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# Recent Developments in the Transmission of Human Life

## PRESERVATION OF FERTILITY IN UTERINE CARCINOMA

Dr.ssa Giorgia Dinoi

# Preservation of fertility in uterine carcinoma

Giorgia Dinoi, MD

Italy



Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

# Faculty Disclosure

**I have no potential conflict of interest to declare**

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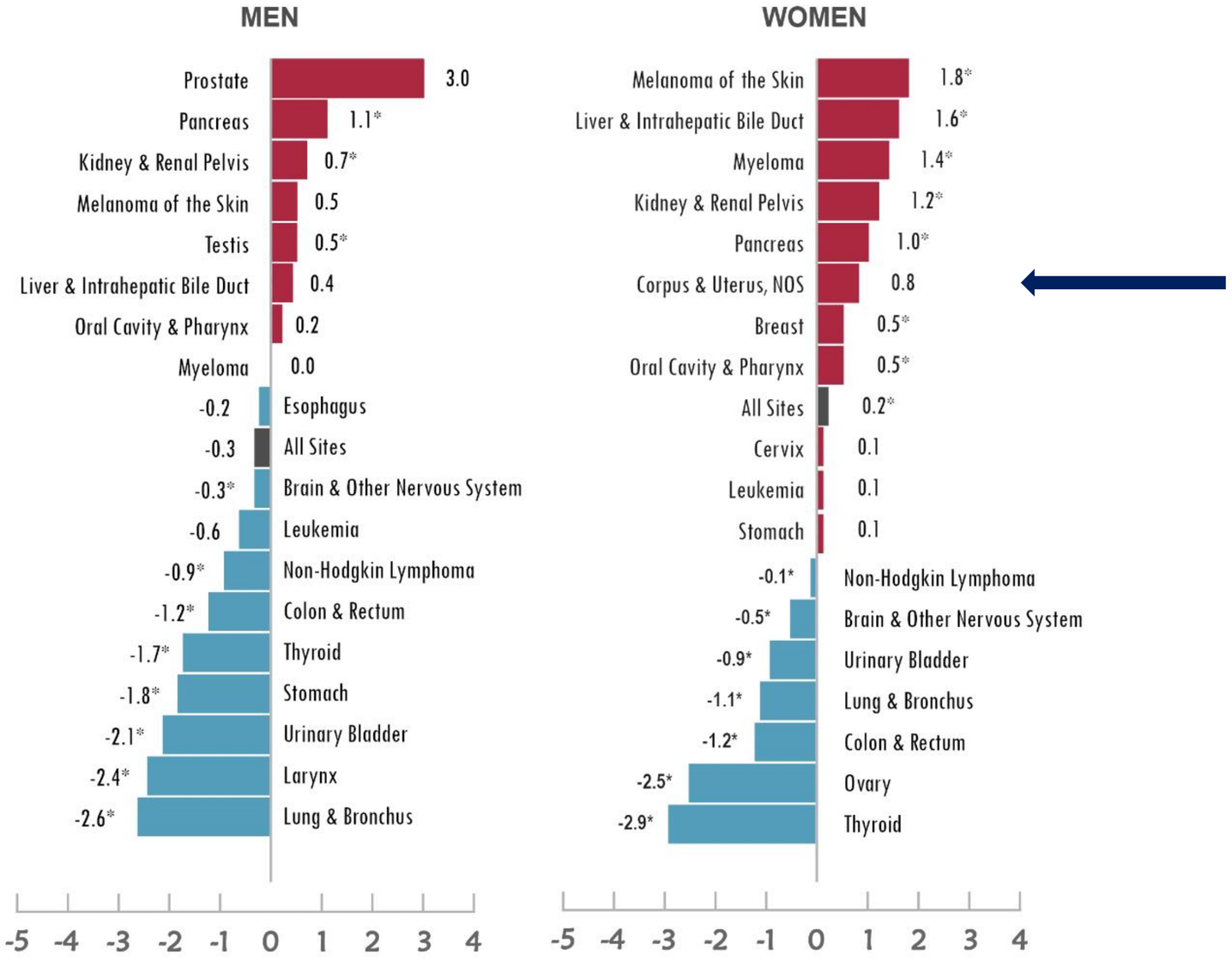
# NATIONAL TRENDS IN RATES OF NEW CANCER CASES




**AVERAGE ANNUAL PERCENT CHANGE (AAPC) 2014-2018**



AAPC = average annual percent change

*AAPC is significantly different from zero ($p<.05$).

seer.cancer.gov

Source: Annual Report to the Nation

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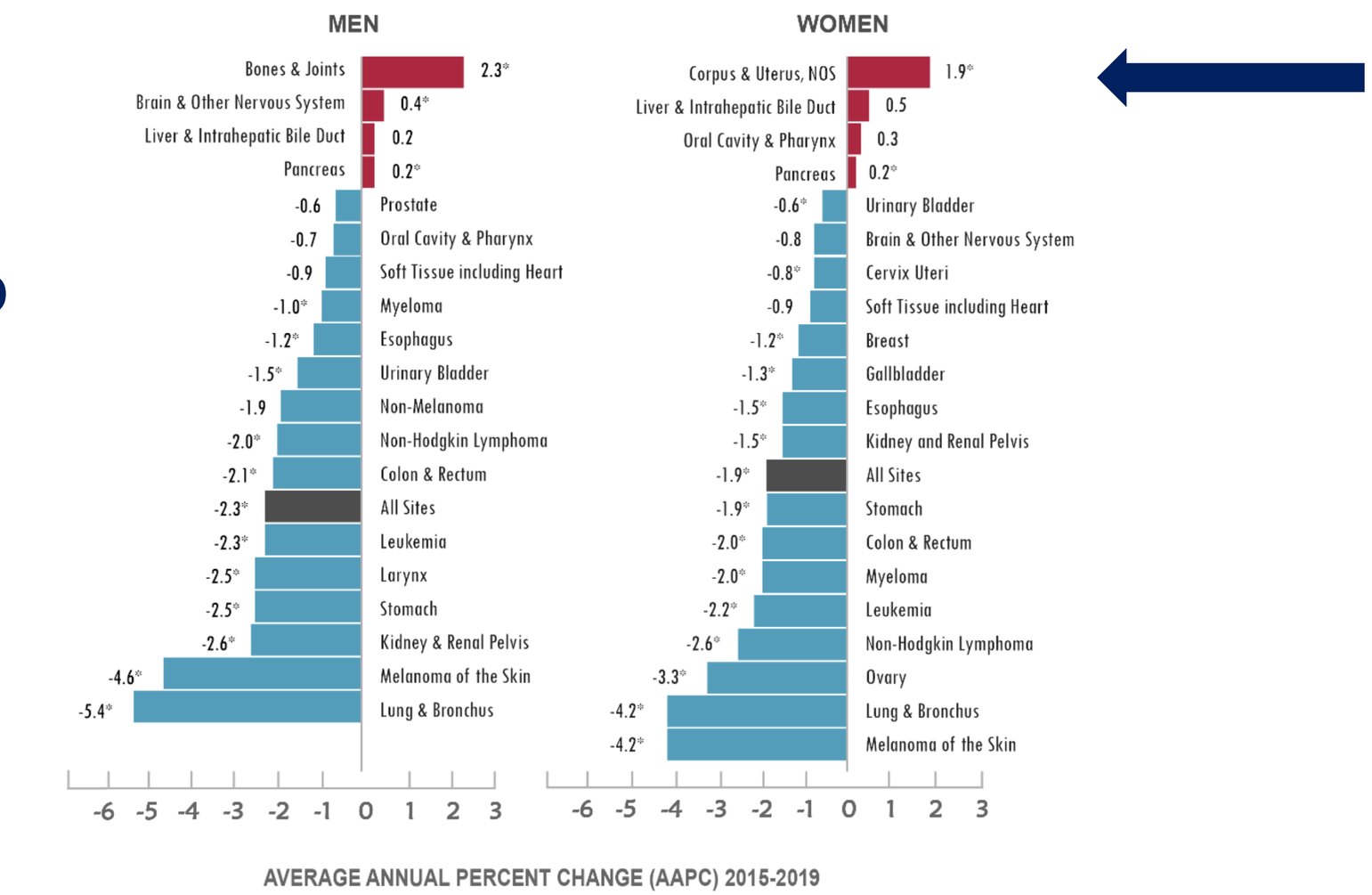
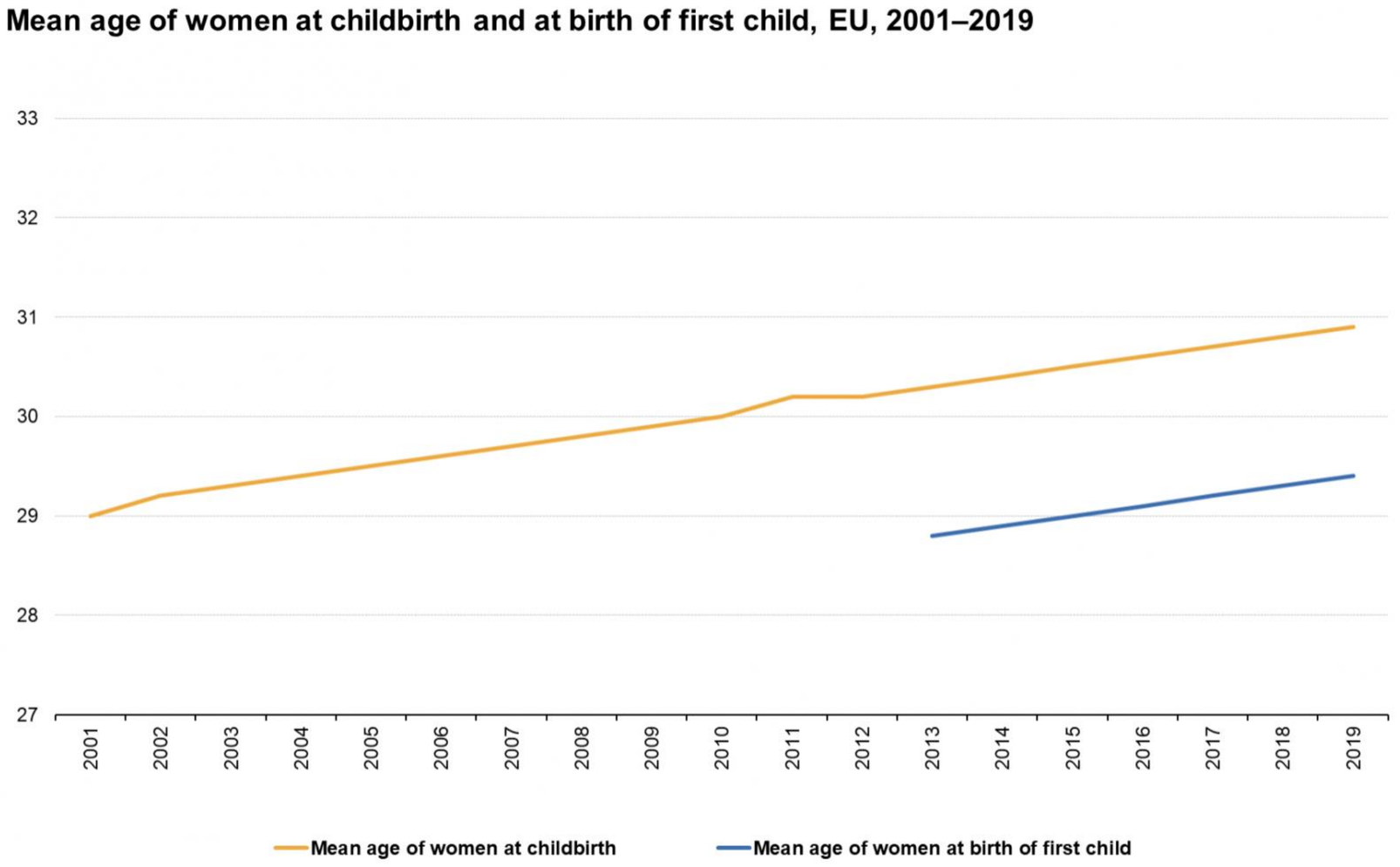
# Annual Report to the Nation 2022: Overall Cancer Statistics






AAPC = average annual percent change
*AAPC is significantly different from zero (p<.05).
seer.cancer.gov
Source: Annual Report to the Nation

# Fertility: mean women age



# Endometrial Cancer Treatment

**STANDARD OF CARE**

**Total Hysterectomty + Bilateral Salpingo-oophorectomy + Lymph node assessment**

**NON-STANDARD OF CARE**

**???**

# NCCN Guidelines Version 1.2023
# Endometrial Carcinoma

**ELIGIBILITY CRITERIA**

**CRITERIA FOR CONSIDERING FERTILITY-SPARING OPTIONS FOR MANAGEMENT OF ENDOMETRIAL CARCINOMA**
**(All criteria must be met)**

- **Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review**
- **Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound[i]**
- **Absence of suspicious or metastatic disease on imaging**
- **No contraindications to medical therapy or pregnancy**
- **Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma**

→

**PRIMARY TREATMENT**

- **Consultation with a fertility expert prior to therapy**
- **Recommend genetic evaluation of tumor and evaluation for inherited cancer risk (See UN-1)**
- **Ensure negative pregnancy test**

→

- **Continuous progestin-based therapy:**
  - **Megestrol**
  - **Medroxyprogesterone**
  - **Progestin IUD**
- **Weight management/ lifestyle modification counseling[t]**

→

**SURVEILLANCE**

**Endometrial evaluation every 3–6 mo (either D&C or endometrial biopsy)**

**Complete response by 6 mo** →

**Encourage conception (with continued surveillance/ endometrial sampling every 6 mo and consider maintenance progestin-based therapy if patient is not actively trying to conceive)** →

**TH/BSO with staging[d,e] after childbearing complete or progression of disease on endometrial sampling (See ENDO-1)**
- **Ovarian preservation may be considered in select premenopausal patients**

**Endometrial cancer present at 6–12 mo[i,u]** →

**TH/BSO with staging[d,e] (See ENDO-1)**
- **Ovarian preservation may be considered in select patients**

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# Comparison of hysteroscopic and hysterectomy findings for assessing the diagnostic accuracy of office hysteroscopy

Oronzo Ceci [1], Stefano Bettocchi, Annarosa Pellegrino, Luigi Impedovo, Raffaella Di Venere, Nicola Pansini

Fertility and Sterility®
2002

**Larger amount of tissue retrieved**

↓

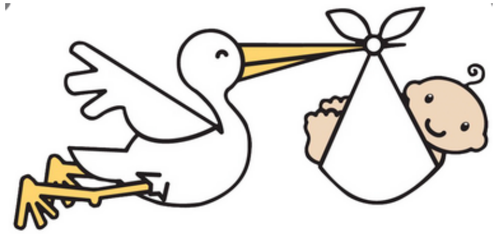
**More accurate histological diagnosis**

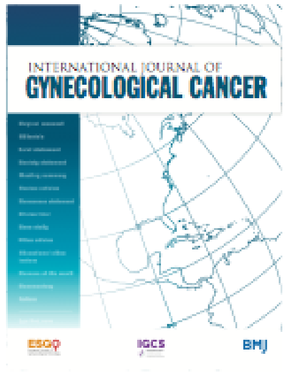
Comparison between the diagnostic accuracy of D&C and of hysteroscopy.

| | D&C vs. histologic findings at hysterectomy (397 patients) | Hysteroscopy vs. histologic findings at hysterectomy (445 patients) | *P* |
|---|---|---|---|
| Sensitivity | 46% | 98% | <.005 |
| Specificity | 100% | 95% | NS |
| Positive predictive value (PPV) | 100% | 96% | NS |
| Negative predictive value (NPV) | 7.1% | 98% | <.005 |

NS = not significant.

# FERTILITY SPARING IN ENDOMETRIAL CANCER






## ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

**Fertility preservation**

Work-up for fertility preservation treatments

Fertility-sparing treatments should be considered in patients with atypical hyperplasia/endometrioid intra-epithelial neoplasia (AH/EIN) or grade 1 endometrioid carcinoma without myometrial invasion.[263–269] There are very few published data on patients with stage IA grade 2 endometrioid carcinoma without myometrial invasion who received fertility-sparing treatment with combined oral medroxyprogesterone acetate/levonorgestrel intrauterine system.[270] Although results are encouraging, this treatment should only be considered by experienced gynecological oncologists using well-defined protocols with detailed patient information and close follow-up.

Hysteroscopic biopsy is suggested, based on its higher agreement with the final diagnosis compared with dilatation and curettage.[271,272] Although hysteroscopy seems to be associated with a higher rate of positive peritoneal cytology, it seems not to have a negative impact on survival.[273] Expert vaginal ultrasound examination can be used instead of pelvic MRI. Its high diagnostic performance allows the detection of myometrial invasion and cervical

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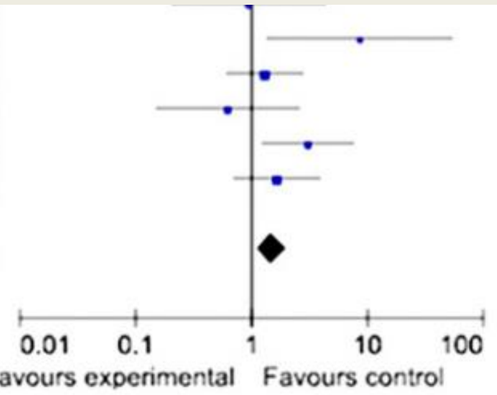
# Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis

Ya-Nan Chang, M.M. • Ying Zhang, M.D. • Yong-Jun Wang, M.D. • Li-Ping Wang, M.M. • Hua Duan, M.D.

Effect of hysteroscopy on positive peritoneal cytology in patients with or without hysteroscopy ($P$=.005).

| Study or Subgroup | HSC Events | HSC Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Ben-Arie A 2008 | 1 | 100 | 0 | 292 | 0.3% | 8.82 [0.36, 218.24] |
| Bradley WH 2004 | 7 | 52 | 14 | 204 | 6.5% | 2.11 [0.81, 5.53] |
| Gao WL 2004 | 2 | 31 | 3 | 39 | 3.3% | 0.83 [0.13, 5.29] |
| Shu W 2008 | 3 | 62 | 4 | 78 | 4.5% | 0.94 [0.20, 4.37] |
| Takac 2007 | 3 | 24 | 2 | 122 | 0.8% | 8.57 [1.35, 54.42] |
| Wang W 2002 | 18 | 51 | 21 | 71 | 15.1% | 1.30 [0.60, 2.80] |
| Wen HW 2000 | 3 | 34 | 7 | 52 | 6.7% | 0.62 [0.15, 2.59] |
| Zerbe 2000 | 11 | 64 | 10 | 158 | 6.4% | 3.07 [1.23, 7.65] |
| Zhang JW 2002 | 12 | 59 | 13 | 97 | 10.4% | 1.65 [0.70, 3.91] |
| **Total (95% CI)** | | **1009** | | **1805** | **100.0%** | **1.51 [1.13, 2.01]** |
| Total events | 110 | | 151 | | | |

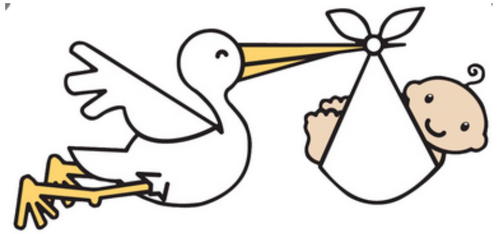
Heterogeneity: Chi² = 15.96, df = 18; I² = 0%
Test for overall effect: Z = 2.82

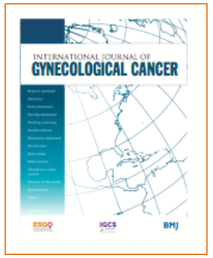



There is **no evidence** to support an **association** between **preoperative hysteroscopic** examination and a worse **prognosis**.

There is no reason to avoid diagnostic hysteroscopy before surgery in patients with endometrial cancer, **especially in early stages.**

# FERTILITY SPARING IN ENDOMETRIAL CANCER






## ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

2021

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- Ensure negative pregnancy test

→

- Continuous progestin-based therapy:
  - Megestrol
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- Weight management/ lifestyle modification counseling[t]

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→ Complete response by 6 mo → Encourage conception (with continued surveillance/ endometrial sampling every 6 mo and consider maintenance progestin-based therapy if patient is not actively trying to conceive) → TH/BSO with staging[d,e] after childbearing complete or progression of disease on endometrial sampling (See ENDO-1)
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→ Endometrial cancer present at 6–12 mo[i,u] → TH/BSO with staging[d,e] (See ENDO-1)
- Ovarian preservation may be considered in select patients

# The role of MRI in Endometrial Cancer

Radiology 2004; 231:372–378

Radiology

Riccardo Manfredi, MD
Paoletta Mirk, MD
Giulia Maresca, MD
Pasquale A. Margariti, MD
Antonia Testa, MD
Gian Franco Zannoni, MD
Deborah Giordano
Giovanni Scambia, MD
Pasquale Marano, MD

## Local-Regional Staging of Endometrial Carcinoma: Role of MR Imaging in Surgical Planning[1]

Statistical Values for Assessment of Myometrial Infiltration, Cervical Invasion, and Lymph Node Metastases with MR Imaging

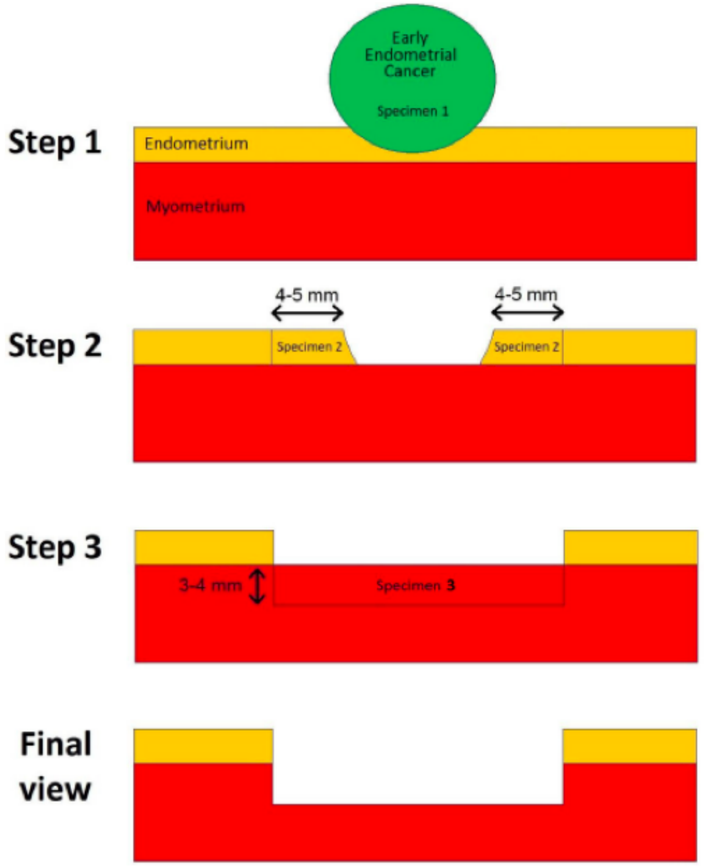
| Finding | Sensitivity (%) | Specificity (%) | Diagnostic Accuracy (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|
| Myometrial infiltration | 87 | 91 | 89 | 87 | 91 |
| Cervical invasion | 80 | 96 | 92 | 89 | 93 |
| Lymph node metastases | 50 | 95 | 90 | 50 | 95 |

***MRI vs hystological evaluation p < 0.01***

# Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection

2005

I Mazzon [1], G Corrado, D Morricone, G Scambia




- **Focal lesion**
- **FIGO Stage IA**
- **Grade I**
- **Reproductive desire**

30 mo. after HSC
→ CS at 39w

FREE OF DISEASE

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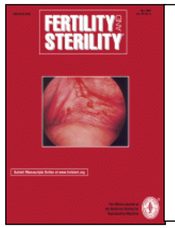
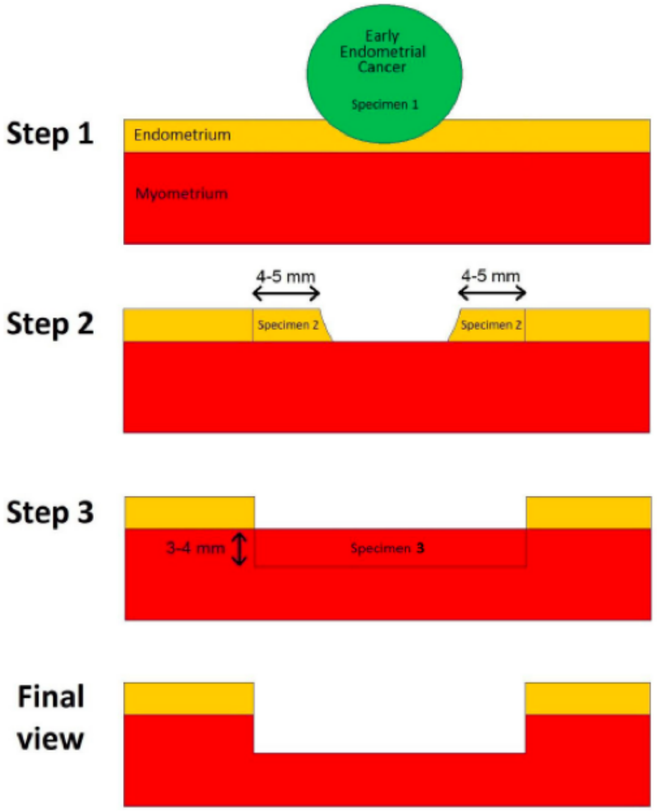


**Conservative surgical management of stage IA endometrial carcinoma for fertility preservation**

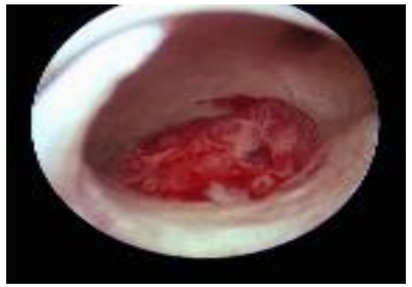
*Ivan Mazzon, M.D.,[a] Giacomo Corrado, M.D., Ph.D.,[b] Valeria Masciullo, M.D., Ph.D.,[c] Daniela Morricone, M.D.,[a] Gabriella Ferrandina, M.D.,[b] and Giovanni Scambia, M.D.[c]*

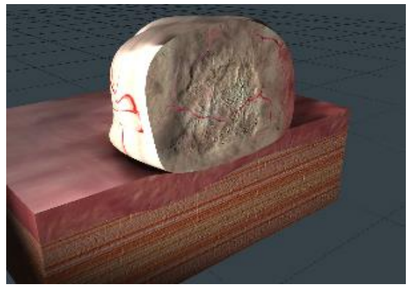
FERTILITY AND STERILITY
The Official Journal of the American Society for Reproductive Medicine

# Mazzon's Technique

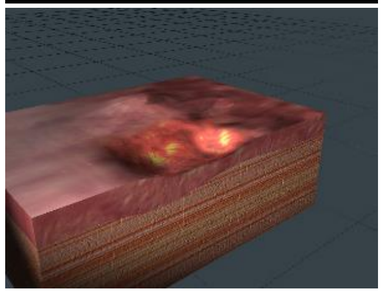



## 1: Visualization

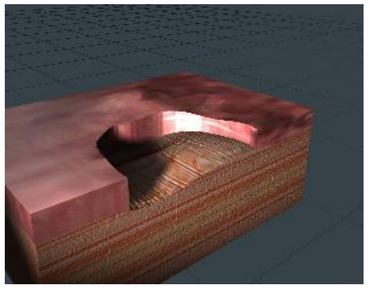




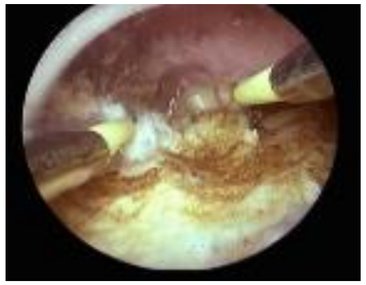
## 2: Removal

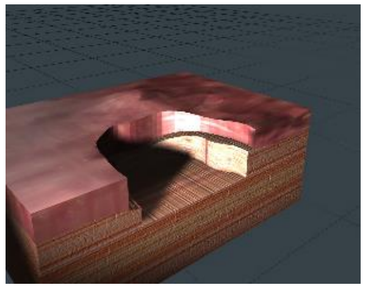


## 3: Removal of peri-lesional endometrium



## 4: Removal of myometrium under lesion





# Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer

Francesca Falcone,[1,2] Giuseppe Laurelli,[1] Simona Losito,[3] Marilena Di Napoli,[4] Vincenza Granata,[5] Stefano Greggi[1]

JOURNAL OF GYNECOLOGIC ONCOLOGY

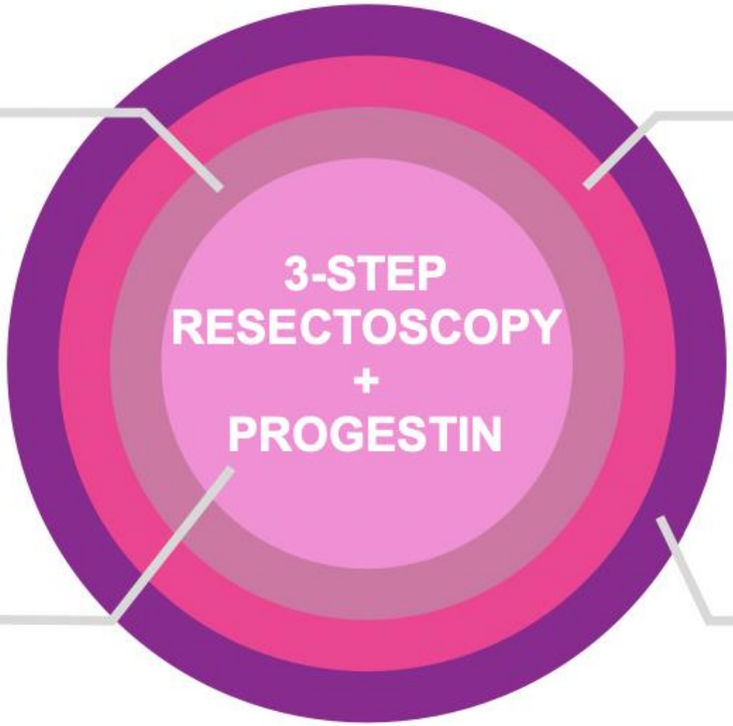
2017

- **Prospective** study
- **28** pts Stage **IA**
- **G1** (N=27), **G2** (N=1)
- **Endometrioid** EC
- Oral **megestrol acetate** or **levonorgestrel IUD** for 6 mo. +

**G1**

**COMPLETE REGRESSION RATE**

**96.3%**




**PREGNANCY RATE**

**93.3%**

**RECURRENCE RATE**

**7.7%**

**LIVE BIRTH RATE**

**86.6%**

Median FUP= 92 mo.

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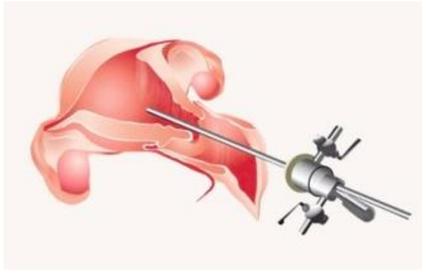
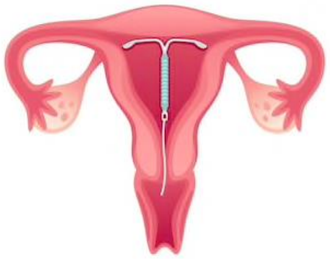




- **Retrospective** case series
- From **2007** to **2017**
- 69 pts (**EEC n=14 – AEH n=55**)
- Mean **age** was **35.1**±4.8 yrs
- **LNG-IUD** inserted in all patients after surgery
- **FU 24 months**

## …PRESERVING THE BASAL LAYER OF THE ENDOMETRIUM

**Similar response and live birth rates compared to those reported in literature for progestins alone, but a considerably lower relapse rate.**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | hysterecto my |

**Table 3.** Oncologic outcomes in patients with AEH.

| FOLLOW-UP | PATIENTS ASSESSED | PATHOLOGICAL REPORTS (%) | | | | | Patients addressed to hysterectomy (%) | Patients lost to follow-up (%) | Changes compared to the previous follow-up |
|---|---|---|---|---|---|---|---|---|---|
| | | complete response CR | partial response PR | stable disease SD | progression of disease P | recurrence of disease R | | | |
| TOTAL | 55 | 51 (92.7) | 3 (5.5) | 1 (1.8) | 0 (0) | 2 (3.6) | 1 (1.8) | 8 (14.5) | 1 R had undergone hysterectomy |

| | | |
|---|---|---|
| (N=25) | | No=0 80%) |
| PREGNANCIES (N=10) 40% | Conception method | Natural=10 (100%) Assisted=0 (0%) |
| | Live birth achieved | Yes=10 (100%) No=0 (0%) |
| | Complications | Yes=0 (0%) No=10 (100%) |
| | Abnormal placentation | Yes=0 (0%) No=10 (100%) |
| DELIVERIES (N=10) | Delivery method | Spontaneous vaginal=7 (70%) Cesarean section=3 (30%) |
| | Delivery time | Full term=10 (100%) Preterm=0 (0%) |
| | Complications | Yes=0 (0%) No=10 (100%) |



Giampaolino P et al , JMIG 2018

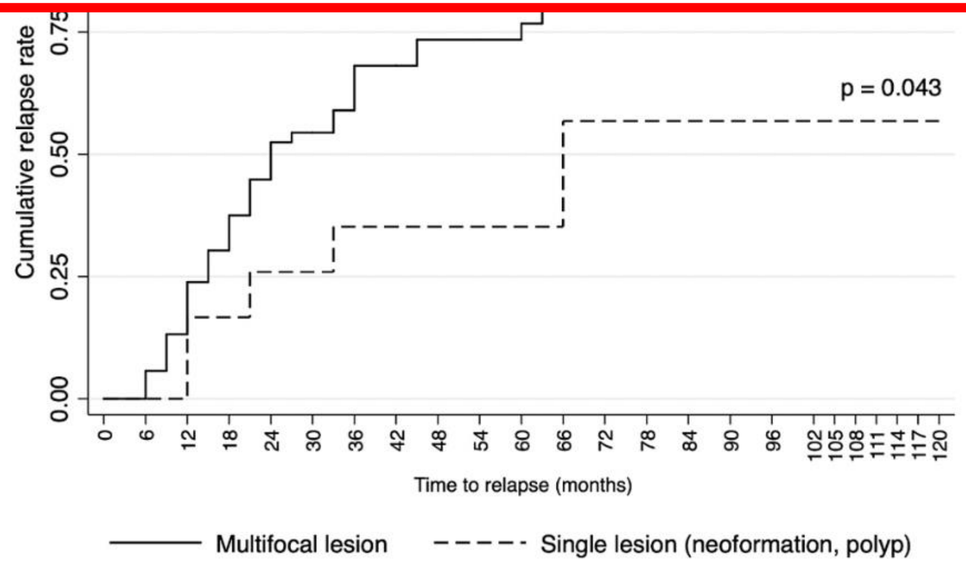
# Prognostic impact of hysteroscopic resection of endometrial atypical hyperplasia-endometrioid intraepithelial neoplasia and early-stage cancer in combination with megestrol acetate

American Journal of Obstetrics & Gynecology

**HSC resection + MA vs. MA alone**

**HSC removal of EAH/EIN or EEC before therapy was the only factor significantly associated with shorter treatment duration to achieve CR**

- **CR= 82 (96.5%)**
- **Mean tx duration for achieving CR**:
  - **HSC resection + MA = 3.4 mo.**
  - MA alone = 4.75 mo.






Masciullo et al, AJOG, 2021

# Fertility-Preserving Treatment in Young Women With Grade 1 Presumed Stage IA Endometrial Adenocarcinoma: A Meta-Analysis

Zunpan Fan, Hui Li, Rui Hu, Yuling Liu, Xinyu Liu, Liping Gu

- **28 Articles**
- **619 patients** with EEC or AEH
  - 456 Oral Progestins
  - 73 HSC resection + Progestins
  - 90 LNG-IUD

| | ORAL PROGESTINS | HSC RESECTION + PROGESTINS | LNG-IUD |
|---|---|---|---|
| COMPLETE RESPONSE RATE | 76.3% | 95.3% | 72.9% |
| RECURRENCE RATE | 30.7% | 14.1% | 11% |



Int J Gynecol Cancer, 2018

# What about G2 Endometrial Cancer?

| Author, year of publication | Country | Study design | Years | FIGO stage/ population | No. of participants | Mean FU (months) |
|---|---|---|---|---|---|---|
| Laurelli et al., 2016 (9) | Italy | Prospective observational monocenter study | 2006–2013 | IA-G1, G2 | 21 | 85.0 |
| Hwang et al., 2017 (10) | Korea | Retrospective observational monocenter study | 2011–2015 | IA-G2 | 5 | 44.4 |
| Chae et al., 2019 (11) | Korea | Retrospective observational monocenter study | 2005–2017 | IA-G1, G2 | 71 | N/A |
| Falcone et al., 2020 (12) | Italy | Prospective observational multicenter study | 2004–2019 | IA-G2 | 23 | 35 |
| He et al., 2020 (13) | China | Retrospective observational monocenter study | 2005–2019 | IA-G2 | 3 | 19.5 |
| Andress et al., 2021 (8) | Germany | Retrospective observational monocentric study | 2006–2018 | IA-G2 | 1 | 16 |

# Combined Oral Medroxyprogesterone/Levonorgestrel-Intrauterine System Treatment for Women With Grade 2 Stage IA Endometrial Cancer

*Ji Young Hwang, MD,* Da Hee Kim, MD,* Hyo Sook Bae, MD, PhD,* Mi-La Kim, MD, PhD,* Yong Wook Jung, MD, PhD,* Bo Seong Yun, MD, PhD,* Seok Ju Seong, MD, PhD,* Eunah Shin, MD,† and Mi Kyoung Kim, MD**

**Combined oral MPA/LNG-IUS is considered a reasonably effective fertility-sparing treatment of G2 stage IA EC.**

**These results are encouraging but preliminary and should be considered with experienced oncologists in well-defined protocol and close FUP**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 25 | 30.5 | 0 | CR | 6 | No | No | No | 19/NED |
| 3 | 29 | 24.2 | 0 | PR | | No | No | No | 10/NED |
| 4 | 31 | 18.5 | 0 | CR | 18 | No | No | No | 55/NED |
| 5 | 39 | 25.7 | 0 | PR | | No | Yes (EA, no myometrial invasion) | No | 69/NED |

BMI, body mass index; NED, no evidence of disease; EA, endometrioid adenocarcinoma.

- PR 2/5
- No cases of SD or PD

**2/3 CR attempted to conceive by IVF.**

# NCCN Guidelines Version 1.2023
# Endometrial Carcinoma

FOLLOW UP

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- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma

→

**PRIMARY TREATMENT**

- Consultation with a fertility expert prior to therapy
- Recommend genetic evaluation of tumor and evaluation for inherited cancer risk (See UN-1)
- Ensure negative pregnancy test

→

- Continuous progestin-based therapy:
  - Megestrol
  - Medroxyprogesterone
  - Progestin IUD
- Weight management/ lifestyle modification counseling[t]

→

**SURVEILLANCE**

Endometrial evaluation every 3–6 mo (either D&C or endometrial biopsy)

→ Complete response by 6 mo → Encourage conception (with continued surveillance/ endometrial sampling every 6 mo and consider maintenance progestin-based therapy if patient is not actively trying to conceive) → TH/BSO with staging[d,e] after childbearing complete or progression of disease on endometrial sampling (See ENDO-1)
- Ovarian preservation may be considered in select premenopausal patients

→ Endometrial cancer present at 6–12 mo[i,u] → TH/BSO with staging[d,e] (See ENDO-1)
- Ovarian preservation may be considered in select patients

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

# Close Surveillance is mandatory

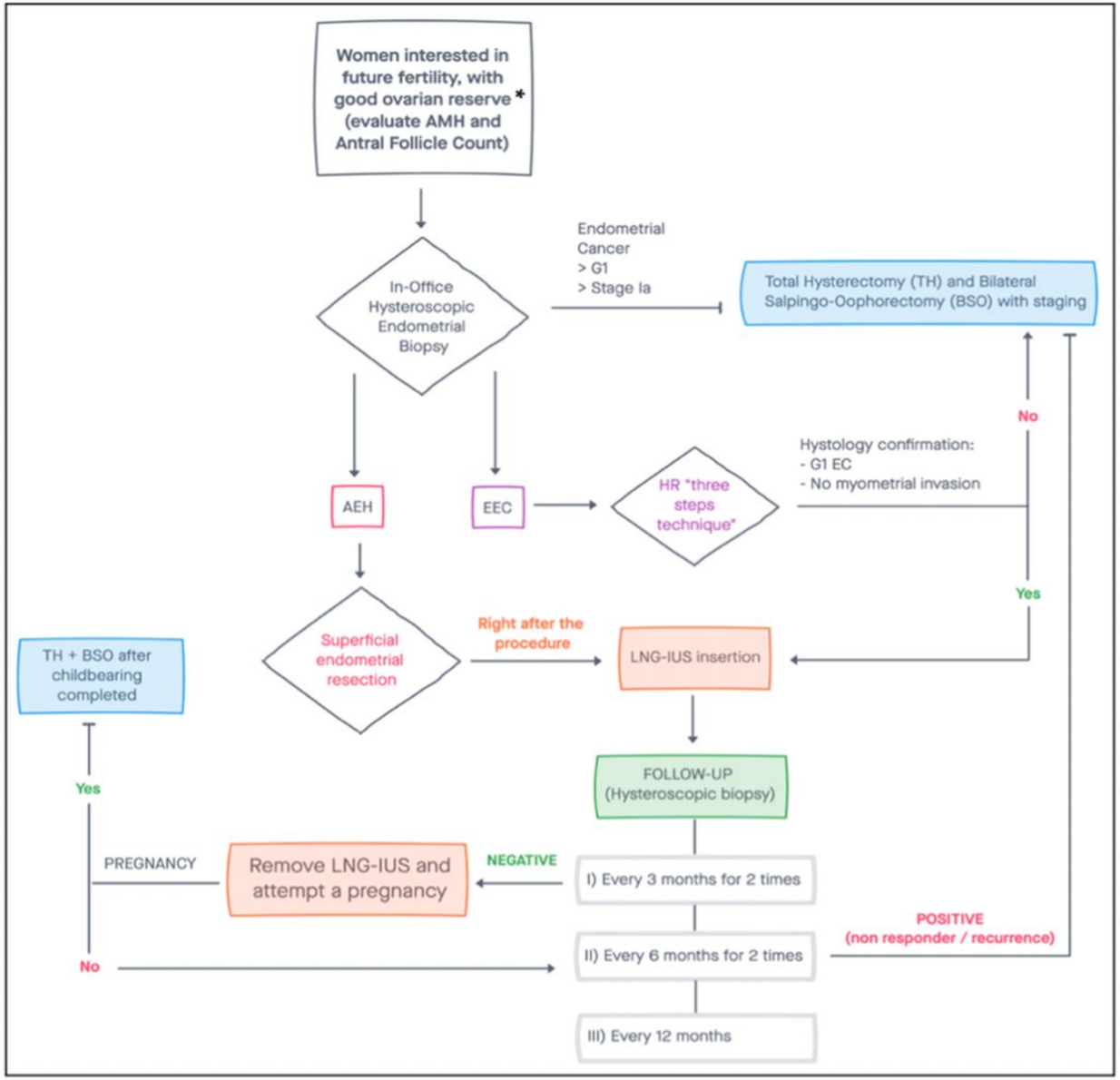
FOLLOW UP

Journal of *Clinical Medicine*

*Review*

## Conservative Surgery in Endometrial Cancer

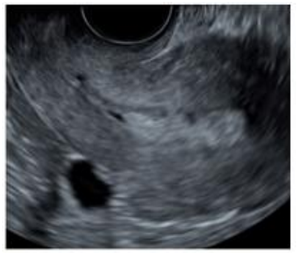
**Alessandra Gallo [1,*], Ursula Catena [2], Gabriele Saccone [3] and Attilio Di Spiezio Sardo**



# Close Surveillance is mandatory

**FOLLOW UP**

- CA 125
- TV-USG or CT-scan or MRI



+

Class
Catholic laparoscopic advanced surgery school

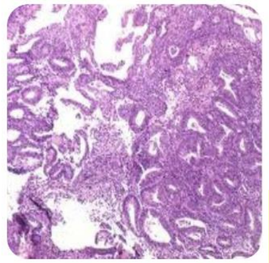
**HYSTEROSCOPY**

Endometrial Biopsy
**every 3 months**

**MULTIDISCIPLINARY TEAM**

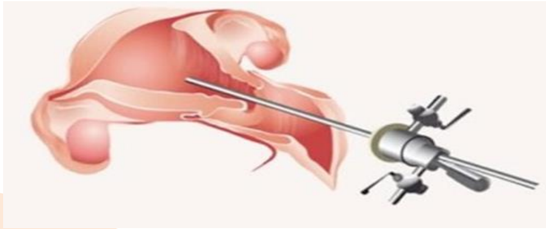
- Gynecologists
- Genetics
- Obesity
- Oncofertility

**And what if we know the molecular profile before surgery?**



**CLINICO/PATHOLOGY:**
- ✓ Histotype

**TGCA:**
- ✓ P53
- ✓ MSI
- ✓ POLE



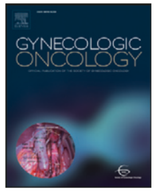
**SURGERY**

# EC Molecular assessment through hysteroscopy

Contents lists available at ScienceDirect

Gynecologic Oncology

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



2016

Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment

Aline Talhouk [a,1], Lien N. Hoang [b,c,1], Melissa K. McConechy [a,d], Quentin Nakonechny [b], Joyce Leo [b], Angela Cheng [e], Samuel Leung [e], Winnie Yang [a], Amy Lum [a], Martin Köbel [f], Cheng-Han Lee [g], Robert A. Soslow [c], David G. Huntsman [a], C. Blake Gilks [b,2], Jessica N. McAlpine [h,*,2]

**57 pts**

- **EXCELLENT AGREEMENT →** sensitivity (0.9), specificity (0.96), PPV (0.9), NPV (0.96) and kappa statistic 0.86 (95%CI, 0.72–0.93)
- ↑ Highest level of concordance for p53 abn.
- **Grade and Histotype → moderate** agreement (kappa = 0.55 and 0.44 respectively)

Comparison of concordance statistics (with 95% confidence intervals) for each ProMisE molecular subgroups.

| | Average | MMR-D | *POLE* EDM | p53 wt | p53 abn |
|---|---|---|---|---|---|
| Sensitivity | 0.9 | 0.94 (0.72–1) | 0.82 (0.52–0.95) | 0.84 (0.62–0.94) | 1 (0.74–1) |
| Specificity | 0.96 | 0.93 (0.81–0.97) | 0.98 (0.89–1) | 0.97 (0.87–1) | 0.98 (0.89–1) |
| Pos Pred value | 0.9 | 0.83 (0.61–0.94) | 0.9 (0.6–0.99) | 0.94 (0.73–1) | 0.92 (0.65–1) |
| Neg Pred value | 0.96 | 0.97 (0.87–1) | 0.96 (0.86–0.99) | 0.92 (0.8–0.97) | 1 (0.92–1) |
| Prevalence | | 0.28 (0.18–0.41) | 0.19 (0.11–0.31) | 0.33 (0.22–0.46) | 0.19 (0.11–0.31) |
| Detection rate | | 0.26 (0.17–0.39) | 0.16 (0.09–0.27) | 0.28 (0.18–0.41) | 0.19 (0.11–0.31) |
| Detection prev | | 0.32 (0.21–0.44) | 0.18 (0.1–0.29) | 0.3 (0.2–0.43) | 0.21 (0.12–0.33) |
| Accuracy | 0.95 | 0.93 (0.83–0.97) | 0.95 (0.86–0.98) | 0.93 (0.83–0.97) | 0.98 (0.91–1) |
| Balanced acc | 0.93 | 0.93 | 0.9 | 0.91 | 0.99 |

SCIENTIFIC SEMINARS
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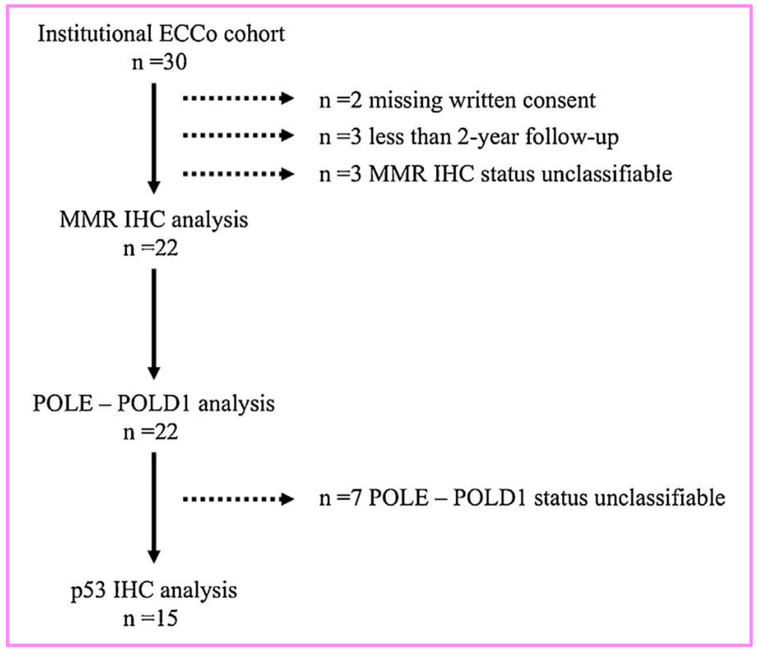
# Application of the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) to patients conservatively treated: Outcomes from an institutional series

Francesca Falcone[a,*], Nicola Normanno[b], Nunzia S. Losito[c], Giosuè Scognamiglio[c], Riziero Esposito Abate[b], Nicoletta Chicchinelli[b], Gennaro Casella[a], Giuseppe Laurelli[a], Cono Scaffa[a], Stefano Greggi[a]




- **15 fully evaluable cases**
- 7/15 (46.7%): abnormal MMR IHC
- 1/15 (6.6%): POLE EDM
- 0/15 (0%): abnormal p53 IHC
- 7/15 (46.7%): p53 IHC wild-type

**In women with EEC, operative HSC could be advantageous to provide samples allowing complete genetic risk assessment**



European Journal of Obstetrics & Gynecology and Reproductive Biology 240 (2019) 220–225

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

# Mismatch repair-deficiency specifically predicts recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment: A multi-center study

Antonio Raffone [a,1], Ursula Catena [b,1], Antonio Travaglino [c,*], Valeria Masciullo [b], Saveria Spadola [d], Luigi Della Corte [a,b], Alessia Piermattei [b], Luigi Insabato [c], Gian Franco Zannoni [d,e], Giovanni Scambia [b], Fulvio Zullo [a], Giuseppe Bifulco [a], Francesco Fanfani [b], Attilio Di Spiezio Sardo [f]

- Multicenter
- Retrospective
- January 2004 - July 2019
- 69 pts (47 AEH, 22 EEC)
- Hysteroscopic resection + progestins

Characteristics of MMR-deficient cases.

| Case no. | AGE, years | BMI, kg/m$^2$ | Familiarity for cancer | Index histological diagnosis | Deficient MMR protein | Progestin administered | Resistance (Diagnosis) | Recurrence (diagnosis) | Time to recurrence, months |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | 19.5 | Yes (colorectal carcinoma) | EEC | MSH6/MSH2 | MA | No | Yes (AEH) | 12 |
| 2 | 43 | 21.4 | No | EEC | MSH6 | LNG-IUD | Yes (EEC) | – | – |
| 3 | 31 | 39.3 | No | EEC | PMS2 | LNG-IUD | Yes (AEH) | – | – |
| 4 | 38 | 22.4 | Yes (endometrial carcinoma) | AEH | MSH6 | LNG-IUD | No | Yes (AEH) | 24 |
| 5 | 37 | 24.6 | No | AEH | MSH6 | LNG-IUD | No | Yes (EEC) | 39 |
| 6 | 34 | 22 | No | AEH | PMS2 | MA | No | Yes (AEH) | 18 |

**Deficient MMR expression in 8.7% of cases**

**Resistance to conservative treatment**

**MMR-deficient** vs MMR-proficient cases (**33.3%** vs 15.9%; RR = 2.1, **p = 0.2508**)

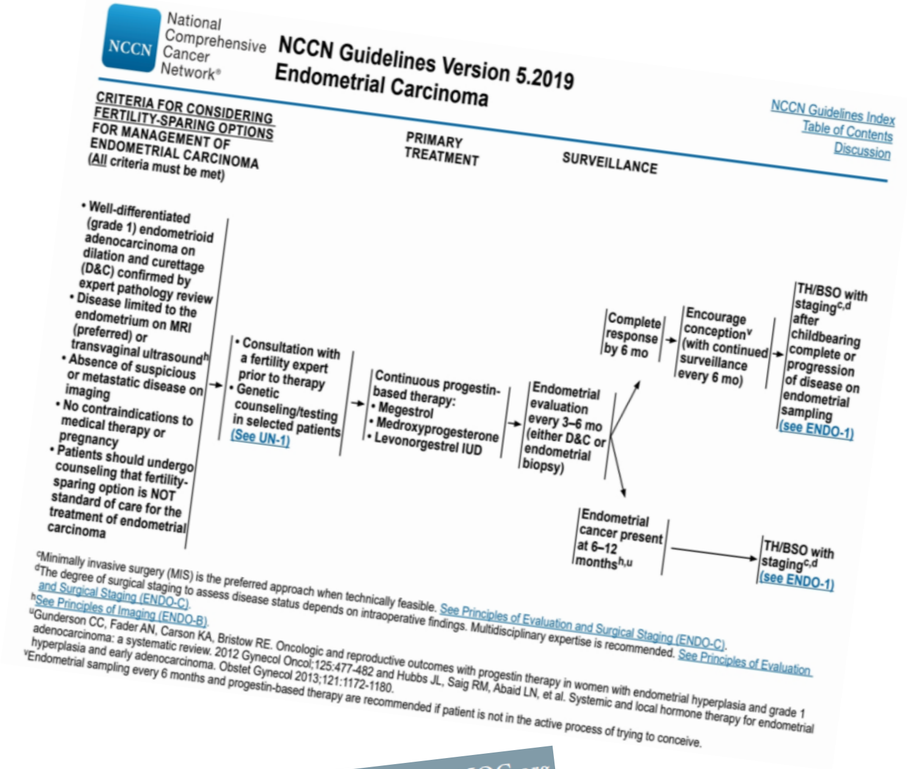
**Recurrence**

**MMR-deficient** vs MMR-proficient cases (**100%** vs 26.4%; RR = 3.8; **p < 0.0001**).

# Lynch syndrome and fertility sparing treatment

- Lynch syndrome accounts for
  - **9% of EC** patients **younger than 50 y**
  - **1.8-2,1%** among **all EC patients**
- Germline mutation in one of the mismatch repair (MMR) genes
  - (**MLH1, PMS2, MSH2, MSH6 and EpCAM**)
- Cumulative life-time risk of EC > 40%, it depends on which gene is mutated:
  - **64% to 71%** for women with **MSH6** mutation
  - **40% to 50%.** for women with **MSH2 or MLH1** mutations *(Corzo et al, 2018)*

# Is Fertility Sparing Treatment In Patients With Ls-related EC An Option?



NCCN Guidelines Version 5.2019
Endometrial Carcinoma

NCCN Guidelines Index | Table of Contents | Discussion

**CRITERIA FOR CONSIDERING FERTILITY-SPARING OPTIONS FOR MANAGEMENT OF ENDOMETRIAL CARCINOMA (All criteria must be met)**

- Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
- Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound[h]
- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma

**PRIMARY TREATMENT**

- Consultation with a fertility expert prior to therapy
- Genetic counseling/testing in selected patients (See UN-1)

Continuous progestin-based therapy:
- Megestrol
- Medroxyprogesterone
- Levonorgestrel IUD

Endometrial evaluation every 3–6 mo (either D&C or endometrial biopsy)

Complete response by 6 mo → Encourage conception[v] (with continued surveillance every 6 mo) → TH/BSO with staging[c,d] after childbearing complete or progression of disease on endometrial sampling (see ENDO-1)

Endometrial cancer present at 6–12 months[h,u] → TH/BSO with staging[c,d] (see ENDO-1)

**SURVEILLANCE**

[c]Minimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[h]See Principles of Imaging (ENDO-B).
[u]Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. 2012 Gynecol Oncol;125:477-482 and Hubbs JL, Saig RM, Abaid LN, et al. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol 2013;121:1172-1180.
[v]Endometrial sampling every 6 months and progestin-based therapy are recommended if patient is not in the active process of trying to conceive.

ESMO-ESGO-ESTRO Consensus guidelines

## ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up ☆

Nicoletta Colombo [a,*], Carien Creutzberg [b], Frederic Amant [c,d], Tjalling Bosse [e], Antonio González-Martín [f,g], Jonathan Ledermann [h], Christian Marth [i], Remi Nout [j], Denis Querleu [k,l], Mansoor Raza Mirza [m], Cristiana Sessa [n], The ESMO–ESGO–ESTRO Endometrial Consensus Conference Working Group [1]

[a] Division of Medical Gynecologic Oncology, European Institute of Oncology and University of Milan-Bicocca, Milan, Italy; [b] Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands; [c] Department of Gynecological Oncology, University Hospital Leuven, Leuven, Belgium; [d] Center for Gynecological Oncology Amsterdam (CGOA), Antoni van Leeuwenhoek, Amsterdam, The Netherlands; [e] Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; [f] Medical Oncology Department, GEICO, Madrid, Spain; [g] MD Anderson Cancer Center, Madrid, Spain; [h] Department of Oncology and Cancer Trials, UCL Cancer Institute, London, United Kingdom; [i] Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria; [j] Department of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands; [k] Department of Surgery, Institut Bergonié, Bordeaux, France; [l] Gynecology and Obstetrics Department, McGill University Health Centre, Montreal, Canada; [m] Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; and [n] Department of Medical Oncology, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland

**Recommendations**

- Patients who are candidates for fertility-preserving treatment must be referred to specialized centers. Fertility-sparing treatment should be considered only in patients with AH/EIN or grade 1 endometrioid endometrial carcinoma without myometrial invasion and without genetic risk factors (V, A).

RESEARCH www.AJOG.org

GENERAL GYNECOLOGY

**Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis**

Ioannis D. Gallos, MD; Jason Yap, MBChB; Madhurima Rajkhowa, MD; David M. Luesley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD

**Does Hormonal Therapy for Fertility Preservation Affect the Survival of Young Women With Early-Stage Endometrial Cancer?**

Zoë R. Greenwald, MSc[1,2]; Lina N. Huang, MD[3]; Michel D. Wissing, MD, PhD[1,2,4]; Eduardo L. Franco, DrPH[1,2]; and Walter H. Gotlieb, MD, PhD[2,5]

**Major articles or guidelines about fertility-sparing treatment in EC do not explore the topic of EC in LS patients**

# ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma

**TO BE PUBLISHED**

- A **combined approach** consisting of **hysteroscopic tumour resection, followed by oral progestins and/or levonorgestrel-intrauterine device (LNG-IUD),** is the **most effective** fertility-sparing treatment both in terms of complete response rate and live birth rate compared to other treatment options [II, B].

- **Weight control** during fertility-sparing treatment is **highly recommended** to increase the chance of response [II, A].

- To date, there are **no randomised controlled trials comparing the different types of medical treatment** in women with AEH or Grade 1 endometrial endometrioid carcinoma.

- If an **early and focal myometrial invasion (1-2 mm) is suspected** from the resection material, a **fertility-sparing approach** may be discussed **on a case-by-case basis**. In this circumstance, complete hysteroscopic lesion resection, followed by oral progestins and/or LNG-IUD, can be proposed as fertility-sparing treatment [IV, C].

- **The maximum time to achieve complete response should not exceed 15 months** [IV, C]. (Shim, *Gynecol Oncol.* 2021)

# ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma

TO BE PUBLISHED

- **Performing the ProMisE molecular classifier in all young patients** with grade 1, low-stage endometrial carcinoma who wish to preserve fertility **is encouraged**, although available data do not allow clinical applicability [IV, B].

- **Immunohistochemistry for the identification of mismatch repair-deficient tumours is mandatory in order to identify patients at high risk for Lynch syndrome** [III, A].

- If a **Lynch syndrome** is identified, patients should have an **appropriate counselling** on the risk of developing additional cancers [III, A].

- In women harbouring **copy number high (p53abn) tumours**, conservative therapy would be **inappropriate** [IV, D].

# Preservation of fertility in uterine carcinoma

## Take-home messages

- ✓ 4% EC < 40yrs
- ✓ Current mean age of first pregnancy is > 30 yrs
- ✓ Fertility-Sparing approach is a non-standard care treatment
- ✓ Hysteroscopic resection + Progestin > 90% CR
- ✓ Issue: heterogeneity of the studies
- ✓ Need for multicenter prospective studies for definition of the proper conservative treatment strategy (for LS and non-LS patients)

# THANK YOU

Questions?

*giorgia.dinoi@guest.policlinicogemelli.it*

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