STUDY PROTOCOL

Study Title:

A randomized clinical trial comparing laparoscopic or robot-assisted radical/simple hysterectomy versus abdominal radical/simple hysterectomy in patients with early-stage cervical cancer

Short title:	G-LACC (German-funded Laparoscopic Approach to Cervical Cancer)
Study design:	Interventional, multicenter, open-label, randomized, controlled non-inferiority trial
Responsible investigator:	Prof. Dr. Peter Hillemanns Hannover Medical School Department of Gynecology and Obstetrics Carl-Neuberg-Str.1 30625 Hannover
Protocol version:	Vs. 2.0
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Protocol SIGNATURES

This clinical study protocol has been approved by the following persons. The following signatures document their approval.

Prof. Dr. Peter Hillemanns Responsible Investigator	Date
Prof. Dr. Armin Koch Trial statistician	Date

INVESTIGATOR'S SIGNATURE PAGE

By my signature, I agree to personally supervise the conduct of the trial and to ensure its conduct in compliance with the protocol, ICH GCP, and the applicable national and European regulations covering the conduct of clinical studies.

Name of study site

Printed name of investigator

Signature of investigator

Date

Version no.: 2.0; dated 15. May 2024; Short study title: G-LACC

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List of Abbreviations and Definitions of Terms

^{99m}TC	Technetium-99m Radiotracer
AGO	Working Group Gynecological Oncology
AH	Abdominal Hysterectomy
ARH	Abdominal Radical Hysterectomy
CC	Cervical Cancer
CI	Confidence Interval
cm	centimeter
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DGGG	German Society for Gynecology and Obstetrics
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
ESGO	European Society of Gynaecological Oncology
EuroQol	EuroQol Research Foundation
FDA	United States Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FPI	First Patient In
FS	Frozen Section
GCP	Good Clinical Practice
G-LACC	German-funded Laparoscopic Approach to Cervical Cancer
HES	Hematoxylin-Eosin-Safran
HPV	Human Papilloma Virus
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICG	Indocyanine Green
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	Immunohistochemistry
ITT	Intention to Treat
LACC	Laparoscopic Approach to Cervical Cancer
LAVRH	Laparoscopic-Assisted Vaginal Radical Hysterectomy
LH	Laparoscopic Hysterectomy
LN	Lymph Node
LPO	Last Patient Out
LRH	Laparoscopic Radical Hysterectomy
LS	Laparoscopic
LVSI	Lymphatic or Vascular Space Invasion
LYMQOL	Lymphoedema Quality-of-Life Questionnaire

MIS	Minimally Invasive Surgery
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Center for Tumor Diseases
OS	Overall Survival
PALND	Paraaortic Lymph Node Dissection
PLN	Pelvic Lymph Node
PLND	Pelvic Lymph Node Dissection
PP	Per Protocol
QALY	Quality-Adjusted Life Years
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RALS	Robot-Assisted Laparoscopic Surgery
RFS	Recurrence-Free Survival
RVT	Radical Vaginal Trachelectomy
SAE	Serious Adverse Event
SAQ	Sexual Activity Questionnaire
SLN	Sentinel Lymph Node
SNB	Sentinel Node Biopsy
SPEC/CT	Single Photon Emission Computed Tomography/ Computed Tomography
TIF	Trial Investigator File
TMMR	Total Mesometrial Resection
TSC	Trial Steering Committee
ZKS	Center for Clinical Trials

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Sub-Committee Quality of Life	[redacted]
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STUDY SYNOPSIS

Title of study	A randomized clinical trial comparing laparoscopic or robot-assisted radical/simple hysterectomy versus abdominal radical/simple hysterectomy in patients with early-stage cervical cancer
Short term	G-LACC (German-funded Laparoscopic Approach to Cervical Cancer)
Responsible investigator	Prof. Dr. Peter Hillemanns Hannover Medical School Department of Gynecology and Obstetrics Carl-Neuberg-Straße 1 30625 Hannover Germany [redacted]
Study design	Interventional, multicenter, open-label, randomized, controlled non-inferiority trial
Subject population	Female patients with operable early-stage cervical cancer: International Federation of Gynecology and Obstetrics (FIGO) stage IA2 - IB2 < 4cm and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma
Participating study sites	20–30 trial sites in Germany and other countries
Number of subjects	To be enrolled: n = 756 women (378 women per treatment arm) The study is event-driven, at least 45 primary endpoint events need to be observed to demonstrate the non-inferiority of laparoscopic or robot-assisted radical/simple hysterectomy compared to abdominal radical/simple hysterectomy with regard to disease-free survival (DFS) using a pre-defined non-inferiority margin of 2.3 for the hazard ratio (HR). To be assessed for eligibility: n = 2100 women
Objectives	<u>Primary Objective</u> To investigate the oncologic safety of laparoscopic or robot-assisted radical/simple hysterectomy compared to abdominal radical/simple hysterectomy using pre-specified surgical techniques and qualitative standards and to demonstrate the non-inferiority with a non-inferiority margin of 2.3 for the hazard ratio (HR) for disease free survival (DFS), defined as the time from randomization to disease recurrence or death from any cause (whichever occurs first). <u>Secondary Objectives</u>

	To evaluate overall survival, disease recurrence, quality of life, complications and treatment-associated morbidity, treatment costs and cost effectiveness.
Inclusion and exclusion criteria	<u>Inclusion criteria</u> • Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix • Patients with FIGO stage IA2, IB1 or IB2 disease (< 4 cm) • Patients undergoing radical hysterectomy according either to Type II or III (Piver Classification) or to Type B or C (Querleu and Morrow classification) OR Simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer (SHAPE criteria: tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone). Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins. • Performance status of Eastern Cooperative Oncology Group (ECOG) 0–1 • Patient must be suitable candidates for surgery with for instance preoperative Magnetic Resonance Imaging (MRI) and available for assessment of serious adverse events up to 3 or 6 months post-surgery • Patients who have signed an approved Informed Consent • Patients with a prior malignancy only if > 5 years previous with no evidence of disease • Females, aged 18 years or older <u>Exclusion criteria</u> • Any histology other than an adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix • Tumor size 4 cm and greater, estimated by either magnetic resonance imaging (MRI) or clinical examination • FIGO stage IB3 - IV • Patients with a history of pelvic or abdominal radiotherapy • Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2 cm, or histologically positive lymph nodes • Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator)

	• Patients unable to withstand prolonged lithotomy and steep Trendelenburg position • Patient compliance and geographic proximity that do not allow adequate follow-up • Women who are pregnant • Patients with contraindications to surgery • Patients with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
Investigational Treatment	Laparoscopic or robot-assisted radical/simple hysterectomy or abdominal radical/simple hysterectomy
Interventions	Experimental intervention: Laparoscopic or robot-assisted, radical or in case of SHAPE criteria simple hysterectomy. Control intervention: Abdominal, radical or in case of SHAPE criteria simple hysterectomy Duration of treatment: Between 150 and 300 minutes (surgical procedure)
Trial duration	Recruitment: 48 months Study duration per subject: a minimum of 60 months (5 years) The duration of the surgical intervention per participant depends on individual circumstances and will take between 150 and 300 minutes followed by a follow-up period of at least 60 Months (5 years). Duration of the entire trial (first subject in to last subject out): 108 months The study is event-driven and can be terminated after 45 primary endpoint events have been observed.
Randomization	Permuted block randomization with randomly selected block sizes stratified by: • tumor size (< 2 cm vs 2 - < 4 cm) • sentinel node mapping only (Yes vs No) • radical vs simple hysterectomy (SHAPE criteria) • anticipated type of minimally invasive surgery (laparoscopic vs robot-assisted) • center The type of laparoscopic surgery, whether conventional or robotic, is determined by the surgeon based on the surgeon's experience and preference. Patients will be allocated to both treatment arms in a 1:1 ratio. Patients will be randomized using

	the electronic randomization tool provided within the electronic case report form (eCRF)/electronic data capture (EDC) system.
Endpoints/outcomes	Primary endpoint: • Disease-free survival (DFS) Secondary endpoints: • Overall survival (OS) • Disease recurrence • Quality of life including lymphatic side effects • Complications and treatment-associated morbidity • Health care costs
Statistical analysis	Primary endpoints: The primary endpoint disease-free survival (DFS) will be primarily analyzed according to the intention-to-treat (ITT) principle which includes all patients as randomized. The DFS curves will be estimated using the Kaplan-Meier method. A Cox proportional hazards model adjusted for the stratification factors for the randomization will be used for the comparison of minimally invasive and open surgery. Non-inferiority of minimally invasive as compared to open surgery will be declared if the upper boundary of the two-sided 95% confidence interval (CI) for the hazard ratio (minimally invasive/open) is below the predefined non-inferiority margin of 2.3. A sensitivity analysis will be performed according to the per-protocol (PP) principle which includes all randomized patients where surgery has been performed according to the initial randomization. Consistency between results in the ITT and PP analysis is needed to draw meaningful conclusion regarding differences in DFS. Secondary endpoints: Overall survival (OS) will be analyzed in line with the primary analysis of the primary endpoint. Data for other secondary endpoints will be summarized by treatment groups, compared with appropriate statistical tests adjusted in line with the primary analysis of the primary endpoint. Absolute and relative frequencies of serious adverse events (SAEs) will be displayed for the whole population and separately for each treatment group and comparisons between groups using Chi-squared tests will be performed and assessed descriptively. Analyses of DFS and OS in relevant subgroups will also be performed.

1 BACKGROUND AND STUDY RATIONALE

1.1 Overview of disease

Cervical cancer (CC) is the fourth most prevalent form of cancer with more than 530000 women annually and the fourth leading cause of cancer deaths in women worldwide. The burden of disease is mainly centered in developing countries. Despite the major progress in cervical cancer screening and the implementation of preventive Human Papilloma Virus (HPV) vaccination since 2006, cervical cancer is the third leading cause of cancer death among women of the age group 15 to 44 years in Germany.[1–3] With 4600 invasive cervical cancer cases per year, the actual raw incidence rate for Germany in 2014 was 11.3 per 100000 (European standardized for age 9.3 per 100000). About 1560 women die each year. The infection of HPV is necessary but not sufficient in the carcinogenesis leading to cervical cancer. Amongst the high-risk HPV subtypes, 16 and 18 are regarded to be the major triggers of cervical cancer in Europeans.[4] Age, multiple pregnancies, environmental factors such as smoking and use of oral contraceptives can contribute to increasing the risk of developing cervical cancer.

1.2 Prognosis of the Target Subject Population

The total 5 and 10-year relative survival in Germany is 67% and 63%, and ranges in the Nordic countries between 58–67%.[5] The median age of disease in already invasive carcinoma is 55 years in Germany. About three-quarters of these tumors are squamous cell carcinomas. Adenocarcinomas (approximately 20%) rather indicate a higher origin at the transition between the uterus and neck. Stage of disease at diagnosis strongly correlates to prognosis. More than one in two invasive carcinomas are diagnosed in the early stages of the tumor (T1) in Germany.

Lymph node (LN) metastasis worsens the prognosis with a reported 5-year overall survival (OS) rate of less than 75% whereas early stage (stage $\leq$ B1) of disease without lymphatic spread has an OS of >90%. By utilization of the Surveillance, Epidemiology and End Results (SEER) database, 5-year cervical cancer-specific survival rates were 62% when only pelvic LN metastases and 43% when para-aortic LN metastases were documented.[6,7] Stage plays an important role in IIIC1 disease with positive pelvic LN with 75% for T1, 59% for T2, and 39% for T3 with a 36% difference in absolute survival. Lymphatic or vascular space invasion (LVSI) of tumor, depth of tumor invasion in the cervical stroma and size of tumor are also unfavorable prognostic factors.[8]

1.3 Clinical Experience with treatment

Treatment of CC relies on four pillars with surgery, radiotherapy, chemo- and targeted therapies alone or in different combinations. For early stage tumors, surgery constitutes the primary treatment with or without adjuvant treatment depending on prognostic factors. Advanced stage tumors are treated with primary radiotherapy with concomitant chemotherapy.[9]

Surgical Treatment

The surgical therapy of cervical cancer has a long tradition in the controversy. In the 19th century, it was the two Viennese gynecologists Friedrich Schauta (1849–1919) and his disciple Ernst Wertheim (1864–1920) who fiercely debated the better surgery in cervical cancer. In the 1940s, Joseph Vincent Meigs modified the surgical procedure with parametrial resection to the pelvic side wall and systematic pelvic lymph node dissection. The operative mortality was reduced and the 5-year OS achieved 90% and 63% for stage I and stage II disease.[10,11] In 1974, Piver et al. proposed five classes of extended hysterectomy for women with cervical cancer in an attempt to reduce the surgical morbidity.[12] Several groups supported the effect of less radical surgery upon reduced morbidity while keeping the

oncological safety in their studies.[13–15] The development of nerve-sparing surgical methods for the treatment of cervical cancer began more than 30 years ago by Japanese groups.[16,17] It is directly linked to the understanding of functional anatomy and also led to the development of nerve-saving surgical methods in western countries. In 2008, Querleu and Morrow published a classification with four types of radical hysterectomy, type A being the least radical (only minimal paracervical tissue dissection) and D being the most radical procedure.[18] Höckel et al. published in 2009 the Total Mesometrial Resection (TMMR), a surgical technique based on resection of embryological compartments with reduced radicality and pelvic nerve preservation, however, combined with a very meticulous lymphadenectomy.[19] A recent update of his monocentric prospective cohort with 495 patients resulted in good locoregional tumour control and survival rates (5-year DFS 83%, disease-specific survival 89%) without the need for adjuvant radiotherapy but needs to be investigated further in multicenter trials.[20] In search for less radical surgery for tumors of 2 cm and less, the international SHAPE trial evaluated if a simple hysterectomy is oncologically as good as a radical hysterectomy (ClinicalTrials.gov Identifier: NCT01658930) and presented positive results at ASCO 2023.[21] In summary, there is consensus in the western world that surgery is gold standard treatment for early stage disease (≤ IB1 + IIA1) and radiation with concomitant chemotherapy for advanced stages ≥IB2 (except IIA1).

Minimally Invasive Surgery

A revival of the radical vaginal hysterectomy method of Schauta-Stöckel by combining it with a laparoscopic lymphadenectomy was seen in the concept of laparoscopic-assisted vaginal radical hysterectomy (LAVRH), introduced by the Frenchman Daniel Dargent in 1987.[22] In the following two decades, laparoscopic (LS) radical hysterectomy (TLRH) with pelvic (PLND) and paraaortic lymphadenectomy (PALND) gained slowly more widespread acceptance. In Germany, laparoscopic radical hysterectomy was propagated and prospectively evaluated by Achim Schneider and his group.[23] Hertel et al. published their experience with the first 200 patients undergoing LAVRH in 2003.[24] They and others demonstrated the implementation of this method as a routine surgical approach in experienced hands since the incidence of complications decreased significantly when comparing the first half with the second half of patients.[25,26] Soon thereafter, a prospective clinical multicenter study of early cervical cancer FIGO IB1 (tumor size 2 cm and less), "Uterus 6" of the German Association of Gynecologic Oncologists (AGO), was published showing a low recurrence rate of only 3% for patients treated with pelvic lymphadenectomy and radical vaginal trachelectomy (RVT), which influenced the German Guidelines for Cervical Cancer to accept organ-preserving surgery as an oncological safe procedure for the mainly young women who wanted to preserve their fertility.[27,9]

Robot-assisted laparoscopic surgery (RALS) was approved by the United States Food and Drug administration (FDA) for gynecologic procedures in 2005 and gained a steady increase in the acceptance as a valid technique for radical hysterectomy in early cervical cancer – with no obvious differences regarding oncologic safety.[28,29]

The safety and effectiveness of RALS devices for the treatment of cancer, based on cancer-related outcomes such as overall survival, recurrence, and disease-free survival have not been established.[30]

Sentinel Lymph Node Biopsy

The sentinel node biopsy concept (SNB) is well established in the surgical management of several malignancies including melanoma, breast and vulvar cancer. Mainly driven by laparoscopic surgery, the sentinel lymph node concept was explored by various groups.[31] Schneider, Altgassen et al. evaluated in a prospective, multicenter cohort study with 590 cervical cancer patients of all stages the detection rate and diagnostic accuracy to predict the histopathologic pelvic nodal status which showed that the sensitivity of the sentinel concept above all stages was low, however, patients with tumor diameter less than 20 mm had a high negative predictive value of 99.1% and could profit from this concept.[32] In the Senticol II study, the surgical morbidity was significantly reduced in the sentinel lymph node

(SLN) group (SLN 31.4% vs. PLN 51.5%, p = 0.0046). Additionally, they showed that ultrastaging of SLN led to the detection of 39.1% metastatic LN which were not detected by routine PLN and histological examination. The procedure itself was well accepted by more than 95% of the patients. According to these results, SLN has been added to several national and international guidelines (DGGG, NCCN, ESGO) as an alternative to PLN under restricted conditions and after informed consent of the patient [24–26,33] However, despite all these data, SLN biopsy is not a standard of care in most guidelines. Today, the only missing, however, most important data regard survival. No study demonstrated that patients assessed with SLN biopsy alone have the same prognosis as patients undergoing radical PLN. This information is mandatory before presenting SLN biopsy as a standard of care for early cervical cancer. A Chinese randomized trial (NCT02642471) and a prospective multicenter international randomized study Senticol III (NCT03386734) are ongoing.[33] These studies will compare the outcome of patients with negative SLN (experimental arm) vs. patients with negative SLN + PLN (reference arm). The German S3 guidelines (2020) state that SLN biopsy can be performed for tumors less than 2 cm as an alternative to lymphadenectomy.

1.4 LACC trial and its critical debate

The first large randomized controlled trial comparing abdominal open (ARH) and laparoscopic (LRH) radical hysterectomy in early cervical cancer was published in 2018.[34] The LACC study (Laparoscopic Approach to Cervical Cancer) was ended prematurely after an interim analysis and 631 (319 LRH vs. 312 ARH) patients with early cervical cancer in FIGO stage IA1 tumor with lymphatic invasion up to IB1 were evaluated. These patients were recruited from 33 centers worldwide between 2008 and 2017. The trial was funded in part by a grant from Medtronic with only $121,250. No other support was mentioned in the publication.

Although the groups were comparable in terms of patient and tumor characteristics, there was a significant and clinically relevant difference in disease-free survival after 4.5 years. In the LRH group, 86% were free of recurrence, while in the ARH group, 96% showed no tumor (difference -10.6%; 95% CI -16.4 to -4.7). Overall survival was also significantly worse with 93.8% versus 99% (HR 6.0; 95% CI 1.8–20.3), as was the locoregional recurrence-free survival (RFS) 94.3% vs. 98.3% (HR 4.3; 95% CI 1.4–12.6). Therefore, non-inferiority could not be proven. The results of the robot-assisted operations were no better and comparable to those of laparoscopic surgery. In addition, it was shown that the laparoscopic procedure did not lead to a reduction in intra- and postoperative complications, nor was it associated with a better quality of life.

This data was not anticipated and contradicted previous knowledge from retrospective studies as shown for instance in the meta-analyzes by Cao et al. 2015 and Zhao et al. 2017.[35,36] Until then, there were only three prospective studies (max. 68 participants) and several retrospective analyzes. There was no difference in recurrence-free and overall survival between the two procedures in 2922 evaluated patients, but a lower rate of intra- and postoperative complications when operated by laparoscopy.

International reaction in cervical surgery after LACC publication

The results of the LACC study led to a drastic change in therapy methods even before the full publication. As analyzed by Charo et al., there was a drastic decrease of minimally invasive radical hysterectomies in the USA immediately after the first presentation of the preliminary data (51% to 27%).[37] Within a very short time, various editorials appeared which confirmed the results or critically questioned them. Among the criticisms of the study are the lack of operative standardization and expertise. For example, it was not specified how the uterus would be prepared and extirpated although the study protocol provided a quality assessment of the participating centers, which consisted of the submission of 10 cases and two uncut surgical videos. Uterine manipulators were allowed, the use of which appears to be associated with an increased likelihood of tumor cell spillage. Other criticisms relate to the selection of centers

and the incomplete recruitment. The impressively high disease-free survival of 94% in the ARH arm is worth mentioning.

Soon thereafter, multiple retrospective studies were published, some of which showed the same difference as in the LACC study, but some did not describe any survival difference between the procedures. In principle, two different types of these analyses can be distinguished, register analyses and individual center analyses. Major register studies from the USA (4-year mortality 5.3% for ARH versus 9.1% for LRH; HR 1.6; 95% CI 1.2–2.2) and Canada (5-year disease-free survival 83.8% for LRH vs. 91.6% for ARH; HR 1.97; 95% CI 1.1–3.5) showed reduced survival for the laparoscopic procedure.[38,39] Similar analyses from Sweden and Denmark, on the other hand, showed no survival disadvantage for patients treated by laparoscopic surgery.[40,41] The two Scandinavian analyses differ from the others due to their high proportion of robot-assisted procedures and a strong centralization towards highly specialized centers. For example, the 864 patients evaluated by Alfonzo et al. had 88% disease-free survival for the robot-assisted minimally invasive procedure and 84% for the open approach.[40] Criticism of this study is a low disease-free survival in the abdominal arm, which is 10% below the results of the LACC study. Non-inferiority was also shown by the results of the Danish analysis by Jensen et al. They did a longitudinal register analysis and compared patients treated before robotic radical hysterectomy was performed in the respective centers with patients operated after implementation of robotic surgery. There was no difference in disease-specific survival (94.1% before robotic surgery versus 95.9% after robotic surgery).[41] Multiple individual center analyses also yielded a wide variety of results.

Studies which showed a highly standardized technique with avoidance of uterus manipulators and vaginal closure over the tumor in a large number of patients combined with a high level of experience of the surgeons seem to be of great importance. In the study by Köhler et al., this surgical approach led to outstanding survival data (disease-free survival after 4.5 years 95.8%).[42]

Critical points of laparoscopic surgery

Various points were discussed which are blamed to be responsible for the poor performance of laparoscopy. The current data are briefly summarized focusing on three points:

Tumor hygiene – One of the main criticisms of the LACC study concerns the lack of standardization of the surgical procedure. Uterine manipulators were used routinely. By manipulation of the cervix, a tumor cell spread into the abdominal cavity can be assumed. In a proof-of-principle study, we were able to show the simple way of contamination by means of indocyanine green spillage.[43] The study results by Köhler et al. indicate the importance of the so-called tumor hygiene. As early as 2016, Kong et al. described an increased number of recurrences in cases where intracorporal colpotomy (laparoscopic) was performed, compared to those where this occurred vaginally (16.3% vs. 5.1%, p=0.057).[44] In an updated analysis, theses authors were again able to show that intracorporal colpotomy is an independent predictive factor for reduced disease-free survival.[45] The multivariate analysis showed an HR of 3.1 (95% CI 1.2–7.9), which roughly corresponds to the difference between the abdominal and laparoscopic arm of the LACC study. Interestingly, patients who received a vaginal colpotomy in the cited studies of Köhler (4.5 year 95.8%) and Kong (2 years 98%) also showed very high disease-free survival rates, although a possible selection bias cannot be excluded in these studies.

The learning curve – Especially in the case of technically complex procedures, it seems logical that the experience and technical skills of the surgeon influence the success of the operation. It is critical to question whether this point has been adequately taken into account in the LACC study and in the various register studies, especially in the context of the widespread introduction of laparoscopic surgery within a very short period of time.[37] Interestingly, Cusimano et al. in their analysis of Ontario registry data could not confirm an effect of the learning curve.[39] The analysis by the

American Cancer Registry showed no difference in disease-free survival depending on the volume of surgery either.[46] The data from Eoh et al., which indicated a clear effect of the learning curve in the robot-assisted approach, are interesting.[47] There was a significantly lower survival rate in patients who underwent surgery between 2006 and 2013 compared to those treated between 2013 and 2018, who in turn had no survival disadvantage compared to patients who underwent abdominal surgery. To an even greater extent, Matsuo et al. analyzed survival after laparoscopic radical hysterectomy depending on the operational volume of the hospitals, in a retrospective Japanese registry study.[48] After propensity score matching there was an impressively reduced likelihood of recurrence if the patients underwent surgery in an experienced clinic instead of an inexperienced clinic (HR 0.69, 95% CI 0.57–0.84). The data are supported by the register data from Sweden and Denmark and the study by Köhler et al., as they report all the results of highly specialized centers.[40–42] A German population-based cohort study including 413 patients with early stage IA1-IIB2 showed that minimally invasive surgery was associated with improved RFS and OS compared with the open surgery.[49] However, after adjustment for treatment center, the surgical approach was not associated anymore with significant difference in RFS (HR = 0.61, 95% CI 0.31–1.19; p = 0.143).

Probably not only the learning curve seems to be decisive for success, but also the content of this learning curve and the surgical technique ultimately applied. Important results of a retrospective international multicenter study were published by Chiva et al., which showed a disease-free survival at 4.5 years of 79% for laparoscopy and 89% for the abdominal approach.[50] This work demonstrated that the outcomes of laparoscopic surgery were better when no uterine manipulator was used (4.5 years DFS 83% vs. 73%) or a vaginal cuff closure was performed (4.5 years DFS 93% vs. 74%).

Robotic surgery – A major criticism of the LACC study by robotic surgeons is the low proportion of robot-assisted radical hysterectomies (16%). It is argued that the more accurate preparation by robot-assisted surgery leads to better survival rates. This effect could not be demonstrated in the LACC study. On the other hand, the Swedish and Danish registry studies, which evaluated only robot-assisted surgery, have not been able to demonstrate a difference to the abdominal procedure in their large analyses.[40,41] An analysis by Brandt et al. also showed similar results regarding survival in 196 patients at Memorial Sloan-Kettering Cancer Center and pointed out the benefits in terms of a lower complication rate of this surgical procedure.[51] The retrospective character and the possible selection bias are emphasized as a criticism of these studies. It should also be noted that, in the Scandinavian countries in particular, there is a very strong centralization of a few highly specialized clinics, so that the effects of the learning curve will probably have to be taken into account. The large American registry study of Melamed et al. showed reduced disease-free survival for robotic-assisted radical hysterectomy compared to the abdominal procedure (HR 1.61; 95% CI 1.18–2.21).[38]

Recently, a meta-analysis of observational studies by Nitecki et al. found that minimally invasive radical hysterectomy was associated with an elevated risk of recurrence and death compared with open surgery.[52] This meta-analysis of 15 observational studies revealed a 71% higher hazard of recurrence and death in the minimally invasive radical hysterectomy group compared to the open surgery cohort. As a strength of their meta-analysis the authors described their various methods used to minimize confounding, e.g. by demographic factors, tumor stage or size. Unfortunately, the authors did not evaluate the association of different surgical techniques with survival after laparoscopic radical hysterectomy.

Therefore, we performed a systematic review and meta-analysis where we not only compared the survival rates of open hysterectomy and laparoscopic hysterectomy, but also the results of risk groups including uterine manipulators and prophylactic vaginal suture.[53] 30 studies fulfilled the inclusion criteria. Five prospective, randomized-control trials were included. Patients were analyzed concerning the surgical approach (open surgery AH, laparoscopic surgery LH).

Additionally, three subgroups were created for the LH group: high risk group (manipulator), intermediate risk group (no manipulator, intracorporal colpotomy) and low risk group (no manipulator, vaginal colpotomy). Regarding OS, the meta-analysis showed a superiority of AH (0.96 [0.93; 0.97]) over the whole LH group. Interestingly, OS was significantly higher in LH low risk (0.96 [0.94; 0.98]) compared to LH intermediate risk group (0.93 [0.91; 0.94]). OS rates were comparable in AH and LH low risk group. DFS was higher in the AH group compared to the LH group in general (0.92 [0.88; 0.95] vs. 0.87 [0.82; 0.91]), whereas the application of protective measures (no uterine manipulator in combination with vaginal colpotomy) was associated with increased DFS in laparoscopy (0.91 [0.91; 0.95]). In conclusion, DFS and OS in laparoscopy appear to be depending on surgical technique. Protective operating techniques result in improved minimal invasive survival and seem to be equivalent to open hysterectomy.

Ongoing studies

Further surgical studies are urgently needed to provide greater clarity on this issue, in particular with the exclusion of manipulators and laparoscopic colpotomy.[42,43,45] Especially experienced laparoscopic surgeons want to incorporate their own experiences and data into the joint therapy decision. However, retrospective data should carefully be interpreted and potential selection bias should always be considered. The results of the LACC study cannot be discounted without comparable other randomized trials. On the contrary, the results of the LACC study must always remind everyone of the importance of good scientific work. Surgical medicine should also seek randomized-controlled trials. Specialized surgical procedures should be carried out by experts and should be subject to meticulous quality control.

Under Swedish leadership, the RACC study has already been launched, which compares the robot-assisted with the abdominal-open radical hysterectomy, similar to the LACC study.[54] The Chinese LACC trial plans to randomly assign 1448 patients in 28 centers in China to undergo MIS (robot-assisted or laparoscopic RH) or abdominal RH with the requirement of experienced surgeons.[55] Strict guidelines for preventive maneuvers and possible tumor hygiene are not implemented. Therefore, we see a need for a multicenter study comparing the laparoscopic approach with the requirements under which the procedure was developed earlier with the abdominal procedure. This includes measures that prevent peritoneal contamination with tumor.[56] The Trial of Robotic Versus Open Hysterectomy Surgery in Cervix Cancer (ROCC/GOG-3403) in the US has a similar design, in which only the transcervical manipulators are prohibited and specific surgical techniques for "tumor containment" are necessary (ClinicalTrials.gov Identifier: NCT04831580).

1.5 Study Rationale

Laparoscopic, minimally invasive surgery has become standard treatment for several benign and malignant diseases including endometrial or colorectal cancer because of reduced bleeding, less complication rates, shorter hospital stays and lower costs while achieving same oncological safety. After publication of the LACC study, multiple gynecologic oncologists abandoned LRH from their clinical routine. Others criticize study methodology and surgical techniques which were not standardized and suggest strategies to improve outcomes after LRH. Important results of recently published retrospective national and international studies by Köhler, Chiva and Kong et al. demonstrated that the outcomes of laparoscopic surgery were comparable to open surgery when no uterine manipulator, vaginal colpotomy and vaginal cuff closure were performed.[42,45,50] Although patient and tumor characteristics are not completely comparable between those different studies, these results raise the strong hypothesis that outcomes of laparoscopic radical hysterectomy depend on surgical technique and the possibility of tumor cell spread into the intraperitoneal cavity. The updated German S3 guideline emphasizes these very good oncological results of preventive operative measures which underline the hypothesis of necessary surgical tumor hygiene and recommend the validation by randomized studies.[9] Therefore, only a well-designed, well-powered and stringently conducted study with expert

centers can finally answer the question whether LRH is an oncological equivalent and less invasive alternative to ARH in early stage cervical cancer.

The idea of minimal invasive surgery is that patients gain significant profit from decreased morbidity, less pain, shorter hospital stays and faster recovery. Therefore, potential adjuvant therapies like radiation or chemotherapy can be administered directly after the primary treatment due to decreased risks for perioperative complications such as wound healing disorders. Furthermore, the reduced lower socioeconomic burden of laparoscopy is linked to indirect costs with earlier return to work and increased work productivity. The main aim of the G-LACC trial is to prove that laparoscopic hysterectomy is non-inferior to abdominal hysterectomy with regard to safety and disease-free survival. Thus, the G-LACC trial will have significant clinical impact on the future surgical approach for early cervical cancer.

1.6 Risk Benefit Evaluation

The large randomized LACC study demonstrated that MIS is associated with a higher rate of recurrence and death from disease which was confirmed by a recent meta-analysis of observational studies. This is deeply concerning since no clear cause has been established. Most industrialized countries had abandoned the open approach in favor of MIS because of its general advantages with decreased morbidity, less pain, shorter hospital stays and faster recovery. Furthermore, substantial investments in research, education and equipment were triggered in the field of laparoscopic oncologic surgery which led to impressive developments such as fluorescent-guided sentinel techniques. Our sophisticated meta-analysis showed that oncologic outcome in laparoscopy appear to be depending on surgical technique. Protective operating techniques resulted in improved minimal invasive survival and were equivalent to open hysterectomy.[53]

At the moment, a significant number of centers returned back to open surgery, however, others don´t. Since MIS is a standard approach in gynecologic surgery, the results of this trial will have a major impact upon national/international guidelines and therefore, on daily clinical practice. The use of nation-wide clinical tumor and quality registers should further improve the oncologic management and constitute a reliable data source for research and quality improvements. The preliminary analyses from the German cancer centers support an advantage of MIS over open surgery, however, this should be interpreted with caution due to its retrospective nature.[57]

Since the LACC trial demonstrated an association between MIS and disease recurrence, the risk for similar outcomes in the G-LACC trial cannot be neglected. However, the potential risk should be balanced against the potential benefits of MIS including less complications, improved quality of life, and future developments within the laparoscopic platforms.

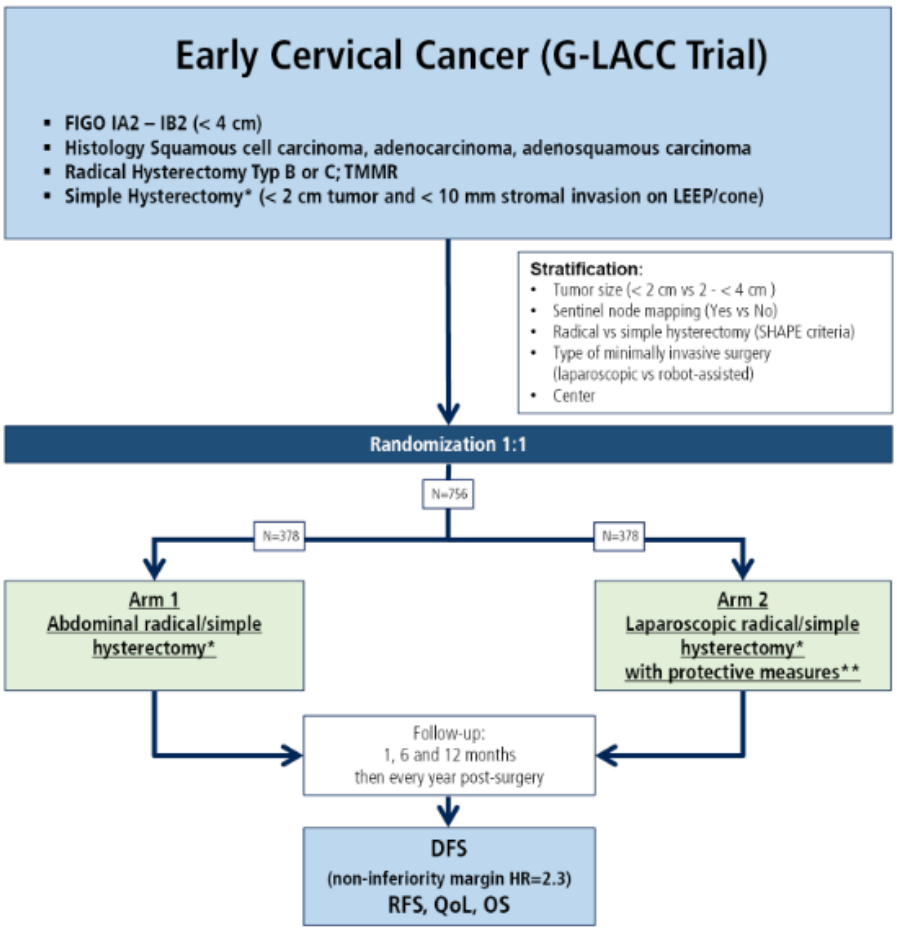
A Data Monitoring Committee (DMC) will be implemented for close supervision of the accruing information, to detect possible harms and to assure continuous risk/benefit assessment. The DMC will review the data in the context of safety, validity and quality on a regular basis and may recommend early termination of the trial in case the DMC observes a significant difference between both treatment groups (see section 7.3 and 9.2).

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

The G-LACC trial is a prospective, interventional, multicenter, open-label, randomized and controlled non-inferiority operative trial.

Eligible patients will be randomly allocated to both treatment arms in a 1:1 ratio. Within an accrual period of 4 years, 378 patients will be included per arm (756 in total) across all sites. The Follow-up period after surgery will take a minimum of 5 years.



Surgery includes pelvic lymph node dissection or optional sentinel lymph node biopsy (SNB) according to current guidelines. Disease-free survival (DFS), Hazard ratio (HR), Recurrence-free survival (RFS), Quality of life (QOL), Overall survival (OS), Sentinel lymph node (SLN).

*1 Simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer (SHAPE-criteria: tumor < 2 cm and < 10 mm depth of stromal invasion (LEEP/cone) BUT has to be determined BEFORE randomization. In case of simple hysterectomy, extrafascial hysterectomy with max. 5 mm vaginal cuff is required to ensure negative margins.

*2 Tumor size assessment: the measurement in any prior specimens (loop/cone excision) has to be taken into account. It is recommended to add together the lateral measurements in different specimens. Tumor size = **loop/cone specimen + surgical specimen.**

** Protective measures: LEEP/conisation before randomization or closure of the vagina before colpotomy. Transcervical manipulators are not permitted. Use of uterus manipulators/cervical adapter (without transcervical device) are allowed only after LEEP/conization

Figure 1: Study scheme of the G-LACC trial

In the standard arm, radical hysterectomy is performed as per standard technique (abdominal radical hysterectomy (Piver type 2 or 3 or Querleu & Morrow Type B or C) with salpingectomy +/- oophorectomy. Ovaries may be removed or preserved +/- transposition. Surgery includes pelvic lymph node dissection or optional sentinel lymph node biopsy (SNB) according to current guidelines in both arms.

In the experimental arm, radical hysterectomy is performed as per standard conventional 2D/3D laparoscopic or robotic assisted technique (Querleu & Morrow Type B or C) with salpingectomy +/- oophorectomy. Ovaries may be removed or preserved +/- transposition. The following protective measures are mandatory for the minimal-invasive arm: LEEP/conization before randomization or closure of the vagina before colpotomy. Transcervical manipulators are not permitted. Use of uterus manipulators/ cervical adapter (without transcervical device) are allowed only after LEEP/conization. Meticulous dissection of pelvic (sentinel) lymph nodes including use of endobags and avoiding the dissemination of cancer cells will be implemented (tumor hygiene).

Due to the positive results of the SHAPE trial presented at ASCO 2023, in both arms simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer[21] (SHAPE-criteria: tumor < 2 cm, < 10 mm depth of stromal invasion (LEEP/cone) BUT has to be determined BEFORE randomization. Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins. Surgery can be performed including removal of the sentinel lymph nodes following the concept of sentinel lymph node biopsy (SNB) and according to the current guidelines.[9]

2.2 Study Objectives

The primary objective is to investigate the oncologic safety of laparoscopic or robot-assisted radical /simple hysterectomy compared to abdominal radical/simple hysterectomy using pre-specified surgical techniques and qualitative standards and to demonstrate the non-inferiority with a non-inferiority margin of 2.3 for the hazard ratio for disease free survival (DFS), defined as the time from randomization to disease recurrence or death from any cause (whichever occurs first).

The secondary objective is to evaluate overall survival, disease recurrence, quality of life, complications and treatment-associated morbidity, treatment costs and cost effectiveness.

2.3 Study Endpoints

2.3.1 Primary Endpoint

Disease-free survival

Disease-free survival (DFS) is defined as the time from randomization to disease recurrence or death from any cause (whichever occurs first). The date of disease recurrence is defined as the date of biopsy.

2.3.2 Secondary Endpoints

Overall survival

Overall survival (OS) is defined as the time from randomization to death from any cause.

Disease recurrence

Local/pelvic recurrence is defined as occurrence of vaginal or pelvic side-wall (including nodal recurrence) recurrence while the occurrence of extra-pelvic lymph nodes, port site metastases, parenchymatous organ, carcinomatosis, bone metastases are defined as distant recurrence at 3 and 4,5 years. A suspicion of disease recurrence (clinical or by imaging) should be verified by histopathological assessment. The date of recurrence of disease is defined as the date of biopsy. Disease recurrence will be assessed and recorded at each follow-up visit starting with 6 months post-surgery (visit 5).

Quality of life including lymphatic side effects

Health Related Quality of Life (HRQoL) will be assessed by using validated questionnaires comprising EORTC QLQ-30, EORTC QLQ-CX24 EuroQoL EQ-5D-3L. Sexual activity will be assessed by using the Sexual Activity Questionaire (SAQ). Additionally, lymphatic side effects will be assessed by the investigator using CTCAE 3.0 and by the patient using the LYMQOL questionnaire. HRQoL and lymphatic side effect assessments will be conducted over the whole course of the trial (see sections 5.3.11 and 5.3.12 and Appendix 0 and 12.2).

Complications and treatment-associated morbidity

Intra- and post-operative treatment-related complications are recorded. In addition, other serious adverse events (SAEs) are captured at each visit starting with surgery (section 6).

Health care costs

Treatment costs and cost effectiveness will be determined as incremental cost-effectiveness ratios. Direct costs will be assessed via internal accounting and billing systems within the hospitals. The quality-adjusted life years (QALYs) gained with the intervention will be calculated based on health status measures for trial participants, with valuations of changes in health status and quality of life based on the EQ-5D questionnaire. QALY calculations will then be used for a cost-utility analysis.

2.4 Number of Subjects / Study Sites

It is planned to assign 756 patients at 20–30 trial sites within a recruitment period of 48 months, which results in about 8 recruited patients per center per year.

The study is event-driven, at least 45 primary endpoint events need to be observed to demonstrate the non-inferiority of laparoscopic or robot-assisted radical/simple hysterectomy compared to abdominal radical/simple hysterectomy with regard to disease-free survival (DFS) using a pre-defined non-inferiority margin of 2.3 for the hazard ratio (HR).

2.5 Study Duration

Study duration is defined as the time from First-Patient-In (FPI) to Last-Patient-Out (LPO). The total duration of the trial will be 108 months (nine years) including a recruitment period of 48 months (4 years).

Study duration per patient will take a minimum of 60 months (5 years). The duration of the surgical intervention per participant depends on individual circumstances and will take between 150 and 300 minutes followed by a follow-up period of at least 60 months (5 years).

The study is event-driven and can be terminated after 45 primary endpoint events have been observed. In addition to that the trial steering committee in cooperation with the DMC may terminate enrolment at any time if this seems to be in the best interest of the patients.

2.6 Randomization

A permuted block randomization with randomly selected block sizes will be conducted to allocate patients to both treatment arms in a 1:1 ratio. The randomization will be stratified by the following factors:

- tumor size (<2cm vs 2-<4 cm)
- sentinel node mapping only (Yes vs No)
- radical vs simple hysterectomy (SHAPE criteria)
- anticipated type of minimally invasive surgery (laparoscopic vs robot-assisted)
- center

Treating physicians will determine the type of minimally invasive surgery (laparoscopic or robot-assisted) upfront randomization to enable stratification. The type of laparoscopic surgery, whether conventional or robotic, is determined by the surgeon based on the surgeon's experience and preference.If a simple hysterectomy is to be considered for patients with low-risk early-stage cervical cancer meeting the SHAPE-criteria (tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone) this must already be determined before the randomization process.

Randomization will only be performed after verification of the patient's eligibility and signed written informed consent. All inclusion criteria and no exclusion criteria must be met. Furthermore, baseline assessment of quality of life questionnaires will be performed prior to randomization.

Patients will be randomized using the electronic randomization tool provided within the eCRF/electronic data capture (EDC) system.

2.7 Protocol Deviations (PD)

All PDs will be tracked and actions will be defined, as feasible. All PDs classified as major will be reviewed in Data Review Meetings by the TSC for the final analysis for assessment of their influence on the quality of the study analysis.

Protocol deviations (PD) are defined as follows:

Major PD:

- Informed consent procedure: ICF not signed and dated by subject/investigator
- Violation of an in- or exclusion criterion
- Deviations affecting the primary endpoint of the study
- Absence of source data in the patient's medical records/absence of the patient file
- Non-compliance with the protocol and protocol amendments (e.g. study visits not in accordance with protocol
- Missing or delayed reporting of serious adverse events (SAE)

2.8 Premature Discontinuation of the Study

The responsible investigator can decide to terminate the trial at his/her study site at any time for reasonable medical or administrative reasons. Stopping rules for individual patients are listed in section 3.4. A DMC will evaluate the trial and the obtained data in the context of safety, validity and quality on a regular basis and can recommend early termination (see section 9.2). If the study is prematurely terminated for any reason, the investigator has to ensure appropriate therapy and follow-up of subjects included in the clinical trial.

3 STUDY POPULATION

3.1 Study Population/Condition

For this trial female patients, aged 18 years or older, with operable early-stage cervical cancer FIGO stage IA2 to IB2 (< 4 cm tumor size) and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma can be recruited. In Germany there are about 4500 cervical cancer cases per year with a percentage of 60% stage I cervical cancer diagnoses.

According to sample size calculation it is necessary to include at least 286 women with early-stage cervical cancer per treatment arm in order to determine the minimally invasive surgery's non-inferiority compared to ARH. For more relevance of the results we plan to recruit 378 patients per arm. Therefore, it is planned to assign 756 patients at 20–30 trial sites within a recruitment period of 48 months, which results in about 8 recruited patients per center per year. It is estimated that 2100 women need to be assessed for eligibility to achieve full patient recruitment.

Participants will be primarily recruited from the centers' patient pools. After obtaining oral and written informed consent all women who undergo screening will be documented in a screening and enrollment log. Patients who sign an informed consent form but do not meet eligibility criteria are defined as screening failures. Eligible patients meeting all inclusion and no exclusion criteria will be randomly allocated to one of both treatment arms. A subject-ID will be assigned which will also be documented in the screening and enrollment log. It is composed of two digits for the site and 3 digits for the sequential number of the patient in the site, e.g. 02-004.

Additionally, it is planned to collect biomaterials at different time-points during the course of the trial. This includes urine samples and pap smear (thin prep) from the cervix either at visit 2 or visit 3 as well as blood samples and tumor material at visit 3. Biomaterials will be labeled with the subject ID as well. The following abbreviations will be used: B = blood sample, T = tumor material, L = lymph node material, P = pap smear from cervix (thin prep), U = urine. The final label will be composed as follows: **CENTER (_ _) _ Randomization Number (_ _ _) _ BIO _ Visit No. _ Material (T = Tumor/B = Blood/L = Lymph/P = Pap Smear/U = Urine)**

e.g. 01_001_BIO_1_T, indicating a probe from: center 1, randomized patient 1, drawn at visit 1, Tumor Material. Furthermore, registration data has to be entered to an electronic Case Report Form (eCRF).

These biomaterials will then be used to enable accompanying scientific projects related to the treatment of cervical cancer in the future. Biomaterials will only be collected if the patient agrees to these procedures and signs a separate consent for the collection of biomaterials.

3.2 Inclusion Criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

1. Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix
2. Patients with FIGO stage IA2, IB1 or IB2 disease (< 4 cm)
3. Patients undergoing radical hysterectomy according either to Type II or III (Piver Classification) or to Type B or C (Querleu and Morrow classification)

   OR

   Simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer (SHAPE criteria:

tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone). Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins.

4. Performance status of ECOG 0-1
5. Patient must be suitable candidates for surgery for instance with preoperative MRI and available for assessment of serious adverse events up to 3 or 6 months post-surgery
6. Patients who have signed an approved Informed Consent
7. Patients with a prior malignancy only if > 5 years previous with no evidence of disease
8. Females aged 18 years or older

3.3 Exclusion Criteria

Patients eligible for inclusion in this study must not meet any of the following criteria:

1. Any histology other than an adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix
2. Tumor size 4 cm and greater, estimated by either magnetic resonance imaging (MRI) or clinical examination
3. FIGO stage IB3 - IV
4. Patients with a history of pelvic or abdominal radiotherapy
5. Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2 cm, or histologically positive lymph nodes
6. Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator)
7. Patients unable to withstand prolonged lithotomy and steep Trendelenburg position
8. Patient compliance and geographic proximity that do not allow adequate follow-up
9. Women who are pregnant
10. Patients with contraindications to surgery
11. Patients with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)

3.4 Premature Subject Discontinuation (Drop-Out)

Participation in the clinical trial is voluntary. Subjects have the right to withdraw consent and discontinue participation in the study at any time for any reason and without prejudice to further treatment. Subjects are not obliged to state a reason for discontinuation but investigators are asked to try to identify the reason. During the initial informed consent procedure subjects will be asked for their consent to be contacted for a final examination irrespective of whether they have discontinued their study participation prematurely or not.

The investigator has the right to withdraw a subject from the study if the subject's safety or wellbeing is compromised or if the subject is not compliant. Subjects who discontinue the treatment for any reason will remain in the study to be evaluated for efficacy and safety endpoints and will be expected to continue study visits.

Concern for the interests of the subject must always prevail over the investigator's/study interests. The investigator must ensure appropriate treatment of the subject after withdrawal.

Whenever possible, investigators should discuss discontinuation of an individual subject with the responsible investigator in advance.

Medical circumstances that may lead to exclusion of the subject include but are not restricted to:

- Occurrence of AEs or SAEs which preclude study treatment or further study participation
- Occurrence of any of the predefined exclusion criteria
- Significant protocol violation including non-compliance with study assessment
- Subject requests to discontinue for any reason; it is important to determine whether the request is primarily due to an SAE, lack of efficacy or other reason.

4 TREATMENT PLAN

4.1 Treatment plan

The screening/baseline evaluations are performed to determine the subject's eligibility for study participation and for determination of the baseline status. In the actual treatment period, an abdominal radical hysterectomy or minimally invasive surgery (conventional laparoscopic or robot-assisted) will be performed with pelvic lymphadenectomy (LNE) or optional sentinel lymphadenectomy during visit 3 (day 0). As diagnostic test sentinel lymph node biopsy and/or complete lymphadenectomy is recommended before radical hysterectomy to assess the lymph node status (frozen section) in order to avoid the combination of radical surgery and radiochemotherapy by abandoning the radical hysterectomy in case of lymphatic spread. Following the recent presentation of the SHAPE trial results at ASCO 2023: if a simple hysterectomy is to be considered for patients with low-risk early-stage cervical cancer meeting the SHAPE criteria (tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone) this must already be determined before the randomization process. Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins. Patients meeting the inclusion criteria and not fulfilling the exclusion criteria will be randomized (see section 2.6) to one of the following arms:

Experimental Treatment

In the standard arm, radical hysterectomy is performed as per standard technique (abdominal radical hysterectomy (Piver type 2 or 3 or Querleu & Morrow Type B or C) with salpingectomy +/- oophorectomy. Ovaries may be removed or preserved +/- transposition. Surgery includes pelvic lymph node dissection or optional sentinel lymph node biopsy (SNB) according to current guidelines in both study arms.

In the experimental arm, radical hysterectomy is performed as per standard conventional 2D/3D laparoscopic or robotic assisted technique (Querleu & Morrow Type B or C) with salpingectomy +/- oophorectomy. Ovaries may be removed or preserved +/- transposition. The following protective measures are mandatory for the minimal-invasive arm: LEEP/conization before randomization or closure of the vagina before colpotomy. Transcervical manipulators are not permitted. Use of uterus manipulators/ cervical adapter (without transcervical device) are allowed only after LEEP/conization. Meticulous dissection of pelvic (sentinel) lymph nodes including use of endobags and avoiding the dissemination of cancer cells will be implemented (tumor hygiene).

Due to the positive results of the SHAPE trial presented at ASCO 2023, in both arms simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer (SHAPE-criteria: tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone) BUT has to be determined BEFORE randomization. Surgery can be performed including removal of the sentinel lymph nodes following the concept of sentinel lymph node biopsy (SNB) and according to the current guidelines. Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins.

The Follow-Up period begins 1 month (+/- 7 days) after surgical treatment and will take a minimum of 5 years per patient.

4.1.1 Surgical treatment

A pelvic examination will be performed under anesthesia, to verify the clinical stage. The operative treatment starts with injection of tracer (^{99m}Tc and blue dye and/or ICG and/or blue dye) subepithelially in the uterine cervix, and SLN biopsy with frozen section which is recommended for all patients to allow (secondary) pathological ultrastaging. For laparoscopic treatment an intrauterine manipulator is not allowed. The abdomen is then entered according to the

result of the randomization. After extirpation of the sentinel nodes, pelvic lymphadenectomy is performed according to current guidelines followed by the radical hysterectomy. Ovaries may be removed or preserved +/- transposition. In case of leaving the ovaries *in situ* it is recommended that the salpinges are extirpated. If surgery is performed by laparoscopy (conventional or robotic assisted can be chosen according to the discretion of the surgeon) the lymph nodes are retrieved via specimen retrieval bags and the hysterectomy specimen is retrieved via the vagina. Closure of the vagina to cover the cervix (vaginal cuff) before colpotomy is mandatory in the laparoscopic group unless LEEP/conization has been performed before randomization. Transcervical manipulators are not permitted. Use of uterus manipulators/ cervical adapter (without transcervical device) are allowed only after LEEP/conization (with clinical R0 resection).

If a simple hysterectomy is to be considered for patients with low-risk early-stage cervical cancer meeting the SHAPE criteria (tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone) this must already be determined before the randomization process. The technique of simple hysterectomy follows the classical procedure either in the standard arm (abdominal) or experimental arm (laparoscopy) according to randomization result. Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins.

Definition of radical hysterectomy

The surgical treatment is based on the valid local guidelines for the treatment of cervical cancer.[58,59] The extend of surgery should be linked to the classification of Querleu & Morrow and/or Piver.[18,60]

Definition of anatomical boundaries for pelvic (and paraaortic) lymphadenectomy

The lymphadenectomy is defined as resection of all fatty tissue and lymph nodes in the areas according to Marnitz et al. (Figure 2).[61] The extent of lymphadenectomy includes for the pelvis the common iliac (2), external iliac (3), internal iliac nodes (5) and obturator fossa (4). If a paraaortic lymph node dissection is necessary the paraaortic lymphadenectomy includes the paracaval, interaortocaval and paraaortal tissue (1) up to the renal veins.

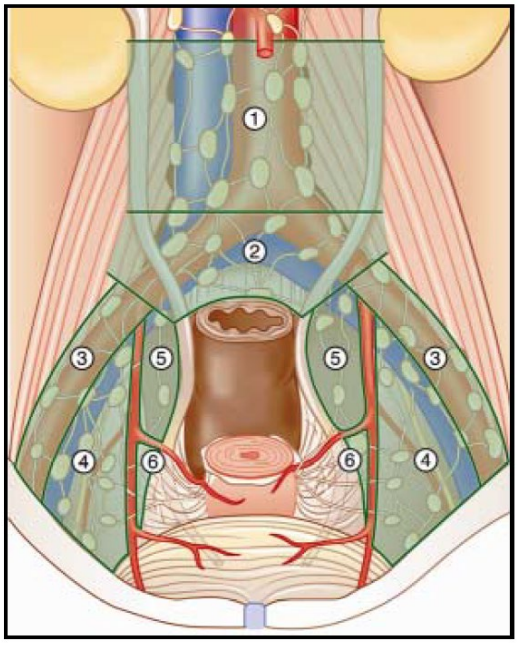


Figure 2: Areas of lymph node dissection[61]

4.1.2 Sentinel Node Biopsy procedure

The surgical procedure starts with marking, identification and dissection of the sentinel lymph nodes and should be performed described as below regardless the treatment arm.

Cervical injection of isotope (^{99m}Tc), will be performed on the day before (long protocol) or on the morning of surgery (short protocol). The report provided by the nuclear physician will detail number and location of SLN according to the Marnitz classification.[61] Intracervical injection for sentinel lymph node detection with blue dye and/or ICG will be performed directly before operation.

The surgical access will be obtained according to the result of the randomization (laparoscopy or open surgery). Once the nodal pelvic and para-aortic areas are visible (especially after adhesiolysis), the areas are explored with the Gammaprobe to detect radio-labelled SLN. If ICG is used an endoscope with fluorescence imaging is mandatory (i.e. FireFly®). The "hot" and/or "coloured nodes" are biopsied by a specific incision. Laparoscopic extraction of the SLN must be performed with an extraction bag or through a port to avoid port-site contamination. A correlation should be performed with the result of the lympho-scintigraphy or SPECT/CT. Radioactivity and colour of the nodes is verified again after extraction. Number and location of SLN has to be noted on histopathological examination requirement form and surgical report according to the classification of Marnitz.[61] SLN are given to the pathologist for frozen section (FS).

Safety algorithm of sentinel lymph node biopsy

All the preoperative lympho-scintigraphy or SPECT/CT mapped nodes must be harvested. All suspicious nodes must be removed. In case of unilateral pelvic non-detection of SLN, a complete lymphadenectomy on that site should be performed. Inspection of the nodal areas during the radical /simple hysterectomy (especially parametria) is necessary. Nodes macroscopically suspect of metastatic disease are defined as such regardless of ICG uptake or technetium/Patent Blue positivity, and must be resected and noted in the study file.

Pathology of sentinel lymph nodes – frozen section

SLNs will be cut in half along their long axis. One of the two parts will be examined in FS in one level after staining with Hematoxylin-Eosin (HE). The other half of the node will be immediately fixed for the definitive examination.

Definitive examination and ultrastaging

Histological examination of all SLNs will be performed after staining with hematoxylin-eosin (HE) on sections of 200 microns. Negative SLNs with HE, will undergo immunohistochemistry (IHC) with anti-cytokeratin AE1-AE3.

Non-sentinel lymph nodes will be examined after staining with HE. Histological analyses will be carried out systematically in the same center by the same pathologist expert for SLN biopsy.

The isolated tumor cells are defined as < 0.2 mm, micrometastases, between 0.2 mm and 2 mm and macrometastases as > 2 mm.[62]

4.1.3 Sentinel Lymph Node algorithm

The sentinel lymph node algorithm includes;

- Intracervical injection of ICG and/or blue dye and Technetium-Isotope (^{99m}Tc)
- Planar lympho-scintigraphy or SPECT/CT with report of number and location of SLN according to the Marnitz classification[61] if available at the study center

- Removing of SLN according to the result of the lympho-scintigraphy or SPECT/CT or as visualized by ICG/blue staining
- Using extraction bag for SLN in laparoscopic approach
- Resection of all macroscopic suspicious lymph nodes regardless of mapping success or not

4.2 Duration of Treatment

The duration of the surgical intervention per participant depends on individual circumstances and will take between 150 and 300 minutes followed by a Follow-Up period of at least 60 months (5 years).

5 STUDY PROCEDURES / EVALUATIONS

5.1 Study Calendar

Study phase	**Screening/ Baseline**		**Treatment**	**Follow-up**						
Procedures	**Visit 1** – Screening (Day –28 to –1	**Visit 2** – Enrollment (Day -28 to - 1)	**Visit 3** – Surgery (Day 0)	**Visit 4** – FU 1 (1 month +/- 7 days)	**Visit 5** – FU 2 (6 months +/- 3 weeks)	**Visit 6** – FU 3 (1 year +/- 1 month)	**Visit 7** – FU 4 (2 years +/- 1 month)	**Visit 8** – FU 5 (3 years +/- 1 month)	**Visit 9** – FU 6 (4 years +/- 1 month)	**Visit 10** – FU 7 (5 years +/- 1 month)
Informed Consent	X									
Eligibility Criteria	X									
Pregnancy Test[1]	X									
Demographics and medical history	X									
Randomisation[2]		X								
Record surgical procedure performed and localization of sentinel lymph node			X							
Record intra-operative complications[3]			X							
Pap smear from cervix[4]		X[5]	X[5]							
Urine sample[4]		X[5]	X[5]							
Length of stay				X						
Record post-operative complications				X	X	X				
Record pathology of the uterus				X						
Record adjuvant treatment						X				
Collection of blood for biobank[4]			X							
Collection of tumor material (Hysterectomy and lymph nodes) specimens)[4]			X							

Quality of life questionnaires[6]	X			X	X	X	X	X	X	X
Lymphatic side effects[7]	X			X	X	X	X	X		
Follow-up care (according to national guidelines)				X	X	X	X	X	X	X
Record if recurrence					X	X	X	X	X	X
Serious Adverse Events			X	X	X	X				

[1] Serum pregnancy testing at screening for women of childbearing potential only; [2]Randomisation only after completed quality of life questionnaires; [3] According to Rosenthal (Appendix 12.1); [4]Biomaterials will only be collected if separate Informed Consent is signed by the patient; [5]These assessments can be carried out either at visit 2 (enrollment) or visit 3 (surgery) [6]EORTC QLQ-C30 + EORTC QLQ-CX24, EuroQol EQ-5D-3L + SAQ (Appendix 0); [7] Lymphatic side effects according to the CTCAE 3.0 and LYMQOL Questionnaire (Appendix 12.2). The LYMQOL needs to be completed only if the patient reports that she has lymphedema

5.2 Study Evaluations

5.2.1 Screening/Baseline Evaluations (Visit 1, Day -28 to -1)

The beginning of the screening period per subject is defined by the date of written consent. Screening and baseline assessments (Visit 1) will be performed as close as possible to inclusion and all results will be available for inclusion. The Investigator will complete the inclusion checklist prior to enrolling the patient in the trial. Results of any tests available apart of routine care, which may have been performed by the referral hospital within the specified time window but prior to informed consent, do not need to be repeated.

The following screening/baseline evaluations are performed to determine the subject's eligibility for study participation and for determination of the baseline status:

- Check of Inclusion/Exclusion criteria
- Medical History
- Recording of demographic and medical history
- Completion of Quality-of-life questionnaire (Appendix 0)
- Completion of Lymphatic side effects questionnaire (Appendix 12.2)

For a detailed description of the assessments, please see section 5.3.

Patients meeting the inclusion criteria and not fulfilling the exclusion criteria will be randomized to one of the treatments arms at visit 2 (day -28 until -1). It is not necessary for the subject to be present at visit 2.

Each subject must be comprehensively informed about the clinical trial and must give her/his written consent before inclusion in the clinical trial.

A subject who has given informed consent and failed to meet all inclusion criteria and/or meet at least one exclusion

criterion is defined as a screening failure.

5.2.2 Enrollment (Visit 2, Day -28 to -1)

Permuted block randomization will be performed with randomly selected block sizes stratified by:

- tumor size (<2cm vs 2-<4 cm)
- sentinel node mapping only (Yes vs No)
- radical vs simple hysterectomy (SHAPE criteria)
- anticipated type of minimally invasive surgery (laparoscopic vs robot-assisted)
- center

Randomization will only be performed after verification of the patient's eligibility and signed written informed consent. All inclusion criteria and no exclusion criteria must be met. Furthermore, baseline assessment of quality of life questionnaires will be performed prior to randomization.

Please note: if a simple hysterectomy is to be considered for patients with low-risk early-stage cervical cancer this must already be determined before the randomization process.

Patients will be allocated to both treatment arms in a 1:1 ratio. Patients will be randomized using the electronic randomization tool provided within the electronic case report form (eCRF)/electronic data capture (EDC) system.

In addition, the following evaluations are performed:

- Collection of urine sample for biobank (first void urine, self-collected by patient)
- Collection of pap smear from cervix (thin prep)

5.2.3 Treatment Visit (Visit 3, Day 0)

After enrollment in the trial and randomization in one of the treatment arms the surgery takes place at visit 3 (day 0). The duration of the surgical intervention per participant depends on individual circumstances and will take between 150 and 300 minutes. The surgical procedure is recorded and the sentinel lymph node localized. For a detailed description of the treatment procedure please see section 4.1. In addition, the following evaluations are performed:

Before surgery and desinfection:

- Collection of blood for biobank
- If not done at visit 2: Collection of urine sample for biobank (first void urine, self-collected by patient)
- If not done at visit 2: Collection of pap smear from cervix (thin prep)

During/after surgery:

- Record surgical procedure performed and localization of sentinel lymph node
- Record of intraoperative complications
- Collection of tumor material (if available) and lymph node specimens

- Recording of serious adverse events

5.2.4 Follow Up Visits

The Follow Up period begins with visit 4 (1 month after surgery +/- 7 days) and lasts for at least 5 years. Completed assessments will be collected either in connection to the visit at the clinic, electronically (eCRF) or per conventional mail.

The following evaluations are performed during the Follow-up period:

- Length of stay (visit 4)
- Recording of post-operative complications (visits 4–6)
- Recording of pathology of the uterus (visit 4) *
- Record of adjuvant treatment (if applicable, visit 6)
- Quality of life questionnaire (visits 4–10)
- Lymphatic side effects questionnaire (visits 4–8)
- Record of recurrence (if applicable, visits 5–10)
- Adverse events (visits 4–8)

* Tumor size assessment in case of prior LEEP/cone excision should be estimated according to the College of American Pathologists (CAP). In providing the final tumor dimensions, the measurements in any prior specimens, for example LEEP/cone excision, will need to be taken into account. Although it may overestimate the maximum horizontal extent, it is recommended to add together the maximum lateral measurements in different specimens when calculating the final horizontal extent.[63,9] For a detailed description of the assessments, please see section 5.3.

5.3 Assessments

5.3.1 Informed Consent

Each subject must be comprehensively informed about the clinical trial and must give her/his written consent before inclusion in the clinical trial. The investigator should explain that trial participation is voluntary and that withdrawal from the trial is possible without any disadvantages to the patient's further treatment at any time and for any reason. The patient information/informed consent form has to be signed by the patient and the investigator. One document (may be a copy) will be given to the patient, the other remains at the trial site. No study procedures are allowed to be conducted until patient's signed and dated informed consent has been obtained. It is planned to collect biomaterials during the study at pre-defined time points. Patients will be asked at study inclusion to give separate (independent of participation in the primary interventional trial) informed written consent before collection of biomaterials.

5.3.2 Eligibility Criteria

The investigator will assess patients for eligibility at the screening visit after the written informed consent has been obtained. Patients eligible for trial participation have to meet all of the inclusion criteria and none of the exclusion criteria (for details see section 3.2 and 3.3).

5.3.3 Demographics and Medical history

Demographic data and medical history will be recorded at screening/baseline visit (visit 1) after written and oral informed consent was obtained. Demographic data includes gender, year of birth, height, weight and ethnic origin. For medical history please record the following data: FIGO stage (IA2, IB1 or IB2), preoperative LEEP/cone excision (yes/no). In case of preoperative LEEP/cone excision, please record: histology according to cone excision (primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma), tumor size (horizontal extent in mm), depth of invasion (in mm), tumor grading (G1-G3), ECOG performance status (0 or 1).

5.3.4 Record surgical procedure performed and localization of sentinel lymph node

Hospital:	City:		Country:	
Date of surgery:				
Surgical approach according to randomization:	Laparoscopic/robot-assisted approach		Abdominal approach	
Operation time (skin to skin):				minutes
Estimated blood loss:				ml
Transfusion	Yes -> Number of erythrocyte concentrates		no	
Simple or type of radical hysterectomy according to Querleu-Morrow classification:	Simple	B1	B2	C1
Complete/radical lymphadenectomy performed	complete left side		complete right side	
Sentinal lymph node procedure only?	yes		no	
Localisation of sentinel lymph nodes:	left common iliac		right common iliac	
	left external iliac		right external iliac	
	left internal iliac nodes		right internal iliac nodes	
	left obturator fossa		right obturator fossa	
Type of uterus manipulator:				
Vaginal closure before colpotomy? (Indicate method)	Vaginal cuff			
	Stapler			
	Sling			
	Other			
	None			
Salpingectomy:	yes		no	
Oophorectomy:	yes		no	
Transposition of ovaries:	yes		no	
Nerve sparing surgery:	yes		no	
Conversion to open surgery:	yes		no	
Intraoperative complications - indicate what kind	yes		no	
Organ injury (please indicate below):				
Urinary Bladder:	yes		no	
Ureter:	yes		no	
Small Bowl:	yes		no	
Colon:	yes		no	
Blood vessel:	yes		no	
Nerve:	yes		no	
Other (please mention):	yes		no	

5.3.5 Record intraoperative complications

Please record intraoperative complications according Rosenthal classification (see Appendix 12.1 for further information).

5.3.6 Length of stay

Please record the number of days spent in hospital.

5.3.7 Record post-operative complications

Please record post-operative complication and state if any of the following adverse events occurred: abdominal pain, constipation, fatigue, paresthesia, peripheral sensory neuropathy, urinary incontinence, urinary retention, dyspareunia, pelvic pain, lymphedema, hot flashes.

5.3.8 Follow-up care according to national guidelines

Please record if a Follow-up care according to national guidelines has been performed. Follow-up care includes physical examination and medical consultation among other optional procedures (e.g. tumor marker or cytology).

5.3.9 Record pathology of the uterus

Please state the pathology report of the uterus as given from the pathology department of your institution. The report should include tumor type, tumor horizontal extent, depth of invasion, grading, presence of lymph vascular involvement (L-Status), presence of vascular involvement (V-Status) perineural invasion (Pn-Status), parametria (left and right in mm), nodal status (number of positive sentinel lymph nodes out of total sentinel lymph nodes for left and right pelvis; number of positive lymph nodes out of total lymph nodes; number of positive paraaortal lymph nodes out of total paraaortal lymph nodes), presence of micrometastasis and presence of isolated tumor cells.
Tumor size assessment in case of prior LEEP/cone excision should be estimated according to the College of American Pathologists (CAP). In providing the final tumor dimensions, the measurements in any prior specimens, for example LEEP/cone excision, will need to be taken into account. Although it may overestimate the maximum horizontal extent, it is recommended to add together the maximum lateral measurements in different specimens when calculating the final horizontal extent.[63,9]
State the final estimated tumor size (in mm), final estimated depth of invasion (in mm) and final TNM status.

5.3.10 Record adjuvant treatment

Adjuvant treatment of patients is recommended according to national guidelines. Please record the adjuvant treatment. E.g. adjuvant post-operative treatment (Yes/No), chemotherapy only (Yes/No), radiation therapy (Yes/No), chemoradiation (Yes/No).

5.3.11 Biosampling (Collection of biomaterials)

An optional translational research component is included within the study. Prospectively collected blood and tumor samples will be collected from the participating centers. Additionally, already processed tumor material can be requested from the individual pathological departments.

These biomaterials will be used to enable accompanying scientific projects related to the treatment of cervical cancer in the future. Biomaterials will only be collected if the patient agrees to these procedures and signs a separate consent for the collection of biomaterials.

Tumor material will be collected during surgery (visit 3) to allow correlation of molecular tumor characteristics with clinically relevant endpoints. Hysterectomy and lymph node specimens will be collected at visit 3 and processed

according to the current valid German S3 guideline [9] (or national equivalent) and sections 4.1.1 and 4.1.2. In addition, blood samples will also be collected at visit 3 and pap smear from cervix (thin prep) as well as urine samples will be collected either at visit 2 or at visit 3 (see section 5.1).

A subject-ID will be assigned which will also be documented in the screening and enrollment log. It is composed of two digits for the site and 3 digits for the sequential number of the patient in the site, e.g. 02-004. Biomaterials will be labeled with the subject ID as well. The following abbreviations will be used: B = blood sample, T = tumor material, P = pap smear/ smear from cervix (thin prep), U = urine. The final label will be composed as follows: **CENTER (_ _) _ Randomization Number (_ _ _) _ BIO _ Visit No. _ Material (T = Tumor/L = Lymph/B = Blood/P = Pap Smear/U = Urine)**

e.g. 01_001_BIO_1_T, indicating a probe from: center 1, randomized patient 1, drawn at visit 1, Tumor material. Furthermore, registration data has to be entered to an electronic Case Report Form (eCRF).

The aims of the translational studies are to evaluate and validate novel prognostic and predictive biomarkers for lymph node metastasis, recurrence and survival. The investigated biomarkers will be correlated with clinically relevant endpoints. Additionally, biomaterials will be analyzed with regard to structure and composition of the immunological tumor microenvironment and the expression level of biomarkers that represent promising targets for cellular immunotherapy. Adoptive immunotherapy will play a major role in future therapeutic strategies for cervical cancer and large collections of biomaterials are missing. In selected cases viable tumor material will be collected to generate cell models to investigate novel immunotherapeutic approaches against cervical cancer.

5.3.12 Quality of Life Assessments

In order to compare the grade of short- and long-term effects on the patients' HRQoL between both treatments (ARH und LRH) all participants will be asked to complete QoL questionnaires at different times over the course of the trial. The QoL assessments' focus will be on late side-effects such as bladder dysfunction, sexual activity, physical-, emotional, and role functioning as well as fatigue and pain.

Patients will complete HRQoL questionnaires in an appropriate language either as electronical patient reported outcome measures or during the clinic visits (by manually filling in hardcopy forms, by accessible computer (eCRF) or by mail). Study personnel, e.g. investigator or study nurses, will not have access to the QoL-forms while answered by the patient in order to avoid any influence.

Eligible patients will be informed orally and in writing about the HRQoL assessment before inclusion in the trial. Baseline assessment will be performed before randomisation to one of both treatment arms at visit 1 but only after written and oral informed consent is obtained. Post-surgery assessments will be conducted 1 and 6 months as well as 1, 2, 3, 4 and 5 years after treatment at visits 4 to 10 (see section 5.1). Completed questionnaires will be collected either in connection to the visit at the clinic, electronically via eCRF or per conventional mail and are always considered as source documents.

The following questionnaires will be completed by all patients included in the G-LACC trial as stated above (see Appendix 0):

<u>EORTC QLQ-C30</u>

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0 (EORTC QLQ-C30) is a questionnaire developed to assess the quality of life of cancer patients participating in clinical trials and has been used in a wide range of cancer trials and by a large number of research groups. The EORTC QLQ-

C30 is composed of both multi-item scales and single-item measures. The nine multi-item scales include five functional scales (physical, social, role, cognitive and emotional), three symptom scales (fatigue, nausea/vomiting and pain) and an overall health status / QoL. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. The six single-item scales include dyspnea, sleep, disturbances, appetite loss, constipation, diarrhea and financial impact.[64]

EORTC QLQ-CX24

The EORTC QLQ Cervical Cancer Module (CX-24) is a cervical cancer specific questionnaire developed to assess the quality of life of women with cervical cancer participating in clinical trials. The EORTC QLQ-CX24 is composed of 24 items divided into four functioning scales (body image, sexual activity, sexual enjoyment and sexual/vaginal functioning) and five symptom scales (symptom experience, lymphoedema, peripheral neuropathy, menopausal symptoms, sexual worry).[65]

EuroQol EQ-5D-3L

The EuroQol EQ-5D-3L is a questionnaire to assess the health-related quality of life in clinical trials and real-world clinical settings not specific to any patient group or health condition. The EQ-5D-3L comprises a descriptive system part and visual analogue scale. The descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three levels each (no problems, some problems or extreme problems). The 20 cm visual analogue scale records the patient's self-rated health where the endpoints are labeled with 100 (best imaginable health state) and 0 (worst imaginable health state).[66]

SAQ (Sexual Activity Questionnaire)

The Sexual Activity Questionnaire (SAQ) is a patient self-administered tool to assess the impact that any treatment may have on sexual functioning. The SAQ has been used in several clinical trials of gynecological diseases and is divided into three sections focusing on the relational, emotional, and behavioral characteristics of sexual activity.[67]

5.3.13 Lymphatic side effects

Lymphatic side effects with specific assessment for lymphatic and lower limb complications will be conducted by both, the investigator and the patient. The investigator will assess lymphatic side effects according to the Common Terminology Criteria (CTC) version 3.0 [68], patients will complete the LYMQOL questionnaire [69] (see Appendix 12.2) in an appropriate language either as electronical patient reported outcome measures or during the clinic visits (by manually filling in hardcopy forms, by accessible computer or by mail) and are always considered as source documents. Study personnel, e.g. investigator or study nurses, will not have access to the LYMQOL-form while answered by the patient in order to avoid any influence.

Baseline assessment will be performed before randomization to one of both treatment arms at visit 1 but only after written and oral informed consent is obtained. Post-surgery assessments will be conducted 1 and 6 months as well as 1, 2, 3, 4 and 5 years after treatment at visits 4 to 10 (see section 5.1). Completed assessments will be collected either in connection to the visit at the clinic, electronically or per conventional mail and are always considered as source documents.

LYMQOL

The Lymphoedema Quality-of-Life Questionnaire (LYMQOL) is a validated disease-specific tool which was developed to measure the impact of lymphoedema on patients' quality of live. The LYMQOL needs to be completed only if the

patient reports that she has lymphedema. The LYMQOL questionnaire assesses the impact of lymphoedema on several aspects of the patient's life and covers four domains (symptoms, body image/appearance, function and mood).[69]

5.3.14 Record if recurrence

In addition to the follow-up visits as scheduled in the study calendar (see section 5.1), patients will receive follow-up care according to national guidelines. Follow-up care includes physical examination and medical consultation among other optional procedures (e.g. tumor marker or cytology). In case of abnormal findings during follow-up or clinical suspicion of disease recurrence, imaging diagnostic should be performed. Recurrence of disease must be verified by histopathological assessment. The date of biopsy counts as the date of recurrence. State where the recurrence occurred:

- Type of analysis (CT, MRT, Biopsy, other)
- pelvic recurrences (vaginal vault, parametrium, pelvic lymph nodes, or other)
- extra pelvic recurrences (abdomen, para-aortic lymph nodes, supraclavicular lymph nodes, or other)
- if possible, an additional blood sample should be collected

5.3.15 Safety assessments (intra-/post-operative complications, SAEs)

Treatment related intra-operative complications will be recorded on the day of surgery (visit 3) according to the definition of Rosenthal[70] (see Appendix 12.1).

Treatment related post-operative complications will be recorded starting directly after surgery up to one year thereafter with a first assessment 30 days post-surgery (visits 4 to 6).

Furthermore, other particularly not treatment related serious adverse events (SAEs) will be captured from the day of surgery until one year post surgery (visits 3 to 6). For a detailed definition of SAEs and the recording procedure see sections 6.1 and 6.2. Note that the reporting of all serious adverse events is mandatory for the investigator within 24 hours after awareness (see section 6.2).

SAEs have to be reported in the eCRF. Serious adverse events will be reported anually to the Ethics Committee according to the Declaration of Helsinki.

6 ADVERSE EVENTS

6.1 Definition of Serious Adverse Events

Serious Adverse Event Definition

A Serious Adverse Event (SAE) is defined as any undesirable medical occurrence according to the FDA definition[71]:

- Results in death
- Is life threatening

Report if you suspect that the death was an outcome of the adverse event and include the date. Report if suspected that the patient was at substantial risk of dying at the time of the adverse event.

- Requires hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Results in disability or permanent damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.~~)~~

- Other serious (important medical events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include for instance the development of drug dependence or drug abuse as a result of the study treatment.

6.2 Adverse Event Monitoring and Reporting

SAE Monitoring

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant SAE information in the eCRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the SAE.

SAEs including a risk-benefit evaluation of the study by the responsible investigator will be reported periodically to the Ethics Committee according to the Declaration of Helsinki.

Assessment of Intensity and Causality

The investigator will assess the intensity for each SAE reported from day of surgery until the follow up visit 6. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Furthermore, the investigator is obligated to assess the relationship between trial treatment and each occurrence of SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment will be considered and investigated. For each SAE, the investigator must document in the medical notes that he/she has reviewed the SAE and has provided an assessment of causality. The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment to the responsible investigator.

SAE Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the responsible investigator with a copy of any postmortem findings including histopathology.

7 STATISTICAL METHODS

7.1 Trial Objective and Hypotheses

7.1.1 Hypotheses

The primary objective of the G-LACC trial is to demonstrate the non-inferiority of laparoscopic or robot-assisted radical/ hysterectomy (minimally invasive surgery) compared to abdominal hysterectomy (open surgery) with regard to disease-free survival (DFS) in patients with early-stage cervical cancer. The non-inferiority margin defined for the hazard ratio (HR) for DFS (minimally invasive surgery / open surgery) is 2.3 (for more details about the non-inferiority margin, please see section 7.2). The statistical hypotheses are as follows:

$$H_0: \lambda_{minimal}/\lambda_{open} = HR \geq 2.3$$

$$H_1: \lambda_{minimal}/\lambda_{open} = HR < 2.3$$

where $\lambda_{minimal}$ and λ_{open} are the hazards for the primary endpoint event in the minimally invasive and open surgery arm, respectively.

As soon as the null hypothesis is rejected, the non-inferiority of minimally invasive surgery compared to open surgery with regard to DFS will be concluded.

7.1.2 Primary endpoint

The primary endpoint disease-free survival (DFS) will be analyzed according to the intention-to-treat (ITT) principle which includes all patients as randomized. The DFS curves will be estimated using the Kaplan-Meier method. A Cox proportional hazards model adjusted for the stratification factors for the randomization will be used for the comparison of minimally invasive and open surgery. Non-inferiority of minimally invasive as compared to open surgery will be declared if the upper boundary of the two-sided 95% CI for the hazard ratio (minimally invasive / open) is below the predefined non-inferiority margin of 2.3. A sensitivity analysis will be performed according to the per-protocol (PP) principle which includes all randomized patients where surgery has been performed according to the initial randomization. Consistency between results in the ITT and PP analysis is needed to draw meaningful conclusion regarding differences in DFS.

7.1.3 Secondary endpoints

Overall survival (OS) will be analyzed in line with the primary analysis of the primary endpoint.

Data for other secondary endpoints will be summarized by treatment groups, compared with appropriate statistical tests adjusted in line with the primary analysis of the primary endpoint.

Absolute and relative frequencies of serious adverse events (SAEs) will be displayed for the whole population and separately for each treatment group and comparisons between groups using Chi-squared tests will be performed and assessed descriptively.

Analyses of DFS and OS in relevant subgroups will also be performed for the following subgroups:

- tumor size (<2cm vs 2-<4 cm)
- sentinel node mapping only (yes vs no)
- radical vs simple hysterectomy (SHAPE criteria)

- anticipated type of minimally invasive surgery (laparoscopic vs robot-assisted)
- histological type (squamous cell carcinoma vs. adenocarcinoma, adenosquamous carcinoma)
- grading (G1-2 vs G3)
- center

7.2 Determination of Sample Size

The sample size calculation for the LACC trial was based on an expected DFS rate of 90% in the open surgery group at 4.5 years and a non-inferiority margin of -7.2% for the difference in DFS rate at 4.5 years (minimally invasive surgery minus open surgery). In the end, the observed DFS rate in the open surgery group at 4.5 years was 96.5%, which was much higher than the assumed DFS rate of 90%, and the difference in DFS rate at 4.5 years (minimally invasive surgery minus open surgery) was -10.6% (95% confidence interval [CI]: -16.4% to -4.7%). The hazard ratio for DFS was estimated to be 3.74 (95% CI: 1.63 to 8.58). Thus, the non-inferiority of minimally invasive surgery compared to open surgery could not be concluded in the LACC trial.

The G-LACC trial is planned to demonstrate that the negative impact of minimally invasive surgery on DFS in the LACC trial was the consequence of an inappropriate minimally invasive surgical procedure.[34] Based on previous studies and clinical experience, the 4.5 year DFS rate for patients undergoing open surgery is expected to be 94% in the German / European context, which is more in line with the outcome of the LACC trial than the initially assumed 90% DFS rate in the LACC trial. In accordance with the LACC trial, a non-inferiority margin of -7% for the difference in DFS rate at 4.5 years (minimally invasive surgery minus open surgery) is considered to be clinically acceptable and was therefore also used for the G-LACC trial. Assuming exponentially distributed event times, the hazard rate for DFS in the open surgery group is estimated to be 0.0138, and the respective non-inferiority margin for the hazard ratio for DFS (minimally invasive surgery/open surgery) is calculated as 2.3. This margin is much lower than the observed upper limit of the hazard ratio for DFS of 8.58 in the LACC trial. A DMC is implemented for close supervision of the accruing information. If similar trends as observed in the LACC trial would be observed in the G-LACC trial, it is the obligation of the DMC to stop the trial for futility.

Sample size estimation for the G-LACC trial was performed in nQuery Advisor version 9 using the non-inferiority test for two survival curves using Cox regression. The one-sided type I error is set to 2.5% and the aimed power is set to 80%. With an assumed probability of primary endpoint event of 6% (=1-94%) at 4.5 years in both arms and each patient will be followed-up for about 4.5 years, a sample size of 378 patients per arm (756 patients in total) will be required to observe 45 primary endpoint events to declare the non-inferiority of minimally invasive surgery compared to open surgery with a non-inferiority margin of 2.3 for the hazard ratio for DFS. The study is event-driven and can be terminated after 45 primary endpoint events have been observed.

7.3 Interim Analysis

No statistical interim analysis is planned. As the study objective is to demonstrate that both operation techniques are equivalent regarding the primary outcome, it is important that this equivalence can also be assessed in relevant subgroups with adequate precision. A DMC is implemented that will carefully oversee the conduct of the study and if one type of surgery is substantially superior to the other the study needs to be terminated.

8 DATA MANAGEMENT

8.1 Data recording and record keeping

All study data will be collected by the investigator and/or other study personnel. A clinical trial data base is provided, in which the data are entered via an eCRF. Authorized and trained staff of the study sites will enter the data in the eCRF. Serious adverse events will be documented in the eCRF. Verification of the data in the eCRF occurs by monitoring as well as via range, validity and consistency checks programmed in the system. In certain cases, queries can be detected from the study software or from authorized study staff. Based on the queries, the investigator can review and answer the found discrepancies directly in the system. All changes of data entered in the eCRF can be followed by an audit trail. A quality control will be performed before the database is closed. This procedure is documented. Finally, data transfer takes place for statistical evaluation.

The data management plan contains further details about data management processes.

The investigator agrees to keep the trial investigator file (TIF), including the identity of all participating patients, all original signed informed consent forms, detailed records of treatment, all other applicable study-related documents as well as source documents. The records should be retained by the investigator for at least 10 years after termination or premature discontinuation of the clinical study. Source data have to be kept according to national regulations.

8.2 Data Protection

All study staff has to give due consideration to data protection and medical confidentiality. The collection, transfer, storage, and analysis of personal study-related data are performed pseudonymized according to national regulations. The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. The declaration of data protection is contained within the patient information/informed consent form. At any time, participants may withdraw their consent for any reason without any negative consequences regarding their treatment. Information about subjects will be kept confidential and managed in accordance with all applicable privacy laws, rules, and EU General Data Protection Regulation (GDPR). Subject confidentiality and privacy are strictly held in trust by the participating investigators, the study site personnel and responsible investigator. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The subject's contact or identifying information will be securely stored at each study site for internal use during the study. After completion or premature termination of the clinical trial, all records will continue to be kept in a secure location for as long as dictated by local regulations.

On CRFs or other documents submitted to the Trial steering committee, patients should not be identified by their names, but by a subject identification number. The investigator should keep a subject enrolment log showing subject identification number, names and addresses. Participating patients will be identified by a study specific subject identification number consisting of two digits for the study site and 3 digits for the subject number within the study site. This subject identification number will be used when registering the patient into the study database. The woman's national identification number will not be entered into the database. The key to the code will be available to the investigator only.

9 QUALITY ASSURANCE

9.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be implemented to provide oversight of the conduct of the trial. This includes the practical aspects of the study as well as ensuring that the study continues to be run in a way which is both safe for the patients and provides appropriate safety and efficacy data to the investigators. In discharging its safety role, the TSC will work in conjunction with the Data Safety Monitoring Board that will also be established for the trial (see section 9.2).

Specific responsibilities of the TSC include, but are not limited to, the following:

- to provide overall supervision of the trial
- to approve the main study protocol and any amendments
- to review, select and train the participating trial sites
- to monitor and supervise the trial towards its objectives and its progress
- to take steps to reduce deviations from the protocol to a minimum
- to review relevant information from other sources
- to consider the recommendations of the DMC

Face-to-face meetings – if not possible then web based – were held at regular intervals determined by need and not less than once a year. Routine business was conducted by telephone, email and post. The TSC will have ultimate responsibility for the trial and will assume primacy over the DMC or responsible investigator. The Trial Steering Committee can prematurely terminate the trial.

9.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be implemented to detect possible harms and to assure continuous risk/benefit assessment. The DMC will be composed of independent experts not involved in the conduct of the trial. Details of the definition of DMC, its composition and its roles and responsibilities can be found in a separate DMC charter.

The DMC will review the data in the context of safety, validity and quality and will carry out the following interim analyses during the course of the trial:

- Evaluation of the study data at least once a year or more often in case of an urgent need e.g. incidence rates of SAEs
- Evaluation of the recruitment rate 3 years after the start of the study (FPI) to ensure the protocol-compliant recruitment after four years

The analyses of the DMC result in one of three recommendations. Thereafter, the DMC may recommend continuing, temporarily halting or early terminating the trial. There commendations will be performed based on blinded data. If the committee determines that it is safe to proceed with the study, the DMC recommendation will remain unknown to everyone except the committee members.

9.3 Sub-Committees

9.3.1 Sub-Committee on Translational Research

The study will include a translational research component, which will have its focus on developing and validating novel prognostic and predictive biomarkers for lymph node metastasis, recurrence, and survival. The investigated biomarkers will be correlated with clinically relevant endpoints. Additionally, biomaterials will be analyzed with regard to structure and composition of the immunological tumor microenvironment and the expression level of biomarkers that represent promising targets for cellular immunotherapy. Adoptive immunotherapy will play a major role in future therapeutic strategies for cervical cancer and large collections of biomaterials are missing. In selected cases viable tumor material will be collected to generate cell models to investigate novel immunotherapeutic approaches against cervical cancer. The investigated biomarkers will be correlated with clinically relevant endpoints. It is the Sub-Committee's task to monitor the sample acquisition and to interpret the corresponding results in close consultation with the Trial Steering Committee.

9.3.2 Sub-Committee on Quality of Life

Women of the G-LACC trial will be requested to complete a variety of questionnaires as part of the study protocol. For more information on the content of these questionnaires, please refer to section 5.3.11. The Sub-Committee on Quality of Life will monitor the data acquisition and interpret the corresponding results in close consultation with the Trial Steering Committee. Patient-reported out-come-measures serve to estimate the occurrence and severity of delayed effects associated with both the standard and the experimental treatment arm. Consequently, it becomes crucial to oversee the data acquisition and to provide these affected women with treatments that minimize the risk of long-term side effects.

9.3.3 Sub-Committee on Surgical Quality

To monitor and to maintain high surgical quality is an integral part of the G-LACC study. Surgical quality of the participating centers will be monitored by the Sub-Committee on Surgical Quality. Throughout the study, the decision to stop further participant recruitment at specific centers due to an elevated occurrence of post-operative major complications or suboptimal surgical quality rests with the coordinating investigators of the Sub-Committee on Surgical Quality and the Trial Steering Committee. This action may be taken either temporarily or permanently, in consultation with the Data Safety Monitoring Board.

9.4 Monitoring

Monitoring is performed for reasons of quality assurance and to verify that the study is conducted according to the protocol as well as to legal and regulatory requirements applicable for clinical trials. This trial will be monitored regularly according to GCP and local regulations. All information reported in the eCRFs will also be documented in the patient´s file unless otherwise specified. The investigator will allocate adequate time for visits performed by the monitor. The investigator will also ensure that the monitor is given access to source documents which support data entered into the eCRF´s. The investigator further assures direct access to source data for possible For-Cause-Audits by the TSC.

The clinical study has to be initiated by the monitor at each study site before study subjects are enrolled. Several study sites may be initiated at a combined Initiation-Meeting. At regular monitoring visits, the monitor reviews the eCRF for completeness and clarity and performs source data verification in a risk-based monitoring approach. The monitor also reviews drug accountability records, reporting of SAEs and the TIF. Furthermore, adherence to the

protocol as well as to regulatory requirements is monitored. Problems will be discussed with the investigator. The monitor has to give due consideration to data protection and medical confidentiality. All original data should be readily available for review during scheduled monitoring visits and the investigator has to provide the monitor direct access to all study-related documents. Close-out visits will be done at the end of the trial, when the last patient has completed the clinical study at a certain study center, and in case a site will prematurely be closed.

The monitoring plan serves as a guiding document and describes quality assurance details including monitoring activities, responsibilities and processes as well as further details about the risk-based monitoring approach.

9.5 Selection of participating trial sites and surgeons

In order to guarantee optimal, representative and reliable study results this trial will be conducted in compliance with strict quality criteria. Therefore, all trial sites and surgeons outside the primary investigating center must be approved by the Trial Steering Committee ensuring adherence to protocol.

Prior to participation each interested trial site has to submit a quality assessment form (see Appendix 12.3) to the TSC indicating the site's annual volume of surgical gynecologic oncology cases and surgical cervical cancer cases as well as information regarding the general infrastructure of the center (e.g. ability to perform ultrastaging). Furthermore, each surgeon must submit 10 anonymized surgery reports accompanied by their histopathology reports (if present) from both abdominal and laparoscopic surgeries including pelvic lymphadenectomies of malignancies of the uterus.

It is at the discretion of the TSC to select or deselect individual surgeons from participating in the trial. Only surgeons stated in the quality assessment form are allowed being lead surgeons, amendments during the trial can be made.

During the study, it is at the discretion of the TSC to request on-site audits (For-Cause-Audits) or videos of procedures, to close centers with a higher than average rate of postoperative major complications or poor quality of surgery, from further accrual, temporarily of irrevocably after consultation with the DMC.

10 ETHICAL, REGULATORY AND ADMINISTRATIVE ASPECTS

10.1 Responsibilities

This study will be conducted in compliance with ICH GCP E6 (R2) guidelines, the Declaration of Helsinki and other applicable ethical and regulatory requirements.

Investigators must have sufficient time to conduct the clinical study in compliance with the study protocol. Furthermore, they have to accurately and completely enter study data in the eCRF. Investigators are responsible for obtaining informed consent of the patients as well as for the preparation and maintenance of adequate case files in order to record observations and other data relevant for this clinical study. Besides, they have to file the study-related records in TIF and have to maintain its actuality. They will permit study-related monitoring visits. The investigator must provide direct access to the study site's facilities, to source documents, and to all other study documents.

10.2 Favorable Opinion of Independent Ethics Committee

The study protocol, patient information and informed consent form as well as subject-related documents (e.g. questionnaires) will be submitted to the ethics committee for approval. The study will only commence after approval by the ethics committee. All substantial protocol modifications must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval before implementation. Once approved by the appropriate IEC, the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

10.3 Subject Information and Informed Consent

The investigator is responsible for obtaining patient's written informed consent after adequate explanation of the aim, study assessments, potential risks, benefits, and consequences of the study, as well as alternative treatment options. The patient information/informed consent form has to be signed (in duplicate) by the patient and the investigator. One document (may be a copy) will be given to the patient, the other (original document) remains in the trial investigator file (TIF) at the trial site. No study procedures are allowed to be conducted until patient's written informed consent has been obtained.

The patient information/informed consent form has to be revised whenever important new information becomes available that may be relevant to the subject's consent. The patients have to be informed and asked to give their consent to continue study participation by signing the updated form.

Additionally, it is planned to collect biomaterials at different time-points during the course of the trial as described in section 5.3.11. These biomaterials will be used to enable accompanying scientific projects related to the treatment of cervical cancer in the future. Biomaterials will only be collected if the patient agrees to these procedures and signs a separate consent for the collection of biomaterials. The optional consent for the collection of biomaterials is not a prerequisite for the patient's participation in the trial.

Participation in this clinical trial is voluntary. Withdrawal from the trial at any time and for any reason is without any disadvantages to the patient's further treatment.

10.4 Definition of the Start and End of the Clinical Trial

The start of the clinical trial is first visit first subject (FVFS). The end of the clinical trial is last visit last subject (LVLS).

10.5 Record Retention

All relevant study-related documents have to be archived for at least 10 years after termination or premature discontinuation of the clinical study.

The investigator agrees to keep the TIF, including the identity of all participating patients, all original signed informed consent forms, detailed records of treatment, all other applicable study-related documents as well as source documents. The records should be retained by the investigator for at least 10 years after termination or premature discontinuation of the clinical study. Source data have to be kept according to national regulations.

10.6 Insurance

The trial will be covered by a participant insurance in case the trial site (clinic) does not cover the study by its liability insurance (Haftpflichtversicherung). In addition a group accident insurance covers injuries sustained by patients during their stay at the trial center and on the direct way to the center. All subjects will be informed about their rights and obligations in regard to insurance policies before participating in the study. A copy of the insurance policies will be handed out to each subject on request.

10.7 Financing

This study is funded by the German Cancer Aid (Deutsche Krebshilfe).

10.8 Adherence to protocol and amendments

The study protocol must be adhered to ICH-GCP E6 (R2). Deviations must be handled according to chapter 2.7. Listings will be created and discussed within the TSC. Changes or supplements to the study protocol can only be decided on and authorized by the responsible investigator, study coordinator, trial steering committee and statistician, respectively. Once approved by the appropriate Independent Ethics Committee the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

10.9 Publication

The data of the study will be published. Publication of results from single study sites is not anticipated. All participating study sites will be entitled for coauthorship.

The study will be registered at the WHO certified ClinicalTrials.gov registry. ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

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12 APPENDICES

12.1 Intra-operative complications

Classification of Intraoperative Complications (CLASSIC) according to Rosenthal et al.[70]

Table 2 Proposed *Class*ification of *I*ntraoperative *C*omplications (CLASSIC)

Grade	Definition
	The classification exclusively relates to any event occurring between skin incision and skin closure and should be rated directly after surgery. Any event during the index-surgery must be considered, regardless whether it is surgery or anesthesia-related[a].
	Prerequisite: the indication for surgery and the interventions conform to current guidelines
Grade 0	No deviation from the ideal intraoperative course
Grade I	Any deviation from the ideal intraoperative course
	• Without the need for any additional treatment or intervention
Grade II	Any deviation from the ideal intraoperative course
	• With the need for any additional treatment or intervention
	• Not life-threatening and not leading to permanent disability
Grade III	Any deviation from the ideal intraoperative course
	• With the need for any additional treatment or intervention
	• Life-threatening and/or leading to permanent disability
Grade IV	Any deviation from the ideal intraoperative course
	• With death of the patient

[a] The following events are not defined as intraoperative complications: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery, or errors in indication

Quality of Life Questionnaires

EORTC QLQ-C30[64]

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-CX24[65]

EORTC QLQ – CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35.	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4

Please go on to the next page

During the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
48.	Have you worried that sex would be painful?	1	2	3	4
49.	Have you been sexually active?	1	2	3	4
Answer these questions only if you have been sexually active during the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
50.	Has your vagina felt dry during sexual activity?	1	2	3	4
51.	Has your vagina felt short?	1	2	3	4
52.	Has your vagina felt tight?	1	2	3	4
53.	Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54.	Was sexual activity enjoyable for you?	1	2	3	4

EuroQol EQ-5D-3L[66]

By placing a tick in one box in each group below, please indicate which statemer describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

2

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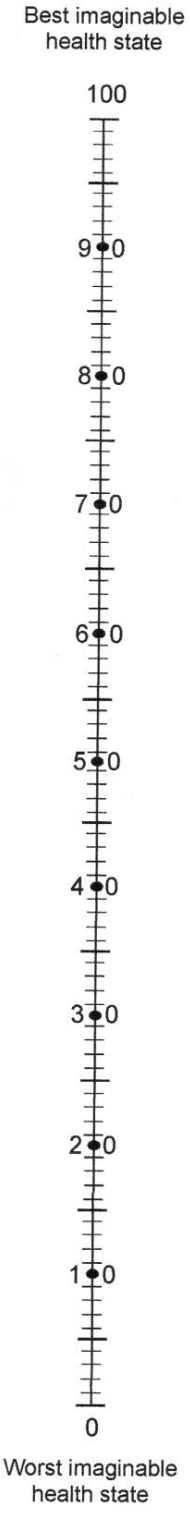
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

SAQ (Sexual Activity Questionnaire)[67]

Age:	Today's date:	Date of birth:

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SEXUAL ACTIVITY QUESTIONNAIRE

Although the following questions are sensitive and personal, please be assured that your responses to these questions will remain confidential.

Section I

	Yes	No
1. Are you currently married or having an intimate relationship with someone?	☐	☐
2. Have you changed your sexual partner in the last 6 months?	☐	☐
3. Do you engage in sexual activity with anyone at the moment?	☐	☐
	If 'Yes' please go to next page	**If 'No' please answer remaining questions on this page**

Section II

I answered 'No' to question 3. I am not sexually active at the moment because:
(Please tick as many of these items as apply)

a) I do not have a partner at the moment ☐
b) I am too tired ☐
c) My partner is too tired ☐
d) I am not interested in sex ☐
e) My partner is not interested in sex ☐
f) I have a physical problem which makes sexual relations difficult or uncomfortable ☐
g) My partner has a physical problem which makes sexual relations difficult or uncomfortable ☐
h) Other reasons (please describe) ☐

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PTO
Page 2

Please complete this section if you are sexually active (i.e. you answered 'Yes' to question 3).

Please read each of the following questions carefully and tick the box that best indicates your sexual feelings and experiences during the past month.

Section III

During the past month:

	very much	somewhat	a little	not at all
1. Was 'having sex' an important part of your life this month?	☐	☐	☐	☐
2. Did you enjoy sexual activity this month ?	☐	☐	☐	☐
3. In general, were you too tired to have sex ?	☐	☐	☐	☐
4. Did you desire to have sex with your partner(s) this month?	☐	☐	☐	☐
5. During sexual relations, how frequently did you notice dryness of your vagina this month?	☐	☐	☐	☐
6. Did you feel pain or discomfort during penetration this month?	☐	☐	☐	☐
7. In general, did you feel satisfied after sexual activity this month?	☐	☐	☐	☐
	5 times or more	**3-4 times**	**1-2 times**	**not at all**
8. How often did you engage in sexual activity this month?	☐	☐	☐	☐
	much more	**somewhat more**	**about the same**	**not as much**
9. How did this frequency of sexual activity compare with what is usual for you?	☐	☐	☐	☐
	very much	**somewhat**	**a little**	**not at all**
10. Were you satisfied with the frequency of sexual activity this month?	☐	☐	☐	☐

Any other comments?

Thank you very much for answering these questions.

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

12.2 Lymphatic side effects

Common Terminology Criteria for Adverse Events (CTCAE) version 3.[68]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Lower extremity lymphedema	5%–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; pitting edema	10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference	>30% inter-limb discrepancy in volume; lymphorrhea, interfering with activities of daily life	Progression to malignancy (i.e. lymphangiosarcoma), amputation indicated, disabling
Truncal/genital lymphedema	Swelling or obscuration of anatomic architecture on close inspection, pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds	Lymphorrhea; interfering with activities of daily life; gross deviation from normal anatomical contour	Progression to malignancy (i.e. lymphangiosarcoma); disabling
Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	-

LYMQOL[69]

LYMQOL LEG
Lymphoedema Quality of Life Tool

This questionnaire has been designed and validated for patients with chronic oedema/ lymphoedema of one or both legs to measure quality of life.
Please tick the box that best describes how you feel about each of the questions.

Name: ..... **Hospital Number:**.....
Date: .....

(Q1) How much does your swollen leg affect the following activities? If any of the items are not applicable to you, please write N/A in the relevant answer box(es)	Not at all	A little	Quite a bit	A lot
a) your walking				
b) your ability to bend, e.g. to tie shoelaces or cut toenails				
c) your ability to stand.				
d) your ability to get up from a chair.				
e) your occupation				
f) your ability to do housework				
(Q2)Does the swelling affect your leisure activities/ social life?				

Please give examples of this .....

.....

	Not at all	A little	Quite a bit	A lot
(Q3) How much do you have to depend on other people?				
(Q4) How much do you feel the swelling affects your appearance?				
(Q5) How much difficulty do you have finding clothes to fit?				
(Q6) How much difficulty do you have finding clothes you would like to wear?				
(Q7) Do you have difficulty finding shoes to fit?				
(Q8) Do you have difficulty finding socks/ tights/ stockings to fit?				
(Q9) Does the swelling affect how you feel about yourself?				
(Q10)Does it affect your relationships with other people?				

LYMQOL LEG Version 2.0 November 2007

	Not at all	A little	Quite a bit	A lot
(Q11) Does your lymphoedema cause you pain?				
(Q12) Do you have any numbness in your swollen leg(s)?				
(Q13) Do you have any feelings of "pins & needles" or tingling in your swollen leg(s)				
(Q14) Does (do) your swollen leg(s) feel weak?				
(Q15) Does (do) your swollen leg(s) feel heavy?				

In the past week….	Not at all	A little	Quite a bit	A lot
(Q16) Have you had trouble sleeping?				
(Q17) Have you had difficulty concentrating on things, e.g. reading?				
(Q18) Have you felt tense?				
(Q19) Have you felt worried?				
(Q20) Have you felt irritable?				
(Q21) Have you felt depressed?				

(Q22) Overall, how would you rate your quality of life at present?
Please mark your score on the following scale:

0 1 2 3 4 5 6 7 8 9 10
poor **excellent**

Thank you for completing this form.
If you have any comments or queries about it, please discuss these with ……...

Dr V L Keeley, Consultant

Questions 16 to 21 have been reproduced with permission from the EORTC.
These questions are only a part of the QLQ-C30 Questionnaire.

12.3 Site Quality Assessment Form

Name of investigator	
Institution	

Information on the clinical trial (must be in accordance with the full proposal)

Trial title	**German Laparoscopic Approach to Cervical Cancer Trial (G-LACC)** A phase III randomized clinical trial comparing laparoscopic or robot-assisted radical hysterectomy versus abdominal radical hysterectomy in patients with early-stage cervical cancer
Inclusion criteria	☐ Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix (≤ 4cm) ☐ Patients with FIGO (2014) stage IA1 (with lymph vascular space invasion), IA2, IB1 disease ☐ Patients undergoing either a radical hysterectomy Type II or III (Piver Classification) or either a Type B or C radical hysterectomy (Querleu and Morrow classification) or either a TMMR procedure and the use of pre-specified endoscopic surgical techniques ☐ Performance status of ECOG 0-1
Exclusion criteria	☐ Any histological type other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix ☐ Tumor size greater than 4 cm ☐ FIGO stage II-IV ☐ Patients with a history of pelvic or abdominal radiotherapy ☐ Patients who are pregnant ☐ Patients with contraindications to surgery ☐ Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes ☐ Unfit for Surgery: serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator)
Recruitment period (months)	First patient in to last patient out (months): 96 Duration of the entire trial (months): 96 Recruitment period (months): 48

Strategy for the determination of recruitment figures

How many patients with the condition specified above have you seen in your institution during the last 12 months?	
How many of these patients would fulfil the inclusion criteria of the above-mentioned trial?	
Approximately how many of these patients would agree to participate in the above-named clinical trial per year?	
Approximately how many patients will be recruited during the entire trial?	
Trials currently recruiting at this institution (please provide the total number and registration no. of trials)	

No. of patients this institution has recruited to the above mentioned trials during the last 12 months	

Which source did you use to estimate potential participants in the above-named clinical trial?

☐ Individual estimate
☐ Hospital data management system
☐ Patient registry
☐ Other

If other, please specify.

Are there any other ongoing clinical trials/projects competing for the same patients?

☐ Yes ☐ No

If yes: How will this affect recruitment for the above-named clinical trial?

Please mention the surgeon/s who will perform the operation (minimal-invasive and open) and provide the certificate Gynäkologische Onkologie

☐

☐

Commitment to Participate

I hereby agree to participate in the above-named clinical trial and to support the trial by recruiting patients.

_____

Date / Signature