the 1st EAGOT annual meeting in Niigata
2023.5.26
Trial in Progress Development Session: JGOG 2051/KGOG 2031

JGOG2051/KGOG2031：
Phase II trial of repeated high dose luteal hormone therapy for intrauterine recurrence following fertility preserving therapy for atypical endometrial hyperplasia or endometrial cancer

Kensuke Sakai / Wataru Yamagami

Department of Obstetrics and Gynecology,

Keio University School of Medicine, JAPAN

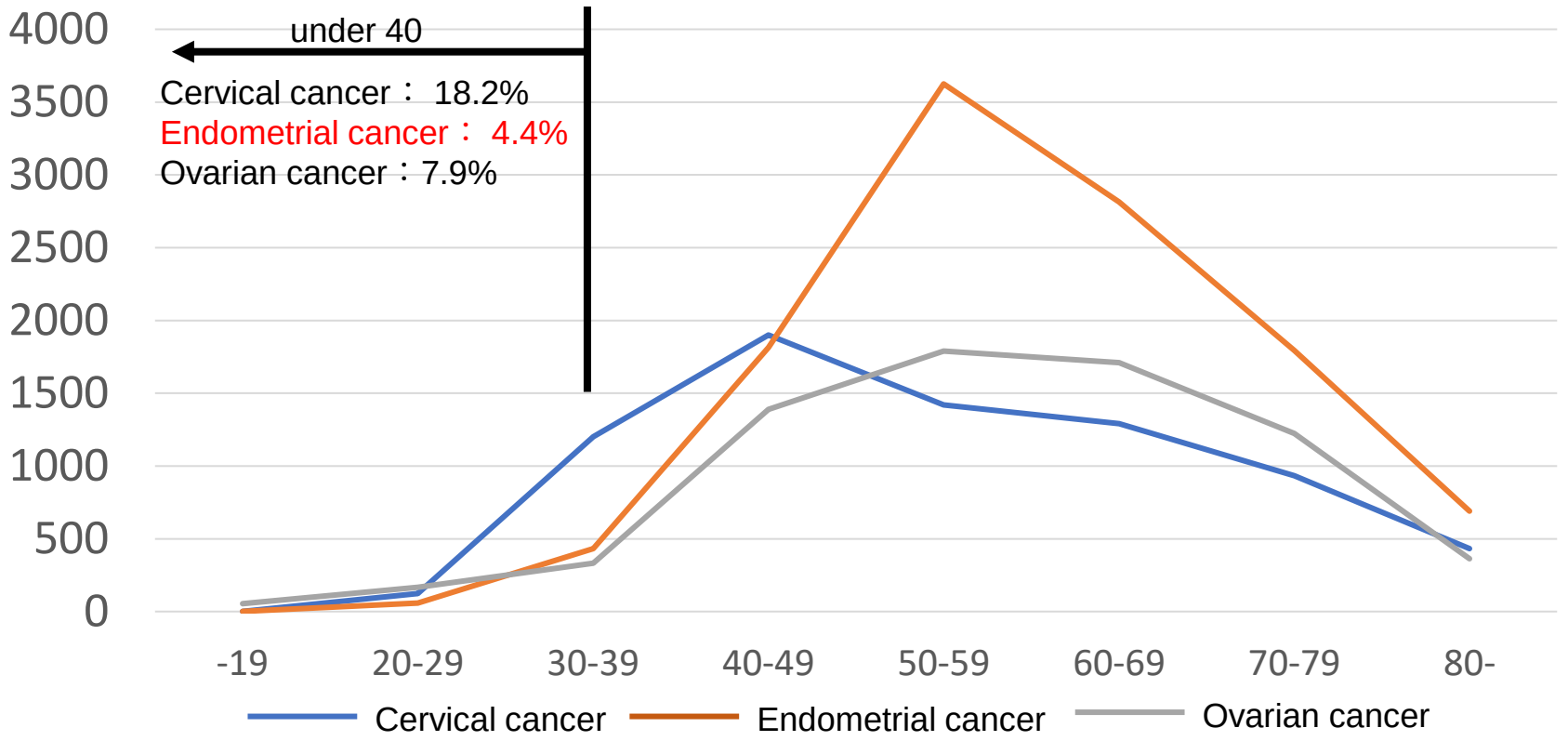
Disclosure of COI

Presenter: Wataru Yamagami
Keio University School of Medicine

I have no COI with this presentation.

Backgrounds

The number of patients with endometrial cancer has been increasing throughout Japan. Additionally, the number of young endometrial cancer patients who desire fertility-sparing treatment has also increased.



Annual report of gynecologic cancer from JSOG 2018

Standard treatment for endometrial cancer

- **Stage I～III (some of stage IV)** → Loss of fertility
  - **hysterectomy + bil. salpingo-oophorectomy ± pelvic lymphadenectomy ± para-aortic lymphadenectomy ± omentectomy**
  - **adjuvant radiotherapy or chemotherapy for patients with high recurrence risk**

- **Stage IV (unable to surgical resection)**
  - **chemotherapy ± radiotherapy**
  - **immune check point inhibitor (dMMR or MSI-high)**

- **Low grade endometrioid carcinoma, stage IA without myometrial invasion / atypical endometrial hyperplasia**
  - **fertility preserving luteal hormone therapy**

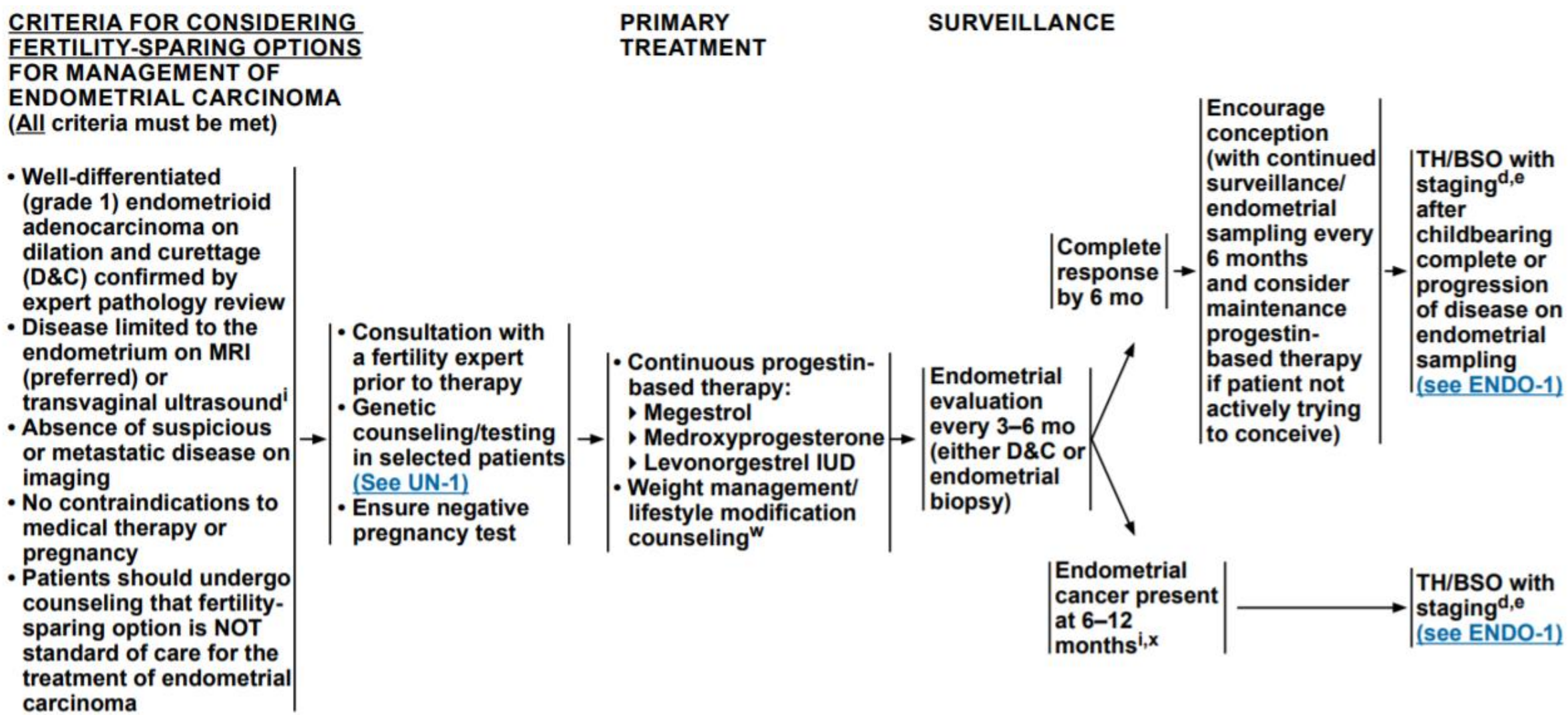
The characteristics of Fertility-Preserving therapy

- The hormonal therapy using progesterone has been considered effective for patients with stage IA non-myoinvasive endometrioid carcinoma Grade 1 or AEH who desire fertility preservation.

- Although the CR rate is high, recurrence rate is also high.

AEH; atypical endometrial hyperplasia
CR; complete response
MPA; medroxyprogesterone acetate

NCCN guideline



NCCN guideline Uterine neoplasms ver 3.2021

ESGO/ESTRO/ESP guideline

Recommendation

- Patients who are candidates for fertility-preserving treatment must be referred to specialised centres. 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].
- Radiologic imaging to assess the extension of the disease must be performed. [III, B].
- Patients must be informed that fertility-sparing treatment is not a standard treatment. Only patients who strongly desire to preserve fertility should be treated conservatively. Patients must be willing to accept close follow-up and be informed of the need for future hysterectomy in case of failure of treatment and/or after pregnancies [V, A].

Concin N, et al. Radiother Oncol 2021

ESGO/ESTRO/ESP guideline

Recommendation

- Medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) is the recommended treatment. Treatment with levonorgestrel intrauterine device in combination with oral progestins with or without GnRH analogues can also be considered [IV, B].
- In order to assess response hysteroscopic guided biopsy and imaging at 3–4 and 6 months must be performed. If no response is achieved after 6 months, standard surgical treatment is recommended [IV, B].
- Continuous hormonal treatment should be considered in responders who wish to delay pregnancy [IV, B].
- Strict surveillance is recommended every 6 months with TVUS and physical examination. [IV, B].
- Fertility-sparing treatment can be considered for intrauterine recurrences only in highly selected cases under strict surveillance [IV, C].
- Hysterectomy and bilateral salpingo-oophorectomy is recommended after childbearing due to a high recurrence rate. Preservation of the ovaries can be considered depending on age and genetic risk factors [IV, B].

Concin N, et al. Radiother Oncol 2021

Japanese guideline

CQ33. What treatments are recommended for patients with a residual tumor or a recurrent lesion after fertility preservation therapy?

Recommendation:

1. Total hysterectomy is recommended (Grade B).
2. If a patient strongly desires preservation of fertility, retreatment with progesterone can be considered for a recurrent lesion, but only under strict control (Grade C1).

[See **Fig. 6**]

Yamagami et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J gynecol Oncol 2020

Repeated fertility-preserving hormonal therapy for endometrial cancer and AEH could be considered as **grade C1**, **but only under strict control.**
Multicenter prospective study of MPA therapy for recurrent disease has not been performed.

JGOG2051：
Phase II trial of repeated high dose luteal hormone therapy for intrauterine recurrence following fertility preserving therapy for atypical endometrial hyperplasia or endometrial cancer

Principal Investigator; Wataru Yamagami

Study Secretariat; Kensuke Sakai

Department of Obstetrics and Gynecology,

Keio University School of Medicine, JAPAN

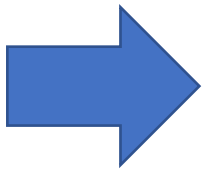
Scheme

115 cases

- registration period：3 years
- follow-up period：2 years

Single arm phase II trial

The patients with intrauterine recurrence following Initial treatment for
Atypical endometrial hyperplasia
or
Endometrial ca IAG1
（without myometrial invasion）



High dose MPA therapy
600mg/day

- No more than twice of recurrences
- Confirmation of histological type by total curettage
- No myometrial invasion
- No extrauterine lesion

Primary endpoint：2y RFS rate
Secondary endpoints:
RFS, OS, AE, CR rate, pregnancy rate, number of D&C, rate of hysterectomy, pregnancy and perinatal outcome, rate and contents of fertility treatment etc.

Major Eligibility criteria

1. Intrauterine recurrence after high-dose luteal hormone therapy for atypical endometrial hyperplasia (AEH) or endometrioid carcinoma G1 without myometrial invasion nor extrauterine lesions（≦2 times recurrence）
2. Histologically confirmed Endometrioid carcinoma G1 or AEH by total endometrial curettage
3. No myometrial invasion, cervical stromal invasion, extrauterine lesion by pelvic MRI
4. No lymph node metastasis, distant metastasis by chest-pelvic CT
5. 20-42 years old
6. Strongly desire of fertility-preserving
7. ECOG performance status 0-1
8. Normal hematological findings, liver function, renal function

Major Exclusion criteria

1. Endometrioid carcinoma G2, G3, non-endometrioid or endometrial hyperplasia without atypia
2. More than 3 times of recurrence
3. Patients previously enrolled in this study
4. Patients who have not been pathologically confirmed to have disappeared endometrial hyperplasia by total endometrial curettage after previous treatment
5. Patients with uterine lesions (such as uterine adenomyosis or leiomyoma) who cannot perform accurate uterine myometrial assessment on pelvic MRI
6. Patients with thromboembolism or with a history of thromboembolism
7. BMI>45kg/m^2 (changed by latest revision)
8. Patients with allergy of luteal hormone agents

Protocol treatment

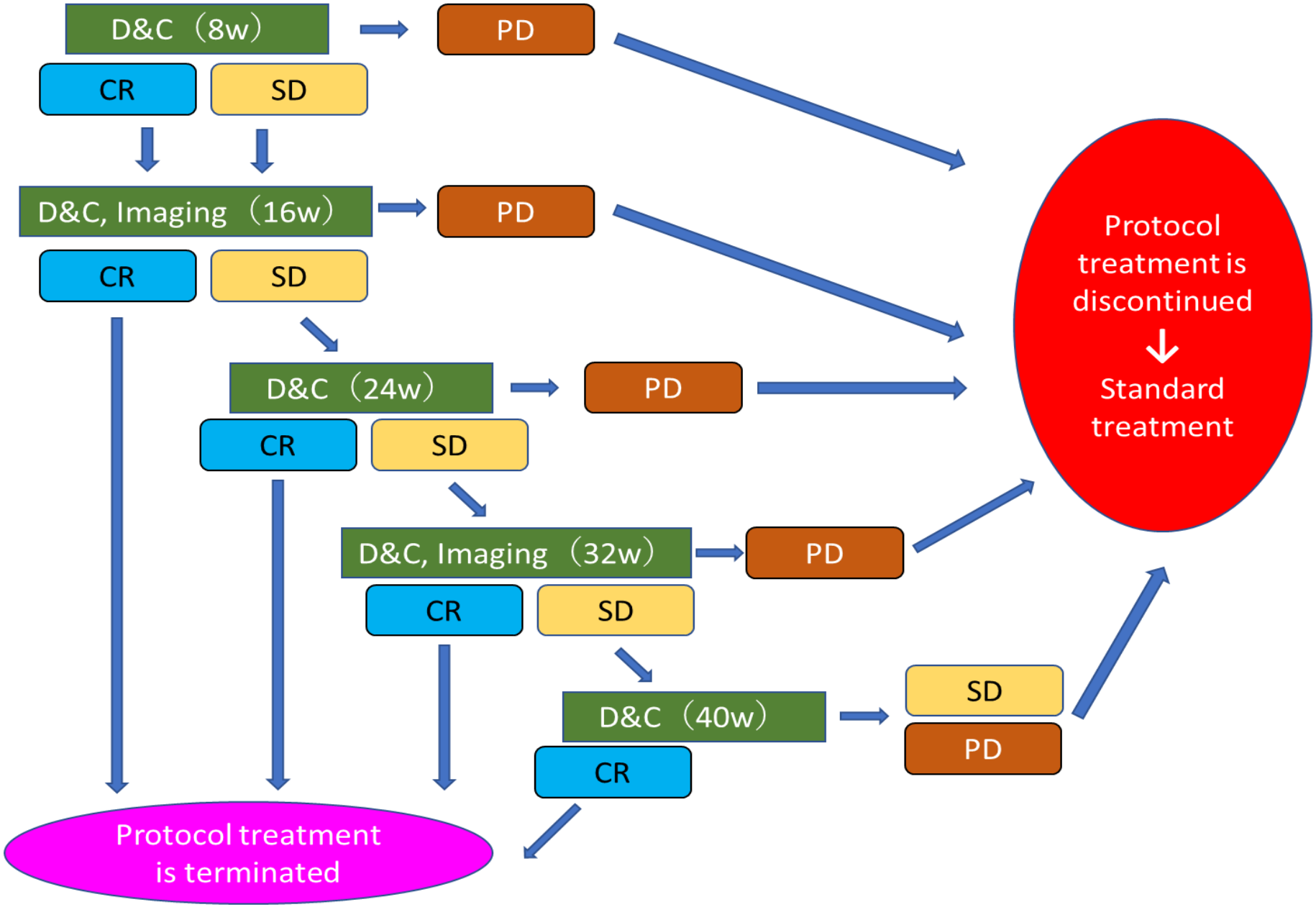
- Oral administration of MPA 600 mg/day in Japan
  - It is possible to reduce the dose to 400 mg/day because of adverse events
  - Oral administration of aspirin 100mg/day for anticoagulation is acceptable
- Interviews, pelvic examinations, blood tests, and vaginal ultrasonography are performed every 4 weeks (±1 week).

- D&C under anesthesia is performed every 8 weeks (± 2 weeks).
  If no lesions of endometrial hyperplasia or worse are found by D&C, it is judged that the lesions disappeared, and the protocol treatment is terminated.

- Pelvic MRI and chest to pelvic CT are performed after 16 and 32 weeks to confirm no progression.
- Patients with residual lesions diagnosed with D&C after 40 weeks are transferred to standard treatment.

D&C; dilatation and curretage

Scheme of Protocol treatment



Current status of JGOG2051

- The JGOG2051 trial
  accepted approval in December 2020.
  started from December 2020.
- As of May 2023, 80 institutions are participating in this study.

However, only 56 patients were enrolled 29 months after the initiation.

Only 56/115 cases (48.7%)

Collaboration between KGOG and JGOG

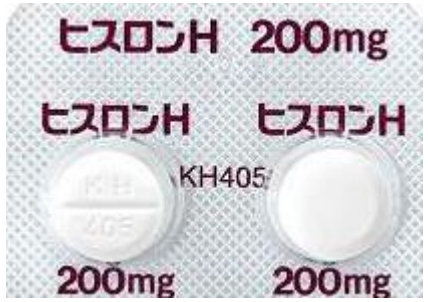
Problems to collaborate with KGOG

1) Difference in MPA dose between Korea and Japan
2) Criteria of Dose Reduction

On November 30th, these revision was permitted in IRB in Keio University in Japan.

1) Difference in MPA dose between Korea and Japan

In Japan



MPA　200mg/T
→ 2T～3T / day

In Korea

MPA　500mg/T
→ 1T / day

In revised and approved protocol,
“the administration dose of MPA is 400-600mg/day”.

2) Criteria of dose reduction

In previous protocol,

If the adverse effects (Non-hematological toxicity ≧ G3) are occurred,

However, few cases need reduction of MPA dose.

In revised protocol,

“The recommended initial dose of oral high-dose medroxyprogesterone acetate is 200mg administered 3 times daily (Japan)/ 500m administered once daily (Korea) ”

Level	Initial dose (Japan)	Initial dose (Korea)
Level 0	600mg/day	500mg/day
Level -1	400mg/day	discontinue
Level -2	discontinue	

Organization Structure in Korea (Permitted in IRB on Nov 30, 2022)

【Principal investigator】

- Dr Yung-Taek Ouh
- Affiliations：Kangwon National University Hospital
  Assistant Professor、Department of Obstetrics & Gynecology

【Monitoring and Study Office】

KGOG：Korean Gynecologic Oncology Group

【Data Center】

Common with Data Center in Japan : Medical Edge Inc

【Audit】

- Audits in Korea will be subject to KGOG regulations.
- Visiting audits from Japan will not be enforced in principle.

【Pathological Central Review】

The virtual slide of the specimen before and after treatment will be used.

Laws and regulations in Korea (Permitted in IRB on Nov 30, 2022)

【Laws and regulations】

- In accordance with ICH-GCP.
- Safety report information required by the “Clinical Research Act” in Japan.

【Adverse effect】

Evaluated using NCI-CTCAE v5.0.

【Reporting of serious Adverse effects or diseases】

When a serious adverse event occurs, the doctors at each facilities must promptly report to principal investigator in Korea/KGOG.

The principal investigator in Korea/KGOG will report to the JGOG/Study Office without delay.

Current Status of collaboration

- On November 30th, the strategy and these revision of international collaboration between JGOG and KGOG was permitted in IRB in Keio University in Japan.

- We sent KGOG the final English protocol by January 2023.

- EAGOT uterine cancer committee meeting was held in Feb 2023.
- JGOG-KGOG web meeting was held on 26th April 2023.

Monitoring Procedure Manual

Main Table of Contents

We only had Japanese version of manual which consists of 8 pages.

→ We made English version and send to KGOG.

Excerpts from Monitoring Procedure Manual

■Before the start of the study

Necessary procedures and documents must be prepared and properly kept

■During Research

1) Informed Consent is obtained appropriately.
2) All selection criteria are met, and research subjects who do not conflict with the exclusion criteria are enrolled.
3) The study treatment, examination, and observation are being conducted appropriately.(drugs to be used, examination/observation items, and reasons for discontinuation and termination, etc)
4) Adverse events are properly recorded and reported appropriately.

etc

Central, off-site, or on-site monitoring is acceptable.
In JGOG, central monitoring is conducted by data center.

Excerpts from Audit Procedure Manual

Selection of the facility to be audited

(1) with many serious adverse events (SAEs), protocol deviations, etc.
(2) with investigators with limited experience in clinical research
(3) with a large number of cases

- We only have Japanese version of manual which consists of 14 pages.
- The audit was conducted by document review, source date access, interview, or tours

→ We made English version and send to KGOG.

EDC system for JGOG 2051/KGOG2031

- We are now preparing EDC system in English version.
- Registration is available 24 hours a day.
- Inquiries to data center will be supported by email.

Points of problems for JGOG2051/KGOG2031 trial

1. Current status: finding hurdle, difficulty, opportunity and chance.

2. Legal issue comparison between Two countries: IRB, Approval process & Monitoring, and Auditing.

3. Do you have “Difficulty” in hormone treatment enrollment: Are we competing with “Easy” surgery? -evidence review.

4. Lesson from shared Case presentation; My difficult case

Points of problems for JGOG2051/KGOG2031 trial

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Intrauterine recurrence following MPA therapy

1st line

AEH or G1

Without MI

Without extrauterine lesion

2nd line

AEH or G1

Without MI

Without extrauterine lesion

JGOG2051

3rd line

AEH or G1

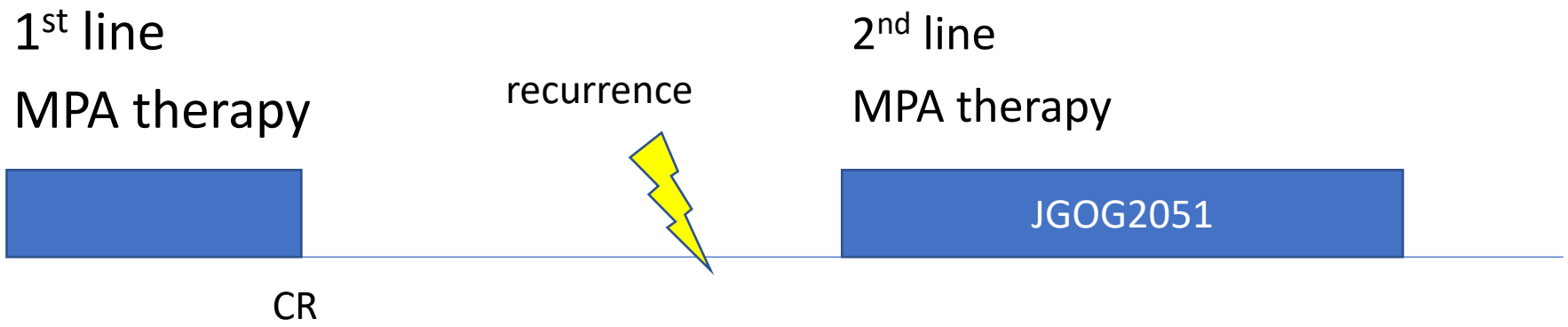
Without MI

Without extrauterine lesion

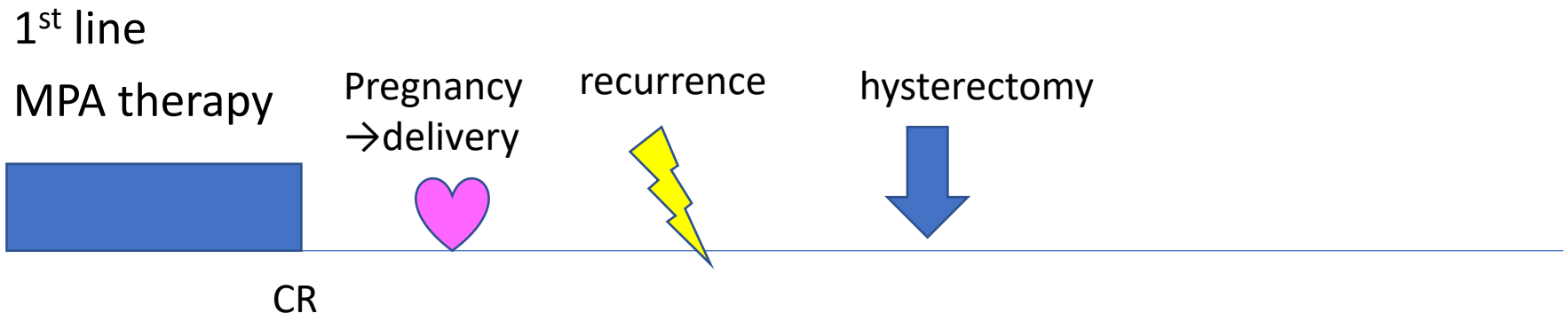
JGOG2051

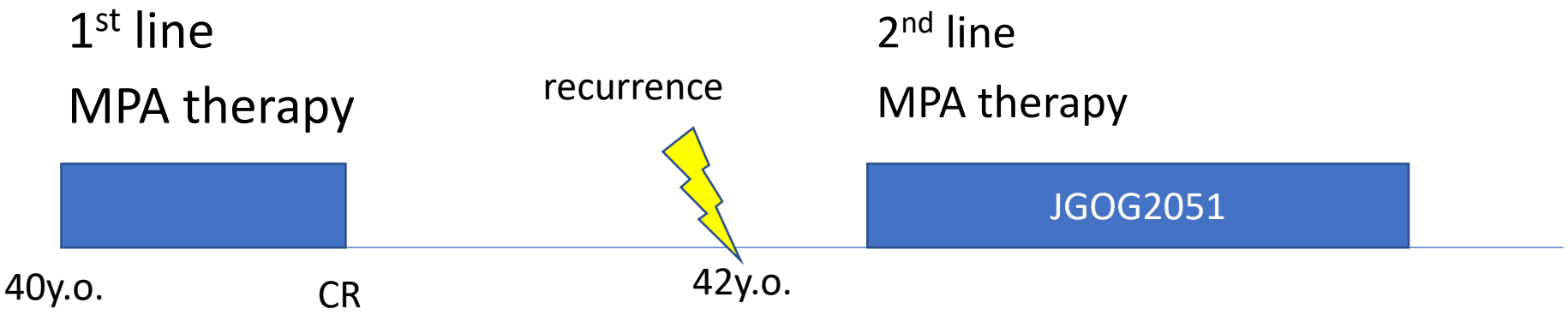
One patient = twice chance

One patient ≠ twice enroll

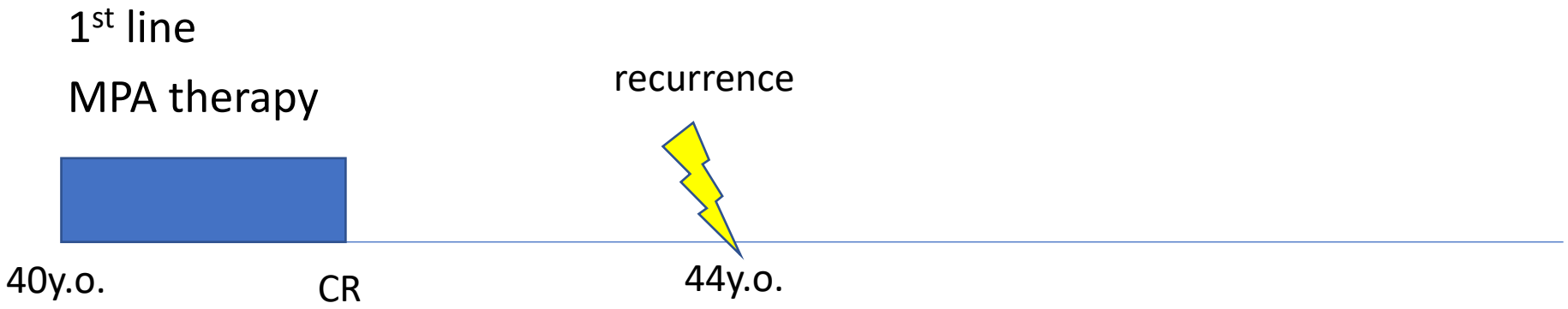


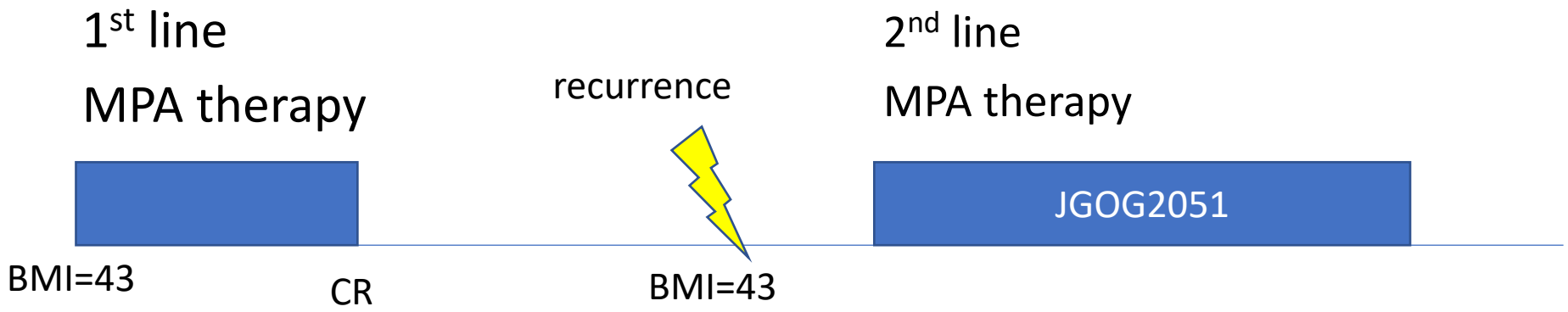
Loss of hope to preserve fertility



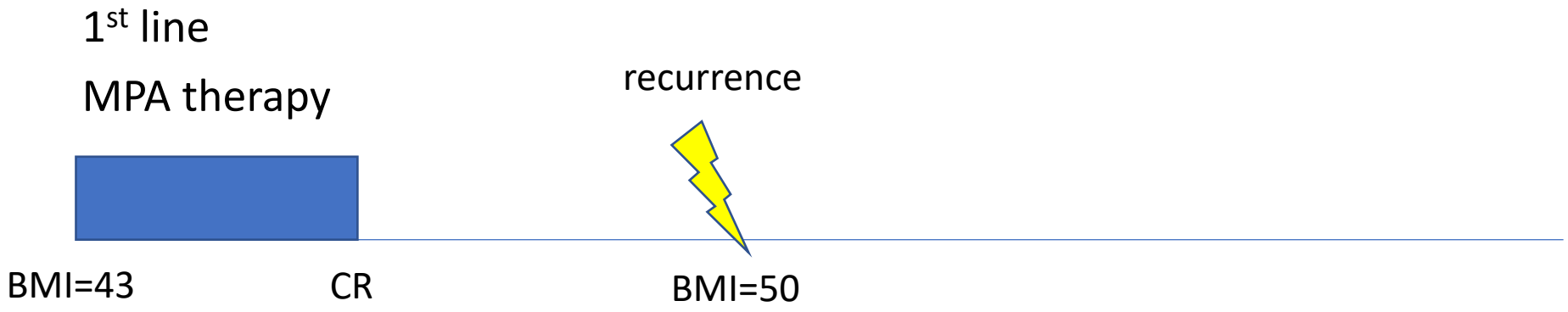

1st line
MPA therapy
recurrence
2nd line
MPA therapy
JGOG2051
40y.o.
CR
42y.o.

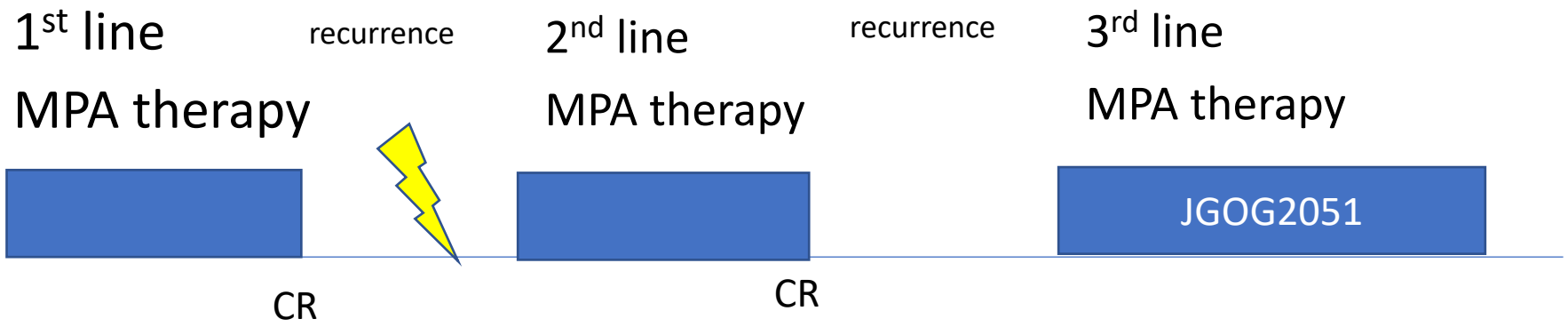
Elder case


1st line
MPA therapy
recurrence
40y.o.
CR
44y.o.

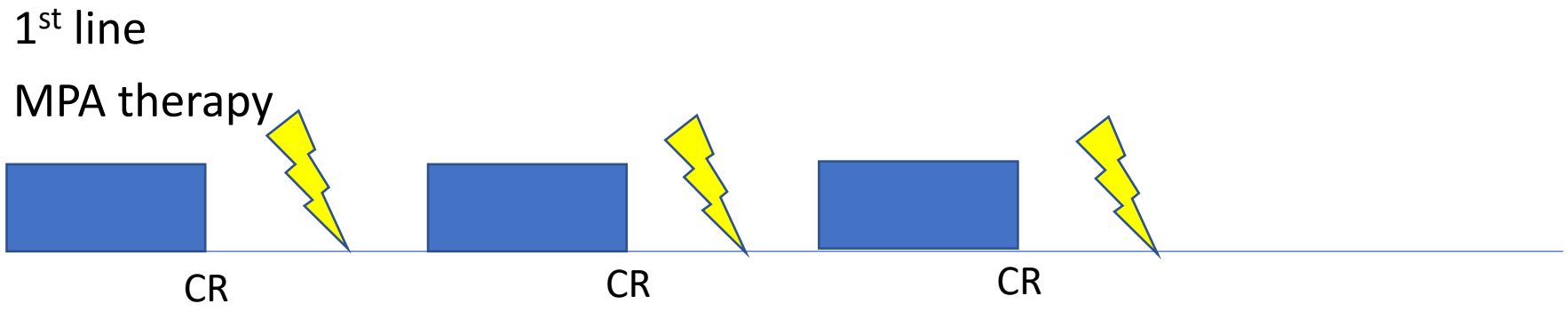

1st line
MPA therapy
recurrence
2nd line
MPA therapy
JGOG2051
BMI=43
CR
BMI=43

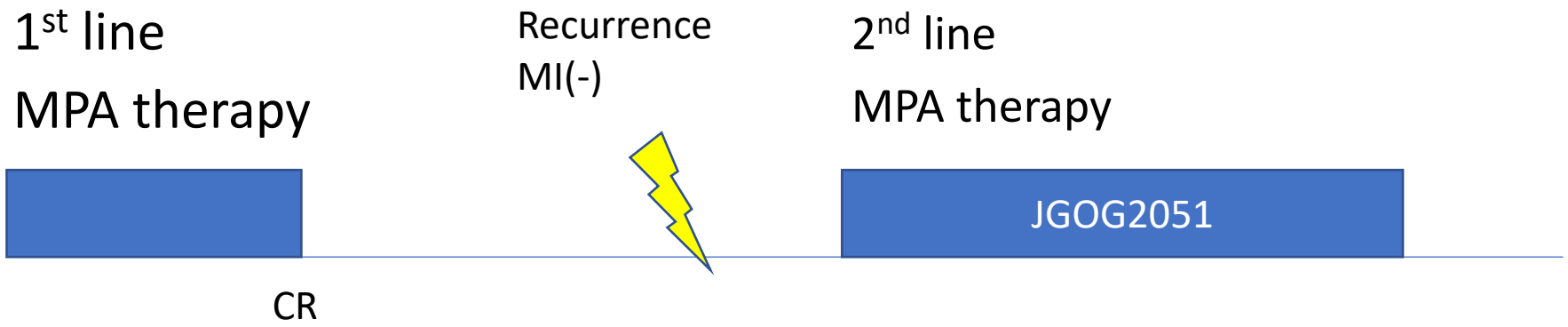
Higher BMI


1st line
MPA therapy
recurrence
BMI=43
CR
BMI=50

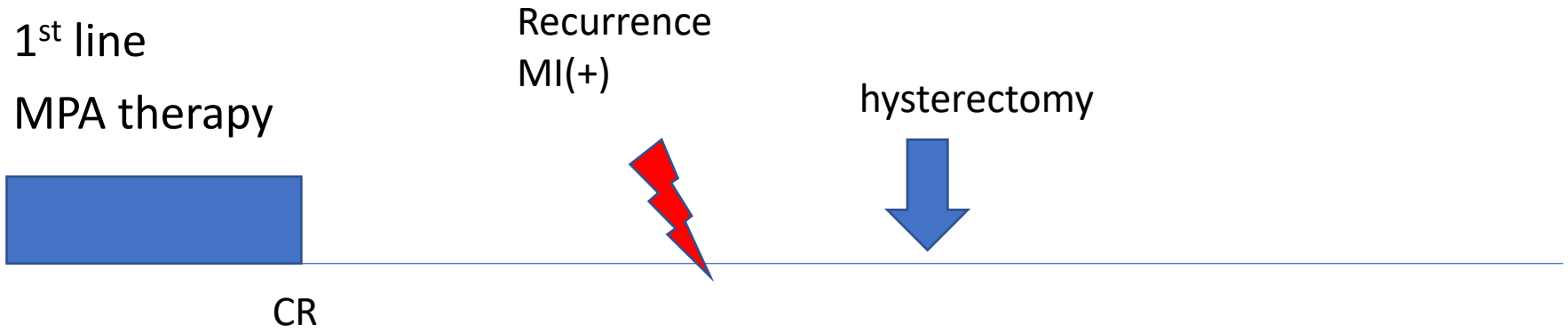

1st line
MPA therapy
recurrence
2nd line
MPA therapy
recurrence
3rd line
MPA therapy
JGOG2051
CR
CR

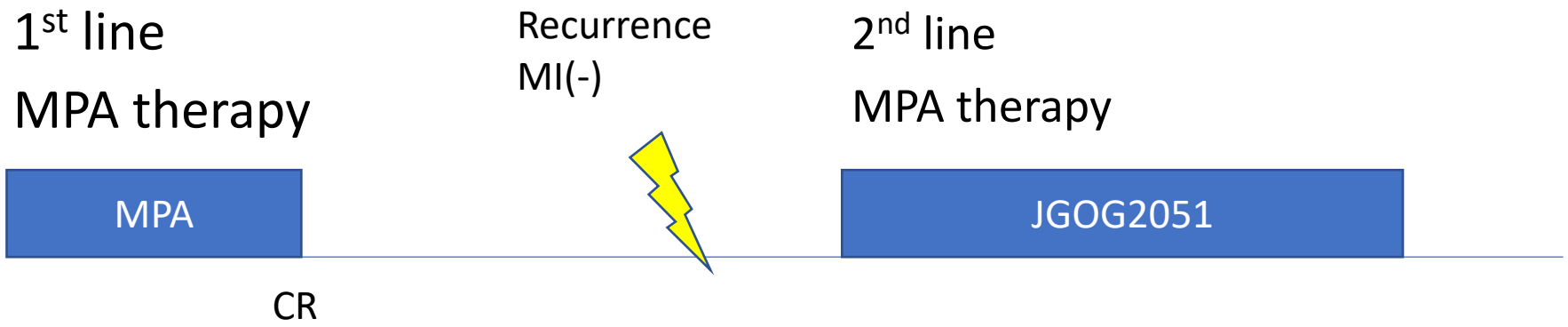
>3rd line


1st line
MPA therapy
CR
CR
CR

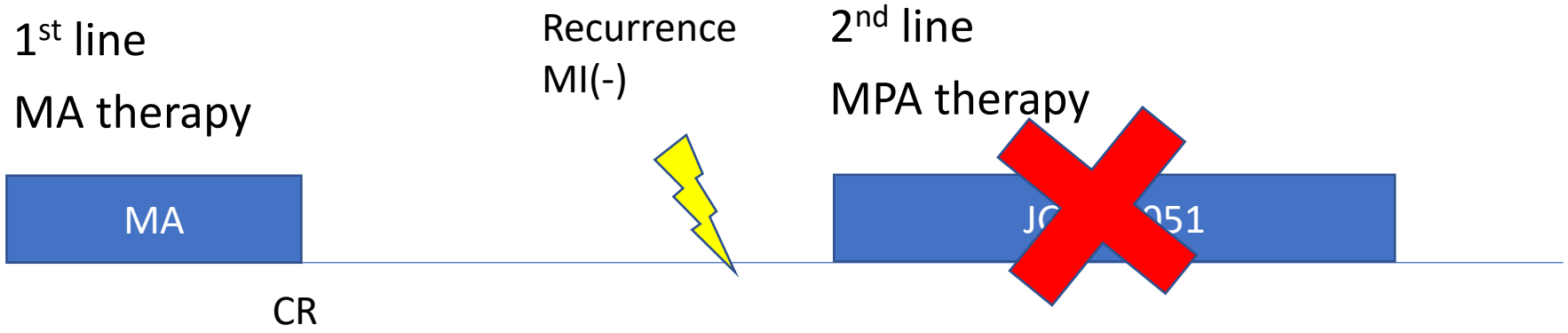


Local advanced case





MPA only at first line therapy



Points of problems

1. Current status: finding hurdle, difficulty, opportunity and chance.

2. Legal issue comparison between Two countries: IRB, Approval process & Audit.

3. Do you have “Difficulty” in hormone treatment enrollment: Are we competing with “Easy” surgery? -evidence review.

4. Lesson from shared Case presentation; My difficult case

Central IRB request us whether “Same Protocol, same quality” between Korea and Japan

- Same treatment protocol
- Same examination (Image, Pathology, Blood test…)
- Same analysis and evaluation (Central Pathological Review)

- Similar level of monitoring and auditing

Points of problems

1. Current status: finding hurdle, difficulty, opportunity and chance.

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IRB ,Approval process & Audit.

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Retrospective analysis of Hysterectomy after MPA therapy

Of 56 patients who underwent hysterectomy in 2019-2022 after high-dose progestin therapy for fertility preservation for EC or AEH at our hospital

Clinicopathological factors and prognosis were extracted from the medical records with the approval of the Ethics Committee.

IRB approval no.：20120243

Our indication of hysterectomy after MPA therapy

Total hysterectomy is recommended in the following cases

- Loss of hope to preserve fertility due to age or delivery
- Recurrence
- Progress disease (worse histological type or upstage)
- Others (if the patient wishes)

In principle, preoperative EMB is performed to check for recurrence. In cases of recurrence, imaging diagnosis is performed to assess the lesion.

If stage IA, minimally invasive surgery is performed.
If stage IB or above, laparotomy is performed.

Indication of hysterectomy

	Open Laparotomy	Laparoscopic	Robot assisted	Total
Patient wishes	–	12	4	16(29%)
Recurrence No desire to preserve fertility	–	13	10	23(41%)
No effect of MPA	–	1	–	1(2%)
Progress disease	5	7	–	12(21%)
With other disease	3	1	–	4(7%)

The most common indication (41%) for total hysterectomy is the absence of hope to preserve fertility at the time of recurrence.

Indication of surgical procedure

[Preoperative Diagnosis]	[Surgical procedure]
No recurrence Hyperplasia without atypia Atypical hyperplasia	Hysterectomy+Bil. salpingectomy
Endometrial carcinoma G1 without myometrial invasion	Hysterectomy+BSO <42y.o. ovarian preservation (under informed consent)
G1 with myometrial invasion (<1/2)	Hysterectomy+BSO+PLN

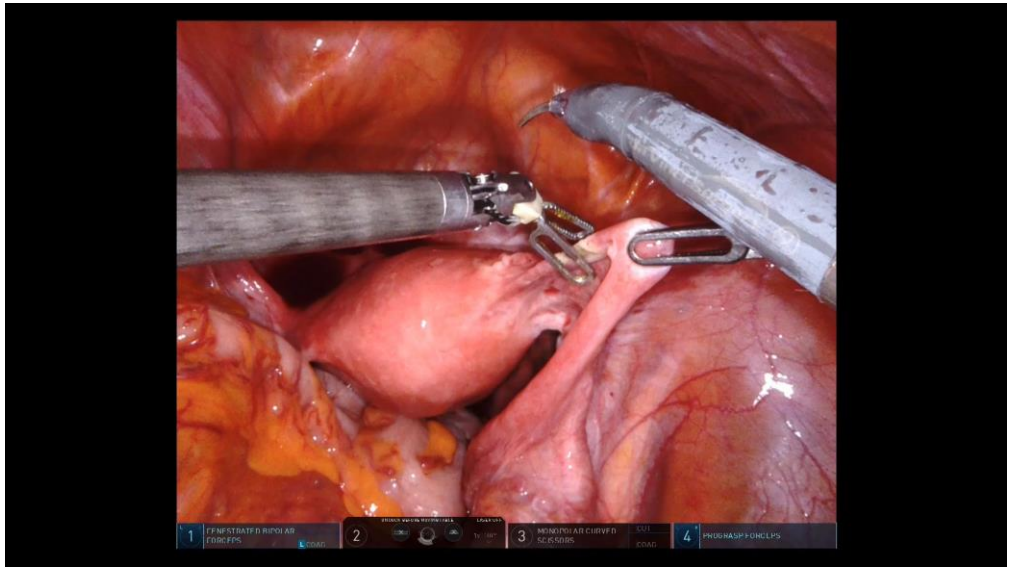
BSO:bilateral salpingo-oophorectomy, PLN: Pelvic lymadenectomy

Detail of surgical procedure of minimal invasive surgery

In the cases with recurrence following MPA therapy

- Sealing or clipping to the fallopian tube
- No Uterine manipulator
- Washing peritoneal cytology specimen is collected
- Removed in a bag
- Do not crush

No recurrence cases are the same as above in principle.



Surgical procedure of cases with minimal invasive surgery

	Laparoscopic	Robot assisted	Total
Ovary preservation	25	11	36 (75%)*
Bilateral salpingo-oophorectomy	9	3	12 (25%)

No case with ovarian metastases or recurrence

	Laparoscopic	Robot assisted	Total
Lymphadenectomy(-)	33	13	46 (96%)
PLN	1	1	2 (4%)
PLN+PAN	0	0	0 (0%)

No case with lymph node metastasis

PLN: Pelvic lymphadenectomy
PAN: Para-aortic lympadenectomy

Pre and post operative pathological diagnosis

		Post		
		No tumor Without atypia	Hyperplasia with atypia	G1 or more
Pre	No tumor Without atypia	13	3	1
	Hyperplasia with atypia	–	11	10 (2 cases with myometrial invasion less than half)
	G1 or more	–	–	9 (1 case with stage II)

About half of cases with AEH preoperatively → G1 or more postoperatively

Postoperative diagnosis of uterine specimen

Hysterectomy before the recurrence

- Benign (without atypia): 69.2%
- Atypical hyperplasia: 23.1%
- Endometrioid carcinoma: 7.7%

} 31.8% of patients had recurrence

Hysterectomy after the recurrence with atypical hyperplasia

- Atypical hyperplasia: 52.4%
- Endometrioid carcinoma: 47.6%

→ 47.6% of patients had recurrence with adenocarcinoma

Even though the recurrence lesion is not detected, the patient should be performed hysterectomy when she lost the hope to preserve fertility.

Points of problems

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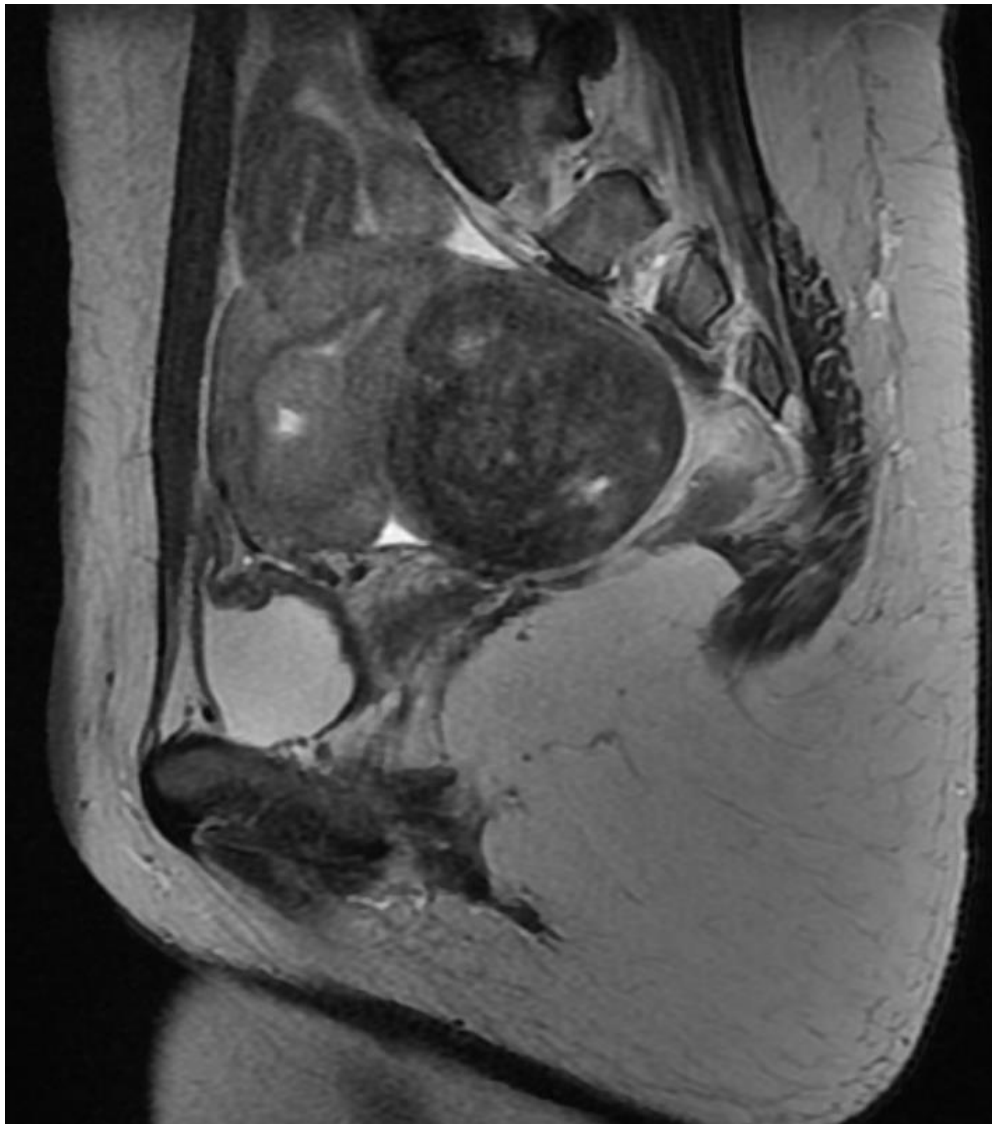
Case report

Case 1: 36 years female

Chief complaint: uterine cancer, fertility preservation treatment
Past history: Ovarian cyst (at age 28)
Pregnancy history: G0P0, never married
Current history: Previous physician said she had atypical polypoid adenomyoma combined with uterine cancer or atypical endometrial hyperplasia;
MRI showed less than 1/2 myometrial invasion and recommended a total hysterectomy;
The patient was referred for a second opinion to be explained whether fertility preservation treatment was possible.

Pelvic MRI



Suspected findings of less than 1/2 myometrial invasion in part of the posterior endometrial wall.
Complicated by myoma
No apparent abnormalities in bilateral ovaries

What is atypical polypoid adenomyoma（APAM）

Atypical polypoid adenomyoma (APAM) is itself a benign tumor, but it is prone to complications such as uterine cancer and atypical hyperplasia, which may look like myometrial invasion on MRI. It is sometimes difficult to differentiate it from uterine cancer or AEH.

Risk of lymph node metastasis with superficial myometrial invasion

	Histological type			
	EMG1	EMG2	EMG3	Not EM
pT1a (no MI)	**0/81**	0/14	0/2	0/6
pT1a (MI<1/2)	**3/102**	3/53	1/8	1/17
pT1b	2/25	6/31	7/18	1/10
pT2	3/14	3/7	3/6	1/9
pT3a	0/3	1/3	0/5	1/6
pT3b	0/2	0/0	1/1	3/3

pT1a(no MI) with endometrioid G1: 0%

pT1a(MI<1/2) with endometrioid G1: 2.9% (3/102)

Risk of PLN metastasis with superficial myometrial invasion

	Histological type			
	EMG1	EMG2	EMG3	Not EM
pT1a (no MI)	**0/81**	0/14	0/2	0/6
pT1a (MI<1/2)	**3/102**	2/55	1/8	1/17
pT1b	2/25	6/31	6/18	1/10
pT2	3/14	3/7	3/6	1/9
pT3a	0/3	1/3	0/5	1/6
pT3b	0/2	0/0	1/1	3/3

pT1a(no MI) with endometrioid G1: 0%

pT1a(MI<1/2) with endometrioid G1: 2.9% (3/102)

Risk of PAN metastasis with superficial myometrial invasion

	Histological type			
	EMG1	EMG2	EMG3	Not EM
pT1a (no MI)	**0/81**	0/14	0/2	0/6
pT1a (MI<1/2)	**2/102**	2/55	1/8	1/17
pT1b	1/25	2/31	**4/18**	0/10
pT2	3/14	1/7	1/6	1/9
pT3a	0/3	0/3	0/5	1/6
pT3b	0/2	0/0	0/1	3/3

pT1a(no MI) with endometrioid G1: 0%

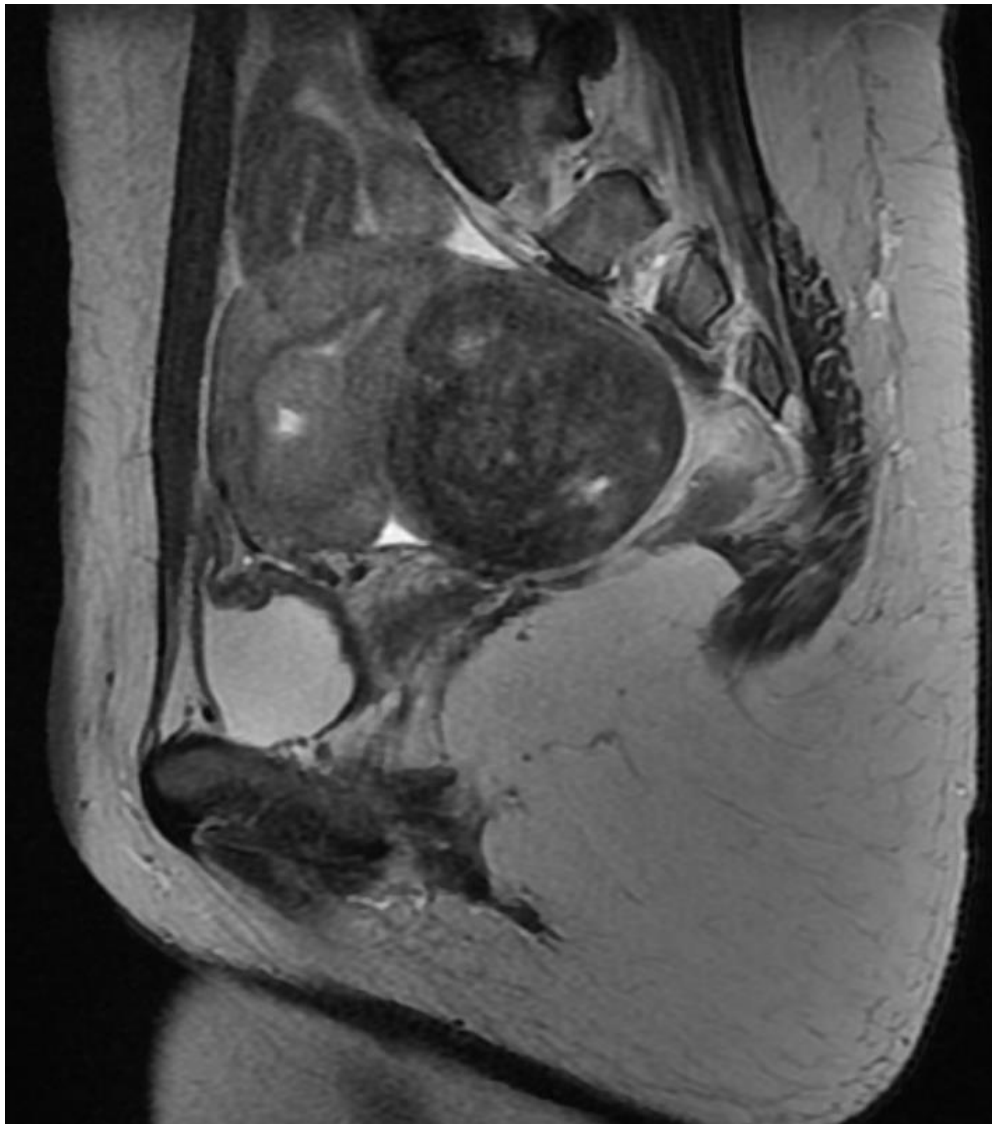
pT1a(MI<1/2) with endometrioid G1: 2.0% (2/102)

Detail of cases with surficial myometrial invasion and lymph node metasatis

Case	Age	Pre Histo type	Pre-MI	CA125	Tumor size (mm)	PostMI	Post Histo Type	LN metastasis	Number of metastatic node /dissection node
1	39	G1	(+)<1/2	12	30	32%	G1	Bil Obturator	3/84
2	49	G1	(-)	31	0	32%	G1	Bil. Obturator、Rt PAN	9/110
3	40	G1	(+)<1/2	22	30	33%	G1	Lt Obturatoer Lt PAN	7/85
4	50	G1	(+)<1/2	35	41	7%	G2	Rt PAN	1/42

Adjuvant chemotherapy was done in all cases
They did not have recurrence

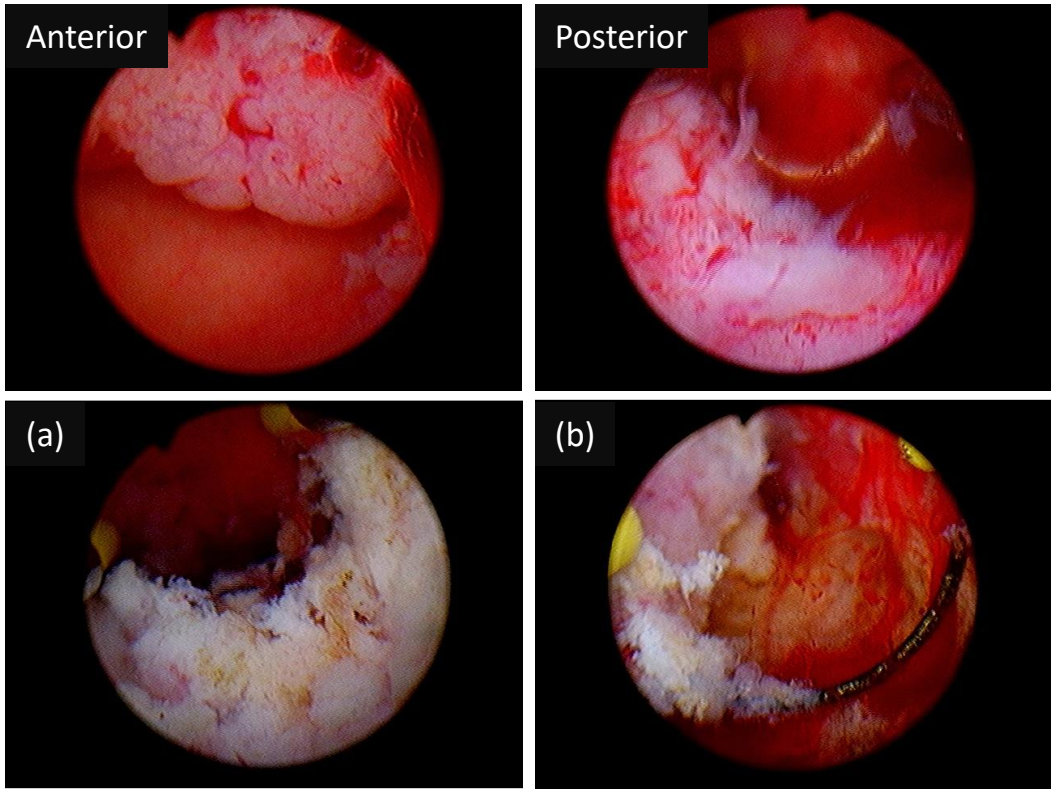
How shall I do?



D&C: endometrioid G1

MRI: less than half myometrial invasion

Hysteroscopic resection to detect myometrial invasion



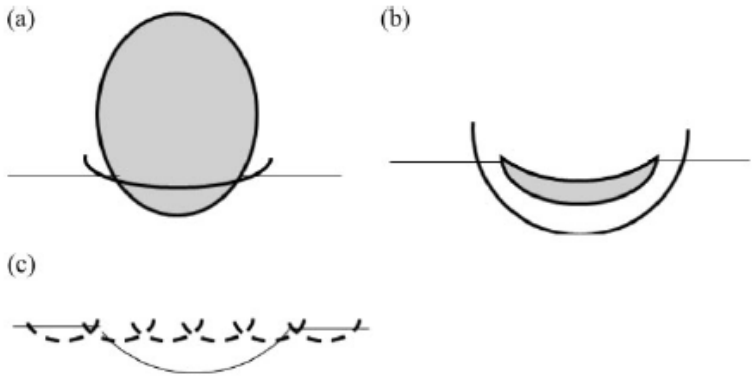


Figure 1 Hysteroscopic surgical procedure to diagnose myometrial invasion. (a) Remove the polypoid lesion; (b) remove a 3–5 mm-thick layer of normal muscle layer at the root of the polypoid lesion; and (c) perform total endometrial curettage. ⌣, transcervical resection; '- - ', dilatation and curettage.

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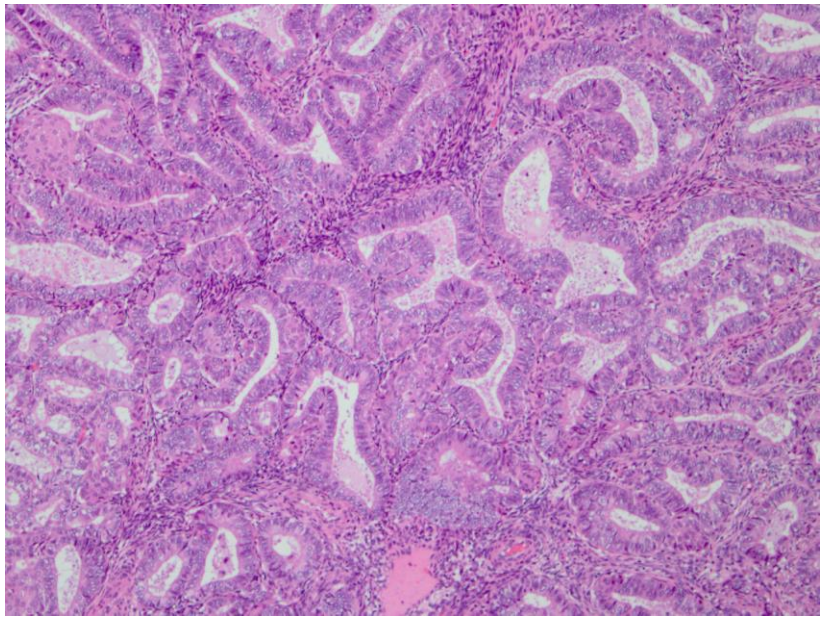
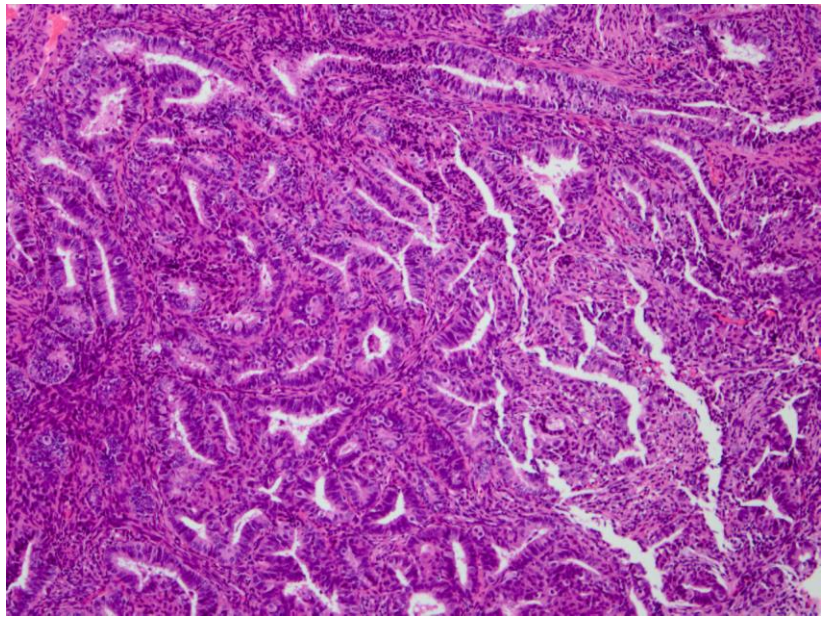
Pathological findings of specimen by TCR

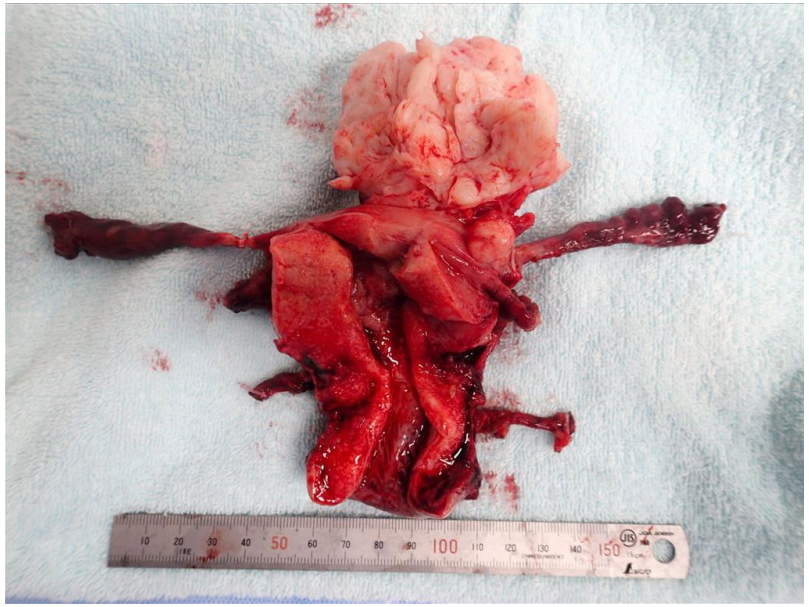




Where APAM is complicated by atypical hyperplasia or more and the possibility of myometrial invasion cannot be ruled out.

The risk of myometrial invasion could not be ruled out, so a total hysterectomy was recommended

Hysterectomy was performed

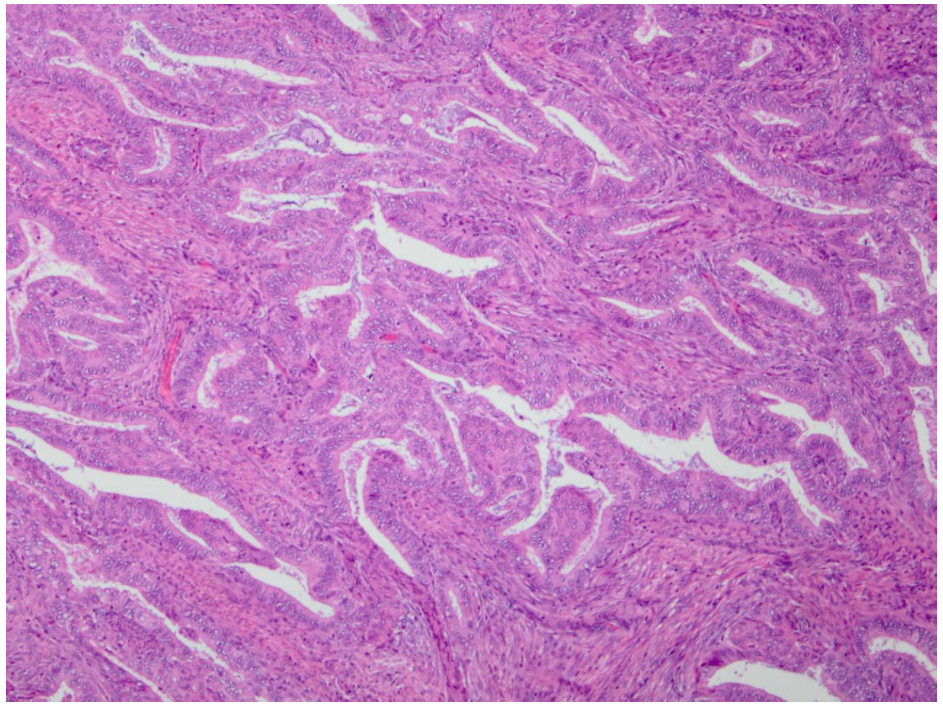


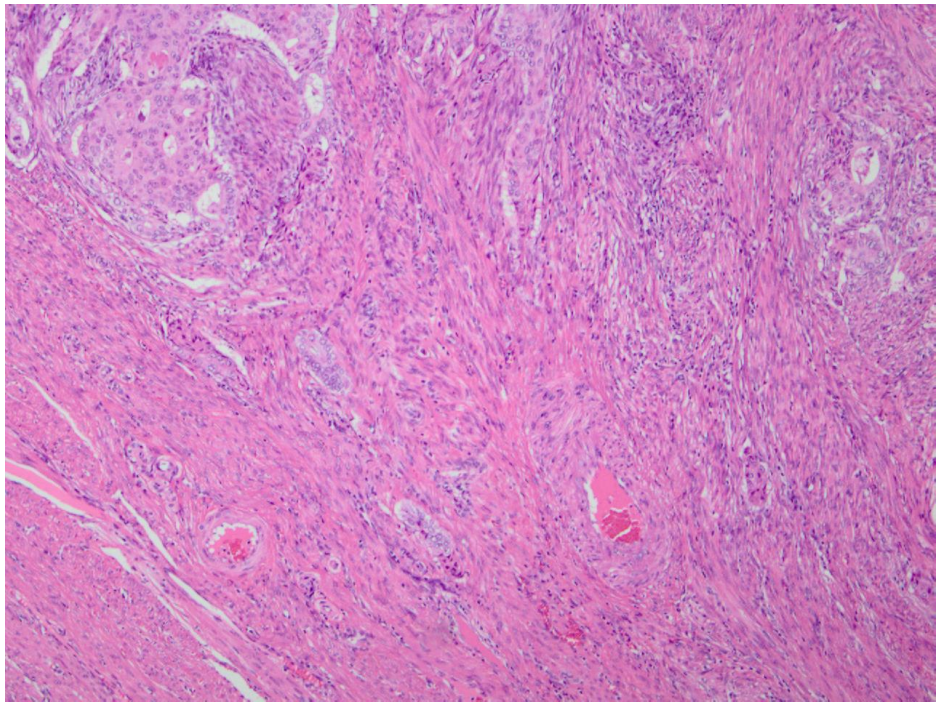
Laparoscopic hysterectomy+Bil. salpingectomy

Frozen section: APAM
No evidence of carcinoma

➡ Oophorectomy was not performed

Final diagnosis of pathology





Endometrioid ca G1

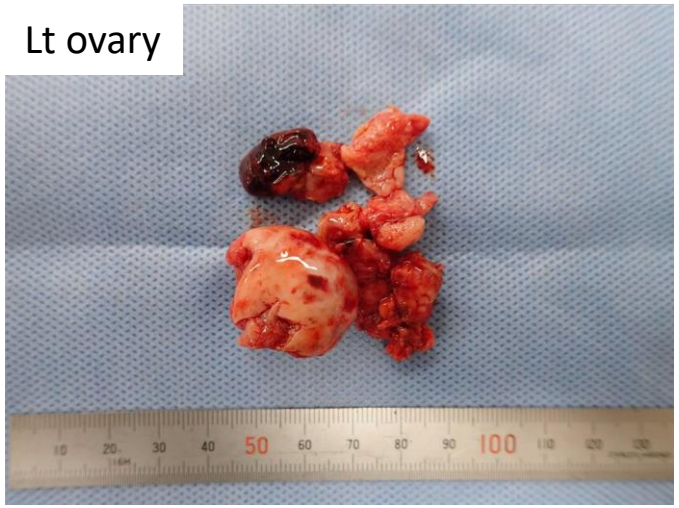
With myometrial invasion

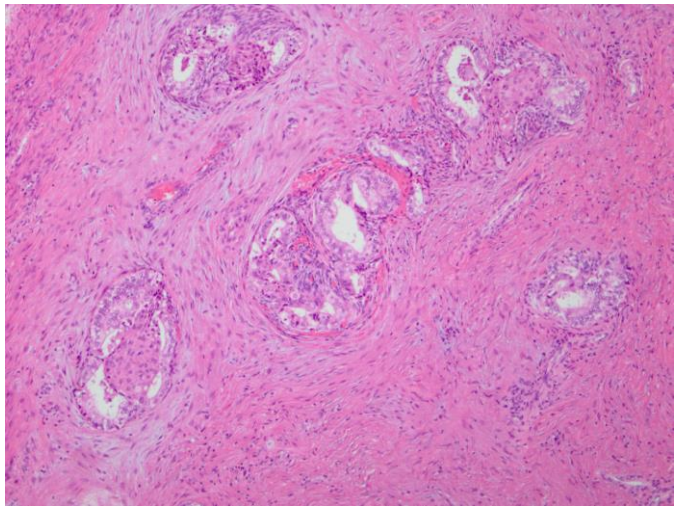
5/11mm

We recommended to add bil. oophorectomy and pelvic lymphadenectomy

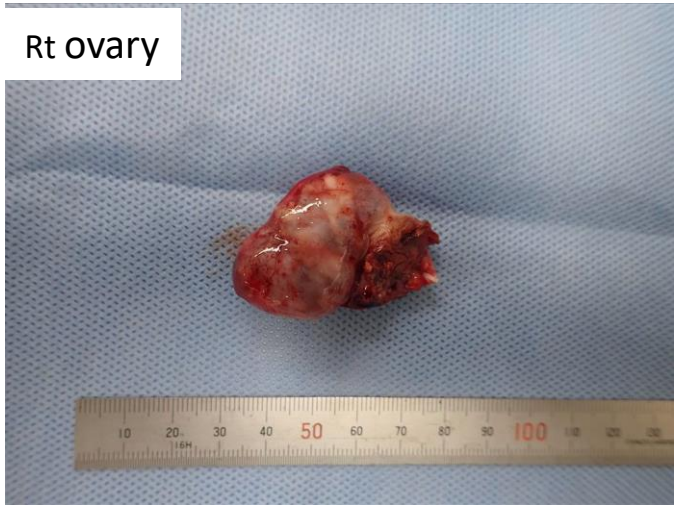
Oophorectomy and Lymphadenectomy

Lt ovary

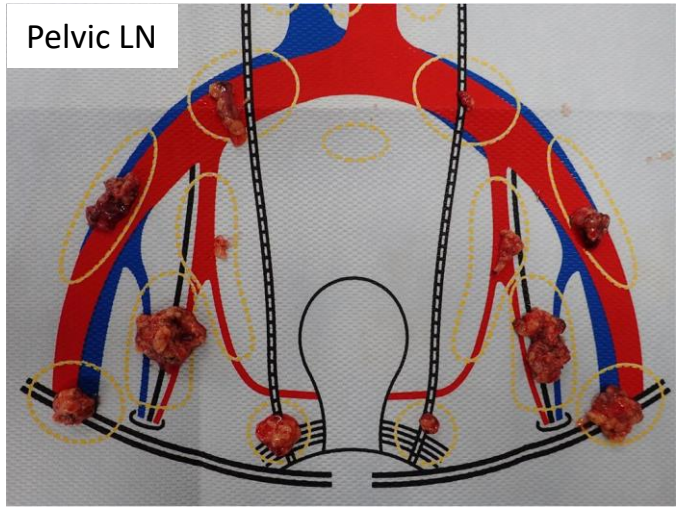




Rt ovary



Pelvic LN



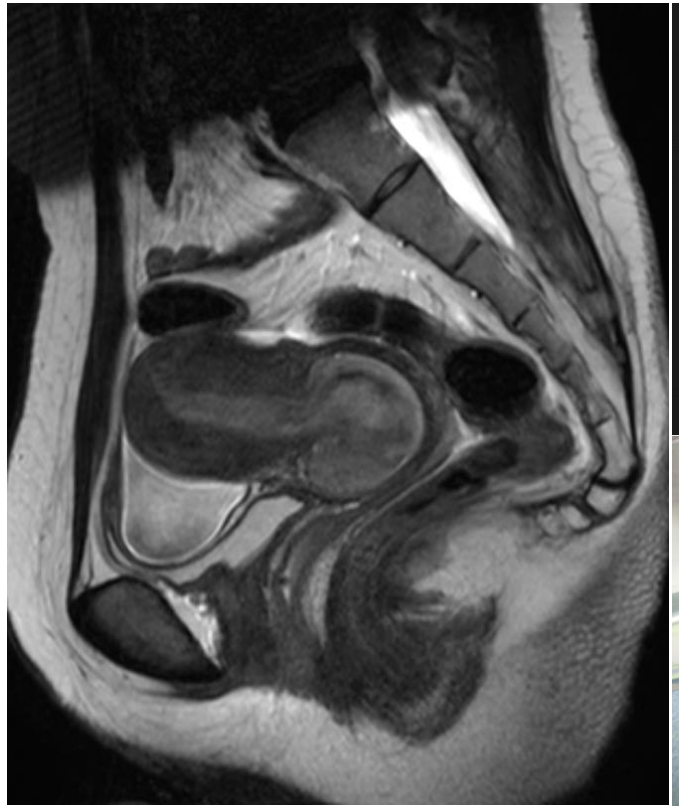
Lt ovarian metastasis (+)

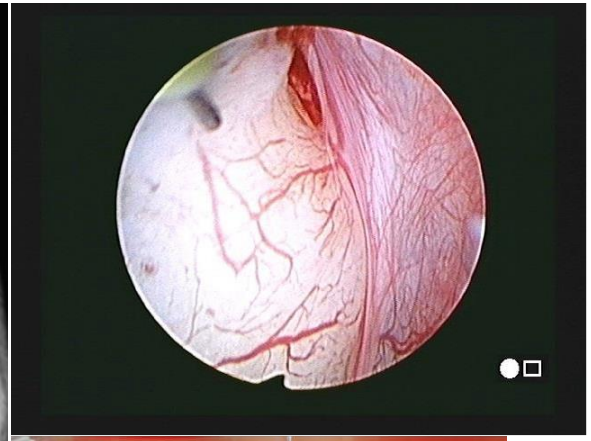
Uterin cancer stage IIIA (pT3aN0M0)

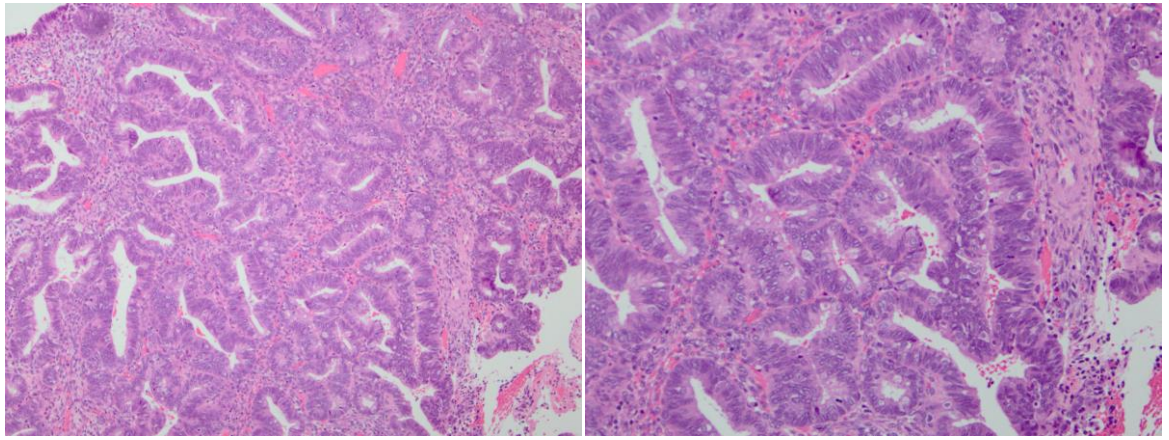
Cervical cancer?

Case 2

31 years female
G0P0



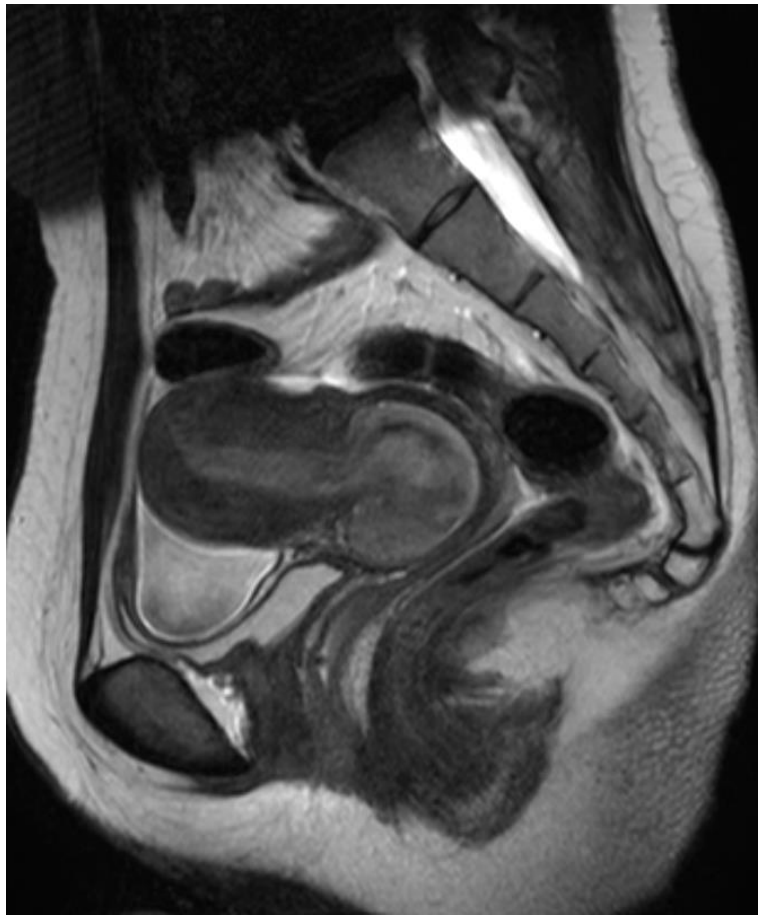




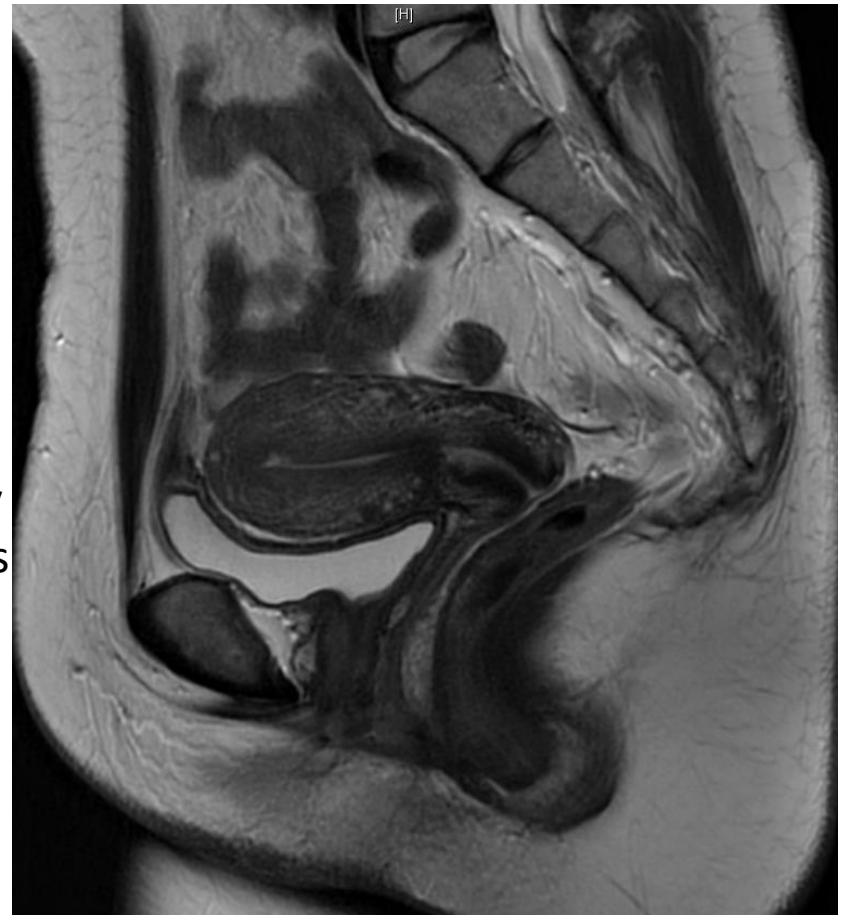
Hysteroscopic resection was performed

APAM only
No evidence of carcinoma

Cervical cancer? →APAM



MPA therapy
For 7 months



2x pregnancy
↓
2x delivery

Thank you for your attention ！

Olympic stadium near Keio University School of Medicine

Points of problems

1. Current status: finding hurdle, difficulty, opportunity and chance.

2. Legal issue comparison between Two countries:
IRB ,Approval process & Audit.

3. Do you have “Difficulty” in hormone treatment enrollment: Are we competing with “Easy” surgery? -evidence review.

4. Lesson from shared Case presentation; My difficult case