Gynecologic Cancer InterGroup
Cervix Cancer Research Network

Conservative surgery in early-stage cervical cancer

Dr Marie Plante
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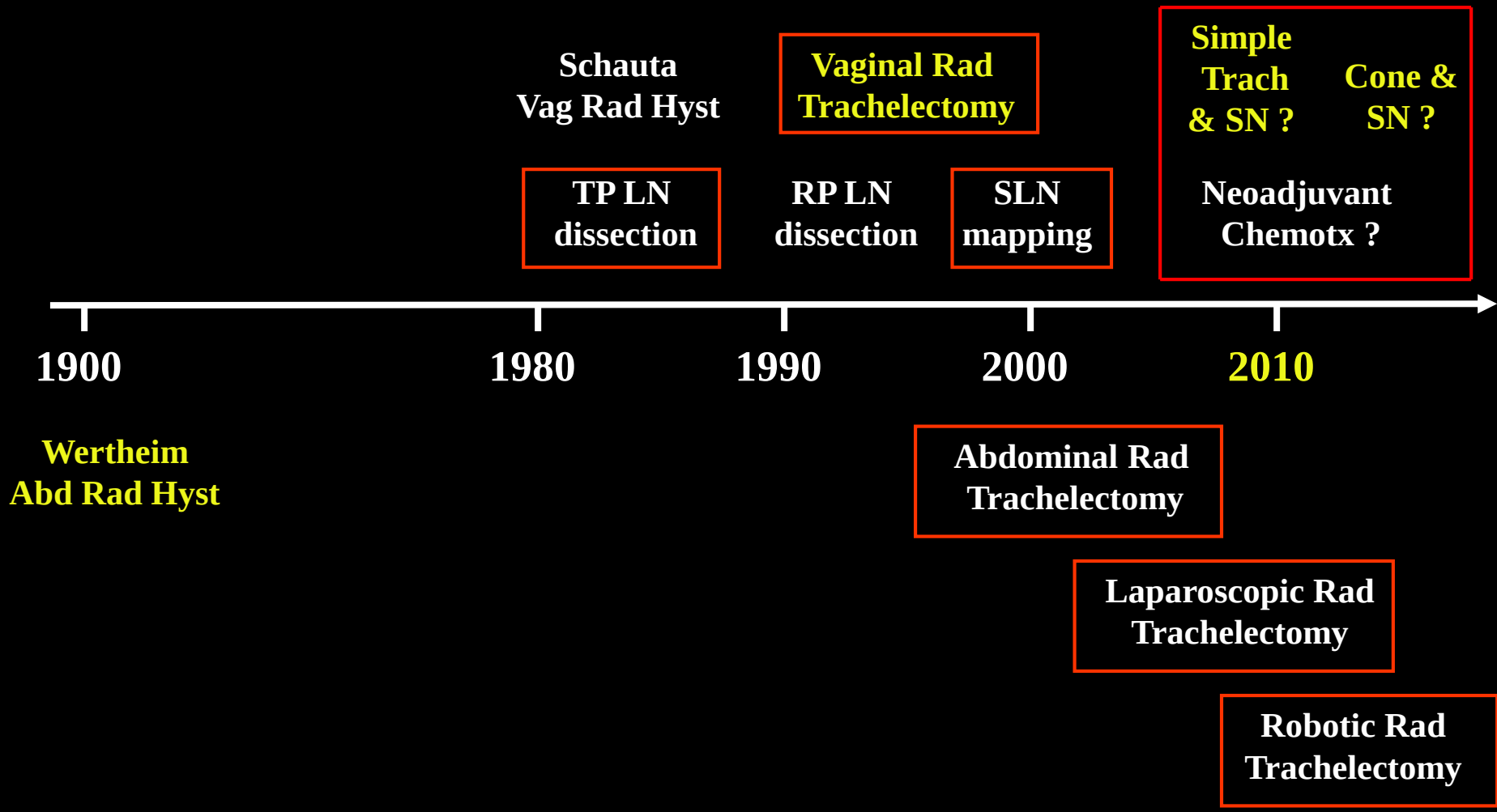
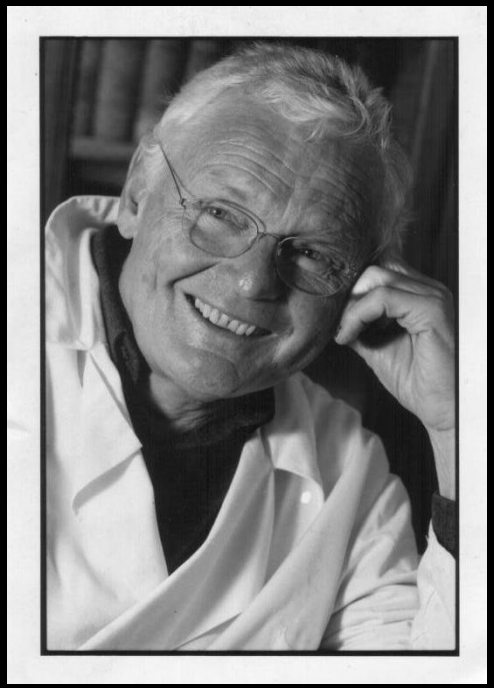
Cervix Cancer Education Symposium, January 2019

Evolution in the management of cervical cancer



Radical Trachelectomy

- VAGINAL approach



Professor Daniel Dargent

Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review

Enrica Bentivegna, Sebastien Gouy, Amandine Maulard, Cyrus Chargari, Alexandra Leary, Philippe Morice

159 studies
3098 patients

	Dargent's procedure	Abdominal radical trachelectomy		
		Laparotomic	Laparoscopic	Robot-assisted
Series and case reports				
Number series or case reports*	21	28	18	9
Number of patients	1523	866	252	101
Patients excluded†	159	206	14	12
Tumour characteristics				
Stage‡				
IA	316	153	55	25
IB1				
All	1065	559	215	54
>2 cm	At least 84	At least 167	At least 42	Unknown
IB2	3	19	2	1
IIA	9	4	1	0
Tumour type				
Squamous-cell carcinoma	892	549	167	37
Adenocarcinoma	432	168	50	29
Other, mixed, or unknown	199	44	35	35
LVSI positive	401	At least 198	At least 52	At least 5
Oncological outcomes				
Recurrent disease	58 **3.8%**	31 **3.6%**	15 **6.0%**	2
Died from disease	24	9	3	0

Lancet Oncol. 2016 Jun;17(6):e240-e253

Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review

Enrica Bentivegna, Sebastien Gouy, Amandine Maulard, Cyrus Chargari, Alexandra Leary, Philippe Morice

	Dargent's procedure	Abdominal radical trachelectomy		
		Laparotomic	Laparoscopic	Robot-assisted
Series and case reports				
Number series or case reports*	21	28	18	9
Number of patients	1523	866	252	101
Patients excluded†	159	206	14	12
Fertility outcomes				
Pregnancies	487	175	55	20
Fetal loss (trimester 1 or 2)	103	37	16	2
Preterm delivery	104	21	19	5
Pregnancy rate¶	216/343 (63%)	114/235 (49%)	25/52 (48%)	17/21 (81%)

Lancet Oncol. 2016 Jun;17(6):e240-e253

Gynecologic Oncology 121 (2011) 290–297

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies

Marie Plante *, Jean Gregoire, Marie-Claude Renaud, Michel Roy

Recurrences: **6/125 (4.8%)**

Deaths: **2/110 (1.6%)**

Risk factor associated with recurrence

Size of the lesion > 2 cm (p=0.001)

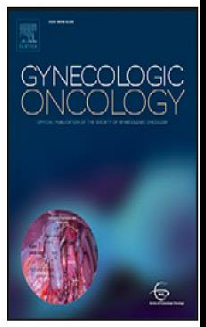
- **10% of ptes had lesions > 2 cm**
- **Represent 50% of the recurrences**

Gynecologic Oncology 138 (2015) 304–310

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy

L. Hauerberg [a,*], C. Høgdall [a], A. Loft [b], C. Ottosen [a], S.F. Bjoern [a], B.J. Mosgaard [a], L. Nedergaard [c], H. Lajer [a]

N=120

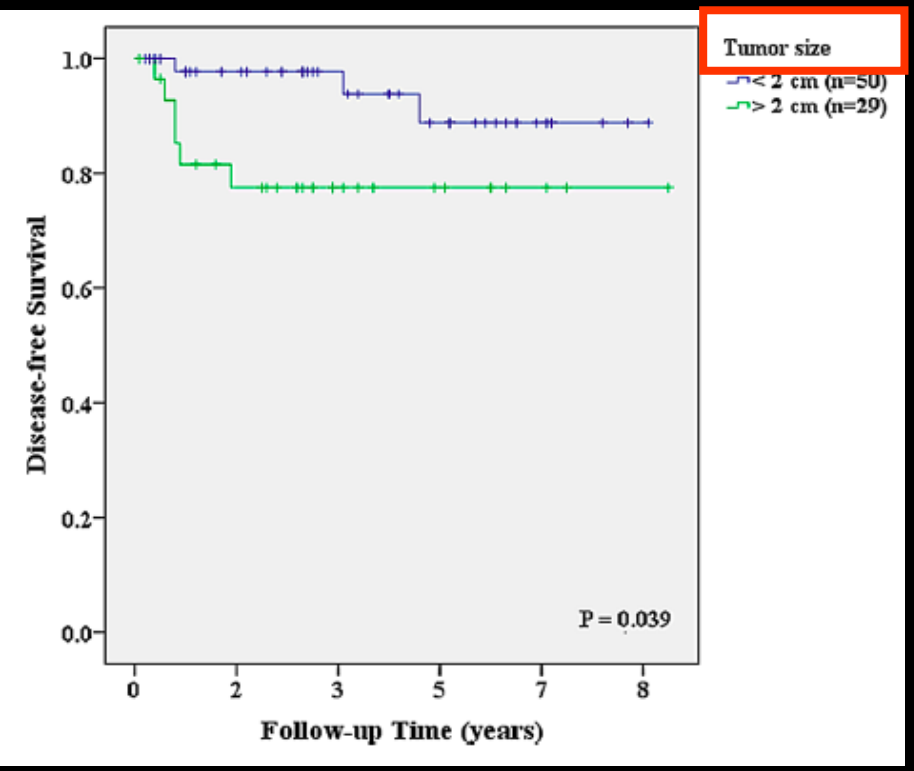
6 recurrences (5.1%); 2 deaths (1.7%)

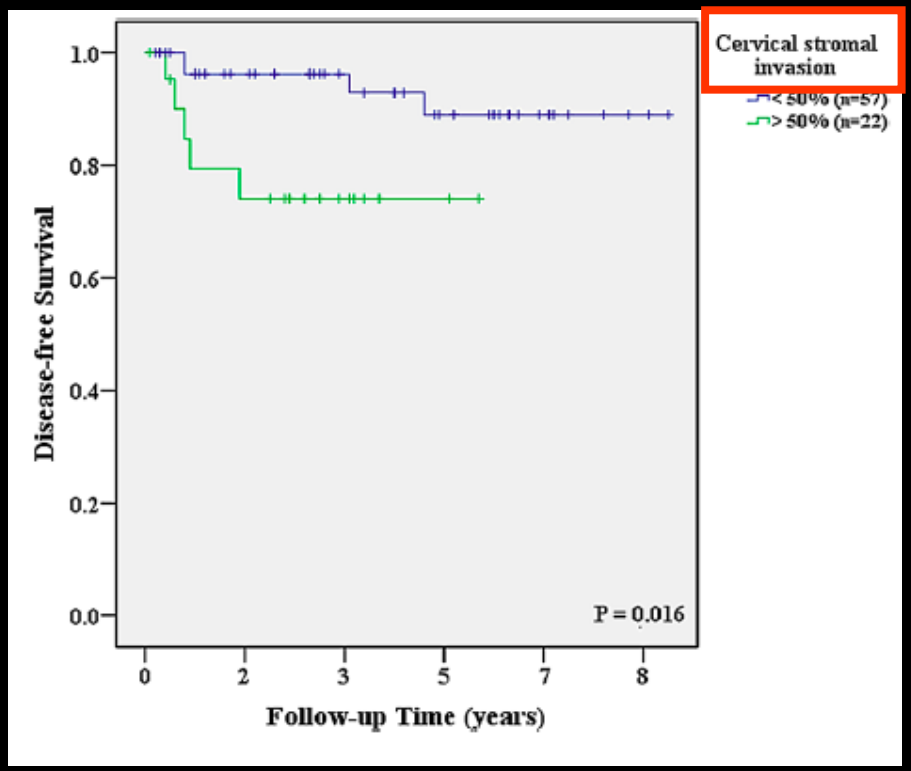
7 patients had lesions >2 cm (5.8 %)

3 recurrences (50%)

Long-Term Outcomes After Fertility-Sparing Laparoscopic Radical Trachelectomy in Young Women With Early-Stage Cervical Cancer: An Asan Gynecologic Cancer Group (AGCG) Study

JEONG-YEOL PARK, MD, PhD,[1] WON DEOK JOO, MD, PhD,[2] SUK-JOON CHANG, MD, PhD,[3] DAE-YEON KIM, MD, PhD,[1] JONG-HYEOK KIM, MD, PhD,[1] YONG-MAN KIM, MD, PhD,[1] YOUNG-TAK KIM, MD, PhD,[1] AND JOO-HYUN NAM, MD, PhD[1]*





Park et al. J Surg Oncol 2014;110:252–257

Radical Trachelectomy

- Careful patient selection
  - SIZE of the lesion
    - Most important prognostic factor
  - Meticulous preoperative evaluation: critical
    - MRI: high quality
    - Pathology review: expert pathologist

Radical Trachelectomy

- **Considerable evolution** in the radical trachelectomy technique (last 30 years)
- **« Proof of concept »**
- Radical Trachelectomy now considered **« standard of care »** in young women who wish to preserve fertility

CLINICAL STAGE[b]	PRIMARY TREATMENT (FERTILITY SPARING)[e]	
Stage IA1 (no lymphovascular space invasion [LVSI])	Cone biopsy[f] with negative margins[g] (preferably a non-fragmented specimen with 3-mm negative margins)[g] (If positive margins, repeat cone biopsy or perform trachelectomy)	See Surveillance (CERV-10)
Stage IA1 (with LVSI) and Stage IA2	Cone biopsy[f] with negative margins[g] (preferably a non-fragmented specimen with 3-mm negative margins[g]) (if positive margins, repeat cone biopsy or perform trachelectomy) + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B) (Consider sentinel lymph node [SLN] mapping)[h] or Radical trachelectomy + pelvic lymph node dissection[h] (± para-aortic lymph node sampling [category 2B]) (Consider SLN mapping)[h]	See Surveillance (CERV-10)
Stage IB1[d]	Radical trachelectomy + pelvic lymph node dissection[h] ± para-aortic lymph node sampling (Consider SLN mapping)[h,i]	See Surveillance (CERV-10)

[b] See Principles of Imaging (CERV-A).
[d] Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and adenoma malignum are not considered suitable tumors for this procedure.
[e] No data to support a fertility-sparing approach in small neuroendocrine tumors, gastric type adenocarcinoma, or adenoma malignum (also known as minimal deviation adenocarcinoma). Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.
[f] Cold knife conization (CKC) is the preferred method of diagnostic excision, but loop electrosurgical excision procedure (LEEP) is acceptable, provided adequate margins and proper orientation are obtained. Endocervical curettage (ECC) may be added as clinically indicated.
[g] Negative for invasive disease or histologic high-grade squamous intraepithelial lesion (HSIL) at margins.
[h] See Principles of Evaluation and Surgical Staging (CERV-B).
[i] For SLN mapping, the best detection rates and mapping results are in tumors <2 cm.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

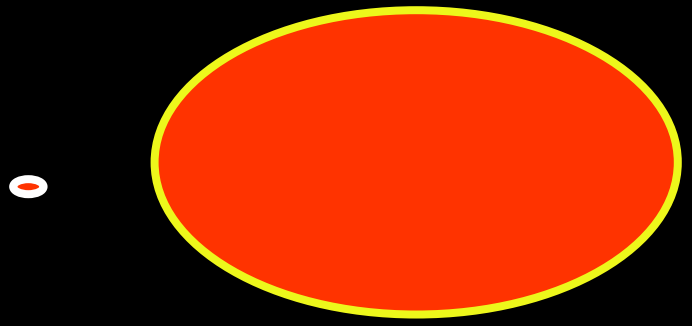
Radical Trachelectomy

- Is radical surgery necessary in low risk small volume disease (< 2 cm) ?

Less radical surgery

Table 2
Carcinoma of the cervix uteri.

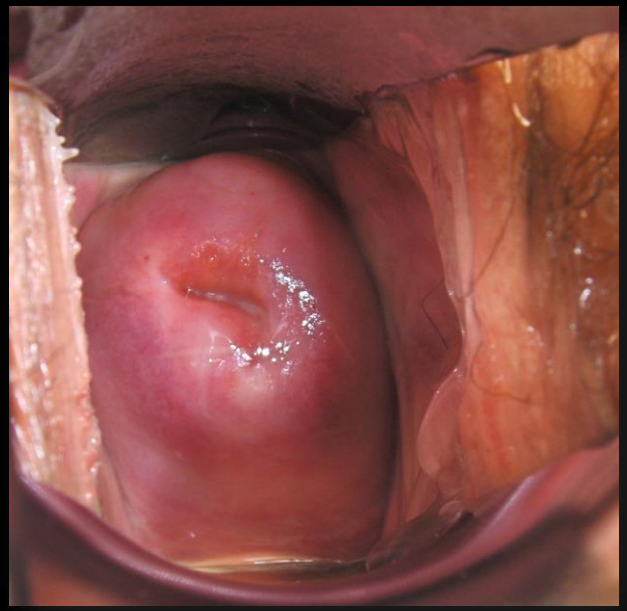
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
	the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs



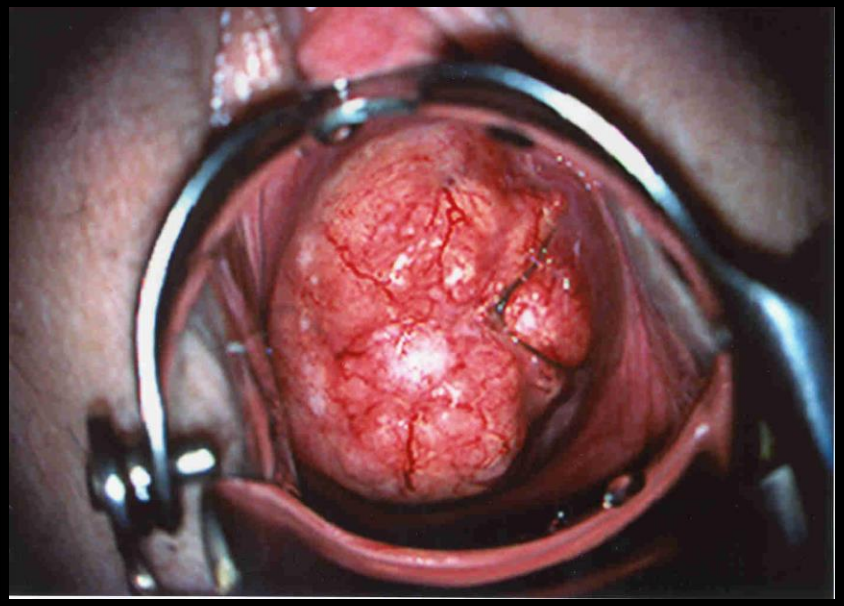
IA2 IB1

FIGO Staging

Less radical surgery



IA2



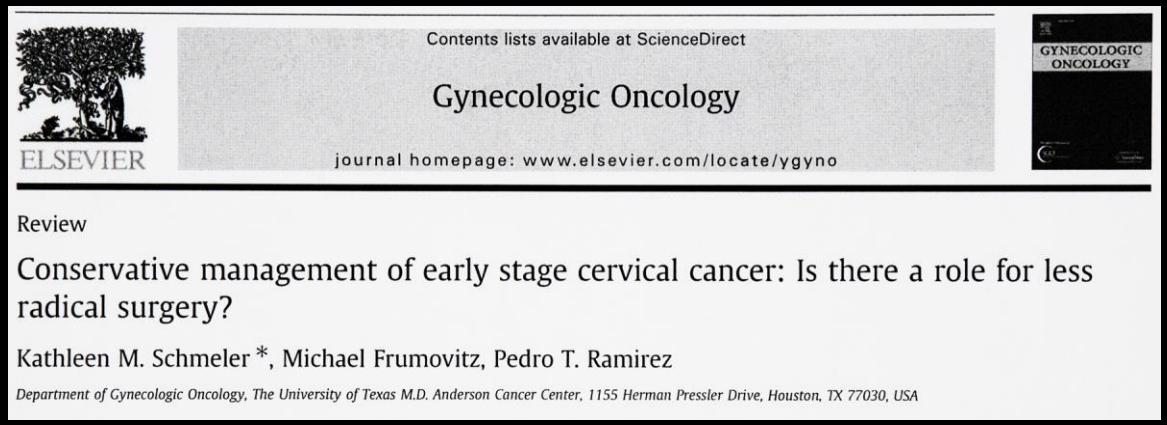
IB1, 3 cm

Less radical surgery

IA2

IB1, 3 cm

Less radical surgery



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Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

Kathleen M. Schmeler *, Michael Frumovitz, Pedro T. Ramirez

Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, 1155 Herman Pressler Drive, Houston, TX 77030, USA

Author	Year	Low-risk criteria	N	Parametrial involvement in low-risk group (%)
Kinney [13]	1995	Squamous histology only, tumor <2 cm, no LVSI*	83	0.0%
Covens [14]	2002	All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes	536	0.6%
Stegeman [15]	2007	Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes	103	0.0%
Wright [16]	2008	All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes	270	0.4%
Frumovitz [19]	2009	Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI*	125	0.0%

*LVSI: lymphvascular space involvement
**DOI: depth of invasion

All retrospective data **N=1117** **< 1%**

Schmeler K et al. Gynecol Oncol 120:321, 2011

Less radical surgery

- All retrospective data
- No prospective randomized trials

The SHAPE Trial

Comparing radical hysterectomy and pelvic node dissection against simple hysterectomy and pelvic node dissection in patients with low risk cervical cancer

Chair: Marie Plante
Laval University, Quebec City

A CCTG Clinical Trials Group proposal for the Gynecological Cancer Inter Group (GCIG)

Trial Schema

Low-risk cervical cancer as defined by:

- squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and modified IB1
- < 10mm stromal invasion on LEEP/cone
- < 50% stromal invasion on MRI
- max dimension of ≤ 20 mm
- Grade 1-3 or not assessable

RANDOMIZE

↗ ARM 1 (Control) Radical Hysterectomy*

↘ Arm 2 (Experimental) Simple Hysterectomy*

→→Pelvic relapse

* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)

Less radical surgery

- Perhaps **radical surgery is NOT necessary** is small volume lesions…

Less radical surgery

- Simple Trachelectomy / Cone

Types of fertility sparing surgery

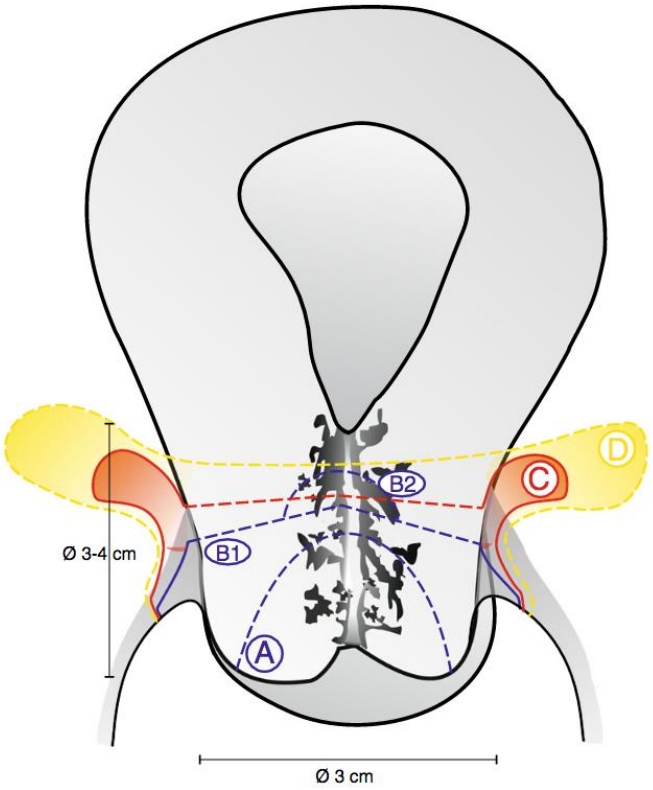
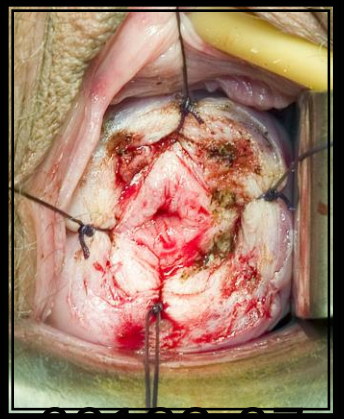


Fig. 1 Types of fertility-sparing surgery: *A* large cone, *B1* simple trachelectomy, *B2* endocervical loop, *C* vaginal radical trachelectomy and *D* abdominal radical trachelectomy or laparoscopic radical trachelectomy

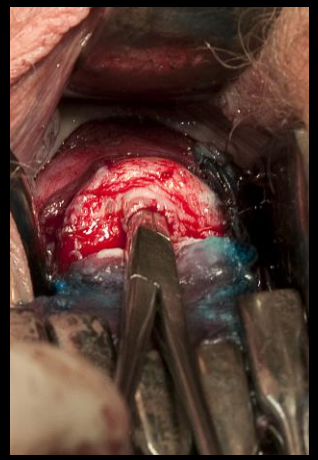
Helena Robova, et al., Curr Oncol Rep (2015) 17: 23

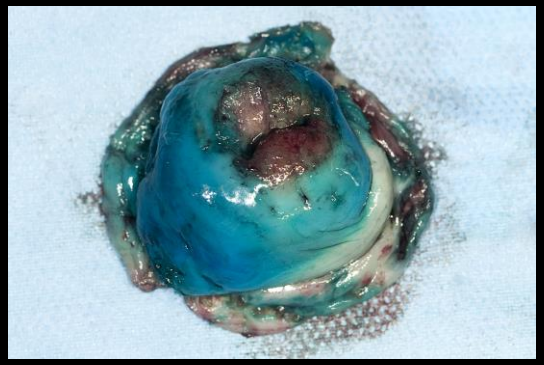
Simple trachelectomy



25 year old woman G0
Very early cervical cancer
Minimal endocervical involvement

Simple trachelectomy





Simple Vaginal Trachelectomy

A Valuable Fertility-Preserving Option in Early-Stage Cervical Cancer

Marie Plante, MD, Marie-Claude Renaud, MD, Alexandra Sebastianelli, MD, and Jean Gregoire, MD

N=35

Nodes : negative except 2 with ITC

2/3 had NRD or in situ disease only

1 recurrence & death

25 pregnancies

72% delivered > 36 weeks

Int J Gynecol Cancer. 2017 Jun;27(5):1021-1027

Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review

Enrica Bentivegna, Sebastien Gouy, Amandine Maulard, Cyrus Chargari, Alexandra Leary, Philippe Morice

	Simple trachelectomy or cone resection
Series and case reports	
Number series or case reports*	13
Number of patients	242
Patients excluded†	12
Tumour characteristics	
Stage‡	
IA	Not included
IB1	
All	228
>2 cm	0
IB2	0
IIA	0
Tumour type	
Squamous-cell carcinoma	60
Adenocarcinoma	25
Other, mixed, or unknown	157
LVSI positive	At least 71
Oncological outcomes	
Recurrent disease	4
Died from disease	0
Fertility outcomes	
Pregnancies	105
Fetal loss (trimester 1 or 2)	15
Preterm delivery	13
Pregnancy rate¶	15/26 (57%)

Gynecologic Oncology 132 (2014) 254–259

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care?☆

Pedro T. Ramirez [a,*], Rene Pareja [b], Gabriel J. Rendón [b], Carlos Millan [c], Michael Frumovitz [a], Kathleen M. Schmeler [a]

[a] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[b] Department of Gynecologic Oncology, Instituto de Cancerología Las Américas, Medellín, Colombia
[c] Department of Gynecology, Hospital Quiron, Murcia, Spain

Less radical surgery

- Meticulous/careful **patient selection** is of utmost importance
  - Preoperative pelvic **MRI**
  - Expert **pathology review**

Preoperative pelvic MRI

Noel P and Plante M. RadioGraphics 2014;34:1099-1119

Expert pathological assessment

- Diagnostic LEEP and cone
  - Several LEEPs…
- Margins status
- Several pieces
- Is the lesion truly < 2cm and < 10mm deep ?
- Danger is to perform conservative treatment in more extensive cervical cancer and end-up with cancer recurrence…

Conization in Early Stage Cervical Cancer

Pattern of Recurrence in a 10-Year Single-Institution Experience

Federica Tomao, PhD, MD,† Matteo Maruccio, MD,*† Eleonora Petra Preti, MD,* Sara Boveri, MD,* Enzo Ricciardi, PhD, MD,*† Vanna Zanagnolo, MD,* and Fabio Landoni, PhD, MD**

TABLE 2. Recurrences

Patient Number	Age*	Stage*	Histotype	LVSI	DFS, mts	Site of Recurrence	Tests Positive	Treatment	Status
1	37	IA2	SCC	−	56	Cervix	SCC clinical examination biopsy	RT + BT	NED
2†	33	IB1	SCC	+	21	Cervix	Papanicolaou test biopsy	RS + CTRT + BT	NED
3	31	IB1	SCC	−	13	Cervix	Papanicolaou test biopsy	Re-coniz	NED
4	37	IB1	Adk	−	14	Cervix	HPV test Papanicolaou test biopsy, PET, MRI	Re-coniz + CTRT + BT	NED
5	24	IB1	Adk	−	22	Cervix	Papanicolaou test biopsy, PET, US, MRI	Reconiz	NED
6	34	IA2	Adenosq	−	21	Cervix	Papanicolaou test biopsy	CTRT	NED
7	34	IB1	SCC	focal	14	Pelvic lymph node	MRI, US, Biopsy	CT	ED

*After surgery she underwent adjuvant chemotherapy with carboplatin (AUC4) and paclitaxel 90 mg/mL on days 1 to 8 every 3 weeks.
†Margins of reconization were positive.
Adenosq, adenosquamous; Adk, adenocarcinoma; CT, chemotherapy; CTRT, chemoradiation; DFS, disease free survival; MRI, magnetic resonance imaging; mts, months; NED, not evident disease; RT, radiotherapy; SCC, squamous cell carcinoma; US, ultrasonographic examination.

N=54; 76% IB1

6/7 recurrence were local (cervix)

Int J Gynecol Cancer 2017;27: 1001-1008

Follow-up

- Post trachelectomy / cone
  - Need for **PROLONGED FOLLOW-UP**
  - Experienced gyn-onc / colposcopists
  - **HPV testing and vaccination**

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 28), pp: 46580-46592

Review

Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis

Qing Zhang[1,2,*], Wenhui Li[1,5,*], Margaux J. Kanis[3], Gonghua Qi[1], Minghao Li[4], Xingsheng Yang[1] and Beihua Kong[1,2]

60 studies: 17 cone and 43 RT

N=2854 patients; 375 cone and 2479 RT

Stage IB1: 44% cone vs 80% RT

Recurrence rate:

- **Stage IA: 0.4% vs 0.7%**
- **Stage IB1: 0.6% vs 2.3%**

CONCLUSION: Fertility-sparing treatment including CON or RT for eCC is feasible and carefully selected women can preserve fertility and achieve pregnancy resulting in live births. CON seems to result in better pregnancy outcomes than RT with similar rates of recurrence and mortality.

Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature

Enrica Bentivegna, M.D.,[a] Amandine Maulard, M.D.,[a] Patricia Pautier, M.D.,[b] Cyrus Chargari, M.D., Ph.D.,[c] Sebastien Gouy, M.D., Ph.D.,[a] and Philippe Morice, M.D., Ph.D.[a,d,e]

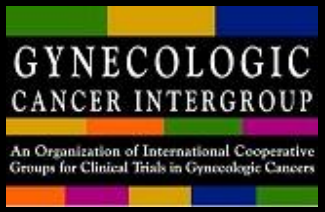
- Review of 2777 patients; 944 pregnancies
- Overall fertility rate: 55%
- Pregnancy rate:
  - Better after vaginal RT compared to abdominal RT
- Prematurity (38%):
  - Significantly lower after ST/Cone versus RT
- Live birth rate: similar (70%)

Fertility and Sterility® Vol. 106, No. 5, October 2016

Prospective trials

- Concerv
- GOG-278

ConCerv (G-GOC)



Cervical Cancer-Conservative Management

Cone/Simple Hysterectomy + SLN Only

Stage IA2-IB1 (<2 cm) LVSI (-); SCC G1-3; ADK G1-2

Study Design: Prospective Phase II

Sponsor(s): None

Planned No. of patients: 100

Other important information: **14 Sites Overall**

Primary: MD Anderson

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PROTOCOL GOG-0278

EVALUATION OF PHYSICAL FUNCTION AND QUALITY OF LIFE (QOL) BEFORE AND AFTER NON-RADICAL SURGICAL THERAPY (EXTRA FASCIAL HYSTERECTOMY OR CONE BIOPSY WITH PELVIC LYMPHADENECTOMY) FOR STAGE IA1 (LVSI+) and IA2-IB1 (≤ 2CM) CERVICAL CANCER

NCI Version Date 07/10/2012

POINTS:
PER CAPITA - 20
MEMBERSHIP - 6

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SCHEMA

Women with IA1– IB1 (≤2cm) carcinoma of the cervix
who have been consented for surgery
will be approached for study participation and entered on study.

N=220

Conization with pelvic lymphadenectomy (fertility preservation) Group

Simple hysterectomy with pelvic lymphadenectomy (no wish for future fertility) Group

Medical Information/Physician Checklist:
Medical extraction form CTCAE v. 4.0 criteria
Preoperative Study Survey (15 min to complete):
Bladder and Bowel Function Items
Female Functioning Index & 2 PROMIS items
GCLQ – Gyn Cancer Lymphedema Questionnaire
Functional Assessment Cancer Therapy FACT-Cx
Impact of Events Scale (IES)
Conization Group only Reproductive Items (ICF & RCS)

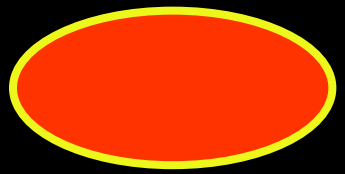
Medical Information/Physician Checklist:
Medical extraction form CTCAE v. 4.0 criteria
Preoperative Study Survey (15 min to complete):
Bladder and Bowel Function Items
Female Functioning Index & 2 PROMIS items
GCLQ – Gyn Cancer Lymphedema Questionnaire
Functional Assessment Cancer Therapy FACT-Cx
Impact of Events Scale (IES)

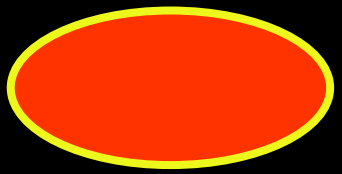
Simple Trachelectomy-Cone

- Valuable less radical option for women with **LOW-RISK small volume** disease
  - < 2 cm
- Patient selection critical
- Long-term follow-up essential

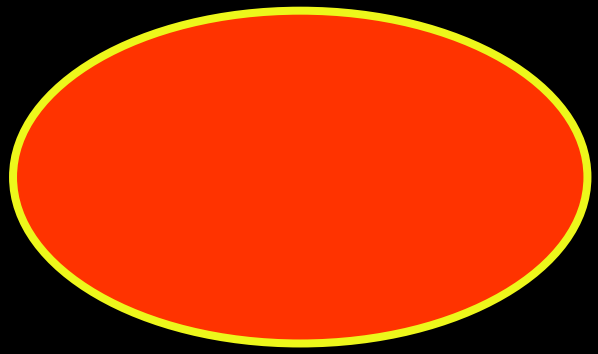
Conclusion

- Change FIGO classification?
  - Sub-divide stage IB1
    - a: < 2 cm





    - b: ≥ 2 cm
      < 4 cm



FIGO CANCER REPORT 2018

Cancer of the cervix uteri

WILEY
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TABLE 1 FIGO staging of cancer of the cervix uteri (2018).

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

ITCs and micromets excluded

Evolution in the management of cervical cancer