Supplementary appendix

Protective Maneuvers Improve the Surgical Outcome in Cervical Cancer

Index:

1.List of participating European Countries and Institutions

Country	Name of your institution/hospital/cancer center
Armenia	NAIRI Medical Center.
Austria	Medical University of Graz
Azerbaijan	National Centre of Oncology
Belgium	Cliniques de l'europe, ucl st luc UNGO
Belgium	University Hospitals Leuven
Belgium	CHU Liège, Site Notre Dame Bruyères
Belgium	Cliniques universitaire Saint-Luc - UNGO
Bulgaria	University hospital of the active treatment of Oncology
Bulgaria	Military Medical Academy
Croatia	Department of Obstetrics & Gynecology, Clinical Hospital Center Rijeka
Croatia	University hospital Zagreb
Czech Republic	General faculty hospital
Czech Republic	University Hospital Hradec Králové
Estonia	East Tallin Central Hospital
Estonia	North Estonia Medical Foundation
Estonia	University Hospital
Finland	University Hospital of Tampere
France	Centre Oscar Lambret
France	Institu Curie
France	Institut Bergonié
France	Georges Pompidou European Hospital
France	Institut Universitaire du Cancer Toulouse Oncopole
Germany	Asklepios Klinik Hamburg Barmbek, Nord Heidberg and Wandsbek
Germany	Kliniken Essen Mitte
Germany	Klinikum Dortmund gGmbH
Germany	Sana Klinikum Lichtenberg
Germany	Klinikum Nürnberg Nord obstetrics
Germany	University Hospital of Cologne, Departement of Obstetrics & Gynecology
Greece	Alexandra Hospital, 1st Department of Obstetris and Gynecology, Gynecologic Oncology Unit
Greece	St. Luke's Hospital,Department of Gynecology oncology
Greece	Metaxa Memorial Cancer Hospital
Greece	Papageorgiou General Hospital
Greece	2nd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki
Greece	3d Dept of Obstet/Gynecol (Aristotle University of Thessaloniki - Greece)
Hungary	Unit.Gynecol.Oncol., Dept.ObGyn, Faculty of Medicine, University of Debrecen
Hungary	national Institute of Oncology
Italy	Fondazione Policlinico A. Gemelli
Italy	San Gerardo Hospital, University of Milan-Bicocca
Italy	EUROPEAN INSTITUTE OF ONCOLOGY
Italy	University of Insubria
Italy	Fondazione IRCCS Istituto Nazionale Tumori - Milan
Italy	Endoscopica Malzoni, Center for Advanced Endoscopic Gynecologic Surgery
Italy	Mauriziano Hospital
Italy	S. Orsola Hospital

Italy	Ospedale Santa Chiara
Italy	"Regina Elena" National Cancer Institute
Kazakhstan	Kazakh Institute of Oncology and Radiology
Macedonia	Clinical Hospital, "Acibadem Sistina", Department of Ob/Gyn
Macedonia	University Clinic for Obstetrics and Gynecology, Clinical Center Skopje
Moldova	Institute of Oncology
Netherlands	Dutch cancer institute AVI/NKI
Netherlands	Leiden University Medical Center
Netherlands	Radboudumc
Netherlands	Amsterdam University Medical Center
Poland	Holycross cancer Center
Poland	Jagiellonian University Medical College
Poland	Lower Silesian Oncology Center and Wroclaw Medical University
Poland	Department of Gynaecology, Oncol. Gyn. & Endoc. Gyn. MU of Gdansk
Portugal	Hospital Beatriz Ângelo
Portugal	Chua-HDF
Portugal	Hospital Prof. Doutor Fernando Fonseca
Portugal	Centro Hospitalar Universitário de Coimbra
Portugal	Instituto Português de Oncologia de Lisboa Francisco Gentil
Portugal	Instituto Português de Oncologia Centro do Porto
Portugal	Instituto Português de Oncologia de Coimbra
Romania	University of Medicine and Pharmacy "Victor Babes"
Romania	Emergency County Hospital Of Tîrgu Mureș - First Obstetrics and Gynecology Clinic
Romania	”Prof. Dr. Ion Chiricuta” Institute of Oncology
Russia	N.N.Petrov National Medical Research Center of Oncology,
Serbia	Clinic of gynecology and obstetrics, Clinical center Serbia
Serbia	Oncology Institute of Vojvodina
Slovakia	II. dpt. of Gynaecelogy and Obstetrics, University hospital Bratislava
Slovenia	UNIVERSITY MEDICAL CENTRE LJUBLJANA
Slovenia	Department for gynecologic and breast oncology, University Medical Center, Maribor
Spain	Hospital Universitari de Bellvitge
Spain	Hospital Universitario Nuestra Señora de Candelaria
Spain	Complejo Hospitalario de Navarra
Spain	Hospital Clinico San Carlos
Spain	Hospital Universitario Cruces
Spain	CLINICA UNIVERSIDAD DE NAVARRA
Spain	Clínica Universidad de Navarra
Spain	Hospitla Universitario 12 de Octubre
Spain	HOSPITAL UNIVERSITARIO DONOSTIA
Spain	FUNDACION JIMENEZ DIAZ UNIVERSITY HOSPITAL
Spain	Hospital General universitario de Castellon
Spain	Hospital Universitario de Getafe
Spain	Hospital Clínico Universitario "Lozano Blesa"
Spain	Hospital del Mar
Spain	Hospital Universitario Central de Asturias HUCA
Spain	University Hospital La fe
Spain	Hospital Universitario Virgen Macarena
Spain	HOSPITAL GENERAL UNIVERSITARIO VALENCIA
Spain	INSTITUTO VALENCIANO ONCOLOGIA
Spain	La Paz University Hospital
Spain	INFANTA LEONOR UNIVERSITY HOSPITAL

Spain	Hospital Universitario Materno Infantil de Canarias
Spain	HOSPITAL PUERTA DE HIERRO MAJADAHONDA
Spain	Hospital Universitario Quironsalud Madrid
Spain	HOSPITAL UNIVERSITARIO DE LA RIBERA
Spain	Hospital Universitario Ramón y Cajal
Spain	HOSPITAL UNIVERSITARI SANT JOAN DE REUS
Spain	Corporació Sanitària Parc Taulí
Spain	HOSPITAL UNIVERSITARIO TORRECARDENAS
Spain	Dr. Josep Trueta University Hospital
Spain	HUA Txagorritxu
Spain	Hospital Universitario Marqués de Valdecilla
Spain	Hospital Álvaro Cunqueiro
Switzerland	Kantonsspital Frauenfeld, Frauenklinik
Switzerland	Hôpitaux Universitaires de Genève
Switzerland	Frauenklinik Luzerner Kantonsspital
Turkey	Zekai Tahir Burak Women's Health Training Hospital
Turkey	Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty, Department of OB&GYN, Division of Gynecologic Oncology
Turkey	Etlik Zübeyde Hanım Women's Health Training and Research Hospital
Turkey	Istanbul Kanuni Sultan Suleyman Education & Research Hospital
Turkey	Saglik Bilimleri University Antalya Research and Training Hospital
Turkey	Yuzuncu Yil University, Medical school, Department of Gynecologic Oncology
Ukraine	LISOD - Israeli Oncological Hospital
Ukraine	Lviv state regional oncology center
United Kingdom	Cheltenham General Hospital
United Kingdom	University Hospitals of Leicester
United Kingdom	Portsmouth Hospital NHS Trust
United Kingdom	University College London Hospital (UCLH)
United Kingdom	The Christie NHS FT
United Kingdom	Northern Gynaecological Oncology Centre
United Kingdom	Royal Cornwall Hospital

2.Participation by Countries

	N	Percent
Italy	188	16,3
Spain	171	14,8
United Kingdom	76	6,6
Turkey	65	5,6
Portugal	61	5,3
Netherlands	55	4,8
Greece	53	4,6
France	50	4,3
Romania	48	4,2
Ukraine	43	3,7
Poland	34	2,9
Belgium	33	2,9
Croatia	30	2,6
Germany	27	2,3
Bulgaria	26	2,2
Hungary	26	2,2
Czech Republic	22	1,9
Estonia	21	1,8
Macedonia	21	1,8
Azerbaijan	20	1,7
Kazakhstan	19	1,6
Austria	13	1,1
Finland	13	1,1
Russia	13	1,1
Serbia	8	,7
Slovenia	6	,5
Switzerland	6	,5
Armenia	5	,4
Slovakia	3	,3
Total	1156	100,0

3.List of inclusion and exclusion criteria

Inclusion Criteria

A. Primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix.
B. FIGO IB1 carcinoma (FIGO 2009)
C. Preoperative pelvic MRI indicating tumor diameter < 4 cm (at least two dimensions,) and no parametrial invasion. Exceptionally, it can be considered acceptable Vaginal Ultrasound, only if your Institution have internally validated this technique for cervical cancer. Otherwise, it cannot be accepted.
D. Preoperative either (Abdominal) CT scan or MRI or PET-CT ruling out extracervical metastatic disease
E. Performance status ECOG 0-1
F. Age 18 years or older
G. Type II-III radical hysterectomy or Type B-C by MIS (laparoscopic or robotic) or open surgery.
H. Operated during the years 2013-2014 within the ESGO area.
I. Bilateral pelvic lymphadenectomy or SNB plus bilateral pelvic lymphadenectomy. At least, a total of 10 pelvic nodes must be reported (considering both sides)
J. Pathologic report shows information on tumor size, vaginal and parametrial margins and bilateral nodal status.

Exclusion Criteria

A. Any histological type other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix
B. Tumor size greater than 4 cm.
C. Past medical history of any invasive tumor
D. History of previous abdominal or pelvic radiotherapy of any type (including braquitherapy).
E. History of preoperative neoadjuvant chemotherapy cervical cancer .
F. Cervical conization previous to surgery.
G. Suspicious positive pelvic or paraaortic nodes nodes or metastatic disease on PET CT, MRI, or CT.
H. Any uterine diameter larger than 12 cm
I. Conversion from MIS to laparotomy
J. Pregnant women.

4.List of excluded patients

116 patients were excluded

41 No Preoperative Imaging
40 Absence of follow- up data
24 Insufficient Lymph Node Dissection
13 Stage <IB1
13 Tumor Size >40 mm
12 No Radical Hysterectomy
8 Conversion to Laparotomy
3 Rare Histology
2 Preoperative Parametrial Invasion

5.Characteristics of patients (No previous cone biopsy. Includes lost of follow-up)

Baseline Characteristics	**Open Surgery (N = 436)**	**Minimally Inv Surgery (N = 297)**	Sig
Age — yr	48.4 ± 10.6	47.8 ± 11.5	0.508
Body-mass index — kg/m2	26.0 ± 4.6	25.4 ± 5.6	0.171
Caucasian Race (%)	354 (89)	247 (94)	**< 0.001**
ECOG performance-status score 0 (%)	377 (89.3)	260 (92.9)	0.161
Smoker >10 cig day (%)	90 (28.8)	64 (26.8)	0.584
Clinical tumor size — mm	24.1 ± 9.7	21.1 ± 10.3	**< 0.001**
MRI largest diameter — mm	25.7 ± 10.1	21.5 ± 10.1	**< 0.001**
MRI-US largest diameter — mm	24.8 ± 10.8	20.6 ± 11.2	**< 0.001**
Type C Rad Hysterectomy (%)	343 (80.6)	192 (69.6)	**< 0.001**
Surgery performed by Senior surgeon (%)	361 (83.2)	218 (75.7)	**< 0.001**
Nerve sparing technique (%)	131 (38.6)	208 (84.6)	**< 0.001**
Sentinel Lymph Node Biopsy (%)	52 (12.9)	107 (38.6)	**< 0.001**
Duration of procedure —min	196.2 ± 55.6	243.3 ± 75.8	**< 0.001**
Estimated blood loss —cc	400.0 ± 373.1	187 ± 206.1	**< 0.001**

Intraoperative complications any grade (%)	42 (9.8)	26 (9.1)	0.759
Histology in the specimen (%)			
Squamous	311 (71.6)	181 (61.6)	**0.007**
Adenocarcinoma	104 (24.0)	102 (34.7)	
Adenosquamous	19 (4.4)	11 (3.7)	
Tumor Largest diameter in Path. Report (mm)	23.8 ± 10.0	22.5 ± 9.5	0.075
Tumor Largest lateral diameter in Path. Report (mm)	24.3 ± 9.0	22.8 ± 91	**0.029**
Largest ant-post diameter in Path. Report (mm)	20.0 ± 8.8	17.1 ± 7.8	**< 0.001**
Depth of invasion (mm)	13.4 ± 7.8	10.6 ± 6.7	**< 0.001**
Uninvolved stroma (mm)	7.4 ± 5.7	7.6 ± 5.2	0.758
Final tumor grade III (%)	129 (32.4)	102 (37.1)	0.421
Lymphovascular Space Invasion (%)	138 (37.3)	69 (32.7)	0.082
Tumor invades >2/3 of the stroma (%)	138 (37.6)	69 (32.7)	0.204
Parametrial invasion (%)	16 (3.7)	16 (5.6)	0.232
Vaginal infiltration (%)	15 (3.5)	10 (3.5)	0.991
Positive Margins (%)	47 (10.9)	23 (7.8)	0.174
Sentinel lymph node biopsy (%)	52 (12.90)	107 (38.6)	**< 0.001**
Mean Retrieved pelvic nodes — N	25.8 ± 14.4	22.2 ± 12.1	**< 0.001**
Mean positive pelvic nodes — N	1.8 ± 0.2	1.0 ± 0,1	**0.044**
Positive pelvic nodes (%)	74 (17.1)	37 (12.60)	0.100
Figo Staging 2018			
IB1 ≥5 mm and <2 cm (%)	135 (31.1)	118 (40.19)	0.041
IB2 ≥2 cm and <=4 cm (%)	214 (49 %)	128 (43.5)	
Mean length of stay — Days	8.9 ± 4.3	5.14 ± 3.4	**< 0.001**
Any Postoperative complications (%)	99 (23 %)	57 (20)	0.338
Readmission (%)	10 (2.3)	7 (2.4)	0.947

Adjuvant therapy after surgery (%)	247 (58.3)	138 (47.1)	**0.003**
Mean size of tumor receiving adjuvant therapy —mm	25.9 ± 9.7	26.1 ± 9.1	0.843
Median time to radiation (days)	61.7 ± 93.0	57.7 ± 23.8	0.681
Median Follow up —months (Range)	57 (0 to 83)	59 (0 to 79).	0.053

6. Open Surgery vs Minimally Invasive Surgery

- Excluded 423 participants with previous conization.
- 34 participants excluded with missing information on relapse.
- 1 participant excluded with missing information on follow-up time.
- New category for missing values except for ADJUVANTCODE because participants with missing value in that variable were dropped out from the Cox regression model (N=5).
- PS covariates: MAXPATHCODE, Finalgradecode, finaLVSIcode, finalDepthcode, MARGINCODE, codeN, ADJUVANTCODE.
- AUC of the PS: 0.81
- Clustered analyses by center (119 centers).
- N=693

DISEASE FREE SURVIVAL

	Open surgery	Minimally Invasive Surgery
Relapse no	355	231
Relapse yes	47	60
total	402	291

MAXPATHCODE=1

	Open surgery	Minimally Invasive Surgery
Relapse no	145	111
Relapse yes	15	17
Total	160	128

MAXPATHCODE=2

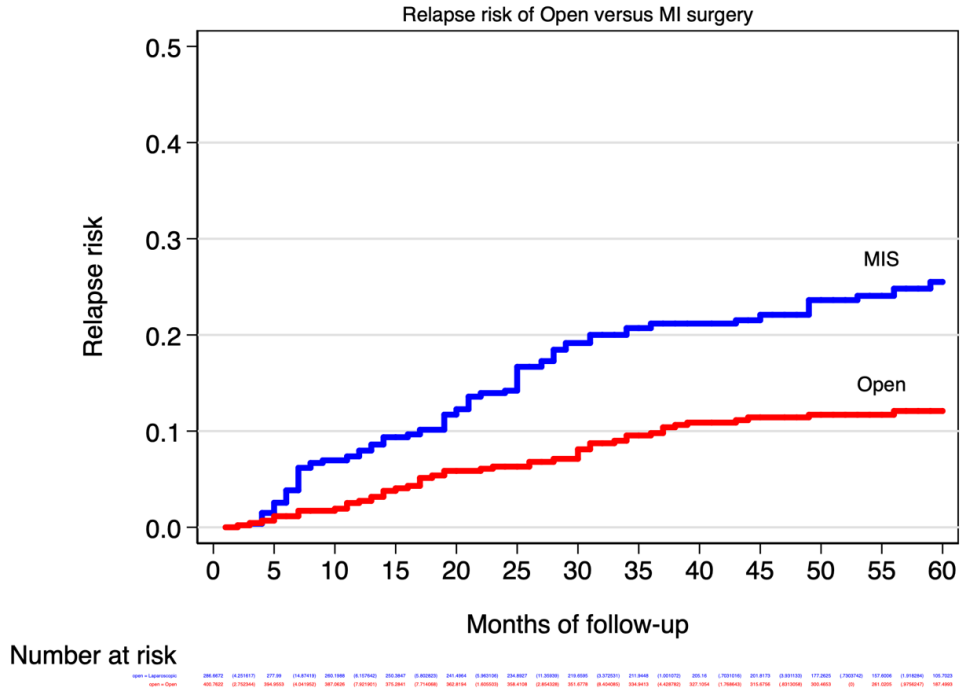
	Open surgery	Minimally Invasive Surgery
Relapse no	210	120
Relapse yes	32	43
total	242	163

Inverse probability weighting-adjusted disease-free survival by type of intervention.

	Open surgery	Minimally Invasive Surgery
12 months	0.97	0.92
24 months	0.94	0.87
54 months	0.89	0.79

Hazard Ratios and 95% Confidence Intervals for the risk of relapse by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery
Incident cases	47	60
Time at risk (person/months)	21651,3	13739,8
HR (95% CI)	1.00 (Ref)	2.07 (1.35–3.15)
p value		0.001
Subgroups analysis:		
MAXPATHCODE 1	1.00 (Ref)	1.63 (0.79-3.40)
		p = 0.19
MAXPATHCODE 2	1.00 (Ref)	2.31 (1.37-3.90)
		p = 0.002



Log-Rank test: p=0.0003

OVERALL SURVIVAL

	Open surgery	Minimally Invasive Surgery
Death no	381	263
Death yes	21	28
total	402	291

MAXPATHCODE=1

	Open surgery	Minimally Invasive Surgery
Death no	155	120
Death yes	5	8
total	160	128

MAXPATHCODE=2

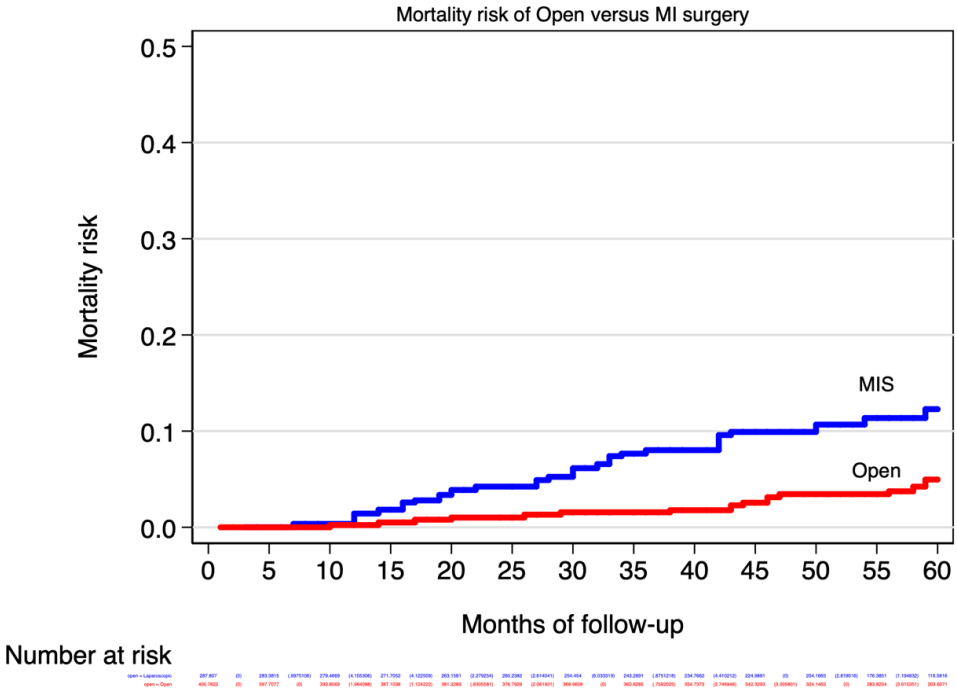
	Open surgery	Minimally Invasive Surgery
Death no	226	143
Death yes	16	20
total	242	163

Inverse probability weighting-adjusted overall survival by type of intervention.

	Open surgery	Minimally Invasive Surgery
12 months	1.00	0.99
24 months	0.99	0.96
54 months	0.97	0.89

Hazard Ratios and 95% Confidence Intervals for the overall survival by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery
Incident cases	21	28
Time at risk (person/months)	22805,9	15133,5
HR (95% CI)	1.00 (Ref)	2.42 (1.34–4.39)
p value		0.004
Subgroups analysis:		
MAXPATHCODE 1	1.00 (Ref)	2.77 (0.91-8.47)
		p = 0.072
MAXPATHCODE 2	1.00 (Ref)	2.26 (1.18-4.36)
		p = 0.014



Log-Rank test: p=0.003

7. Open Surgery vs MIS with uterine manipulator and vs MIS without uterine manipulator

- Excluded 423 participants with previous conization.
- 34 participants excluded with missing information on relapse.
- 1 participant excluded with missing information on follow-up time.
- New category for missing values except for ADJUVANTCODE because participants with missing value in that variable were dropped out from the Cox regression model (N=5).
- PS covariates: MAXPATHCODE, Finalgradecode, finaLVSIcode, finalDepthcode, MARGINCODE, codeN, ADJUVANTCODE.
- AUC of the PS: 1.00
- Clustered analyses by center (119 centers).
- 41 excluded with missing values for uterine manipulator
- N=652

DISEASE FREE SURVIVAL

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Relapse no	355	89	106
Relapse yes	47	17	38
total	402	106	144

Inverse probability weighting-adjusted disease-free survival by type of intervention.

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
12 months	0.97	0.90	0.90
24 months	0.94	0.86	0.83
54 months	0.89	0.83	0.73

MAXPATHCODE=1

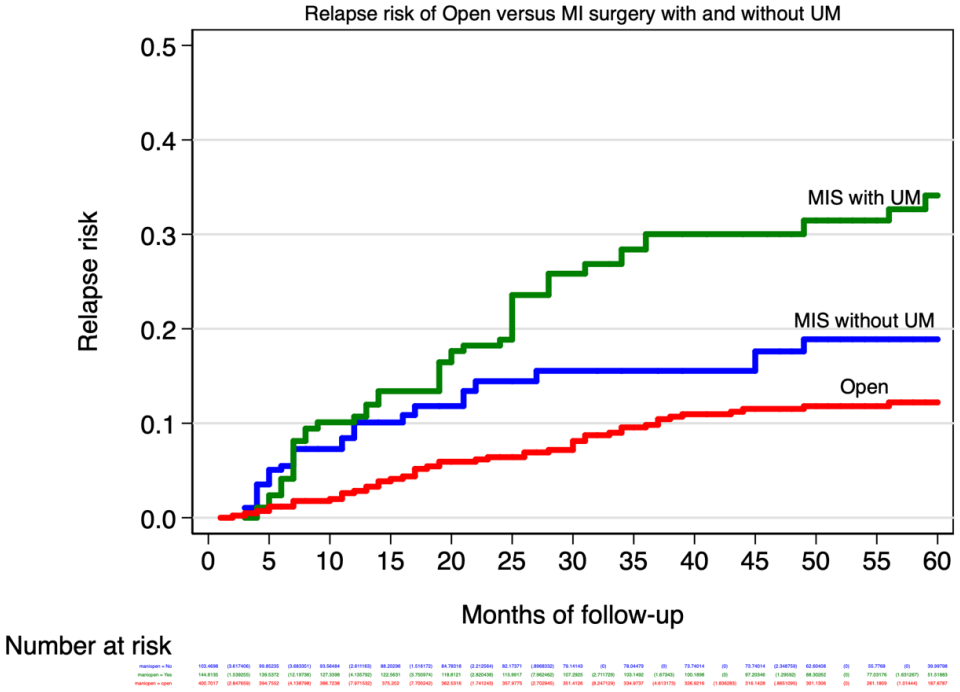
	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Relapse no	145	35	56
Relapse yes	15	4	11
Total	160	39	67

MAXPATHCODE=2

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Relapse no	210	54	50
Relapse yes	32	13	27
Total	242	67	77

Hazard Ratios and 95% Confidence Intervals for the <u>risk of relapse</u> by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Incident cases	47	17	38
Time at risk (person/months)	21664,1	4957,5	6757,7
HR (95% CI)	1.00 (Ref)	1.58 (0.79–3.15)	2.76 (1.75–4.33)
p value		0.20	<0.001
Subgroups analysis			
MAXPATHCODE 1	1.00 (Ref)	0.99 (0.27-3.64)	2.25 (0.96-5.26)
		p= 0.99	p=0.061
MAXPATHCODE 1	1.00 (Ref)	1.83 (0.80-4.18)	3.05 (1.73-5.38)
		p=0.152	P<0.001



OVERALL SURVIVAL

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Death no	381	95	128
Death yes	21	11	16
total	402	106	144

Inverse probability weighting-adjusted overall survival by type of intervention.

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
12 months	1.00	1.00	0.97
24 months	0.99	0.98	0.92
54 months	0.97	0.91	0.86

MAXPATHCODE=1

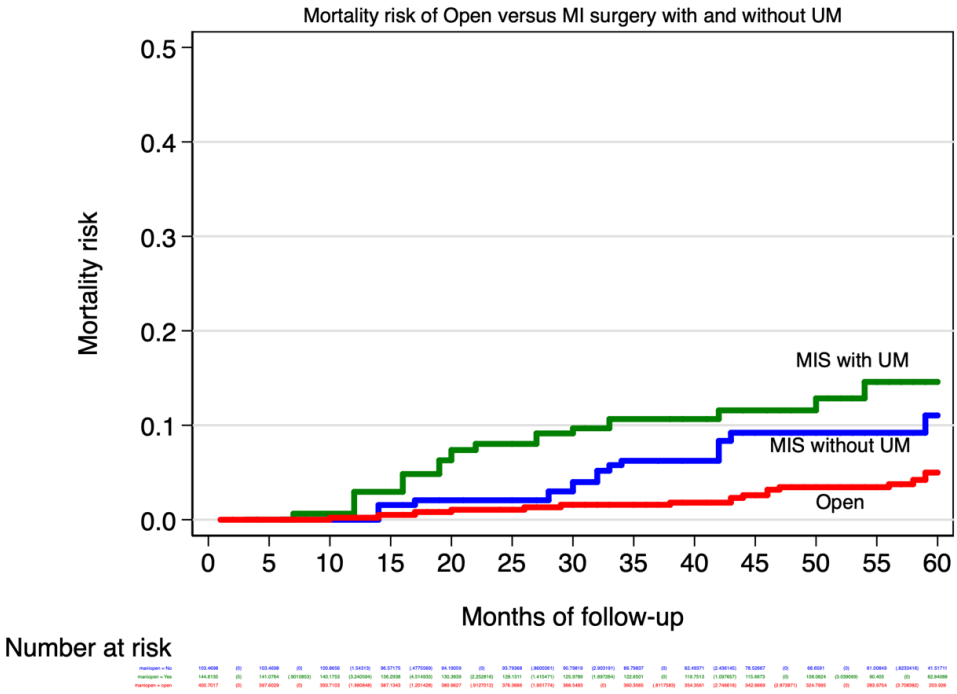
	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Death no	155	36	62
Death yes	5	3	5
Total	160	39	67

MAXPATHCODE=2

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Death no	226	59	66
Death yes	16	8	11
Total	242	67	77

Hazard Ratios and 95% Confidence Intervals for the overall survival by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery	
		Without uterine manipulation	With uterine manipulation
Incident cases	21	11	16
Time at risk (person/months)	22817,8	5396,1	7661,7
HR (95% CI)	1.00 (Ref)	2.03 (0.92–4.48)	3.00 (1.60–5.62)
p value		0.078	0.001
Subgroups analysis			
MAXPATHCODE 1	1.00 (Ref)	2.32 (0.54-10.07)	3.84 (1.11-13.26)
		p= 0.26	p=0.033
MAXPATHCODE 1	1.00 (Ref)	1.89 (0.76-4.67)	2.69 (1.22-5.89)
		p=0.173	p=0.013



Log-Rank test: p=0.004

8. Open Surgery vs MIS with an without protective maneuvers

- Excluded 423 participants with previous conization.
- 34 participants excluded with missing information on relapse.
- 1 participant excluded with missing information on follow-up time.
- New category for missing values except for ADJUVANTCODE because participants with missing value in that variable were dropped out from the Cox regression model (N=5).
- PS covariates: MAXPATHCODE, Finalgradecode, finaLVSIcode, finalDepthcode, MARGINCODE, codeN, ADJUVANTCODE.
- AUC of the PS: 1.00
- Clustered analyses by center (119 centers).
- 41 excluded with missing values for uterine manipulator
- N=652

DISEASE FREE SURVIVAL

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Relapse no	355	155	40
Relapse yes	47	52	3
total	402	207	43

Inverse probability weighting-adjusted disease-free survival by type of intervention.

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
12 months	0.97	0.89	0.97
24 months	0.94	0.82	0.95
54 months	0.89	0.74	0.93

MAXPATHCODE=1

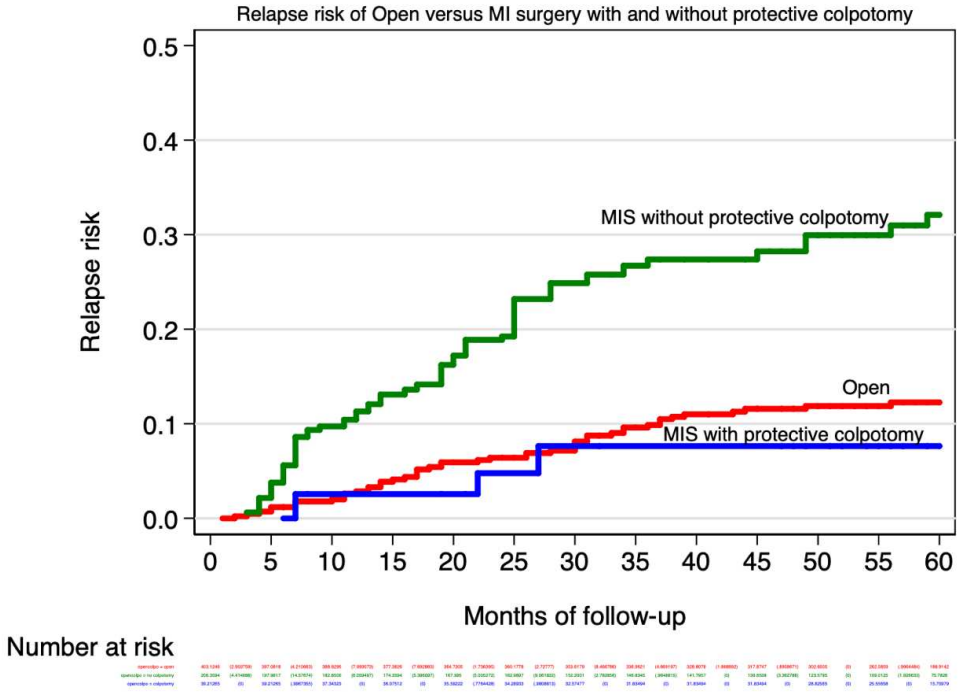
	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Relapse no	145	75	16
Relapse yes	15	14	1
Total	160	89	17

MAXPATHCODE=2

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Relapse no	210	80	24
Relapse yes	32	38	2
Total	242	118	26

Hazard Ratios and 95% Confidence Intervals for the risk of relapse by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Incident cases	47	52	3
Time at risk (person/months)	21792.0	9645.8	2051.6
HR (95% CI)	1.00 (Ref)	2.58 (1.70-3.95)	0.63 (0.15-2.59)
p value		<0.001	0.518
Subgroups analysis			
MAXPATHCODE 1	1.00 (Ref)	1.96 (0.91-4.27)	0.84 (0.10-7.25)
		p=0.09	p=0.87
MAXPATHCODE 1	1.00 (Ref)	2.99 (1.78-5.00)	0.54 (0.18-1.61)
		p<0.001	P=0.27



Log-Rank test: p<0.001

OVERALL SURVIVAL

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Death no	381	183	40
Death yes	21	24	3
total	402	207	43

Inverse probability weighting-adjusted overall survival by type of intervention.

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
12 months	1.00	0.98	1.00
24 months	0.99	0.94	1.00
54 months	0.97	0.87	0.92

MAXPATHCODE=1

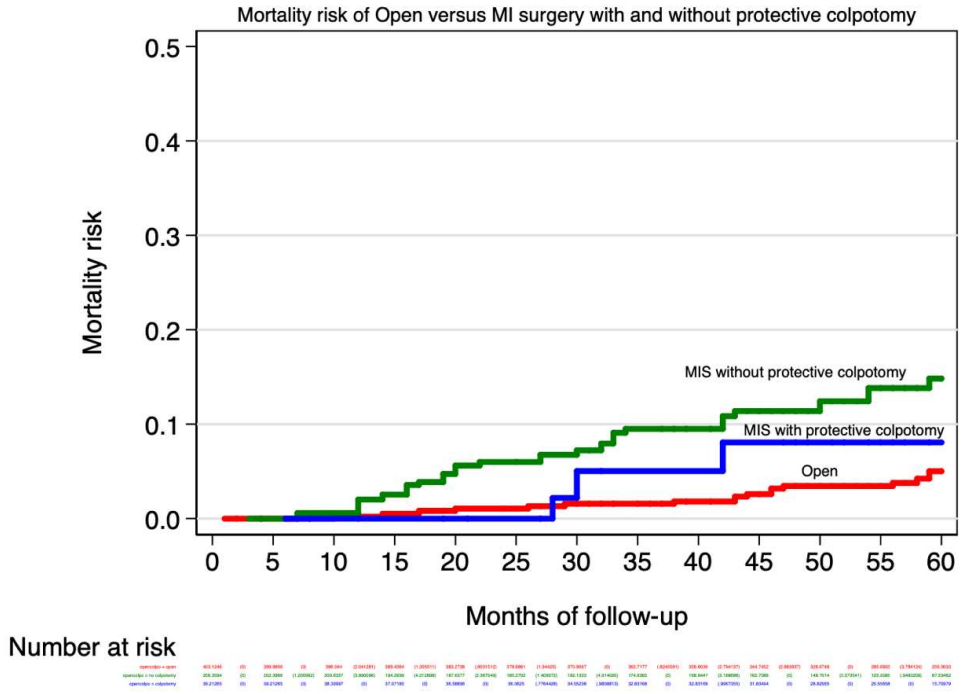
	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Death no	155	82	16
Death yes	5	7	1
Total	160	89	17

MAXPATHCODE=2

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Death no	226	101	24
Death yes	16	17	2
Total	242	118	26

Hazard Ratios and 95% Confidence Intervals for the overall survival by type of intervention. Adjusted using Inverse probability weighting by propensity scores.

	Open surgery	Minimally Invasive Surgery	
		Without protective colpotomy	With protective colpotomy
Incident cases	21	24	3
Time at risk (person/months)	22958.5	10928.7	2094.1
HR (95% CI)	1.00 (Ref)	2.85 (1.59–5.15)	1.59 (0.37–6.90)
p value		p<0.001	0.53
Subgroups analysis			
MAXPATHCODE 1	1.00 (Ref)	3.33 (1.06-10.46)	2.62 (0.3-22.83)
		p= 0.039	p=0.384
MAXPATHCODE 1	1.00 (Ref)	2.71 (1.35-5.46)	1.24 (0.27-5.65)
		p=0.005	p=0.776



Log-Rank test: p=0.002

9.Protocol

Protocol Title

SUCCOR-Surgery in Cervical cancer

Full Protocol Title

An international European retrospective cohort observational study comparing Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer

Indication

Cervical Cancer FIGO Stage 1B1 (FIGO 2009)

Study Chair:

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Study statistician

Juan Arevalo MD, PhD
Department of Internal Medicine
UNIVERSIDAD DE ALCALA DE HENARES

Study design

International, multicenter, observational, retrospective, cohort study of consecutive cervical cancer cases operated in 2013 and 2014 within hospitals belonging to the ESGO area (50 countries) that meet the inclusion-exclusion criteria.

We plan to balance both groups by means of a Propensity Score Matched Cohort Study for the following variables: histology, tumor diameter, tumor volume (MRI and pathology), depth of invasion, LVSI, parametrial invasion, vaginal margins, positive nodes, grade and adjuvant radiation.

Primary endpoint

Compare disease-free survival at 4.5 years in patients who underwent a laparoscopic or robotic radical hysterectomy (MIS) vs. abdominal radical hysterectomy (TARH) for stage IB1 cervical cancer.

Secondary endpoints

Compare overall survival at 4.5 years between groups.

Compare patterns of recurrence between groups.

Compare treatment-associated morbidity (30 days after surgery)

Define association between tumor diameter, tumor volume (by MRI and pathology) with rates of relapse in both groups.

Stablish groups of low and high risk of relapse in both groups.

Explore causal association between specific surgical maneuvers and chance of relapse (Manipulator, vaginal closure, nodes extraction)

Definitions

Disease-free survival is defined as the time from Radical Hysterectomy to disease recurrence or death from cervical cancer.

Progression-free survival is defined as the time from randomization to disease recurrence or death from any cause.

Data regarding patients with no evidence of recurrence or death were censored at the date of last follow-up.

Overall survival is defined as the time from Radical Hysterectomy to death from cervical cancer or last follow up.

Background and Rationale

A recent international randomized trial and two large US retrospective studies have shown the inferiority of minimally invasive surgery vs the open approach in early cervical cancer in terms of DFS, OS and pattern of relapse. Previously, several retrospective studies including patients with early-stage cervical cancer had shown that laparoscopic radical hysterectomy was associated with less intraoperative blood loss, a shorter length of hospital stay, and a lower risk of postoperative complications than open abdominal radical hysterectomy. Furthermore, those studies found that minimally invasive approach obtained similar 5-year rates of disease-free survival or overall survival than the open approach with similar rates and patterns of recurrence.

In Europe, we have not carried out recently any relevant large study comparing the different forms of surgical treatment of early cervical cancer.

On the other hand, the design of any randomized clinical trial in the coming years on this subject will face severe difficulties to convince ethics committees after learning the results of the last clinical trial.

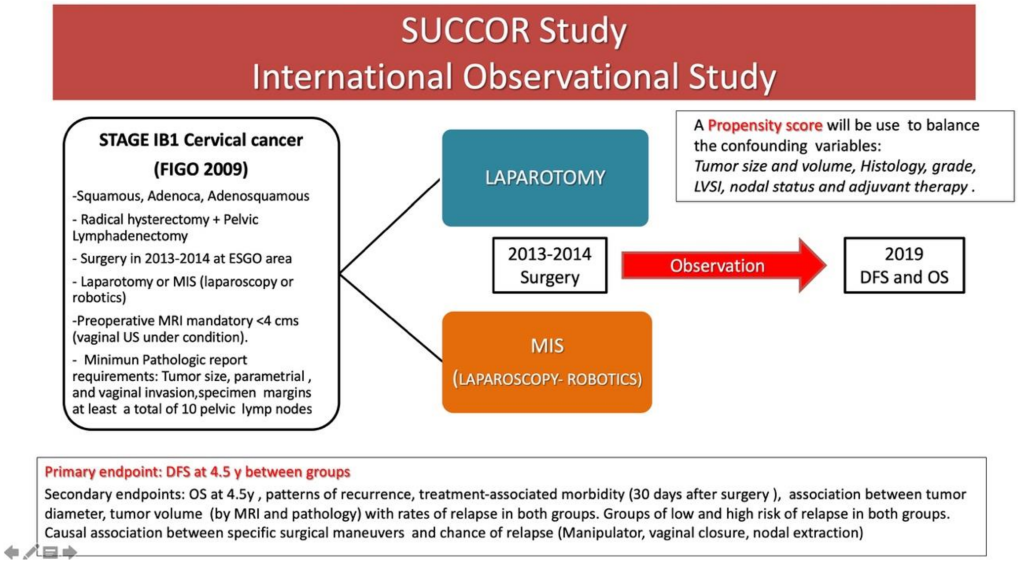
Therefore, we consider it crucial to carry out a highly controlled European retrospective study that allows us to draw sufficient conclusions to make adequate decisions in research on the surgical treatment of early cervical cancer.

A total of 54,517 new cases of cervical cancer cases and 24,874 deaths were reported in Europe in 2008 . Both incidence and mortality rates, are generally higher in Central and Eastern Europe and former Soviet Union countries than in Western Europe. The incidence rate of cervical cancer in Europe is 10.6 per 100,000. The analysis between different parts of Europe shows more than doubled incidence rates in Central/Eastern Europe (14.9/100,000) when compared with Western Europe (6.9/100,000). We have calculated that in Europe approximately over 3400 Radical Hysterectomies are performed annually if we considered a 6 % of surgical candidates.

Our goal is to obtain data from 1000 patients that underwent a Radical Hysterectomy in 2013 and 2014. Approximately 500 patients per arm.

Scope of this study

- To take a real picture of what happened in Europe to those patients with IB1 cervical cancer that underwent a Radical Hysterectomy plus pelvic lymphadenectomy.
- Compare outcomes after MIS vs open technique.
- Study risk factors for relapse.
- Search for preventable maneouvers to lower relapse in the MIS group.



Inclusion Criteria

1. Primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix.
2. FIGO IB1 carcinoma (FIGO 2009)
3. Preoperative pelvic MRI indicating tumor diameter < 4 cm (at least two dimensions,) and no parametrial invasion. Exceptionally, it can be considered acceptable Vaginal Ultrasound, only if your Institution have internally validated this technique for cervical cancer. Otherwise, it cannot be accepted.
4. Preoperative either (Abdominal) CT scan or MRI or PET-CT ruling out extracervical metastatic disease
5. Performance status ECOG 0-1
6. Age 18 years or older
7. Type II-III radical hysterectomy or Type B-C by MIS (laparoscopic or robotic) or open surgery.
8. Operated during the years 2013-2014 within the ESGO area.
9. Bilateral pelvic lymphadenectomy or SNB plus bilateral pelvic lymphadenectomy. At least, a total of 10 pelvic nodes must be reported (considering both sides)

10. Pathologic report shows information on tumor size, vaginal and parametrial margins and bilateral nodal status.

Exclusion Criteria

1. Any histological type other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix
2. Tumor size greater than 4 cm.
3. Past medical history of any invasive tumor
4. History of previous abdominal or pelvic radiotherapy of any type (including braquitherapy).
5. History of preoperative neoadjuvant chemotherapy cervical cancer .
6. Cervical conization previous to surgery.
7. Suspicious positive pelvic or paraaortic nodes nodes or metastatic disease on PET CT, MRI, or CT.
8. Any uterine diameter larger than 12 cm
9. Conversion from MIS to laparotomy
10. Pregnant women

Study Development

1. Submission to ESGO members the study application form.
2. Confirmation of participants to join the study.
3. Accreditation of one Principal Investigator for each medical center and delivery of center codes.
4. Start collecting cases through Google Forms.
5. Deadline for collection of individual cases: Six months after the study release

Screening for the candidate

How to participate in the study

1. Note that only centers belonging to the ESGO area can participate in the study. (Appendix 1)
2. Fill and sign the **online application form** (see the link below) to accept the participation in the study as principal investigator (PI) of your institution (only one PI by each institution) https://forms.gle/2WPhzrkxyFPodmDq5 (Appendix 2)
3. As soon as your center joins the study, you will receive a Center Identification code and e-mail with instructions, allowing the data collection.
4. Then, start to collect data of consecutive cervical cancer patients operated in 2013 and 2014 in your center that meet the inclusion and exclusion criteria.
5. For collecting data, the online questionnaire can be reached in the following link: https://forms.gle/bUpnV2r41fkv8cnY8 (Appendix 3)

6. Every time submit each a complete case form, you will receive an e-mail with the confirmation and a copy of your response. For sending the form, you have to fill at least the required items. You are allowed to re-edit your answers later.
1. We want to complete the data collection in less than six months.
2. As principal investigator, I will be available for any doubt by e-mail (lchiva@unav.es), or also by phone (+34630232947)

Data statistical management

A Propensity score will be calculated to construct a weighted cohort of patients. For comparison of the distributions of categorical variables we will use the chi-square test in the unweighted cohort and weighted logistic-regression models in the weighted cohort. We will compare DFS and OS using the inverse probability of treatment–weighted log-rank test and plotted weighted survival functions. Estimation of the hazard ratio for death from any cause after minimally invasive radical hysterectomy, as compared with open surgery, with weighted Cox proportional-hazards models. Sensitivity analyses to assess the robustness of findings. To ensure that treatment-related survival differences were not confounded by a differential use of adjuvant therapy, the survival model will be refitted with postoperative treatment as a covariate.

To explore whether the observed association differed according to the minimally invasive method (traditional laparoscopy vs. robot-assisted laparoscopy), tumor size in the greatest dimension (≥2 cm vs. <2 cm), or histologic type, we estimated the hazard ratios that were associated with minimally invasive surgery after refitting separate propensity-score–weighted survival models for each subgroup.

Data Publication

Hopefully, the results of this study will be submitted for evaluation to international meetings and publication in a relevant international journal.

Authorship will include investigators following a strict criteria, considering the introduced number of cases in the study by each investigator. We will try to count with as many authors we may.

Furthermore, in order to count with as many authors as possible, we will create a Succor Research Study Group that will offer authorship when the investigators cannot may allocated among the first authors .

At the time of the publication we will follow the STROBE guidelines5 for observational studies.

STROBE stands for an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of STrengthening the Reporting of OBservational studies in Epidemiology.

Study registration

- Succor Study has been registered at ClinicalTrials.gov. ClinicalTrials.gov

References

1. Pecorelli, S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105, 103-104 (2009)
2. Ramirez PT, Frumovitz M, Pareja R, et al Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-1904.
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4. Nancy A, Dreyer, Sean R et al. Why Observational Studies Should Be Among The Tools Used In Comparative Effectiveness Research. Health Affairs 29, 10 (2010): 1818–1825
5. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9.

10.Appendix 1. Countries of the ESGO area are allowed to participate in this study)

Albania	Andorra
Armenia	Austria
Azerbaijan	Belarus

Belgium	Bosnia and Herzegovina
Bulgaria	Croatia
Cyprus	Czech Republic
Denmark	England
Estonia	Finland
France	Georgia
Germany	Greece
Hungary	Iceland
Ireland	Israel
Italy	Kazakhstan
Kosovo	Latvia
Liechtenstein	Lithuania
Luxembourg	Macedonia
Malta	Moldova
Montenegro	Netherlands
Norway	Poland
Portugal	Romania
Russia	San Marino
Serbia	Slovakia
Slovenia	Spain
Sweden	Switzerland
Turkey	Ukraine

11.Appendix 2. SUCCOR STUDY application form

Application form for participation in this project as Principal Investigator (PI) in your institution

SURGERY IN CERVICAL CANCER

AN EUROPEAN MULTICENTRIC OBSERVATIONAL STUDY

CASES OF 2013 and 2014

PI. Luis Chiva MD PhD, CLINICA UNIVERSIDAD DE NAVARRA

* Required

Email address *

First Name *

Last Name *

Position *

Mark only one oval.

- Physician attending
- Fellow
- Resident
- Other:

Country (only countries of the ESGO area are allowed to participate in this study) *

Mark only one oval.

- Albania
- Andorra
- Armenia
- Austria
- Azerbaijan
- Belarus
- Belgium
- Bosnia and Herzegovina
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- England
- Estonia
- Finland
- France
- Georgia
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Israel
- Italy

- Kazakhstan
- Kosovo
- Latvia
- Liechtenstein
- Lithuania
- Luxembourg
- Macedonia
- Malta
- Moldova
- Montenegro
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Russia
- San Marino
- Serbia
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- Turkey
- Ukraine

Name of your institution/hospital/cancer center *

City *

Address *

Zip code *

Telephone number

Type of institution

Mark only one oval.

- Academic public hospital
- Non Academic public hospital
- Academic private hospital
- Non Academic private hospital

On average, How many early cervical cancer do you operate every year in your institution ?

Mark only one oval.

- Less than 5
- 5-10
- 10-20
- 20-30
- >30

Have your Department incorporated minimally invasive surgery for performing Radical Hysterectomy ? *

Mark only one oval.

- Yes, many years ago, before 2014
- Yes, but recently, after 2014
- Not yet, we are still doing open surgery for cervical cancer

Do you use typically Vaginal US as imaging tool of choice instead of MRI , for evaluating a surgical candidate for a radical hysterectomy ?

Remember that Preoperative pelvic MRI indicating tumor diameter < 4 cm (at least two dimensions,) and no parametrial invasion is mandatory in this study . Exceptionally, it can be considered acceptable vaginal ultrasound, only if your Institution have internally validated this technique for cervical cancer. Otherwise, it cannot be accepted.

Mark only one oval.

- Yes
- No
- Other:

If the previous answer was yes, Have you validated Vaginal US in your institution as an accurate option ?

Mark only one oval.

- Yes
- No
- Other:

Final Statement

FINAL STATEMENT After having read the study protocol, I agree with the objectives and methodology of the study, and therefore I want to participate in the study as investigator of my Institution. I understand that I want to collaborate by providing the anonymized data of the questionnaire so the principal investigator cannot identify the patients. Through this document, I acquire the commitment that data that I send to the central investigator will match with those reflected in the clinical history of the patients. I also agree to consecutively include all the patients that meet the inclusion criteria of the study. It has been explained to me that after my inclusion as a researcher in the study, the principal investigator will assign a code to identify my institution. Each patient will be identified with that code followed by a correlative order number. Even though the study has been presented in the Ethical Committee of the central investigator, if necessary it might be presented in a local Ethical Committee. I count with the permission of my institution to participate in this study. I agree with everything previously affirmed.

I wish to participate in Succor study *

Signed (write down your name)

Thank you very much for joining the SUCCOR STUDY, we will contact you shortly.

For any doubt or comment, feel free to contact Dr. Luis Chiva lchiva@unav.es

(phone number +34630232947)

12.Appendix 3. Data Questionarie

SUCCOR STUDY, we want to know why

SURGERY IN CERVICAL CANCER

AN EUROPEAN MULTICENTRIC OBSERVATIONAL STUDY

CASES OF 2013 and 2014

PI. Luis Chiva MD PhD, CLINICA UNIVERSIDAD DE NAVARRA

* Required

Email address *

Local investigator Name *

Local investigator Last name *

Country *

Only cases operated in the ESGO area can be included

Mark only one oval.

- Albania
- Andorra
- Armenia
- Austria
- Azerbaijan
- Belarus
- Belgium
- Bosnia and Herzegovina
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- England
- Estonia

- Finland
- France
- Georgia
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Israel
- Italy
- Kazakhstan
- Kosovo
- Latvia
- Liechtenstein
- Lithuania
- Luxembourg
- Macedonia
- Malta
- Moldova
- Montenegro
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Russia
- San Marino
- Serbia
- Slovakia
- Slovenia
- Spain
- Sweden

- Switzerland
- Turkey
- Ukraine
- Option 51

Basic Data

Center Code (provided by the central investigator) *

Patient consecutive number of order *

For instance, if the provided Center Code is: CUN (Clinica Universidad de Navarra); we will number patients as : CUN1, CUN2, CUN3, CUN4...etc.

Patient´s Date of birth *

Example: December 15, 2012

Date of the surgery (Radical Hysterectomy) *

Example: December 15, 2012

Inclusion criteria and Exclusion criteria

All the power of this study relies on the adequate fulfillment of these strict criteria to avoid confounding variables that may rest value to the conclusions. We have designed these criteria in a similar way to a prospective randomized trial. Please, try to be very meticulous with patient selection.

Inclusion criteria

All the items must be checked to include the patient in the study

Check all that apply.

- Primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix
- Stage IB1 carcinoma, <4 CMS, (FIGO 2009)

- Preoperative pelvic MRI indicating tumor diameter < 4 cm (at least two dimensions,) and no parametrial invasion. Exceptionally, it can be considered acceptable Vaginal Ultrasound, only if your Institution have internally validated this technique for cervical cancer. Otherwise, it cannot be accepted.
- Preoperative either (Abdominal) CT scan or MRI or PET-CT ruling out extracervical metastatic disease
- Performance status ECOG 0-1
- Age 18 years or older
- Radical hysterectomy Type II-III or Type B-C by MIS (laparoscopic or robotic) or open surgery.
- Patient was operated during the years 2013-2014 within the ESGO area.
- Bilateral pelvic lymphadenectomy (+- sentinel LN biopsy). At least, a total of 10 pelvic nodes must be reported (considering both sides)
- Pathologic report shows information on tumor size, vaginal and parametrial margins and nodal status

Exclusion criteria

All the items must be checked to include the patient in the study

Check all that apply.

- Any histological type other than adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix
- Tumor size greater than 4 cm.
- Past medical history of any invasive tumor
- History of previous abdominal or pelvic radiotherapy of any type (including braquitherapy).
- History of preoperative neoadjuvant chemotherapy cervical cancer .
- Cervical conization previous to surgery.
- Suspicious positive pelvic or paraaortic nodes nodes or metastatic disease on PET CT, MRI, or CT.

- Any uterine diameter larger than 12 cm
- Conversion from MIS to laparotomy
- Pregnant women

Does the case fulfill all the inclusion and exclusion criteria? *

This a crucial item. Please try to be precise.

Mark only one oval.

- YES
- NO (patient will be excluded)

Physical exam, biopsies and preoperative evaluation

BMI (kg/m2):

Performance status

Mark only one oval.

- ECOG 0
- ECOG 1
- Not reported

External appearance of the tumor

Mark only one oval.

- Exophytic
- Endophytic ulcerative
- Endophytic barrel-shaped
- Not reported

Estimated tumor size in mm by clinical evaluation in the chart

(inspection and/or palpation; estimation of largest diameter in mm)

Absence of vaginal or parametrial invasion during the pelvic exam

Mark only one oval.

- No vaginal or parametrial invasion
- Vaginal or parametrial invasion (patient will be excluded)

Histology of cervical biopsy:

Mark only one oval.

- Squamous
- Adenocarcinoma
- Adenosquamous
- Not reported
- Other:

Grade of the tumor on cervical biopsy

Mark only one oval.

- Grade I or well differentiated
- Grade II or moderately differentiated
- Grade III or poorly differentiated
- Not reported

Imaging evaluation

Imaging information is crucial for this study If any of the following items are not found in the radiologic report or they are not are clear to you, please, we encourage the investigator to review the MRI images with the Radiology Department. • Preoperative pelvic MRI is mandatory indicating tumor diameter < 4 cm (at least two dimensions, preferably three, to calculate volumes) and no parametrial invasion. This is the imaging tool of choice in this study. • Exceptionally, if a pelvic MRI was not ordered, as second option , we considered acceptable vaginal Ultrasound indicating tumor diameter < 4 cm (at least two dimensions, preferably three to calculate volumes) with no parametrial invasion; only this is allowed if your Institution has internally validated this technique for cervical cancer. Otherwise, it cannot be accepted.

Had the patient a pelvic MRI preoperatively ? *

Mark only one oval.

- Yes
- No, but patient had vaginal US and we have validated this technique in cervical cancer.
- No (patient will be excluded)

MRI (US) tumor diameter (1) in mm *

Preferably MRI rather than US, if it was ordered

MRI(US) tumor diameter (2) in mm *

Preferably MRI rather than US, if it was ordered

MRI (US) tumor diameter (3) in mm

Preferably MRI rather than US, if it was ordered

Parametrial invasion by MRI (US) *

Preferably MRI rather than US, if it was ordered

Mark only one oval.

- Absence of parametrial invasion
- Presence of suspicious parametrial invasion (patient will be excluded)

Extracervical disease by either abdominal CT or MRI or PET-CT *

This a crucial item. Please try to be precise.

Mark only one oval.

- Absence of extracervical disease by CT or MRI or PET-CT:
- Presence of suspicious extracervical disease by CT or MRI or PET-CT, (patient will be excluded)

Surgical procedure

The operating report should be reviewed in detail to understand how was the operation carried out

This Surgeon that performed the procedure can be described as

Mark only one oval.

- Senior surgeon in gyn oncology (>10 years after gyn-onc training)
- Junior surgeon in gyn oncology (<10 years after gyn-onc training)
- Fellow in gyn oncology
- Resident assisted by senior or junior surgeon
- General gynecologist
- Other

How was the surgical approach of this case ? *

This a crucial item. Please try to be precise.

Mark only one oval.

- Open

- Laparoscopic
- Robotic
- Other (patient will be excluded)

The operative report describes a radical hysterectomy with bilateral pelvic lymphadenectomy +- sentinel lymph node biopsy (SLNB) *

To consider the procedure as Radical hysterectomy, the operating report must describe at least the following maneuvers: 1.Developing of pelvic spaces, 2.Ligature of uterine artery in its origin 3. Dissection of the ureter up to the bladder 4.Excision of the paracervical tissue 5. Bilateral pelvic lymph node dissection.

Mark only one oval.

- Yes
- No (patient will be excluded)

What type of radical hysterectomy is described in the operating report?

Type III or type C: transection of paracervix at junction with internal iliac vascular system

Mark only one oval.

- Type II or type B (Transection of paracervix at the ureter ; Modified radical hysterectomy).
- Type III or type C (Transection of paracervix at junction with internal iliac vascular system; Clasical Radical Hysterectomy)
- Not reported
- Other:

Type of nodal evaluation at the time of the procedure *

Remember as inclusion criteria , at least, a total of 10 pelvic nodes must be reported (considering both sides)

Mark only one oval.

- Bilateral Pelvic lymphadenectomy (10 nodes, at least)
- SNB and Bilateral Pelvic lymphadenectomy (10 nodes at least)
- Other:

Was the MIS (laparoscopy or robotics) converted to laparotomy in any moment of the procedure ?

Mark only one oval.

- No

- Yes (patient will be excluded)
- Not aplicable

Duration of the procedure (min)

Estimated blood loss (cc):

Intraoperative complications

Check all that apply.

- Intraoperative bleeding, patient needs transfusion during surgery
- Ureteral injury
- Bladder injury
- Vascular injury
- Bowel injury
- Nerve injury
- Other:

Did the surgeon use any type of uterine manipulator?

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, indicate which type

Did the surgeon report any of the following protective maneuvers during the procedure?

Check all that apply.

- Extraction the lymph nodes in bag.
- Closure the vagina over the tumor at the beginning of the procedure to avoid contamination.
- Colpotomy performed vaginally at the end of procedure.
- Specimen extraction performed vaginally within a bag.
- Another protective maneuver to avoid tumor contamination (explain).
- Other:

Pathological findings

Reporting pathological información is critical for the study. If any of the following items are not found in the Pathology Report, please, we encourage you to review the case with the Pathology Department. At least two diameters of the tumor must be reported, preferably three for evaluating tumor volume

Diameter (1) of the tumour (mm) *

This a crucial item. Please try to be precise.

Diameter (2) of the tumour (mm) *

This a crucial item. Please try to be precise.

Diameter (3) of the tumour (mm)

Final histology in the Pathology report *

This a crucial item. Please try to be precise. Mixed tumours are allowed if they shows these histological types.

Mark only one oval.

- Squamous carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma
- Other (patient will be excluded, explain below)
- Other:

Final tumor grade

This a crucial item. Please try to be precise.

Mark only one oval.

- Grade I or well differentiated
- Grade II or moderately differentiated
- Grade III or poorly differentiated
- Not reported

Lymphovascular space invasion

This a crucial item. Please try to be precise.

Mark only one oval.

- Yes
- No
- Not reported

Depth of invasion (measured from the cervical surface up to cervical canal)

This a crucial item. Please try to be precise.

Mark only one oval.

- Superficial (invades <1/3 of the stroma in any diameter)
- Intermediate (invades between 1/3 and 2/3 of the stroma in any diameter)
- Deep (invades >2/3 of the stroma in any diameter)
- Not reported

Parametrial invasion in the pathological specimen

This a crucial item. Please try to be precise.

Mark only one oval.

- No parametrial invasion
- Unilateral proximal parametrial invasion
- Bilateral proximal parametrial invasion
- Not reported (It will be excluded)
- Other:

Vaginal infiltration in the pathological specimen

This a crucial item. Please try to be precise.

Mark only one oval.

- No vaginal infiltration
- Upper Vaginal infiltration
- Not reported
- Other:

Infiltration of the uterine corpus

Mark only one oval.

- Yes
- No
- Not reported

Infiltration either of the tubes or ovaries

Mark only one oval.

- Yes
- No
- Not reported

Infiltration of pelvic peritoneum

Mark only one oval.

- Yes
- No
- Not reported

Margins on the final specimen *

This a crucial item. Please try to be precise.

Mark only one oval.

- Free margins
- Positive margins
- Not reported (It will be excluded)

If positive , specify which positive margin/s in detail:

Check all that apply.

- Parametrial
- Vaginal
- Other:

Nodal evaluation

Did the surgeon carried out a SLNB?

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, what tracer use the surgeon to look for the sentinel node?

Check all that apply.

- Blue dye
- Technetium
- Indocyanine green
- Not reported

- Other:

if SLNB was done, did the surgeon identify a SLN?

Mark only one oval.

- None
- Only one side
- Both sides
- Not reported

Did the surgeon carried out bilateral pelvic lymphadenectomy? *

Mark only one oval.

- Yes
- No
- Not reported

Did the surgeon order a frozen section of one or more nodes?

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, did the frozen section found any positive node ?

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, how many nodes were found positive at the time of the frozen section ?

Total Number of pelvic nodes in the final pathology report *

This a crucial item. Please try to be precise.

Total Number of POSITIVE pelvic nodes in the final pathology report *

This a crucial item. Please try to be precise.

Number of TOTAL/POSITIVE pelvic nodes in the final pathology report in each side

Check all that apply.

	Leftside total	Left side positive	Right side total	Right side positive
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
>15				

Postoperative period

Postoperative complications (within 30 days after surgery) Several options allowed

Check all that apply.

- No relevant complications

- Post operative bleeding, patient needs transfusion
- Bladder fistula
- Ureteral fistula
- Urinary infection
- Hematuria
- Bladder dysfunction
- Urinary incontinence
- Small bowel fistula or leakage
- Large bowel fistula or leakage
- Constipation/ileus
- Bowel obstruction
- Pelvic or abdominal abscess
- DVT
- Pulmonary embolism
- Pneumonia
- Pleural effusion
- Lymphorrhagia
- Quilous ascites
- Abdominal wall infection of any type
- Moderate/Severe Vaginal bleeding
- Vaginal cuff cellulitis
- Vaginal cuff dehiscence
- Readmission to ICU
- Re-intervention
- Death
- Other:

In case of readmission in ICU, re-operation or death within the 30 period after surgery, please summarise briefly the circumstances and the evolution.

Length of hospital stay (days)

Adjuvant therapy

Did the patient received any adjuvant therapy after surgery? *

This a crucial item. Please try to be precise.

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, when did she start the adjuvant therapy ?

Example: December 15, 2012

If the answer was yes, which type of adjuvant therapy?

Check all that apply.

- Standard external radiation
- Braquitherapy
- Radiation Boost as consolidation
- Concomitant chemotherapy as part of a chemoradiation protocol
- Chemotherapy before or after Radiation, but not concomitant
- Only adjuvant chemotherapy with out external radiation
- Radiation was suboptimal or incomplete
- Chemotherapy could not be completed as planned
- Other:

If patient received external radiation, do you know the total dosis that receive the pelvic volume ?

The standard recommendation for postoperative radiation therapy consist sof external beam radiation therapy to a dose 50.4 Gy in 25-28 fractions using either intensity modulated radiation therapy or 4-field technique. The external beam radiation therapy maybe supplemented by vaginal brachytherapy boost at the discretion of the treating physician.

Mark only one oval.

- Less than 50.4 Gy
- Equal or greater than 50.4Gy

If patient received "No concomitant" adjuvant chemotherapy, how many cycles did she receive?

Did the patient receive Bevacizumab as part of adjuvant therapy ?

Mark only one oval.

- Yes
- No
- Not Reported

Follow up and Recurrences

Accurate description of clinical details of relapse are very important for the conclusions of this study. In fact, central investigator will ask for a copy of patients´ codified reports in case of relapse (MRI report, operating report and pathology report)

Did the patient relapse during her follow up? *

This a crucial item. Please try to be precise.

Mark only one oval.

- Yes
- No
- We don't know, patient was missed after surgery
- Other:

if the answer was yes, when was she diagnosed the first relapse ?

This a crucial item. Please try to be precise.

Example: December 15, 2012

if the patient relapsed, Where was the recurrence?

This a crucial item. Please try to be precise.

Mark only one oval.

- Local (including vagina, parametrial area and pelvic retroperitoneum)
- Distant metastases (any other location)
- Both Local and distance

if the answer was yes, Where was specifically located the relapse?

Check all that apply.

- Vaginal cuff, intracavitary
- Vaginal cuff, peritoneal side
- Parametria
- Lateral pelvic side wall
- Pelvic nodes
- Paraaortic nodes
- Pelvic Peritoneum
- Mid or upper abdominal peritoneum
- Inguinal nodes
- Laparotomy scar
- Trocar sites
- Distant metastases (specify where below in other)
- Other:

How was diagnosed the recurrence?

Check all that apply.

- Physical exam
- Vaginal citology
- Biopsy
- Pelvic MRI
- CT scan
- PET CT
- Abdominal ultrasound
- Vaginal ultrasound
- Chest Xray
- Other:

Any commentary to clarify the location of relapse/s

Date of last contact, last follow up or death *

This a crucial item. Please try to be precise.

Example: December 15, 2012

Status at last follow-up *

This a crucial item. Please try to be precise.

Mark only one oval.

- Alive without disease
- Alive with disease
- Death without disease
- Death of disease
- Missing

Did the patient suffer any sequelae directly related to the surgical procedure at the time of the last follow-up?

Mark only one oval.

- Yes
- No
- Not reported

If the answer was yes, could you briefly describe the sequelae?

Conclusion

Please, share any commentary regarding the case that may help to offer relevant information

Final statement

As a result of this I declare that all the information sent about this case coincides with that is contained in the clinical history, except for an error or unintentional omission.

Mark only one oval.

- Confirmed
- Unconfirmed

Thank you very much for your invaluable collaboration.

As soon as you submit you filled form, you will receive an e-mail with the confirmation and a copy of your response. For submitting the form that you have finished, it is expected to complete at least the required items. You have permission to re-edit your responses later. If you have any doubt, please do not hesitate to contact the central investigator at lchiva@unav.es

To be filled by the central investigator

This Case includes all the requirements to be accepted

Mark only one oval.

- YES
- NO

A copy of your responses will be emailed to the address you provided

13.Appendix 4. Succor study Final Declaration Form

Message From the Central PI

● After the final submission of your cases, they will be thoroughly reviewed by our team, and if there is found any inconsistency, error or mistake, the record/s will be resent to you to for further evaluation.

● It has been an incredible honor and pleasure to count with you in this project. Thank you for your invaluable support.

● I dare to affirm that it is the one most extensive European studies ever done in Radical Hysterectomy.

● I hope that this initiative may help to understand better this disease and consequently to help our patients with cervical cancer.

Investigator

As you want to appear on the Certificate of Participation

2. First Name

3. Last Name

4. Institution

5. Center Code provided by central PI

6. Number of cases submitted to the study

2013-2014 with inclusion-exclusion criteria

7. Ethics Committee Approval

It is necessary to include the cases in the final publication

Mark only one oval.

It has been obtained and already submitted to the central PI

It has been already obtained and shortly it will be submitted to the central PI

It was requested and it will be send as soon as we get it

It has not been accepted by the Ethics Committee (please, contact CENTRAL PI)

Other:

Final Statement

As investigator in SUCCOR STUDY, I Declare that:

(Please check the different statements

Check all that apply.

- **I have included all patients that underwent a Radical Hysterectomy in my Institution from January 1, 2013, to December 31, 2014 and fulfilled the study inclusion criteria.**
- **I only have submitted cases operated in this institution and not in other (to avoid duplicates)**
- **ALL the information submitted matches with the information contained in the records of the included patients.**
- **I have incorporated all the cases of RELAPSE or RECURRENCE and I have not missed any relapse.**
- **At the time of a final publication, I would like to collaborate as author, following the publication criteria included in the protocol.**
- **If due to the number of submitted cases I cannot be within the authorized number of** authors of by the journal, I would like to appear in the publication as a member of the SUCCOR STUDY GROUP

9. Comments and Questions

10. Signed by