



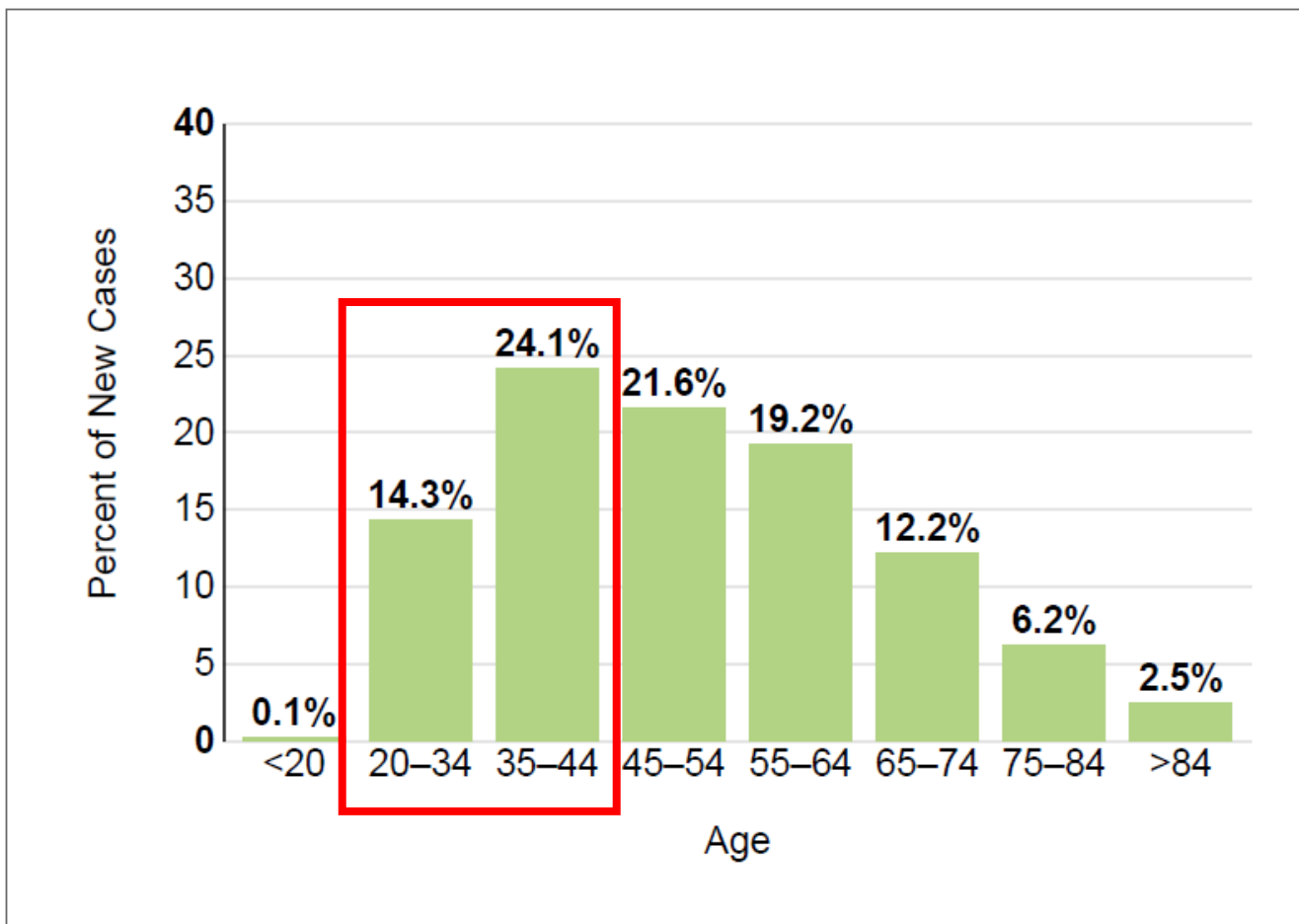
## Terapia Conservativa Fertility Sparing nei carcinomi cervicali

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University of Milan Bicocca

Fondazione IRCCS San Gerardo dei Tintori  
Clinic of Obstetrics and Gynecology

No disclosures



Cervical cancer is most frequently diagnosed among women aged 35-44.

In 2022, approximately 2500 new cases in Italy



## «Elderly Primigravidas»

Women start to find a pregnancy at an ever increasing age

44968 born in 2012 (526.567)

40676 born in 2022 (387.394)

**OVER 40**

Only 0,1 % of babies are born from women younger than 20 years

ISTAT

**MANDATORY**  
© Can Stock Photo

Quality care for AYA patients with cancer is tied to timely detection and initiation of treatment, compliance with and adherence to treatment, and access to a multidisciplinary team of health care

# Carcinoma della cervice: quando la chirurgia fertility sparing



fertility sparing surgery cervical cancer



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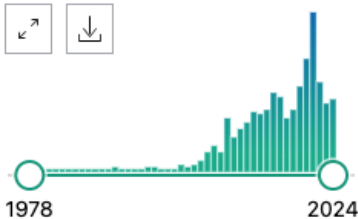
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of 52



RESULTS BY YEAR



TEXT AVAILABILITY

Abstract

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ARTICLE ATTRIBUTE

<https://pubmed.ncbi.nlm.nih.gov/35953599/>

**Fertility-Sparing and Less Radical Surgery for Cervical Cancer.**

1 Batman SH, Schmeler KM.

Cite [Curr Oncol Rep. 2022 Nov;24\(11\):1541-1548. doi: 10.1007/s11912-022-01317-w. Epub 2022 Aug 12. PMID: 35953599](#) [Free PMC article.](#) [Review.](#)

Share PURPOSE OF REVIEW: Patients with early-stage **cervical** cancer who desire future **fertility** may be candidates for less radical **surgery**. ...Furthermore, neoadjuvant chemotherapy is being assessed as an option to extend **fertility-sparing** treatment to ...

**Fertility-sparing Surgery for Patients with Cervical, Endometrial, and Ovarian Cancers.**

2

Cite [Kohn JR, Katebi Kashi P, Acosta-Torres S, Beavis AL, Christianson MS. J Minim Invasive Gynecol. 2021 Mar;28\(3\):392-402. doi: 10.1016/j.jmig.2020.12.027. Epub 2020 Dec 26. PMID: 33373729](#) [Review.](#)

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For these women, although their cancer treatment can be lifesaving, it's also life-altering because traditional **surgical procedures** can cause infertility and, in many cases, induce **surgical**

# The Will Roger phenomenon in medicine



The NEW ENGLAND  
JOURNAL of MEDICINE

**The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer**

A R Feinstein, D M Sosin, C K Wells

N Engl J Med 1985 Jun 20;312(25):1604-8.doi:  
10.1056/NEJM198506203122504.



Will Roger (1879 to 1935)  
Comedian-Humorist

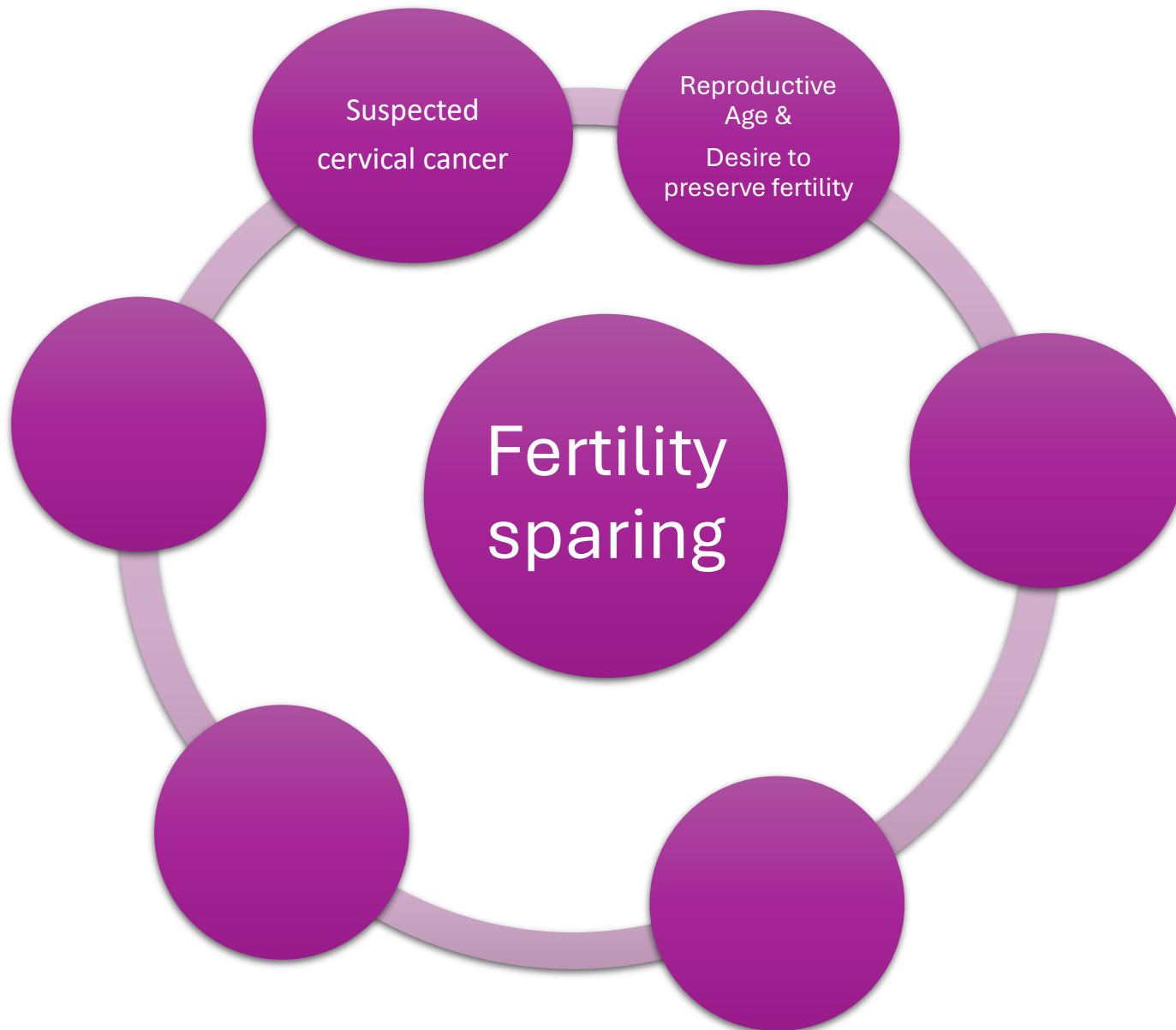
## His Joke:

« When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states»

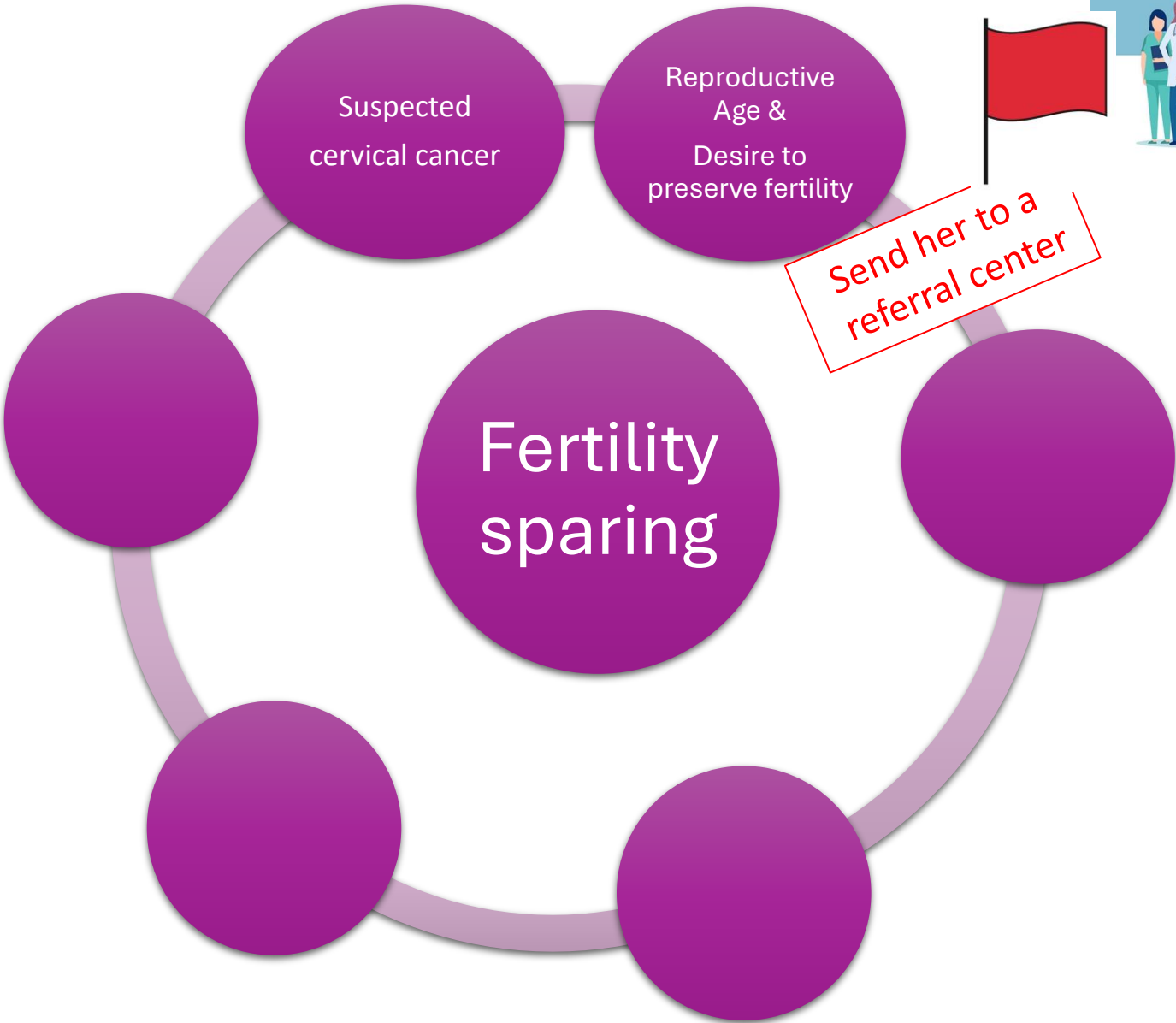
Migration during The American  
Economic depression of the 1930'

A « stage migration» resulted in an improved survival of Patients in both the less and the more severe disease stage

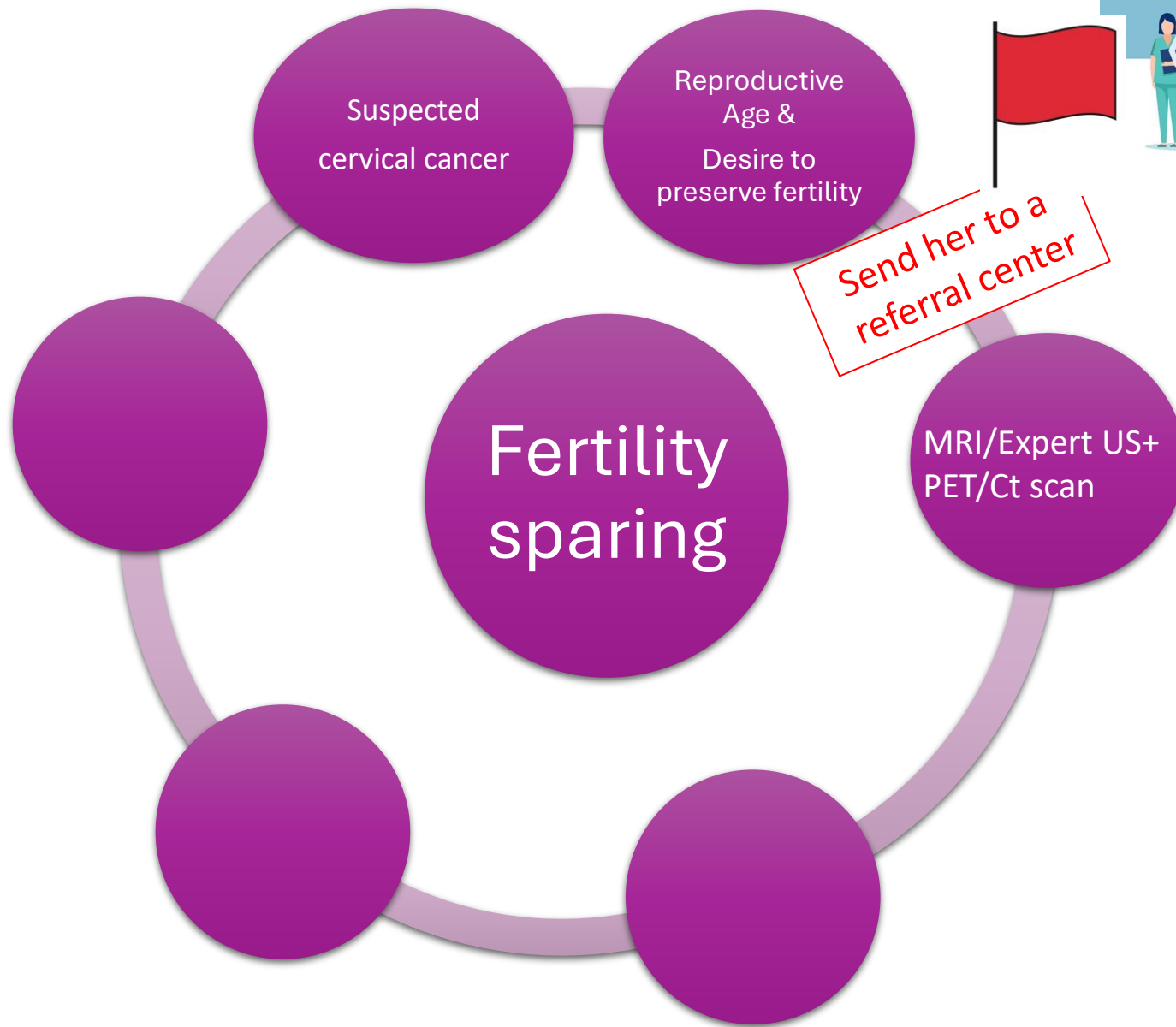
# Carcinoma della cervice: quando la chirurgia fertility sparing



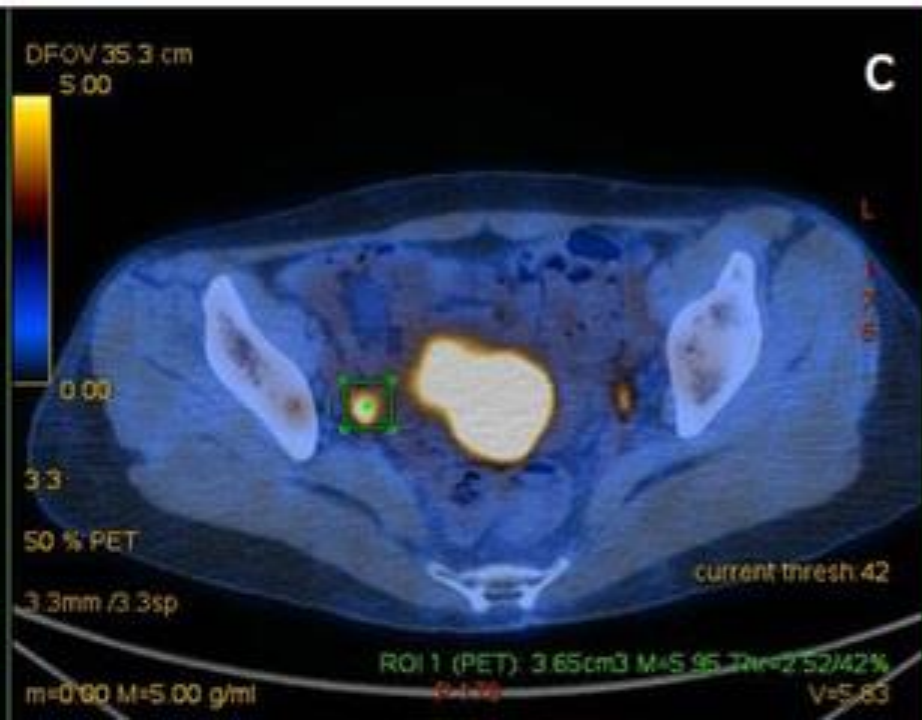
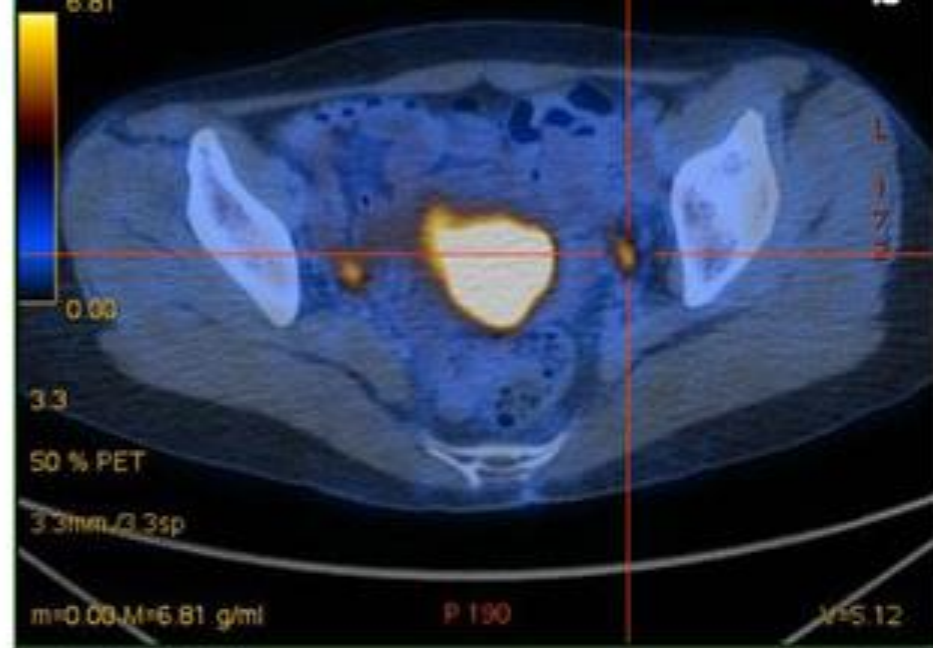
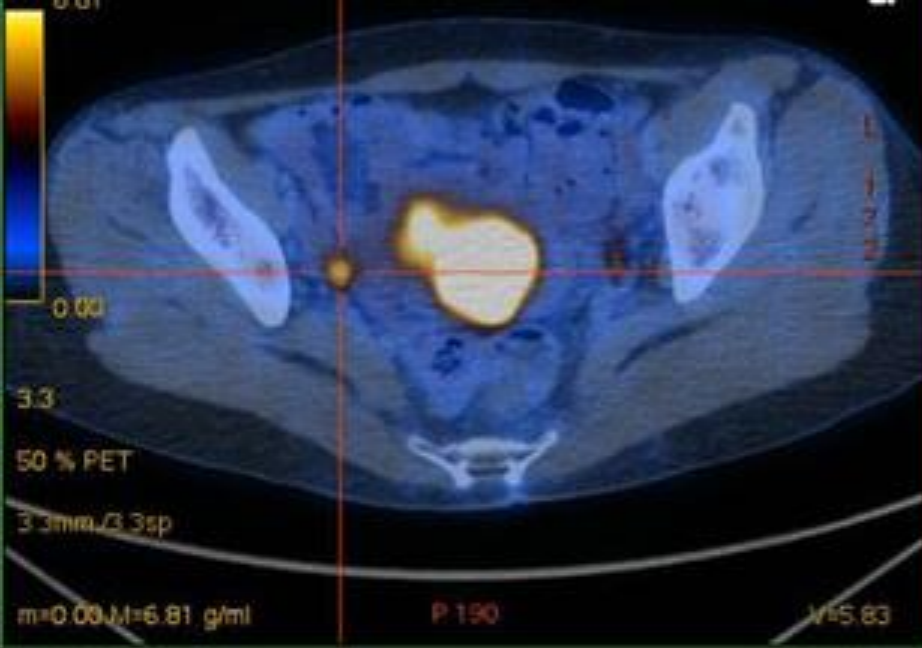
# Carcinoma della cervice: quando la chirurgia fertility sparing



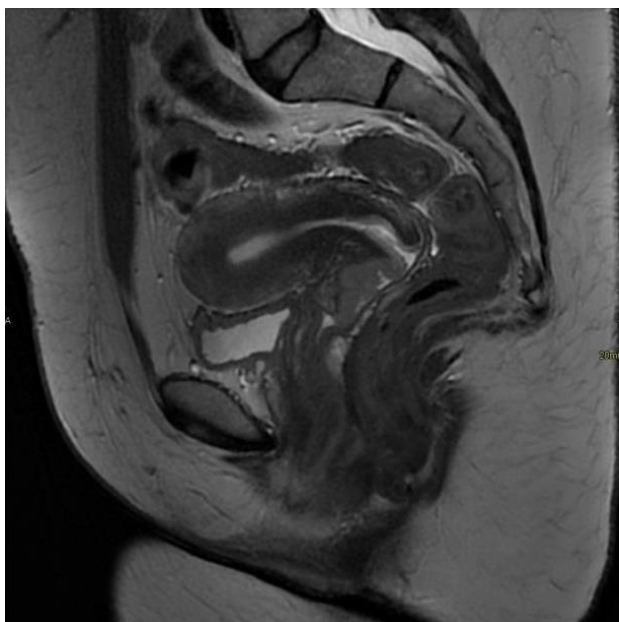
# Carcinoma della cervice: quando la chirurgia fertility sparing







# Carcinoma della cervice: quando la chirurgia fertility sparing



- Size of disease

- Depth of stromal invasion and free margins

- Distance from OUI

## Risk Factor: diameter/invasion/LVSI

Sedlis: always valid criteria after 20 years?

Tumor diameter 25 mm  
Cervix diameter 30m  
LVSI pos  
Out thrid  
25yrs old, P:0000

Tumor diameter 30mm  
Cervix diameter 45mm  
LVSI pos  
Out thrid  
3yrs old P3003



2,5mm free

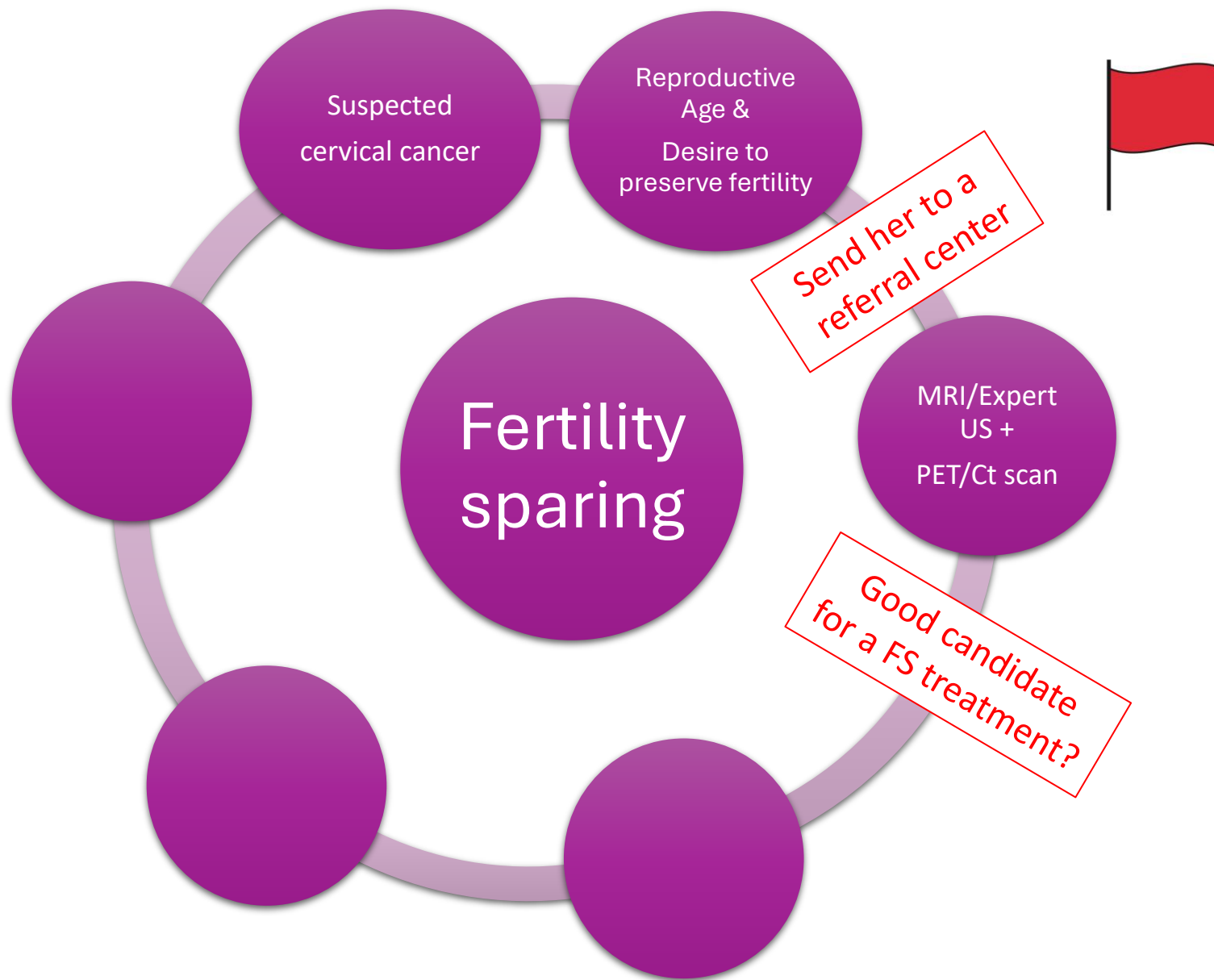
7,5mm free



Melanoma (ESMO): safety margins of 0.5 cm for in situ 1 cm for tumours









Vulva (ESGO): Surgical excision margins of at least 1 cm are advised

# Carcinoma della cervice: quando la chirurgia fertility sparing



## ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023\*



David Cibula,<sup>1,2</sup> Maria Rosaria Raspollini,<sup>3</sup> François Planchamp ,<sup>4</sup> Carlos Centeno,<sup>5</sup> Cyrus Chargari ,<sup>6</sup> Ana Felix,<sup>7,8</sup> Daniela Fischerová ,<sup>1,2</sup> Daniela Jahnn-Kuch,<sup>9</sup> Florence Joly,<sup>10</sup> Christhardt Kohler,<sup>11,12</sup> Sigurd Lax,<sup>13,14</sup> Domenica Lorusso,<sup>15,16</sup> Umesh Mahantshetty,<sup>17</sup> Patrice Mathevet,<sup>18</sup> Raj Naik,<sup>19</sup> Remi A Nout,<sup>20,21</sup> Ana Oaknin ,<sup>22,23</sup> Fedro Peccatori,<sup>24</sup> Jan Persson,<sup>25,26</sup> Denis Querleu ,<sup>15,27</sup> Sandra Rubio Bernabé ,<sup>28</sup> Maximilian P Schmid,<sup>29</sup> Artem Stepanyan ,<sup>30</sup> Valentyn Svintsitskyi,<sup>31</sup> Karl Tamussino,<sup>32</sup> Ignacio Zapardiel ,<sup>33</sup> Jacob Lindegaard<sup>34</sup>

### Fertility Sparing Treatment

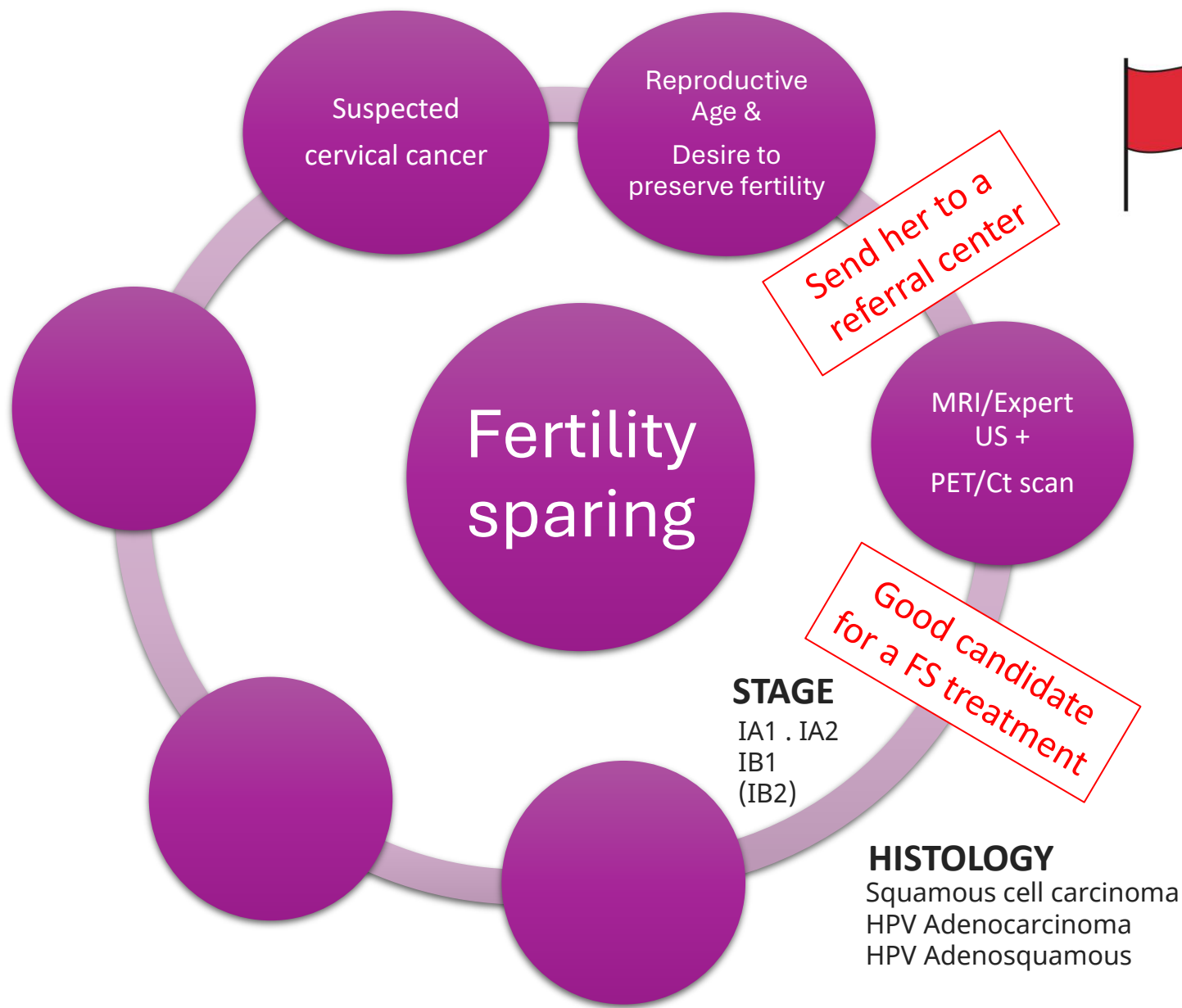
- ▶ Fertility sparing therapy is an oncologically valid alternative to radical hysterectomy for young patients with cervical cancer <2 cm (IA1 to IB1) <2 cm (squamous cell carcinoma and HPV-related adenocarcinoma) who want to preserve the option to have children. Before initiating fertility sparing therapy, consultation at an onco-fertility center and discussion in a multidisciplinary tumor board is recommended [III, B].

# Oncological outcomes

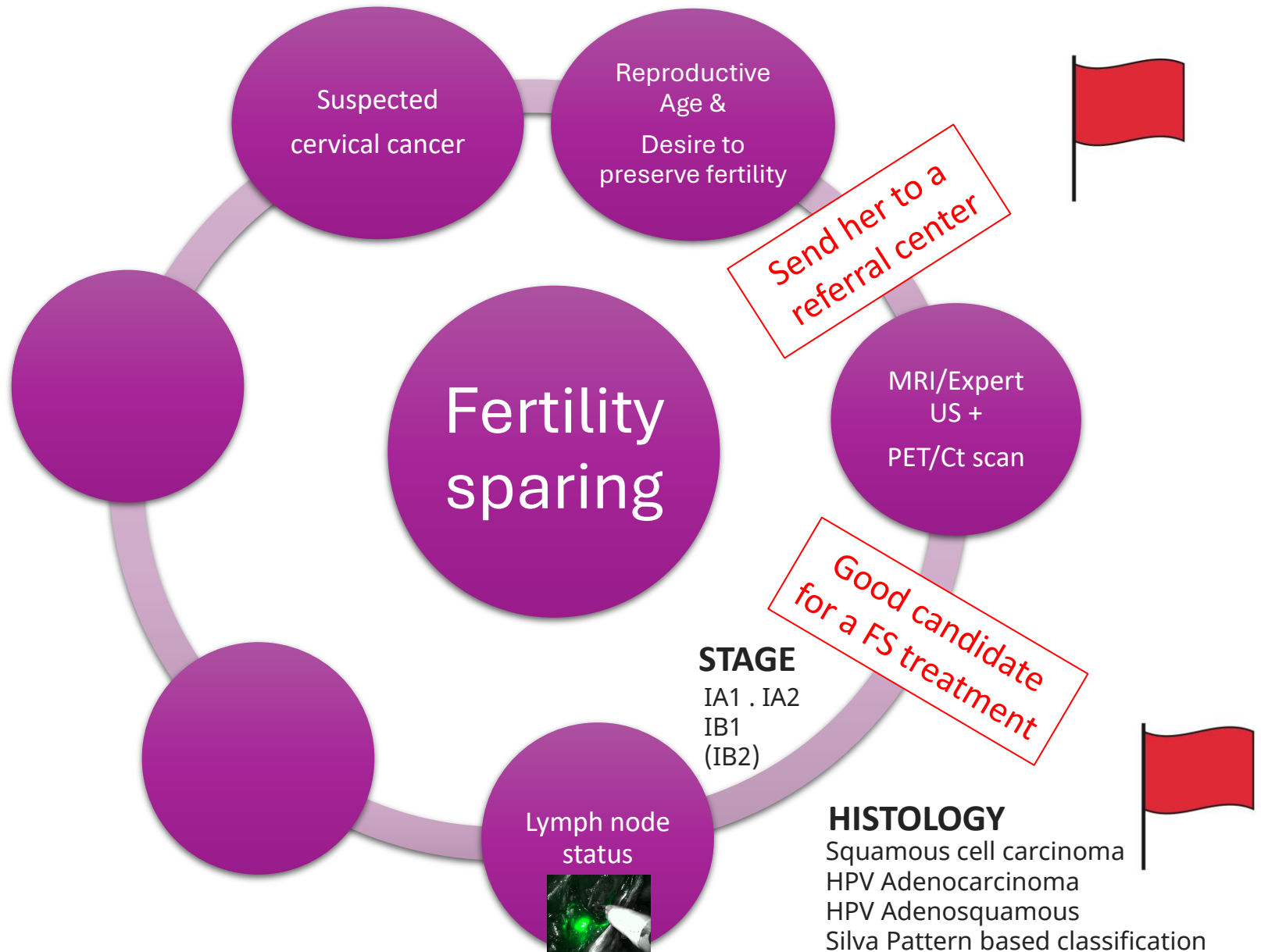
VRT	< than 2 cm - 2.7%
ART	< than 2 cm - 1.6%
Less radical	< than 2 cm - 1.9%

Rob L, et al. *Lancet Oncol.* 2011;12(2):192-200.

# Carcinoma della cervice: quando la chirurgia fertility sparing



# Carcinoma della cervice: quando la chirurgia fertility sparing





# SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study



↓ or LND  
N  
/- LND  
: SLN + LND

# Sentinel lymph node biopsy versus pelvic lymphadenectomy in early-stage cervical cancer: a multi-center randomized trial (PHENIX/CSEM 010)

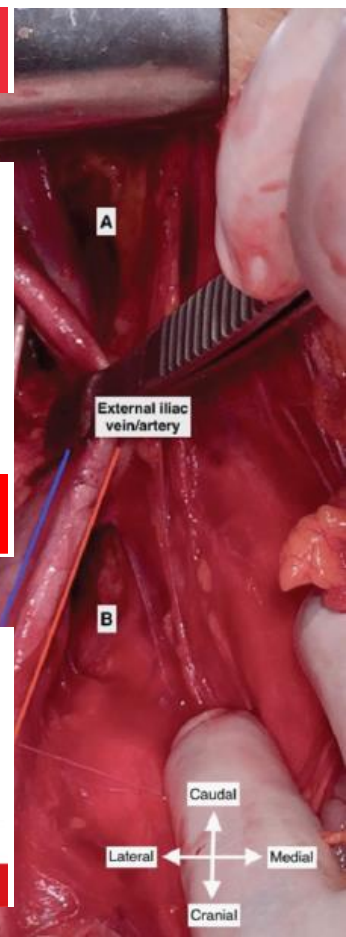


Fro

If positive,

abc

# A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX)

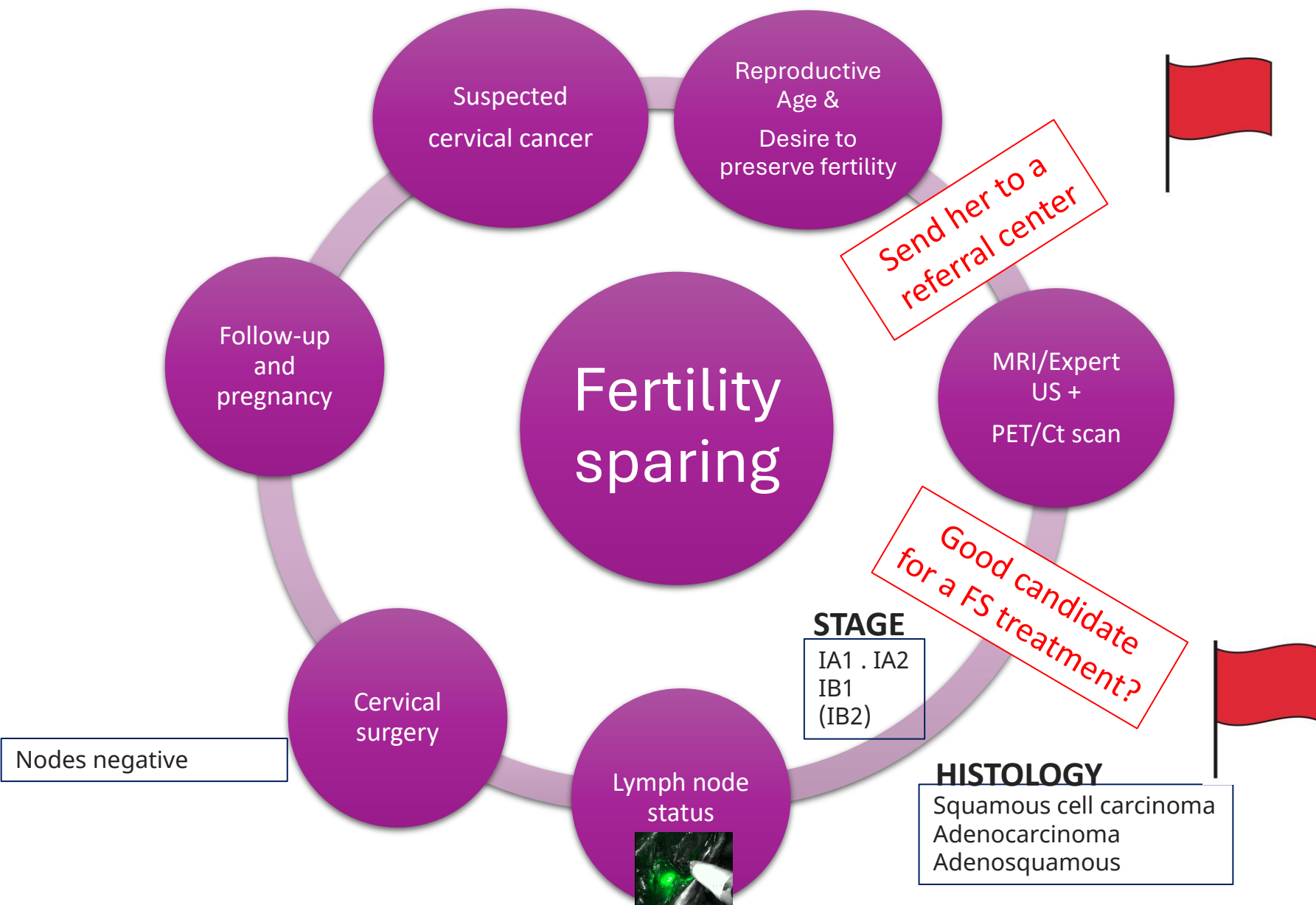


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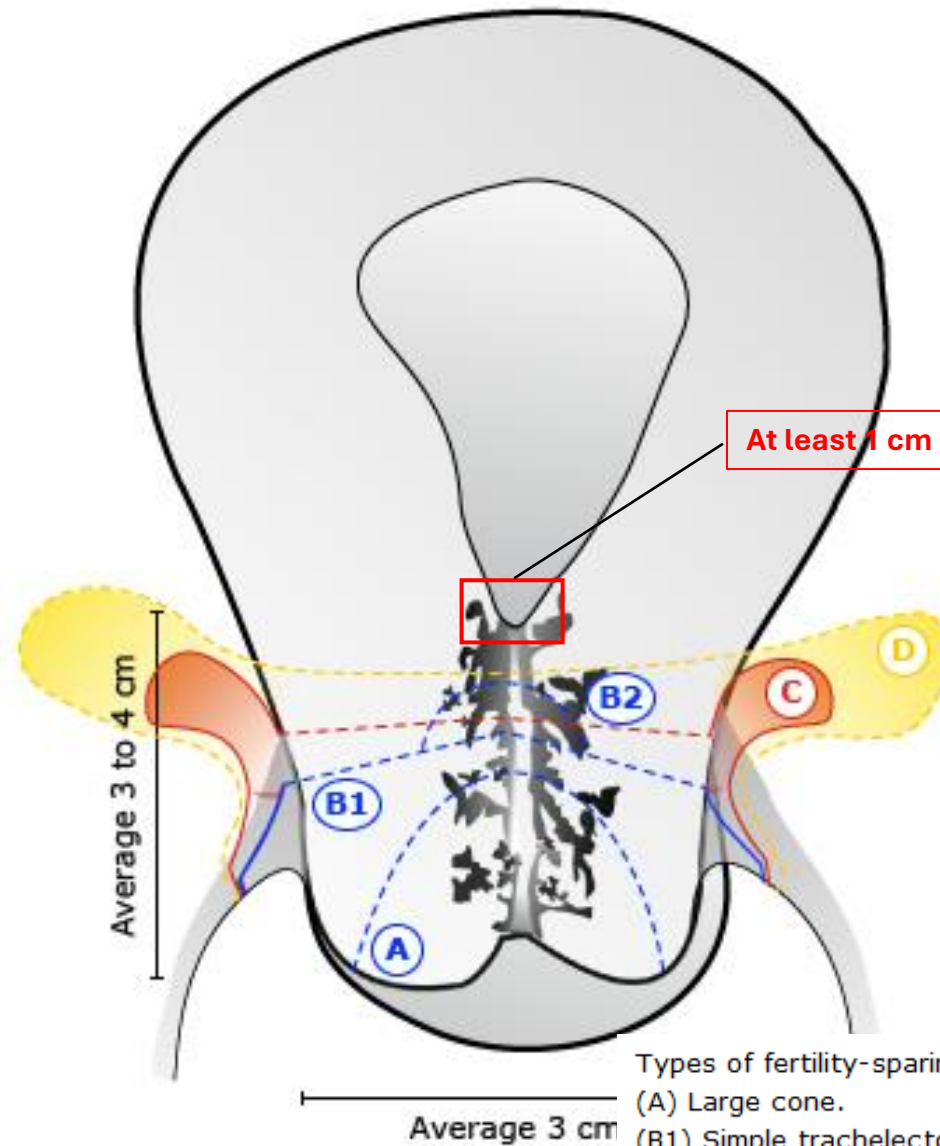


# I TUMORI IN FASE PRECOCE: QUANDO LA GRAVIDANZA È UNA POSSIBILITÀ

## Carcinoma della cervice: quando la chirurgia fertility sparing



# Carcinoma della cervice: quando la chirurgia fertility sparing



Types of fertility-sparing surgery:

(A) Large cone.

(B1) Simple trachelectomy.

(B2) Endocervical loop.

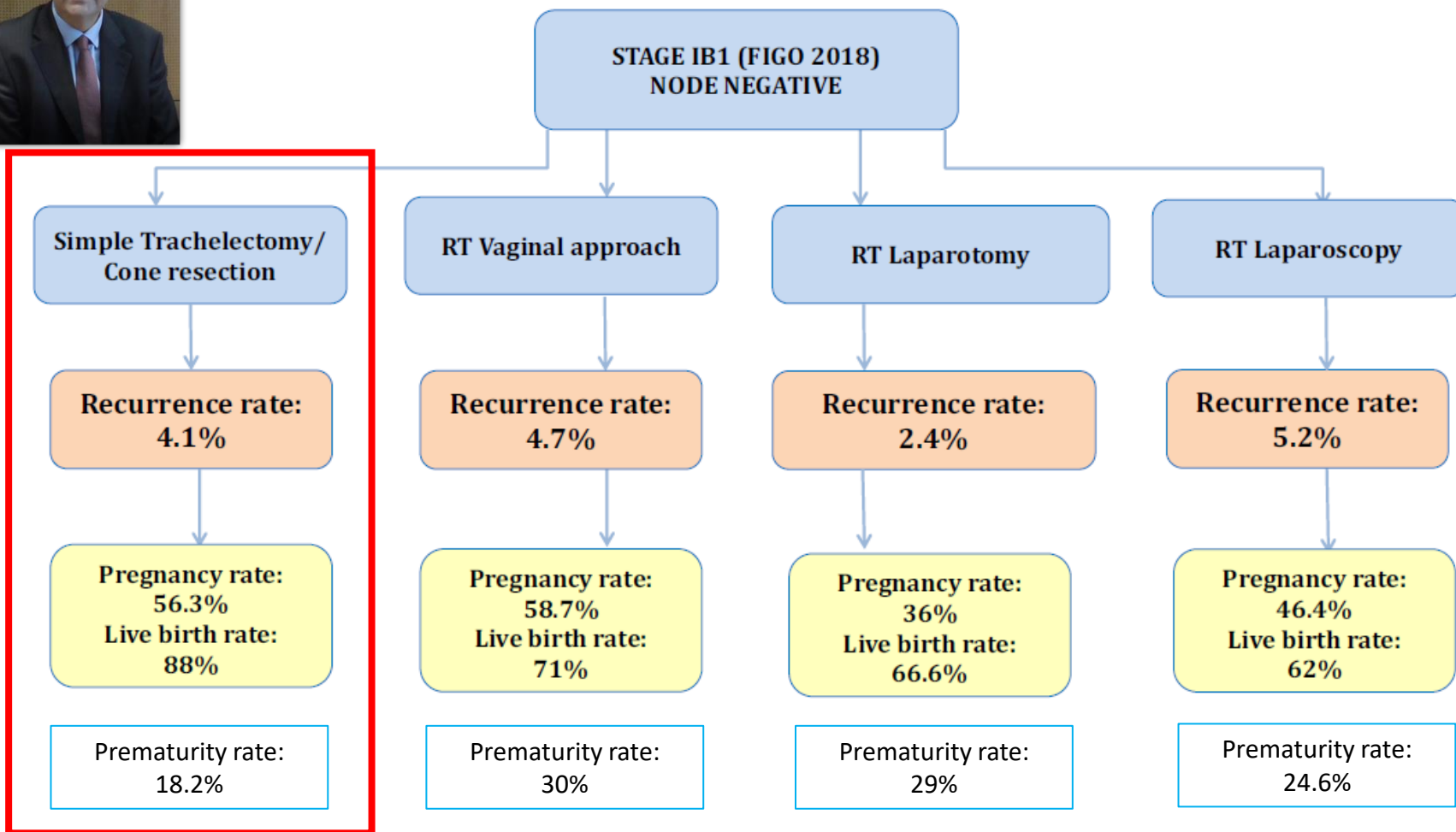
(C) Vaginal radical trachelectomy.

(D) Abdominal radical trachelectomy or laparoscopic radical trachelectomy.

# Carcinoma della cervice: quando la chirurgia fertility sparing



## CERVICAL CANCER < 2CM



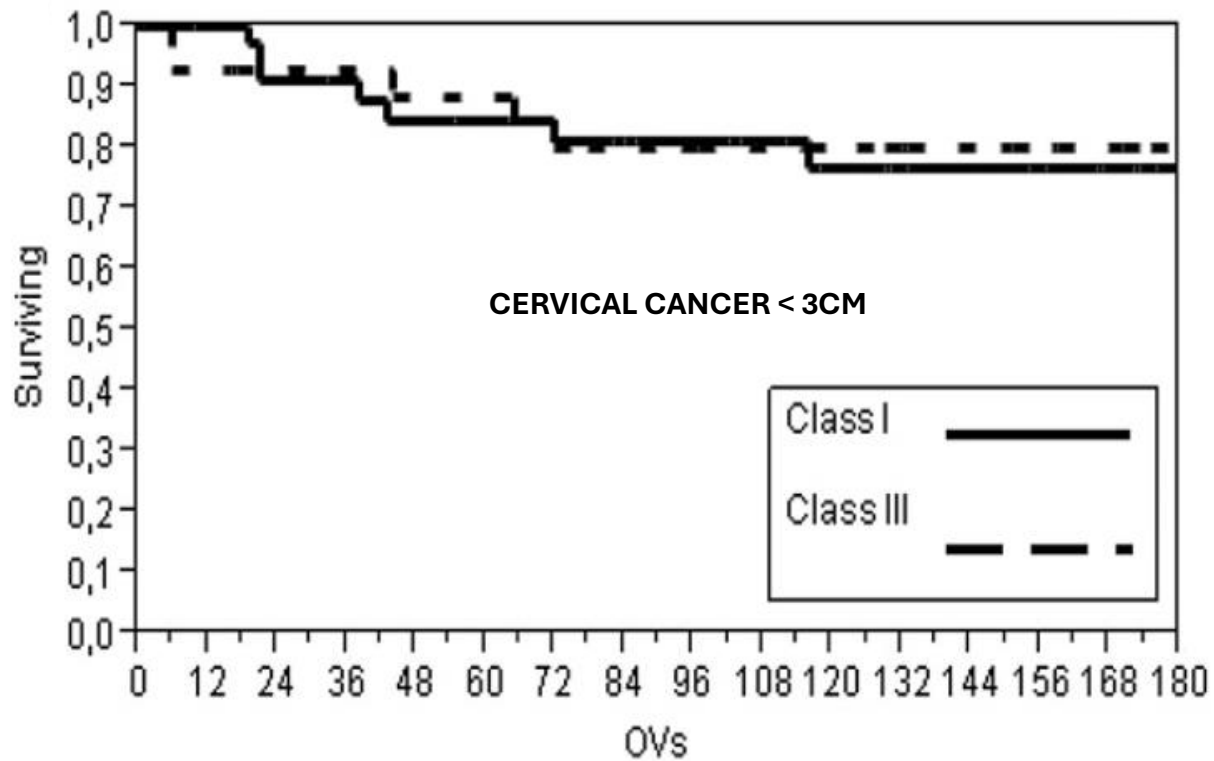
Morice P. et al., *Gyn Onc* 2022

Bentivegna E et al. *Lancet Oncol. & Fertil Steril.* 2016

Rob L, et al. *Lancet Oncol.* 2011

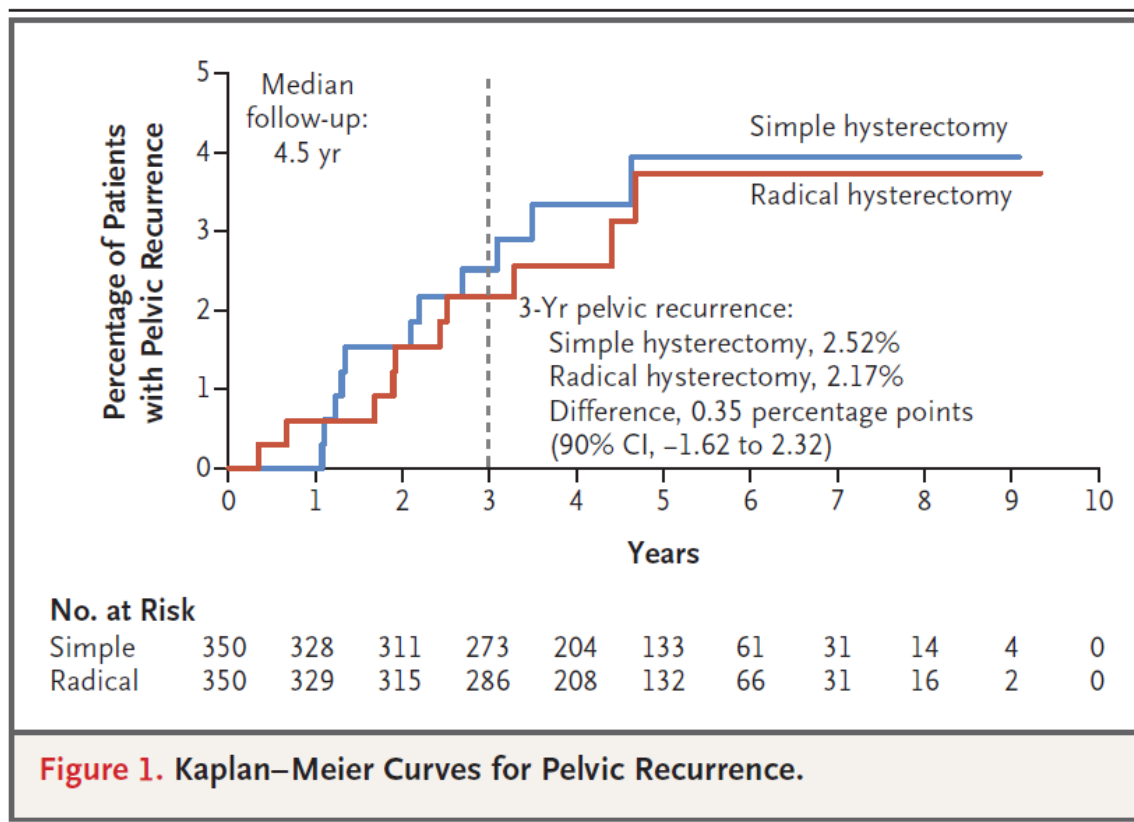
# Carcinoma della cervice: quando la chirurgia fertility sparing

Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer.  
A prospective randomized study





## Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer

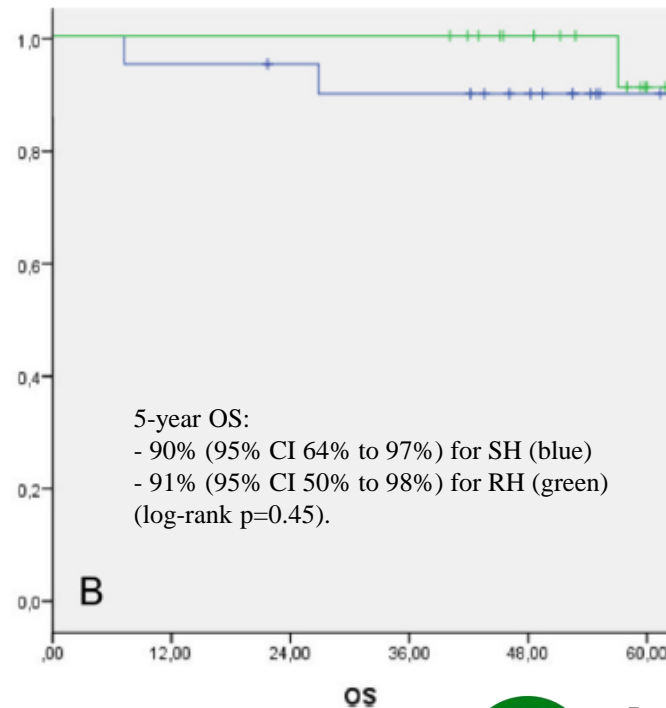
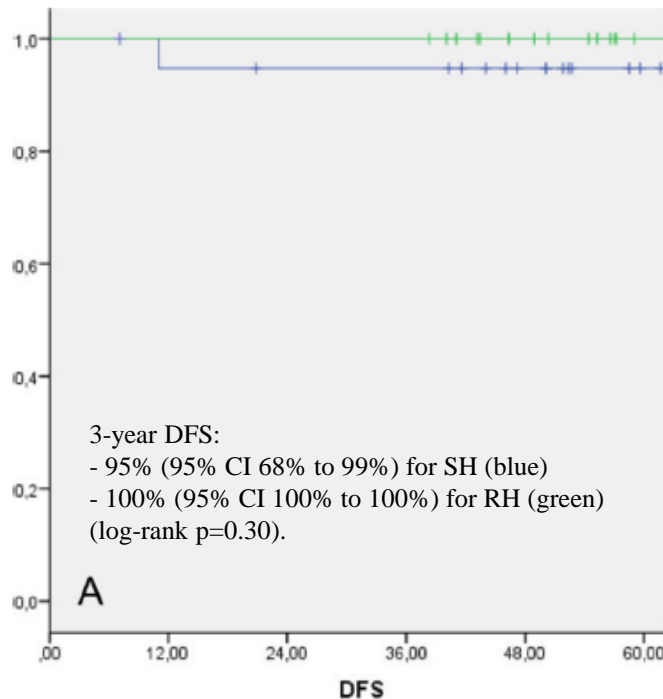


CERVICAL CANCER < 2CM (IA2-IB1)  
 Squamous or adenoca or adenosquamous  
 Depth of invasion < 10 mm  
 or less than 50% of cervical stromal tissue

Figure 1. Kaplan–Meier Curves for Pelvic Recurrence.

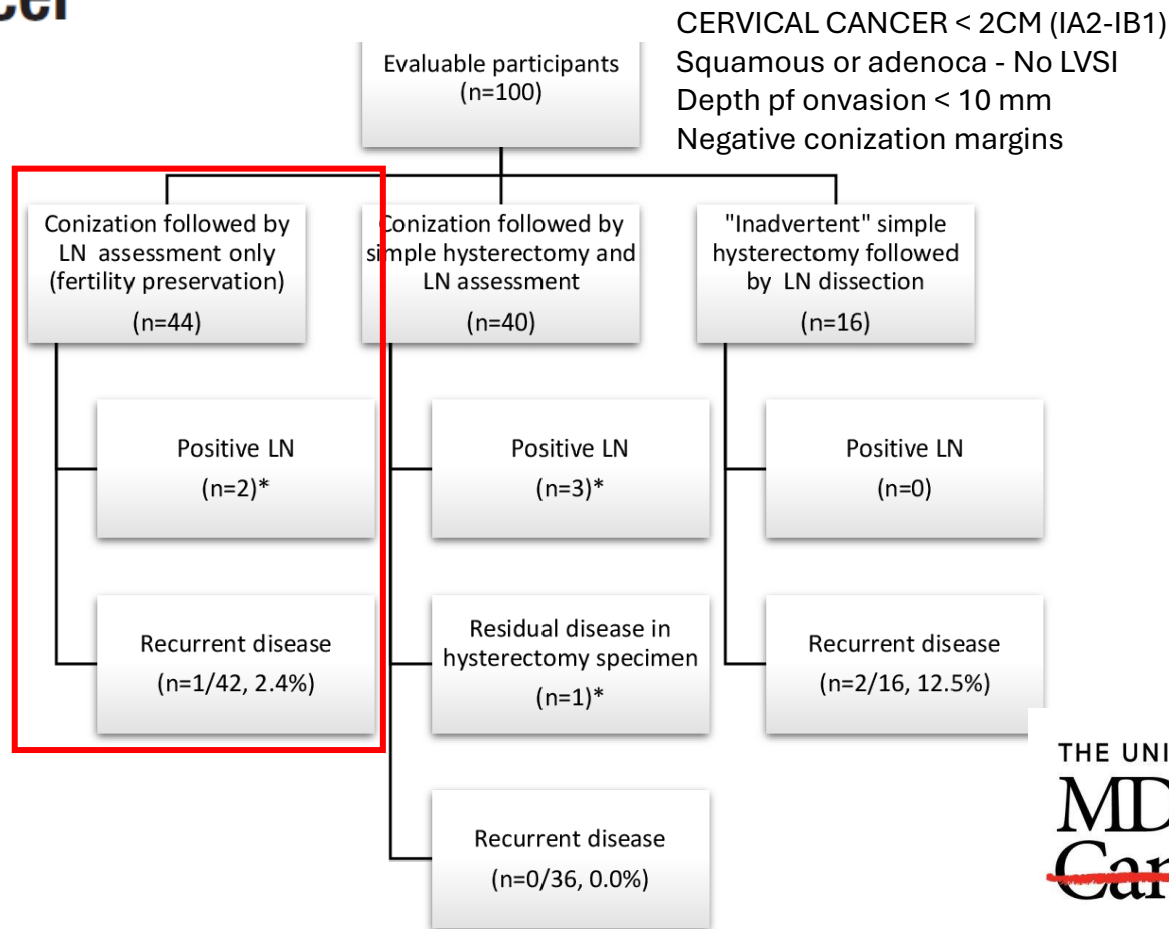


# Proof-of-concept randomized phase II non-inferiority trial of simple versus type B2 hysterectomy in early-stage cervical cancer $\leq 2$ cm (LESSER)



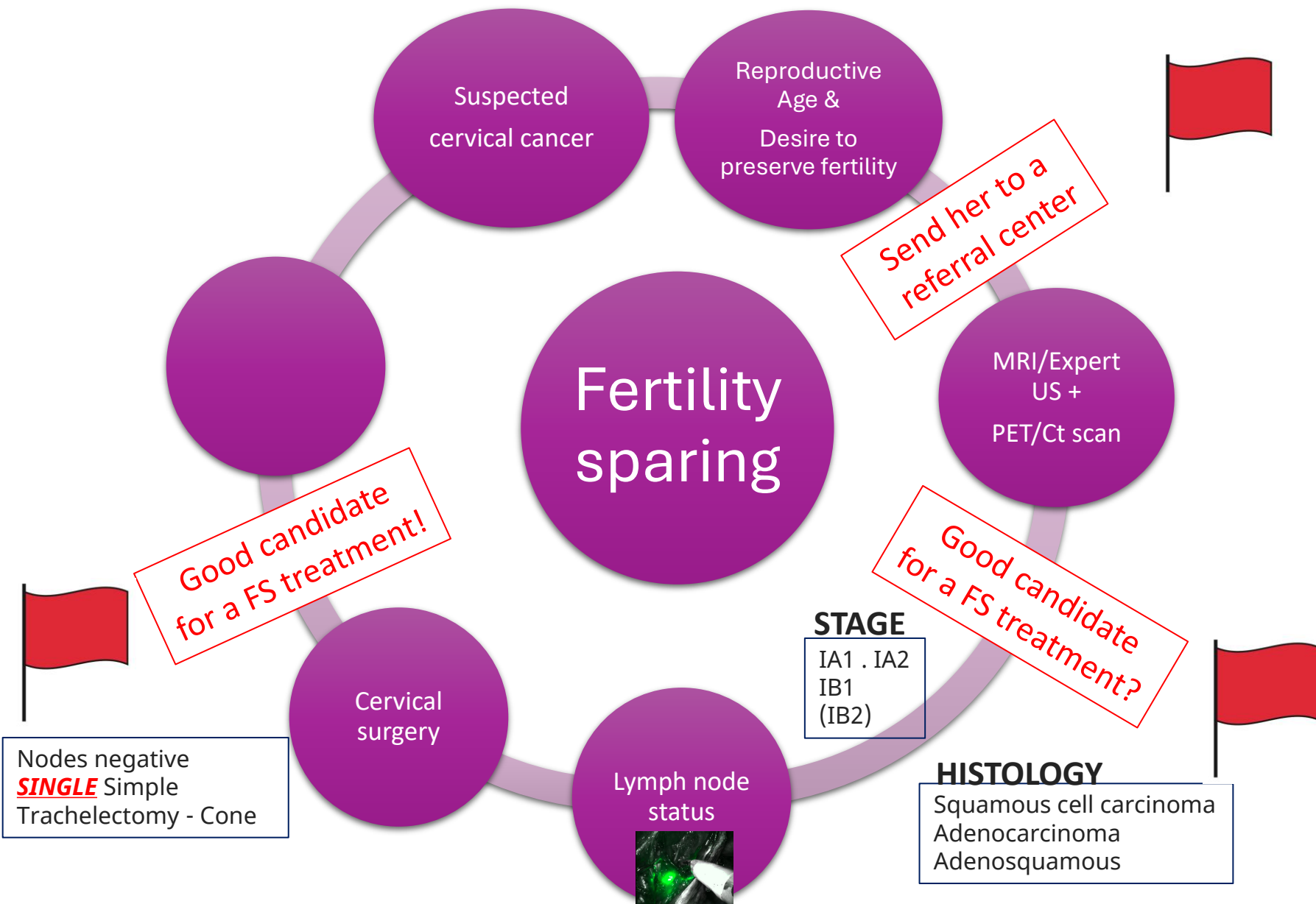


# ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer



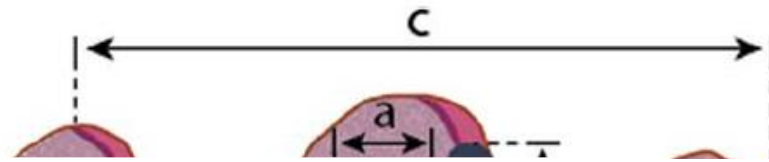
# I TUMORI IN FASE PRECOCE: QUANDO LA GRAVIDANZA È UNA POSSIBILITÀ

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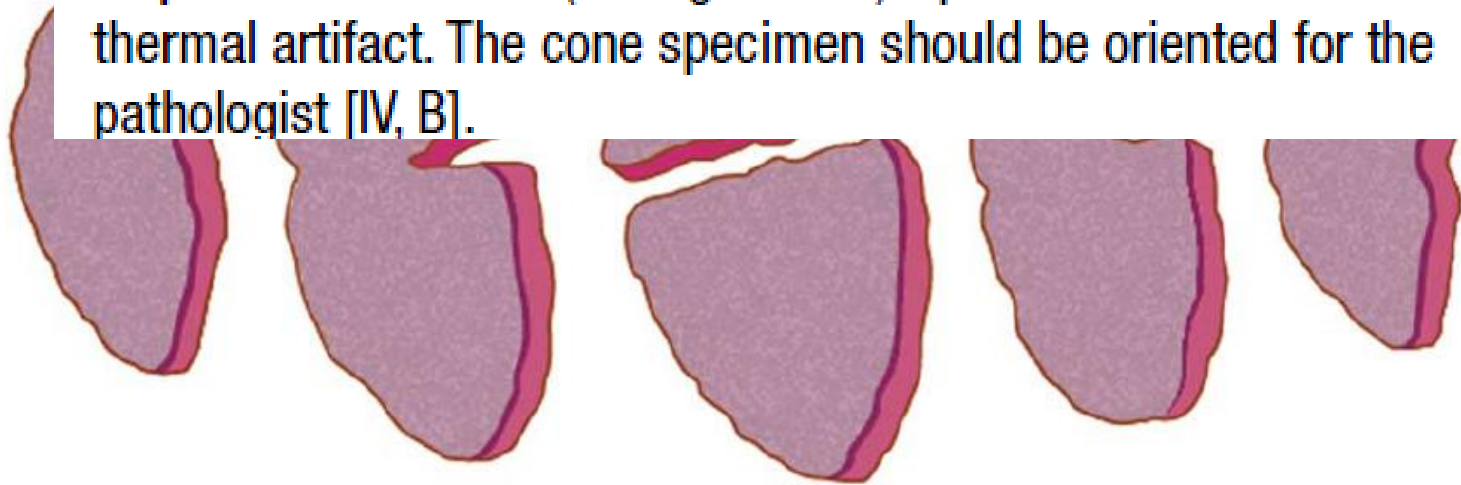




It is often difficult to comprehend the size of disease when the conization is performed outside from a referral center



Care should be taken to provide an intact (unfragmented) specimen with minimal thermal artifact. The cone specimen should be oriented for the pathologist [IV, B].



## Standards and datasets for reporting cancers

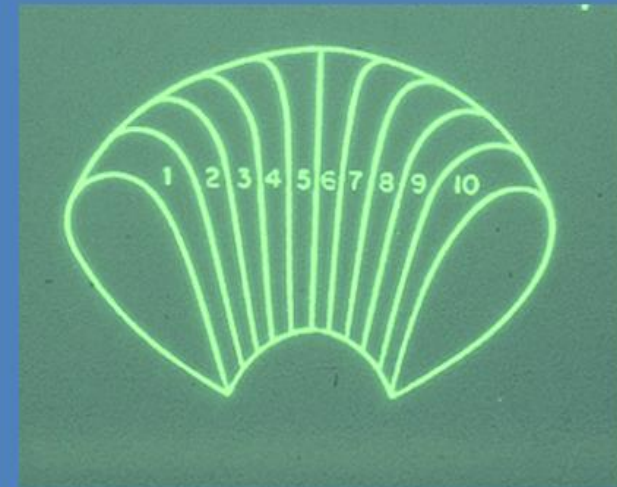
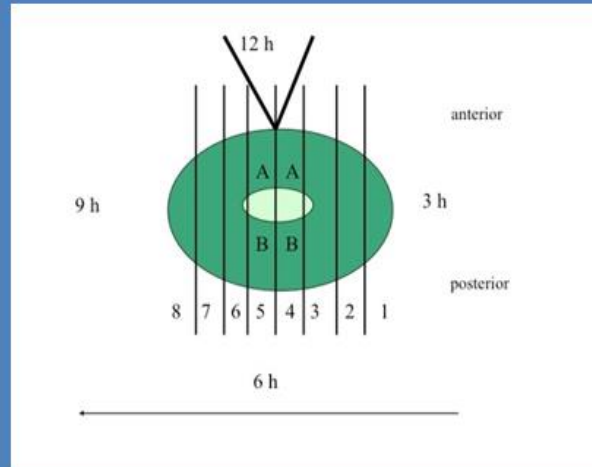
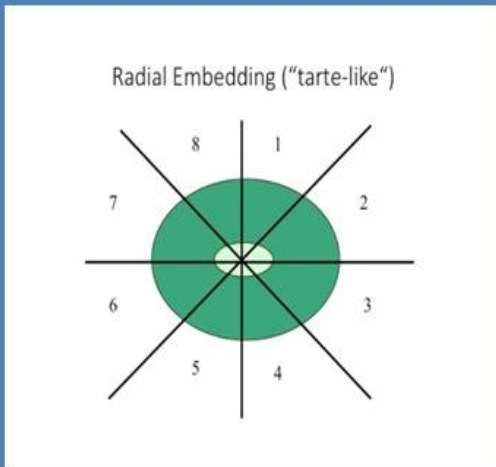
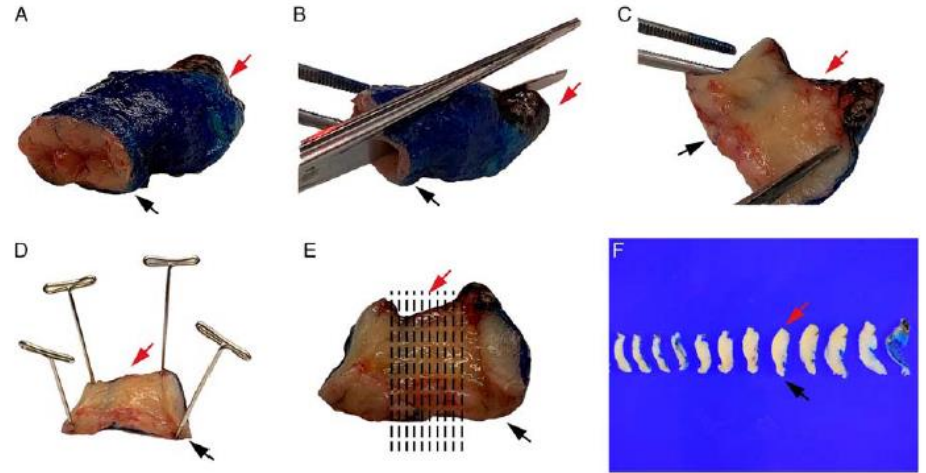
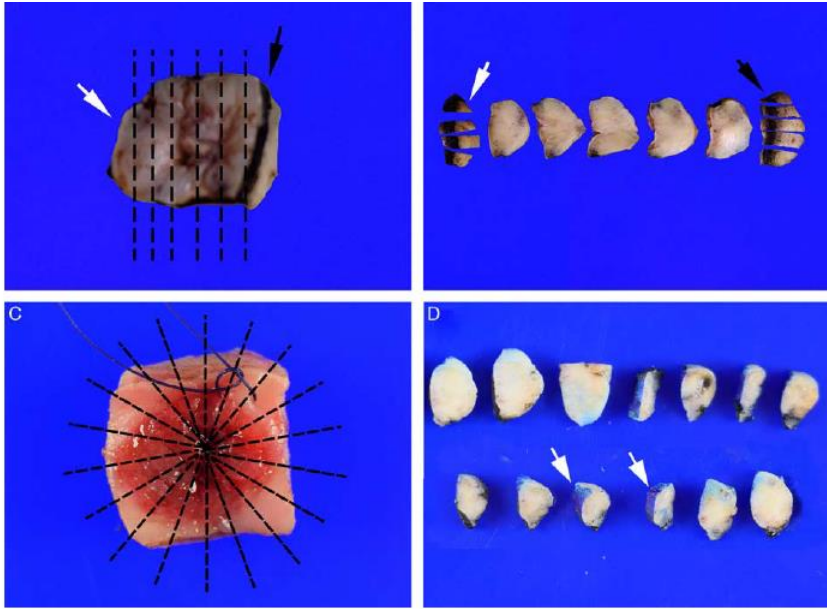
### Dataset for histopathological reporting of cervical neoplasia

March 2021

There are several methods of dissection of cone and loop biopsies . The commonest method is serial slicing at 2–3 mm intervals, from one edge to the other in a sagittal and parasagittal plane (beginning at the three or nine o'clock edge, which should be noted, particularly if the 12 o'clock position has been marked by the surgeon), perpendicular to the transverse axis of the external os. This method avoids the interpretation problems

Tumour measurements are especially important in distinguishing between FIGO (2018) stage IA1, IA2 and IB neoplasms since FIGO IA1 neoplasms are treated by local excision while FIGO IA2 and IB neoplasms are treated by radical trachelectomy or hysterectomy. In the 2018 FIGO staging system, the horizontal dimension is no longer considered when defining the upper boundary of a stage IA carcinoma.<sup>8</sup> It is stated in the 2018 revised FIGO staging article that if the margins of an excision biopsy show invasive carcinoma, FIGO stage IB1 is allocated; this is not, however explicitly tabulated in the staging criteria. In order to avoid over- or under-staging, when small cancers involve resection margins staging should be offered a provisional stage. Staging should be completed at MDT with clinical and radiological assessment or after due correlation with findings on subsequent excision or resection specimens.

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# Prognostic factor related to SCC

## Established prognostic F

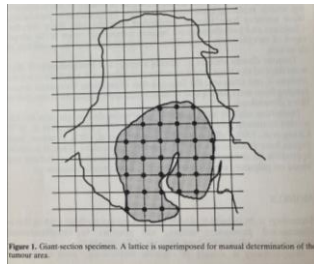
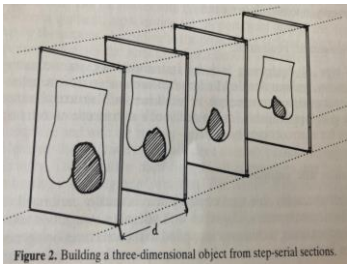
HPV status  
 Depth of stromal invasion  
 LVSI  
 Parametrial extension  
 Margin status

## Novel prognostic F

Tumor Budding/cell nest size  
 Tumor free distance (TFD)  
 Perineural invasion (PNI)  
 TILS

## Uncertain prognostic F

Grading  
 Horizontal spread  
 Extension in canal



### Risk Factor: diameter/invasion/LVSI

Sedlis: always valid criteria after 20 years?

Tumor diameter 25 mm  
 Cervix diameter 30mm  
 LVSI pos  
 Out thrid  
 25yrs old, P:0000

Tumor diameter 30mm  
 Cervix diameter 45mm  
 LVSI pos  
 Out thrid  
 3yrs old, P3003



2,5mm free  
 7,5mm free



Melanoma (ESMO): safety margins of 0.5 cm for *in situ* 1 cm for tumours  
 Vulva (ESGO): Surgical excision margins of at least 1 cm are advised

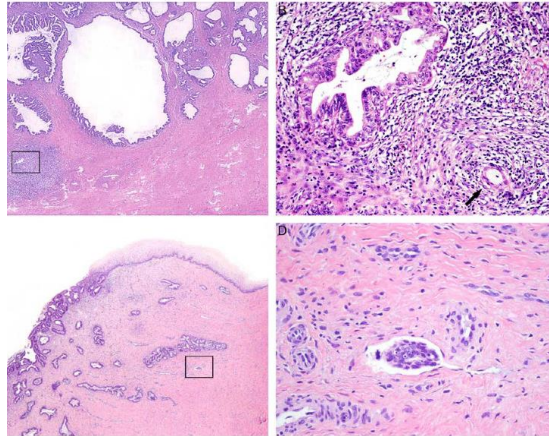
OPEN

Article

The Silva Pattern-based Classification for HPV-associated Invasive Endocervical Adenocarcinoma and the Distinction Between In Situ and Invasive Adenocarcinoma: Relevant Issue and Recommendations From the International Society of Gynecological Pathologists

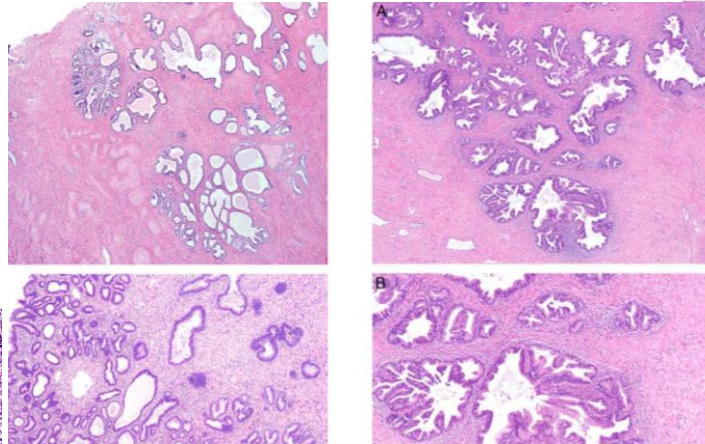
Pattern B

Localized (limited, early) destructive stromal invasion arising from well-demarcated glands (pattern A-like glands)  
 Individual, ragged glands or small clusters of tumor cells, separated from the rounded glands, usually in an inflamed or desmoplastic stroma  
 Foci may be single, multiple, or linear at the base of the tumor, < a 4× field (5 mm in diameter)  
 No solid growth  
 LVI (±)



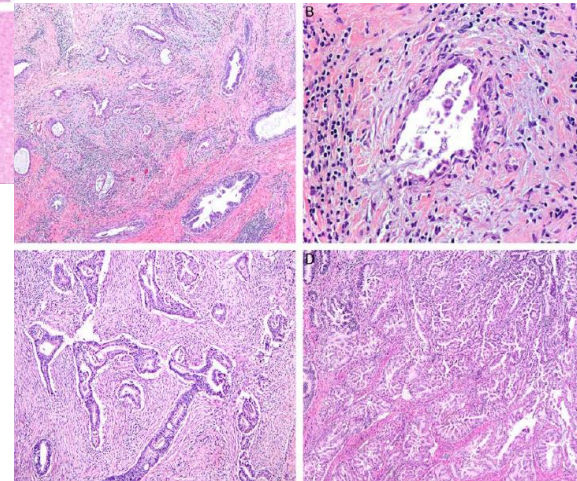
Pattern A

No destructive stromal invasion  
 Well-demarcated glands with rounded contours, commonly forming groups  
 No single cells or cell detachment  
 Complex intraglandular growth allowed (i.e. cribriform, papillae), < a 4× field (5 mm in diameter)  
 No solid growth or high-grade cytology  
 No lymphovascular invasion (LVI)  
 Irrelevant relationship to large cervical vessels or depth of the tumor



Pattern C

Diffuse destructive invasion  
 Infiltrative glands that are variable in shape and size, often angulated or interconnected  
 Confluent growth  
 Glands or papillary structures with little intervening stroma or mucin lakes with tumor cells within the cervical stroma and filling a 4x field (5mm)  
 Solid  
 Poorly differentiated component (architecturally high grade) with sheets of large malignant cells  
 Extensive linear destructive  
 Diffuse laminar EACs ≥ 5 mm. Tumor cells or individual glands are present in a desmoplastic stroma at the base of the tumor  
 Band-like lymphocytic infiltrate  
 Superficial prominent band-like lymphoid infiltrate that obscures the neoplastic aggregates  
 Micropapillary  
 Numerous small clusters of tumor cells  
 LVI (±)



Article

The Silva Pattern-based Classification for HPV-associated Invasive Endocervical Adenocarcinoma and the Distinction Between In Situ and Invasive Adenocarcinoma: Relevant Issues and Recommendations From the International Society of Gynecological Pathologists

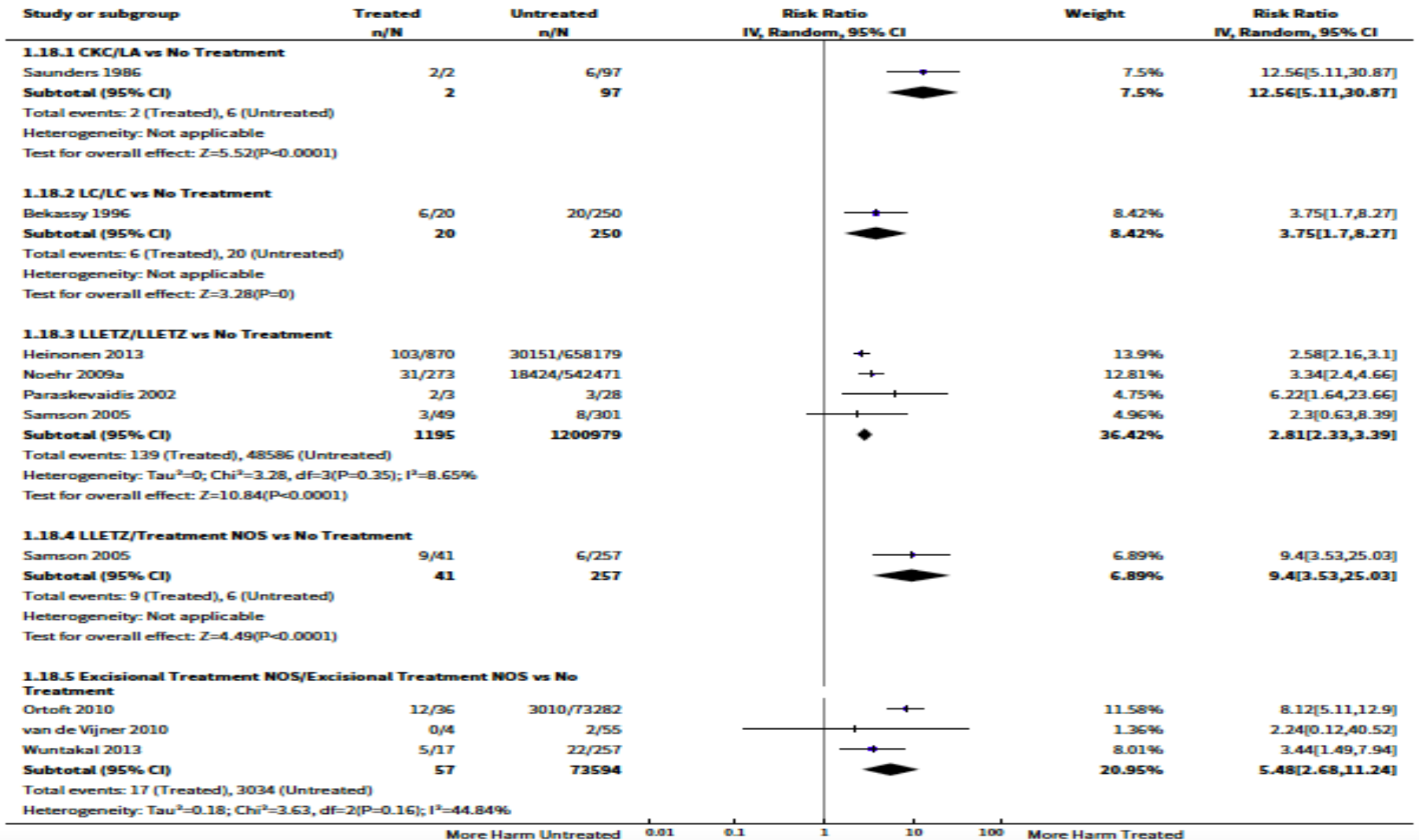
**TABLE 4.** *Cumulative clinico-pathologic features of patients with endocervical adenocarcinoma categorized according to the Silva pattern-based classification*

	Total	Pattern A	Pattern B	Pattern C
No. Pts	1319	253	262	804
LVI	543 (41%)	0	53 (20%)	490 (61%)
With LN mets	191 (14%)	0	14 (5%)	177 (22%)
With stage information	1102	224	241	637
Stage I	981 (89%)	222 (99%)	233 (97%)	526 (83%)
Stage II–IV	119 (11%)	2 (1%)	6 (3%)	111 (17%)
With F/U	776	201	216	359
F/U in months, mean (range)	62 (3–392)	62 (3–252)	69 (5–392)	55 (3–258)
With recurrences	77 (10%)	0	7 (3%)	70 (19%)
DOD	42 (5%)	0	3 (1%)	39 (11%)

DOD indicates dead of disease; F/U, follow-up; LN, lymph node.

# Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease (Review)

## Analysis 1.18. Comparison 1 Maternal Outcomes-PTB, Outcome 18 PTB (<37w)-Repeat cones.



# Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease (Review)

## Analysis 1.25. Comparison 1 Maternal Outcomes-PTB, Outcome 25 PTB (<37w)-Depth≥15-17mm.

Study or subgroup	Treated n/N	Untreated n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
<b>1.25.1 LC vs No Treatment</b>					
Andersen 1999	14/61	7/150		12.54%	4.92[2.09,11.59]
<b>Subtotal (95% CI)</b>	<b>61</b>	<b>150</b>		<b>12.54%</b>	<b>4.92[2.09,11.59]</b>
Total events: 14 (Treated), 7 (Untreated)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.64(P=0)					

## Analysis 1.35. Comparison 1 Maternal Outcomes-PTB, Outcome 35 PTB (<37w)-Depth≥10mm.

Study or subgroup	Treated n/N	Untreated n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
<b>1.35.1 LC vs No Treatment</b>					
Raio 1997	5/23	3/64		4.29%	4.64[1.2,17.88]
<b>Subtotal (95% CI)</b>	<b>23</b>	<b>64</b>		<b>4.29%</b>	<b>4.64[1.2,17.88]</b>
Total events: 5 (Treated), 3 (Untreated)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.23(P=0.03)					

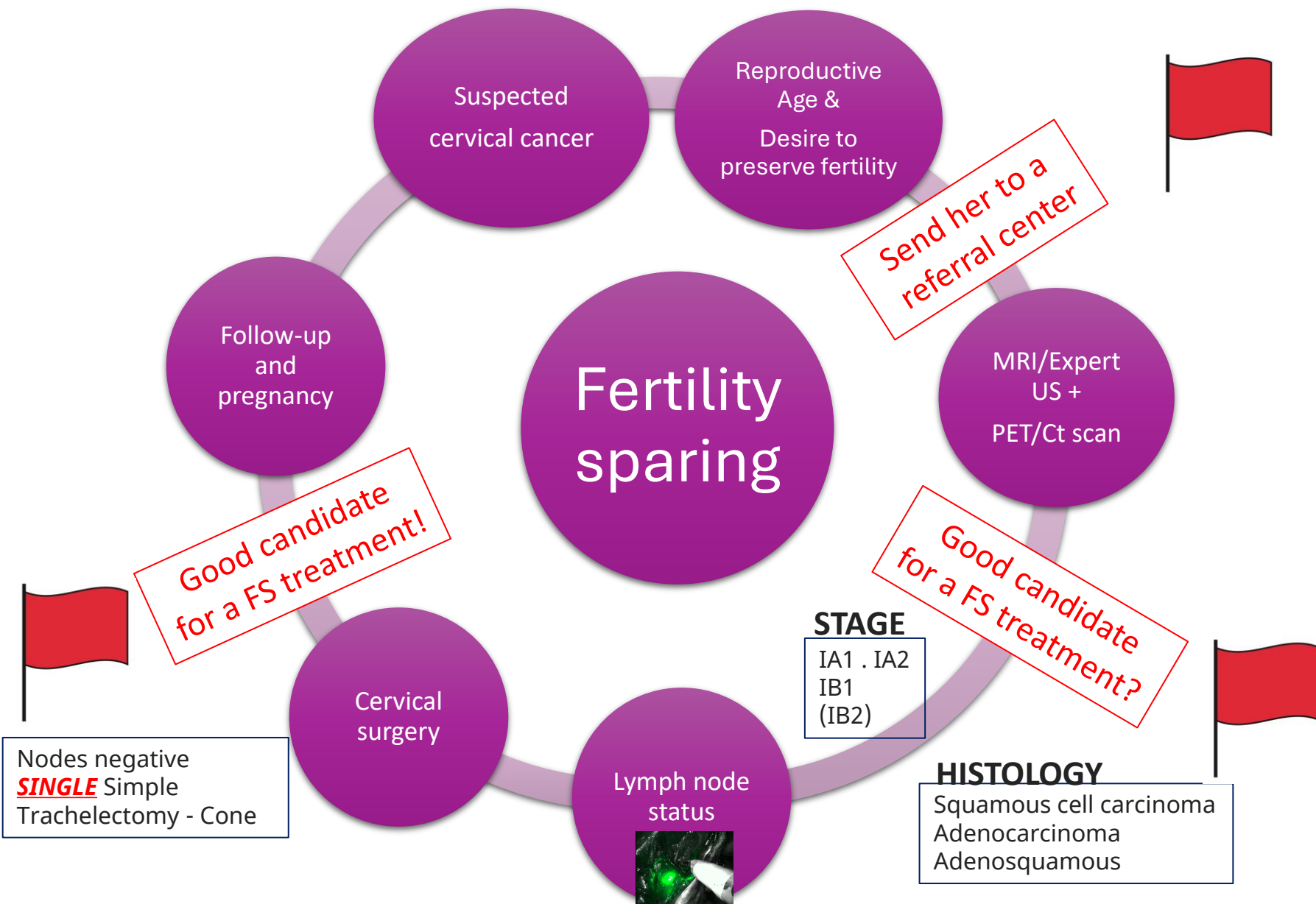
## Analysis 1.26. Comparison 1 Maternal Outcomes-PTB, Outcome 26 PTB (<37w)-Depth≥20mm.

Study or subgroup	Treatment n/N	Untreated n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
<b>1.26.1 LC vs No Treatment</b>					
Andersen 1999	12/42	7/150		30.71%	6.12[2.57,14.57]
<b>Subtotal (95% CI)</b>	<b>42</b>	<b>150</b>		<b>30.71%</b>	<b>6.12[2.57,14.57]</b>
Total events: 12 (Treatment), 7 (Untreated)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.1(P<0.0001)					



# I TUMORI IN FASE PRECOCE: QUANDO LA GRAVIDANZA È UNA POSSIBILITÀ

## Carcinoma della cervice: quando la chirurgia fertility sparing



## Pregnancy Outcomes

	Method	total	N (%)
Number of pregnancies	<i>VRT</i>	621	300 (48)
	<i>ART</i>	194	32 (16)
	<i>Cone ST</i>	32	23 (72)

VRT – vaginal radical trachelectomy, ART – abdominal (laparoscopic) radical trachelectomy, ST – vaginal simplex trachelectomy

Rob L, et al. *Lancet Oncol.* 2011;12(2):192-200.



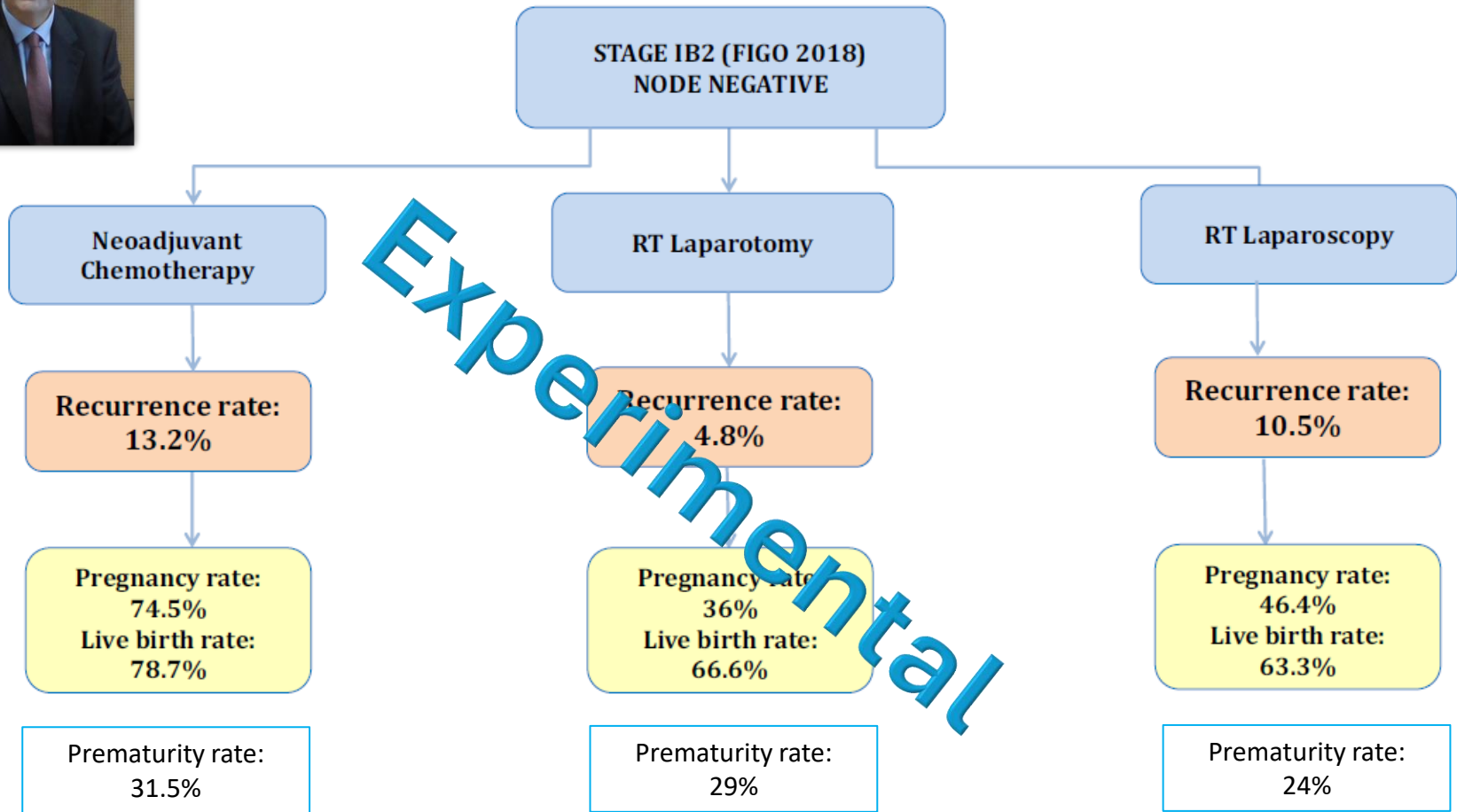
## Fertility-Sparing and Less Radical Surgery for Cervical Cancer

Samantha H. Batman<sup>1</sup> · Kathleen M. Schmeler<sup>1</sup>

Number	Simple trachelectomy/ cone resection	Radical Trachelectomy Vaginal approach	Radical Trachelectomy Laparotomy	Radical Trachelectomy Laparoscopy	Radical Trachelectomy Robot	Neoadjuvant Chemotherapy
Patients	649	1977	2153	538	208	337
Patients excluded*	59	258	249	91	14	36
Number of teams reporting series/cases**	23	35	44	27	15	31
Number of published articles/abstracts	33	67	81	32	20	42
IB < 2 cm***	436	1013	687	118	Unknown	113
IB between 2 and 4 cm***	0	101	375	57	Unknown	147
IB > 4 cm	0	3	21	At least 3	1	At least 27
IIA	0	10	At least 19	At least 1	0	At least 11
LVSI****	191	At least 495	At least 227	At least 61	Unknown	Unknown
Recurrences*****	18	86	76	29	9	25
DOD*****	1	28	27	2	0	5
Recurrence rate (overall)	18/436:4.1%	86/1669:5.1%	73/1836:4%	29/386:7.5%	10/188:5.3%	25/300:8.3%
Recurrence rate IB < 2 cm	18/436:4.1%	48/1037:4.7%	17/687:2.4%	6/114:5.2%	ND****	ND
Recurrence rate IB 2–4 cm	–	21/101:20.7%	18/375:4.8%	6/57:10.5%	ND	16/131:13.2%
Recurrence rate IB < 4 cm	–	–	–	14/254:5.5%*****	–	–
Number of pregnancies	243	689	420	77	79	135
Number of pregnant patients	198	412	339	62	55	112
Pregnancy rate*****	80/142:56.3%	337/574:58.7%	190/527:36%	33/65:50%	53/76:77%	70/94:74.5%
Live birth rate*****	161/183:88%	342/481:71%	258/387:66.6%	46/69:66.6%	53/71:74.6%	111/141:78.7%
Prematurity rate*****	31/170:18.2%	145/481:30%	92/320:29%	17/69:24.6%	12/51:23.5%	18/57:31.5%



## CERVICAL CANCER 2-4CM



Morice P. et al., *Gyn Onc* 2022

Bentivegna E et al. *Lancet Oncol. & Fertil Steril.* 2016

Rob L, et al. *Lancet Oncol.* 2011

## WAITING FOR...

### Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F)

Stage IB1 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility-Sparing Surgery (CONTESSA)

**Sample size** A total of 90 evaluable patients will be needed to complete the study.

**Expected complete accrual** in 2022 with **presentation of results** by 2025.



#### Box 2. Primary objectives and end points

##### Primary objectives

- To evaluate the feasibility of preserving fertility in women with node negative, 2018 FIGO stage IB2 cervical cancer with lesions measuring 2–4 cm

##### Primary end points

- To assess the rate of functional uterus defined as successful fertility-sparing surgery and no adjuvant therapy

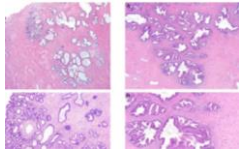
# TAKE HOME MESSAGES

*Remember the red flags*

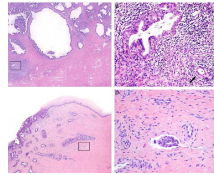
	VRT	SVT/cone	NACTH(adj)/SVT
St Ib1 <2cm LVSI neg	no benefit	indicated	no benefit
St Ib1 <2cm LVSI pos	indicated	indicated	feasible:more
St Ib2	UNSAFE	UNSAFE	FEASIBLE/safety
St Ib3	Contraindicated UNSAFE	Contraindicated UNSAFE	FEASIBLE/safety being assessed
Unusual Histological subtype Nodal status	Contraindicated UNSAFE	Contraindicated UNSAFE	Contraindicated UNSAFE

# TAKE HOME MESSAGES

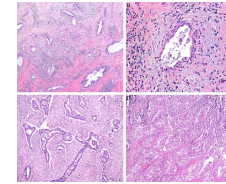
## Remember the red flags



**Pattern A**  
 No destructive stromal invasion  
 Well-demarcated glands with rounded contours, commonly forming groups  
 No single cells or cell detachment  
 Complex intraglandular growth allowed (i.e. cribriform, papillae), < a 4x field (5 mm in diameter)  
 No solid growth or high-grade cytology  
 No lymphovascular invasion (LVI)  
 Irrelevant relationship to large cervical vessels or depth of the tumor

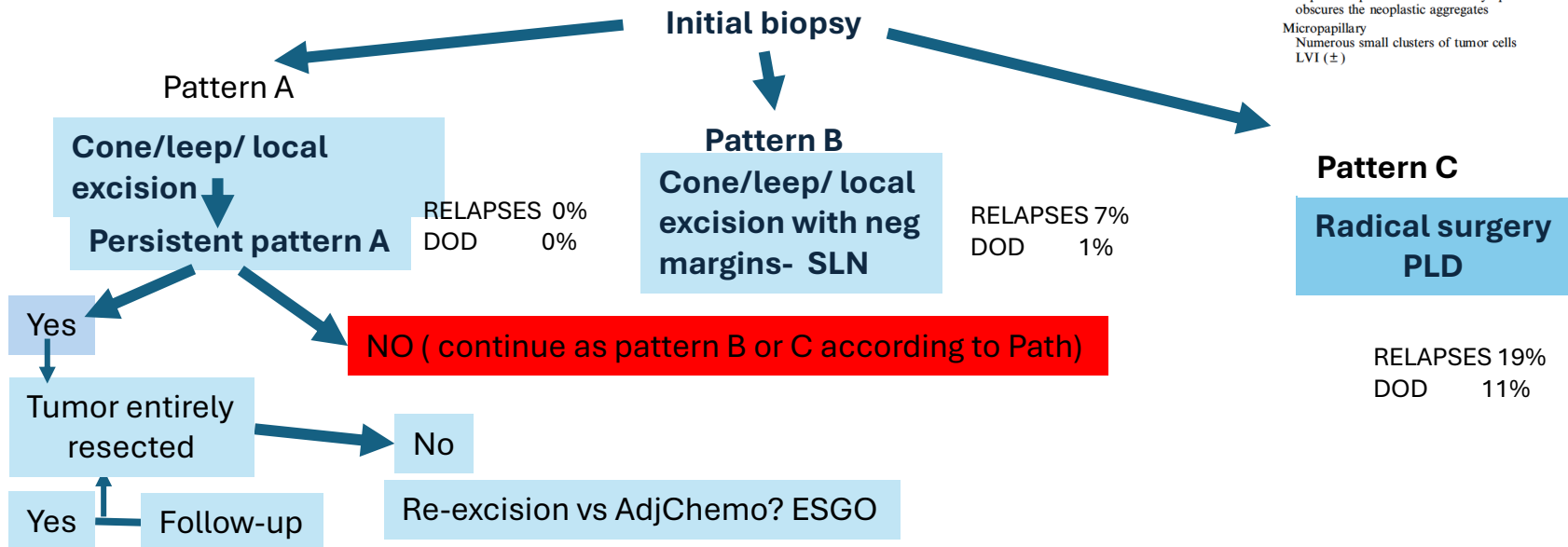


**Pattern B**  
 Localized (limited, early) destructive stromal invasion arising from well-demarcated glands (pattern A-like glands)  
 Individual, ragged glands or small clusters of tumor cells, separated from the rounded glands, usually in an inflamed or desmoplastic stroma  
 Foci may be single, multiple, or linear at the base of the tumor, < a 4x field (5 mm in diameter)  
 No solid growth  
 LVI (±)



**Pattern C**  
 Diffuse destructive invasion  
 Infiltrative glands that are variable in shape and size, often angulated or interconnected  
 Confluent growth  
 Glands or papillary structures with little intervening stroma or mucin lakes with tumor cells within the cervical stroma and filling a 4x field (5mm)  
 Solid  
 Poorly differentiated component (architecturally high grade) with sheets of large malignant cells  
 Extensive linear destructive  
 Diffuse laminar EACs ≥ 5 mm. Tumor cells or individual glands are present in a desmoplastic stroma at the base of the tumor  
 Band-like lymphocytic infiltrate  
 Superficial prominent band-like lymphoid infiltrate that obscures the neoplastic aggregates  
 Micropapillary  
 Numerous small clusters of tumor cells  
 LVI (±)

### Treatment modalities based on tumor pattern





**Perché viaggiare in moto è uno dei viaggi più INTIMI che si possano compiere: si è soli con la strada, con la propria voglia di viaggiare ma soprattutto con i propri pensieri**

