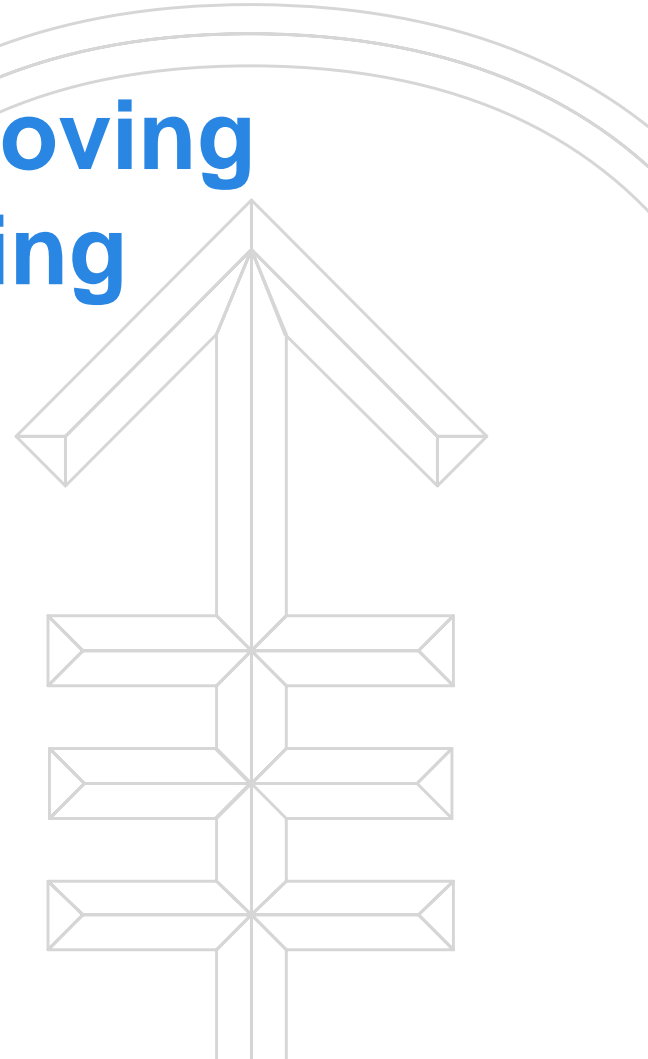




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Endometrial cancer: Improving outcomes while maintaining quality of life

April 18, 2018
Jennifer Mueller, MD
Assistant Attending Gynecologic Oncology
Department of Surgery
[www. MSKCC.org](http://www.MSKCC.org)



Talk Outline

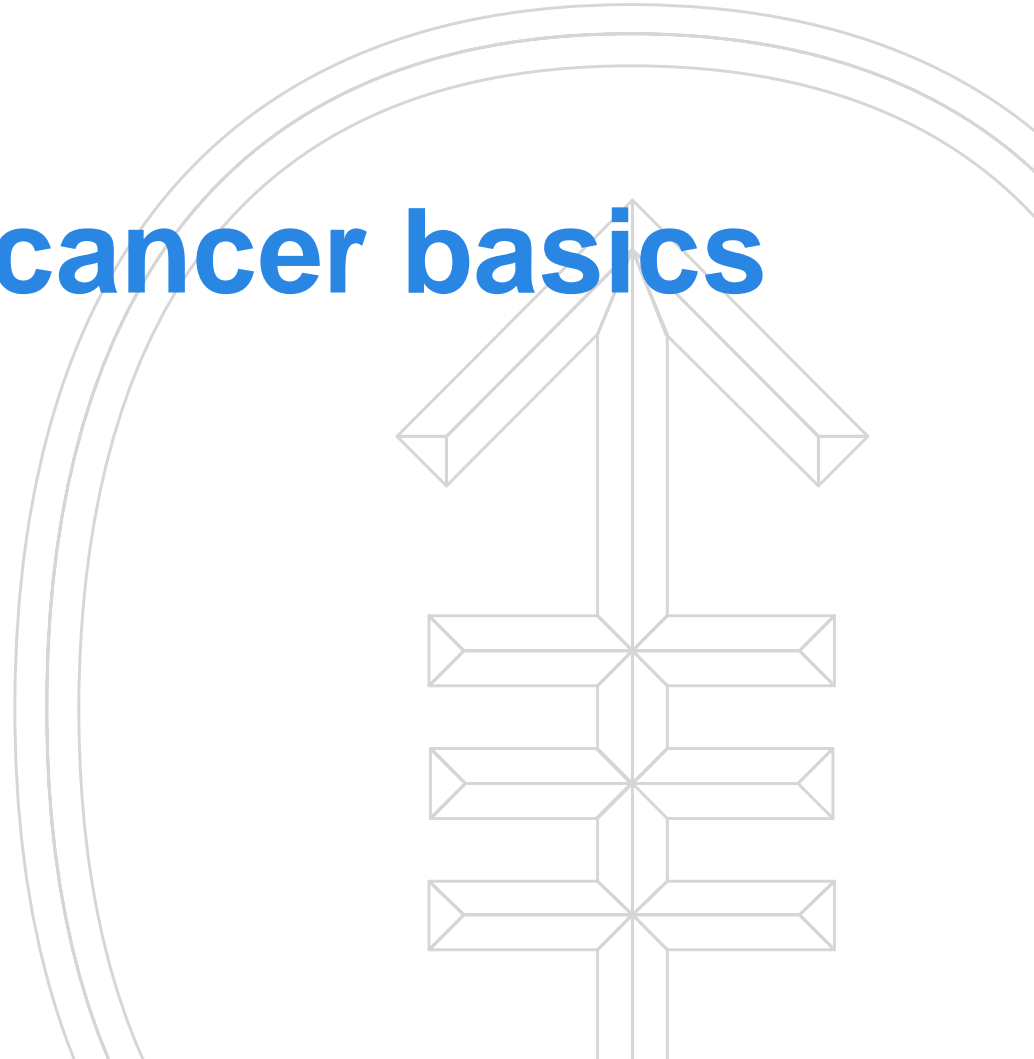
- **Background facts on endometrial cancer**
 - How common is it
 - How we diagnose it
 - How we treat it
- **How surgery has improved quality and oncology outcomes**
 - Robotic and laparoscopic surgery
 - Sentinel lymph node mapping
- **Therapeutic strategies beyond surgery**
 - Adjuvant
 - Recurrent
 - Targetted therapy





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Endometrial cancer basics



Background facts on endometrial cancer

- Most common gynecologic cancer
- Arises in the lining of the uterus



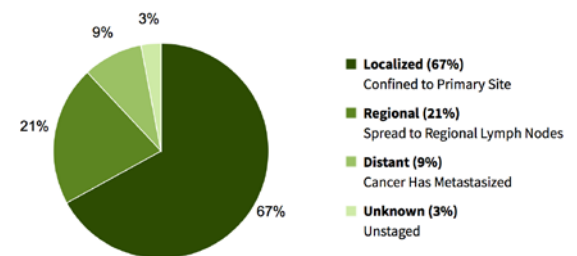
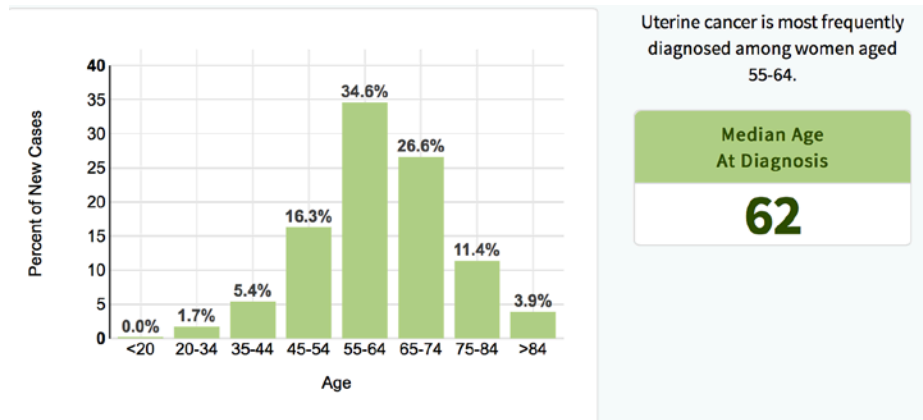
[SEER.cancer.gov/statfacts/](https://seer.cancer.gov/statfacts/)



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Background facts on endometrial cancer

- Most common gynecologic cancer
- Arises in the lining of the uterus
- ~63,230 women will be diagnosed in 2018
 - 3.6% of all cancer cases in the U.S.
- Most women diagnosed 55-74 years of age
- Two-thirds women will be stage I at diagnosis



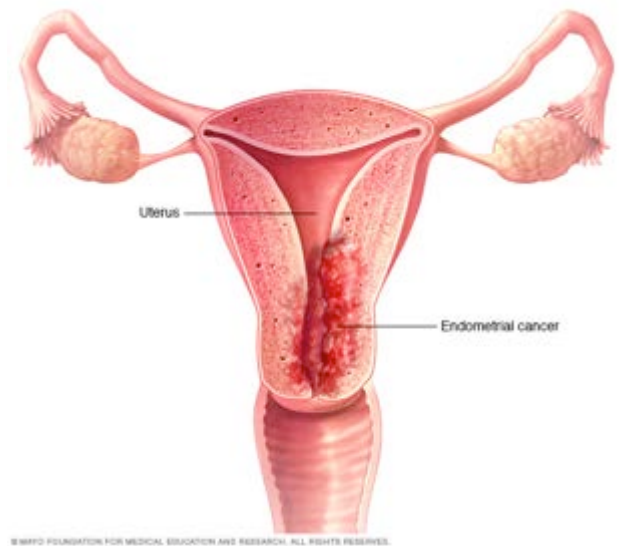
[SEER.cancer.gov/statfacts/](https://seer.cancer.gov/statfacts/)



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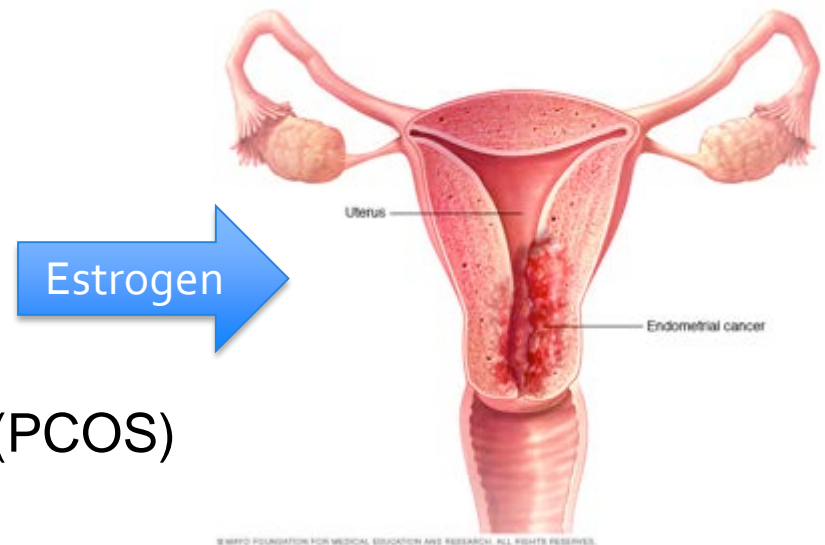
Background facts on endometrial cancer

- Are there any signs or symptoms?
 - Bleeding after menopause
 - Irregular or abnormal periods (new/different)
 - Discharge that isn't relating to periods
 - Gland cells on a pap



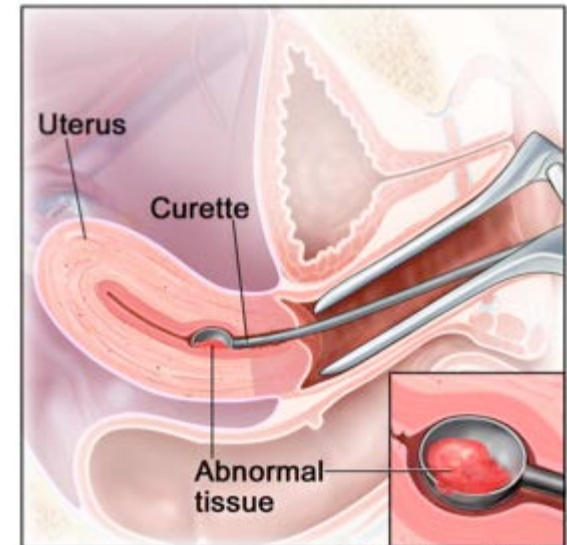
Background facts on endometrial cancer

- Are there any signs or symptoms?
 - Bleeding after menopause
 - Irregular or abnormal periods (new/different)
 - Discharge that isn't relating to periods
 - Gland cells on a pap
- Who is at increased risk?
 - Obesity
 - High blood pressure
 - Diabetes
 - Estrogen Rx
 - Tamoxifen
 - Polycystic Ovarian Syndrome (PCOS)
 - Lynch Syndrome



Background facts on endometrial cancer

- How is endometrial cancer diagnosed?
 - Biopsy
 - Office or operating room
 - Guides surgery plan
 - Cell type
 - Grade

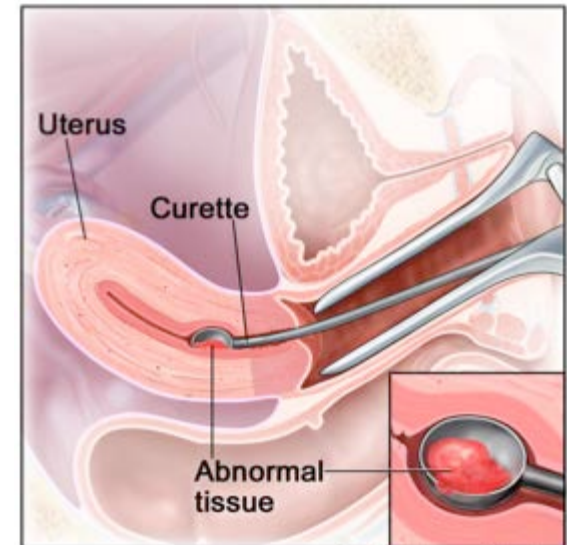


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Background facts on endometrial cancer

- How is endometrial cancer diagnosed?
 - Biopsy
 - Office or operating room
 - Guides surgery plan
 - Cell type
 - Grade



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Low Grade



High Grade

Endometrioid

Serous
Clear Cell
Carcinosarcoma
Endometrioid



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Background facts on endometrial cancer

- How is endometrial cancer diagnosed?
 - Biopsy
 - Office or operating room
 - Guides surgery plan
 - Cell type
 - Grade
- What imaging tests are helpful?
 - Ultrasound can show a thickened endometrium
 - CT scan can help look at lymph nodes and beyond the uterus



Background facts on endometrial cancer

- How is endometrial cancer diagnosed?
 - Biopsy
 - Office or operating room
 - Guides surgery plan
 - Cell type
 - Grade
- What imaging tests are helpful?
 - Ultrasound can show a thickened endometrium
 - CT scan can help look at lymph nodes and beyond the uterus
- Surgery is the mainstay of treatment
 - Surgery provides the staging information
 - Guides next steps in treatment (chemotherapy, radiation)



FIGO 2009 Staging

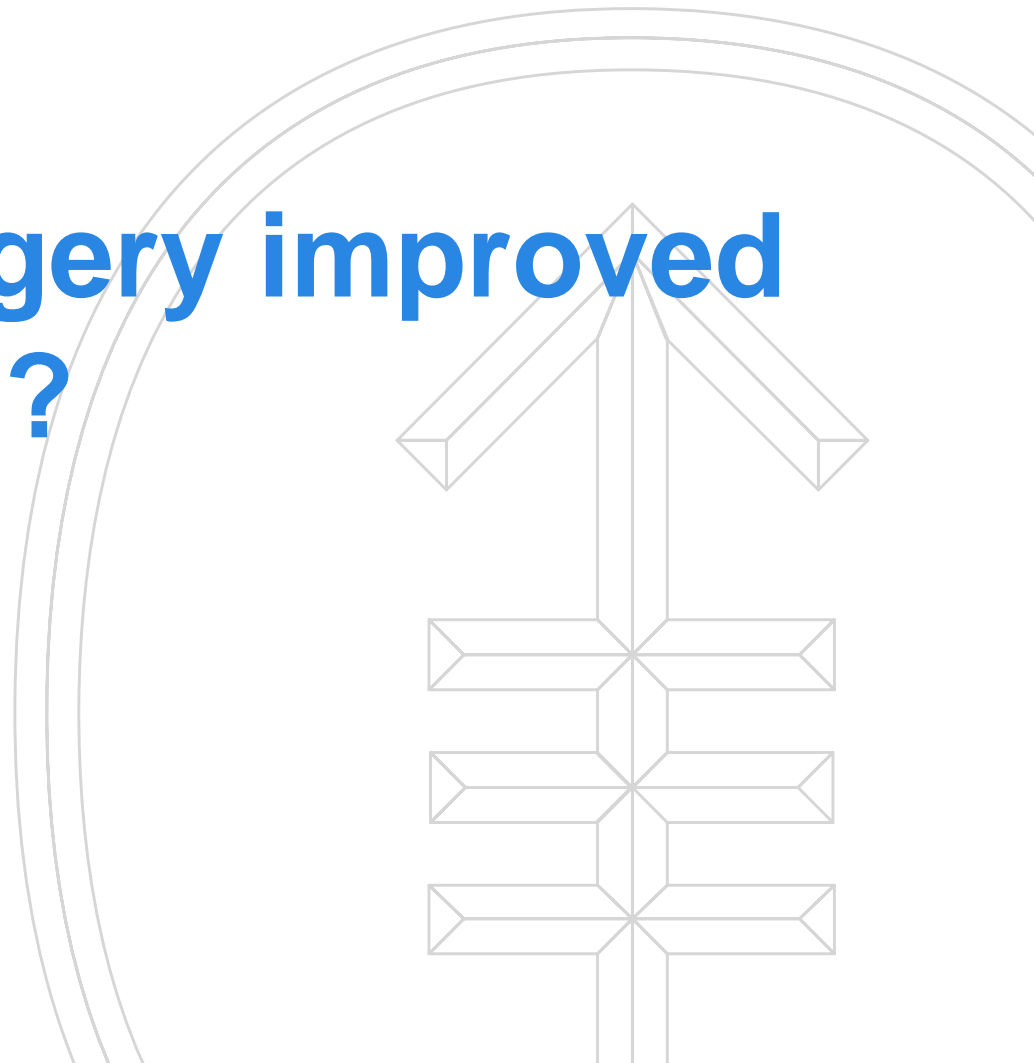
Stage I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastatic to pelvic and/or para-aortic lymph nodes
IIIC ₁	Positive pelvic lymph nodes
IIIC ₂	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases (this includes intra-abdominal metastases and/or inguinal lymph nodes)





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How has surgery improved quality of life?



Sentinel nodes...or all the nodes



Google images



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Little incisions...or big incisions

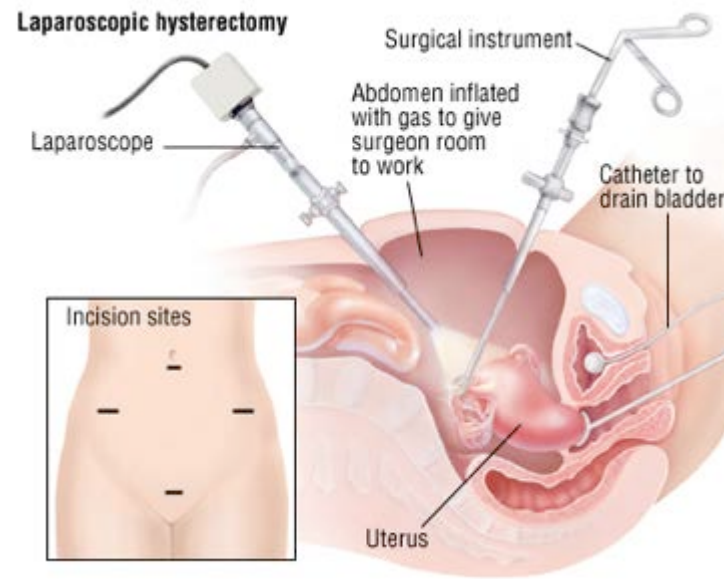


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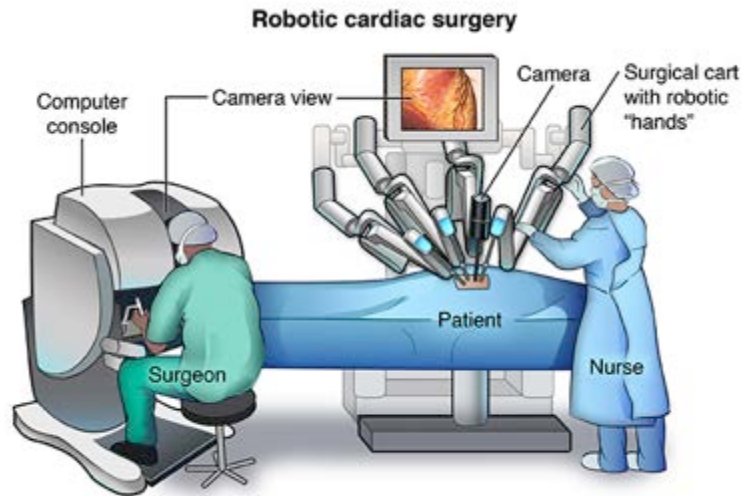


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The basics: laparoscopy



The basics: 'robotic assisted' laparoscopy



How has surgery improved quality of life?

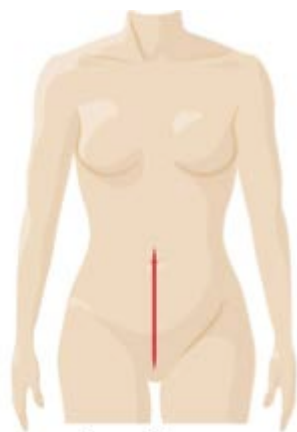
VOLUME 27 • NUMBER 32 • NOVEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Laparoscopy Compared With Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group Study LAP2

Joan L. Walker, Marion R. Piedmonte, Nick M. Spirtos, Scott M. Eisenkop, John B. Schlaerth, Robert S. Mannel, Gregory Spiegel, Richard Barakat, Michael L. Pearl, and Sudarshan K. Sharma



Open Surgery
Incision

Over 2,600 women
Randomized control trial
Early stage endometrial cancer



Laparoscopy
Incisions

Shorter hospital
stay

Fewer
postoperative
complications

Similar stage III
detection



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How has surgery improved quality of life?

VOLUME 30 • NUMBER 7 • MARCH 1 2012

JOURNAL OF CLINICAL ONCOLOGY

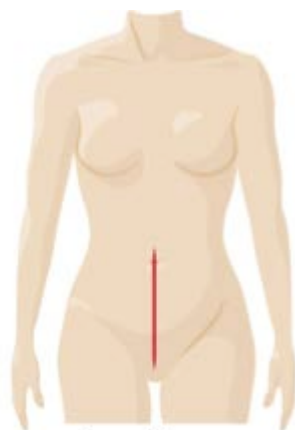
ORIGINAL REPORT

Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group LAP2 Study

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10% 3 yr
recurrence
rate

90% 5 yr
survival



Open Surgery
Incision

Follow up study from LAP2
Five years of follow up
Noninferiority design
Fewer recurrences than anticipated

11% 3 yr
recurrence rate

90% 5 yr survival



Laparoscopy
Incisions



How has surgery improved quality of life?



- 2 years tracking all robotic hysterectomies at MSKCC
- 200 same day cases planned during time period
- 40% endometrial cancer, 50% benign, 8% cervix, 2% ovary
- 80% home within 24 hrs, median time for discharge 5 hrs
- No difference in readmission rates compared with similar cases that were not planned for same day
- Feasible and safe to leave same day



Same day surgery



The Josie Robertson Surgical Center



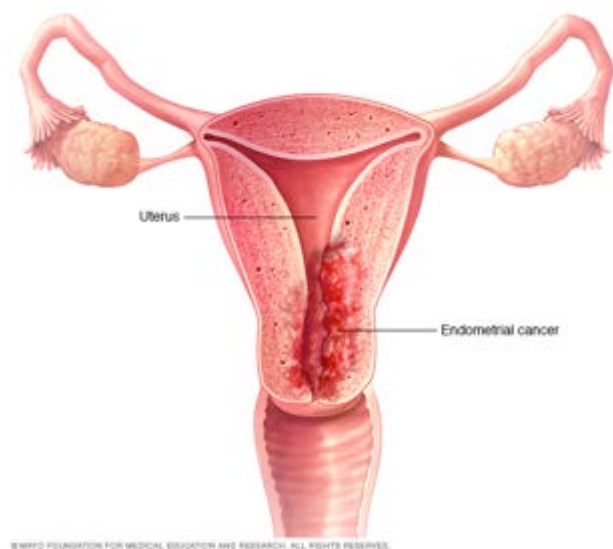


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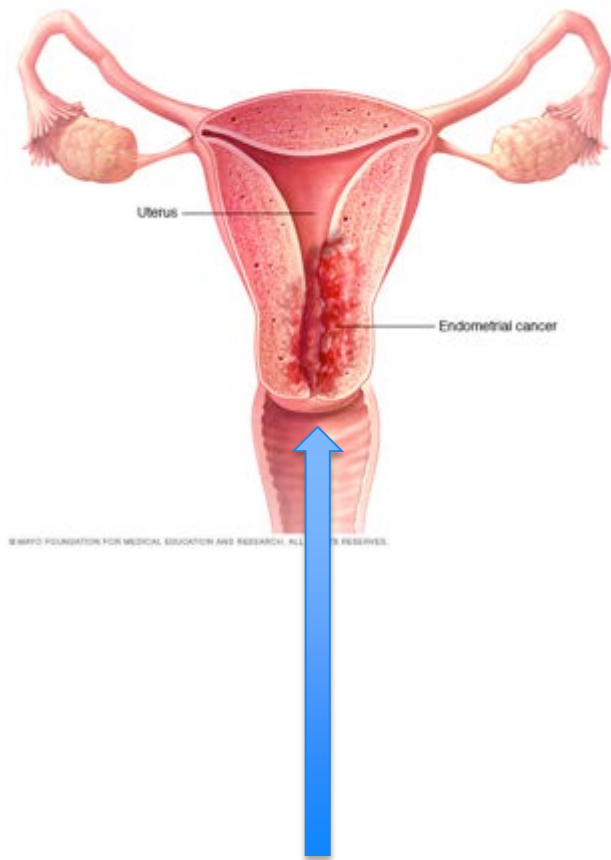
How has surgery improved cancer outcomes?



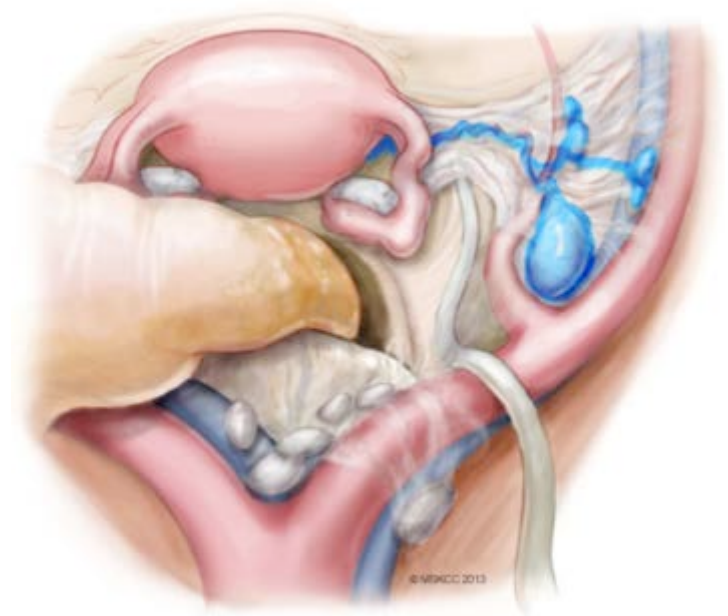
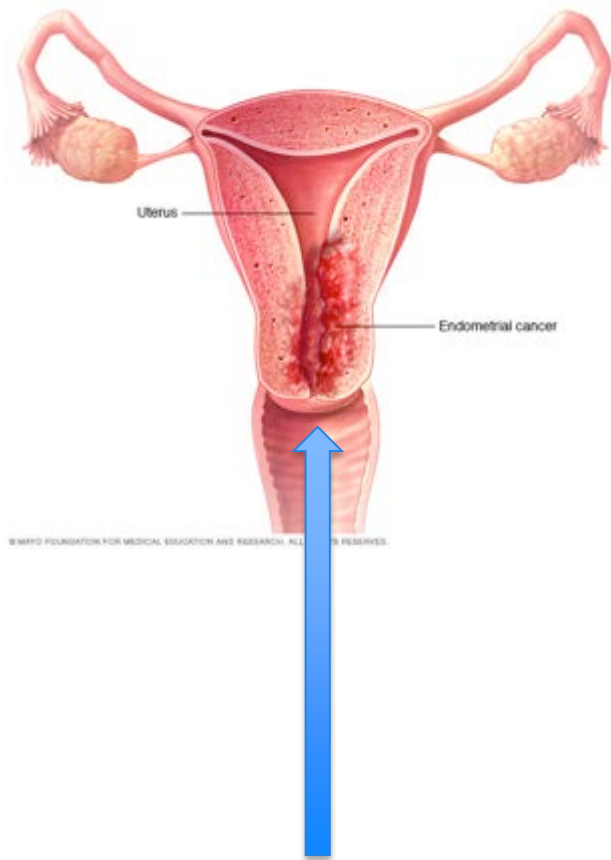
Sentinel lymph node mapping



Sentinel lymph node mapping

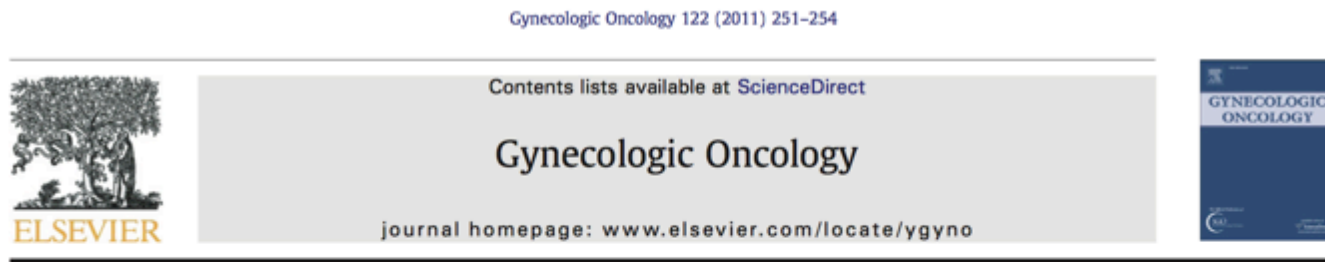


Sentinel lymph node mapping



How has surgery improved cancer outcomes?

- Sentinel lymph node mapping
 - Improves detection of metastatic lymph nodes
 - 3 times more likely to detect metastatic disease in the sentinel node than a non sentinel lymph node



Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes[☆]

F. Khoury-Collado^a, M.P. Murray^b, M.L. Hensley^c, Y. Sonoda^a, K.M. Alektiar^d, D.A. Levine^a, M.M. Leitao^a, D.S. Chi^a, R.R. Barakat^a, N.R. Abu-Rustum^{a,*}

^a Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., N Y, NY 10065, USA

^b Department of Pathology, Gynecology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., N Y, NY 10065, USA

^c Department of Medicine, Gynecology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., N Y, NY 10065, USA

^d Department of Radiation Oncology, Brachytherapy Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., N Y, NY 10065, USA





How has surgery improved cancer outcomes?

- Sentinel lymph node mapping
 - Detects node positive disease 97% of the time
 - Negative predictive value of 99.6%
 - A safe and accurate replacement of full node dissection



A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study

Emma C Rossi, Lynn D Kowalski, Jennifer Scalici, Leigh Cantrell, Kevin Schuler, Rabbie K Hanna, Michael Method, Melissa Ade, Anastasia Ivanova, John F Boggess

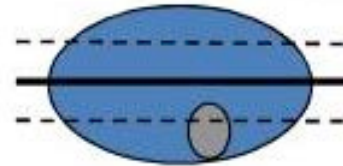




How has surgery improved cancer outcomes?

- Sentinel lymph node mapping
 - Improves detection of metastatic lymph nodes
- Ultrastaging sentinel lymph nodes
 - Increases the detection rate of metastatic lymph nodes

Ultrastaging



NIH Public Access

Author Manuscript

Int J Gynecol Cancer. Author manuscript; available in PMC 2014 July 02.

Published in final edited form as:

Int J Gynecol Cancer. 2013 June ; 23(5): 964–970. doi:10.1097/IGC.0b013e3182954da8.

Pathologic Ultrastaging Improves Micrometastasis Detection in Sentinel Lymph Nodes during Endometrial Cancer Staging

Christine H. Kim, MD¹, Robert A. Soslow, MD², Kay J. Park, MD², Emma L. Barber³, Fady Khoury-Collado, MD¹, Joyce N. Barlin, MD¹, Yukio Sonoda, MD^{1,4}, Martee L. Hensley, MD^{4,5}, Richard R. Barakat, MD^{1,4}, and Nadeem R. Abu-Rustum, MD^{1,4}

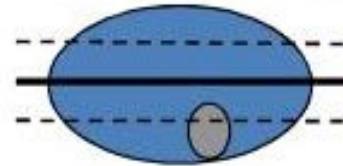




How has surgery improved cancer outcomes?

- Sentinel lymph node mapping
 - Increased precision in identifying node positive disease
- Ultrastaging sentinel lymph nodes
 - Increases detection rate of node positive disease

Ultrastaging



More women are treated (who should be)

Improved outcome and prognosis





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Therapeutic options



Adjuvant Therapy- Early Stage Disease



“High Intermediate Risk”

- Age
- Presence of lymphovascular invasion
- Myoinvasion
- Cell type
- Grade of the tumor





High Intermediate Risk Endometrial Cancer

- **GOG 99 and PORTEC 1**
 - US and Europe, phase 3 data
 - Randomized to no treatment after surgery versus RT to pelvis
 - Fewer recurrences with RT arm of both trials
 - No difference in overall survival
 - *Not to be used in low or intermediate risk endometrial cancer due to side effects (acute and long term) of RT to pelvis*
- **PORTEC 2**
 - Pelvic RT versus Vaginal Brachytherapy after surgery (noninferiority)
 - Recurrence rare in both arms of the trial
 - Fewer side effects with vaginal brachytherapy
- **GOG 249**
 - Pelvic RT versus Vaginal Brachytherapy plus Chemotherapy
 - No difference in recurrence or survival in either arm
 - 50% decrease in node recurrences in the Pelvic RT arm (4% vs 9%)



Adjuvant Therapy-Advanced Stage Disease



Advanced Stage Endometrial Cancer

- **GOG 107**
 - Doxorubicin versus Doxorubicin/Cisplatin
 - Improved response rate and progression free survival with 2 agents
 - No difference in overall survival
- **GOG 177**
 - Doxorubicin/Cisplatin versus Doxorubicin/Cisplatin/Paclitaxel
 - Improved response rate, progression free and overall survival with 3 agents
- **GOG 209**
 - Doxorubicin/Cisplatin/Paclitaxel versus Carboplatin/Paclitaxel
 - Therapeutically equivalent regimens
 - Fewer side effects and better tolerated with Carboplatin/Paclitaxel
- **GOG 258**
 - Randomized to chemo versus RT plus chemo after surgery
 - No difference in overall survival or recurrence free survival
 - Fewer vaginal and nodal recurrences with RT plus chemo arm
 - Fewer distant recurrences with chemo arm



Advanced/Recurrent Endometrial Cancer

Hormonal Therapy



FDA Approved Treatment: Megestrol Acetate

- Approved in 1971 for the palliative treatment of advanced carcinoma of the breast and **endometrium** (i.e., recurrent, inoperable, metastatic disease)
- Response Rate: 14%–33%
- Progression Free Survival: 2.5–3.2 months



Hormonal Therapy

Study	N	Treatment	RR	PFS (months)	OS (months)
GOG 121	58	MA 800 mg daily	24%	2.5	7.6
GOG 81	154	MPA 1000 mg daily vs MPA 200 mg daily	14%	2.5	7
	145		25%	3.2	11.1
GOG 168	23	Anastrozole 1 mg daily	9%	1	6
GOG 81F	68	T 20 mg BID	10%	1.9	8.8
GOG 119	58	T 20 mg BID plus MPA 100 mg BID every other week	33%	3	13
GOG 153	56	MA 80 mg BID x 3 weeks, alternating with T 20 mg BID x 3 weeks	27%	2.7	14
GOG 188	31	Fulvestrant 250 mg IM every 4 weeks ER Positive	16%	10	26
	22	ER Negative	0	2	3

MA (megestrol acetate); MPA (medroxyprogesterone acetate); T (tamoxifen)



Advanced/Recurrent Endometrial Cancer

Chemotherapy



Single Agent Chemotherapy (No Prior Chemotherapy)

Agent	Response Rate (%)	Reference
Doxorubicin	37	Thigpen et al, 1979
Cisplatin	20	Thigpen et al, 1989
Carboplatin	28	Long et al, 1988
	30	Green et al, 1990
Paclitaxel	36	Ball et al, 1996
Ifosfamide	24	Sutton et al, 1996
Topotecan	20	Wadler et al, 2003



Single agent chemotherapy (1 prior chemotherapy)

Study	Agent	N	Response Rate (%)
129-C	Paclitaxel	44	27.3
129-H	Liposomal doxorubicin	42	9.5
129-J	Topotecan	22	9
129-K	Oxaliplatin	52	13.5
129-N	Docetaxel (weekly)	26	7.7
129-P	Ixabepilone	50	12
129-O	Pemetrexed	26	4
129-Q	Gemcitabine	23	4

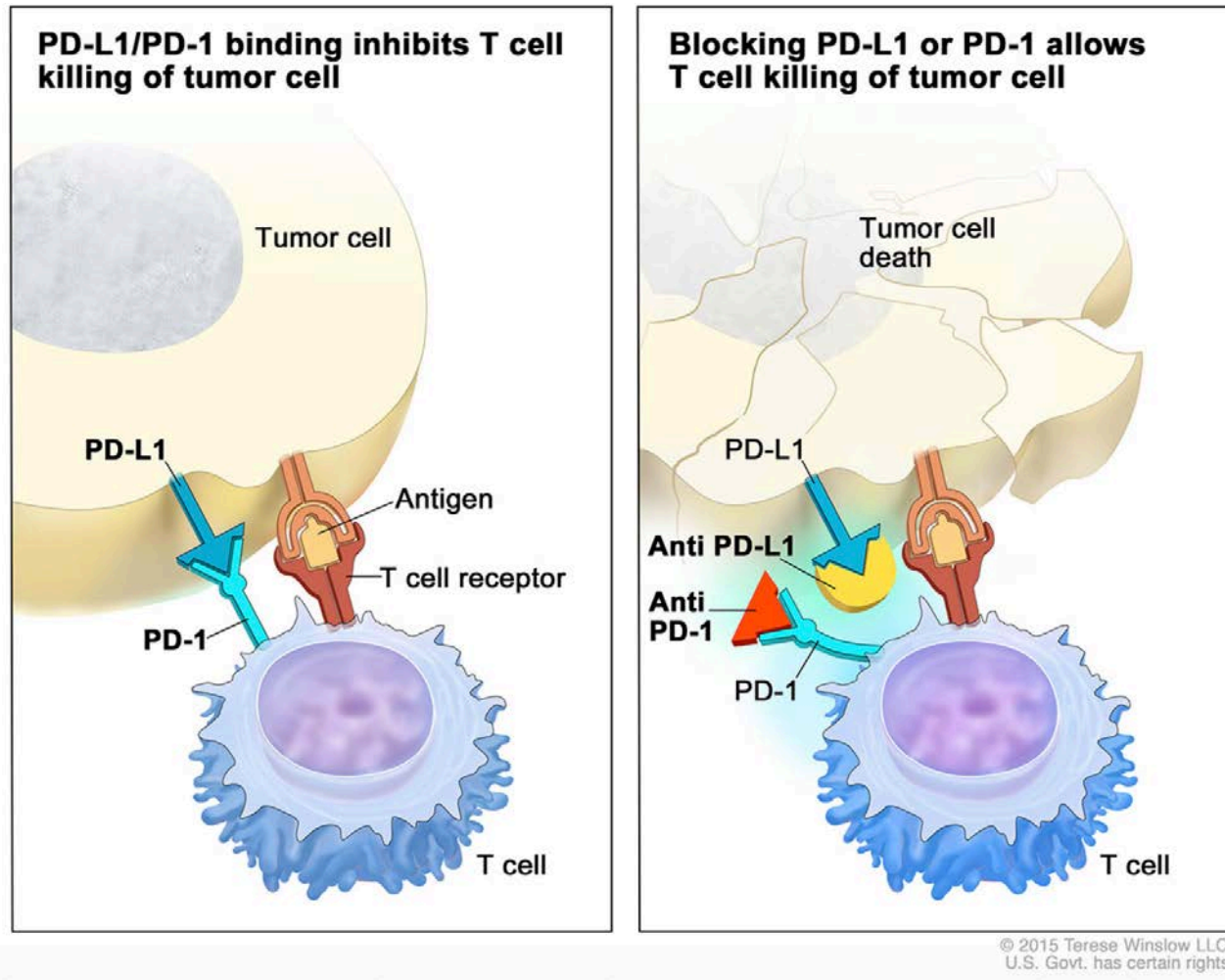


Advanced/Recurrent Endometrial Cancer

Targeted Therapy



PD-1 Inhibitors



PD-1 Inhibitors

- Keytruda (Pembrolizumab)
- FDA Approved 2017
- MSI-High and deficient Mismatch Repair tumors *regardless of site of origin*
 - Molecular profiling (MSI score, somatic mutation testing)
 - Immunohistochemistry (mismatch repair proteins)
- Decision based on 5 clinical trials in multiple tumor types
 - 149 patients total (14 with endometrial cancer)
 - 40% objective response rate, up to 80% durable response to 6 months





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Looking to the future





Looking to the future: personalized medicine



MSK-IMPACT

- Integrated **M**utation **P**rofiling of **A**ctionable **C**ancer **T**argets
 - Detects gene mutations in rare and common cancers
 - Available for MSKCC patients only
 - Tests over 450 genes implicated in cancer development
- Potential benefit of MSK-IMPACT testing
 - Increase our understanding of endometrial cancer
 - Smarter cancer therapy
 - Mutation specific clinical trials
 - How mutations will impact response to treatment

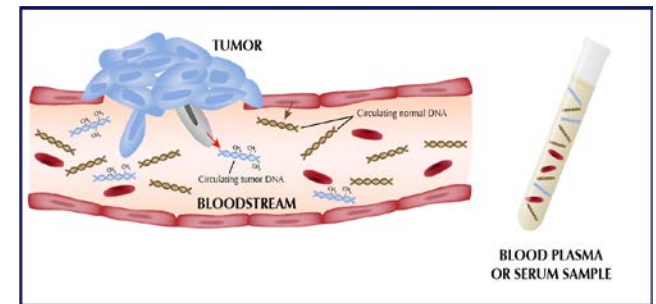
<https://www.mskcc.org/msk-impact#education>



Looking to the future: personalized medicine

GRAIL Study

- The **C**irculating **C**ell-free **G**enome **A**tlas (**CCGA**) Study
 - Creating a library of information for observational study
 - 10,000 patients included
 - Study of cell free nucleic acids (cfNA)
- Offered to ANY eligible patients treated at MSKCC
 - Increase our understanding of cancer
 - Cancer prevention





Looking to the future: personalized medicine



ConFiDenT Study

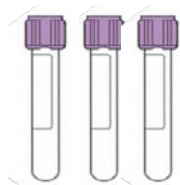
- **Cell Free DNA Tracking in Endometrial Cancer**
 - IMPACT testing
 - Blood also tested for cell free DNA and circulating tumor DNA
 - Pre-surgery MRI to assess the ‘texture’ of cancer on imaging
- Offered to eligible patients with endometrial cancer treated at MSKCC
 - Increase our understanding of endometrial cancer
 - Search for ways to monitor patients after their treatment using a simple blood test



ConFiDenT Study Design



Diagnosis (PST)

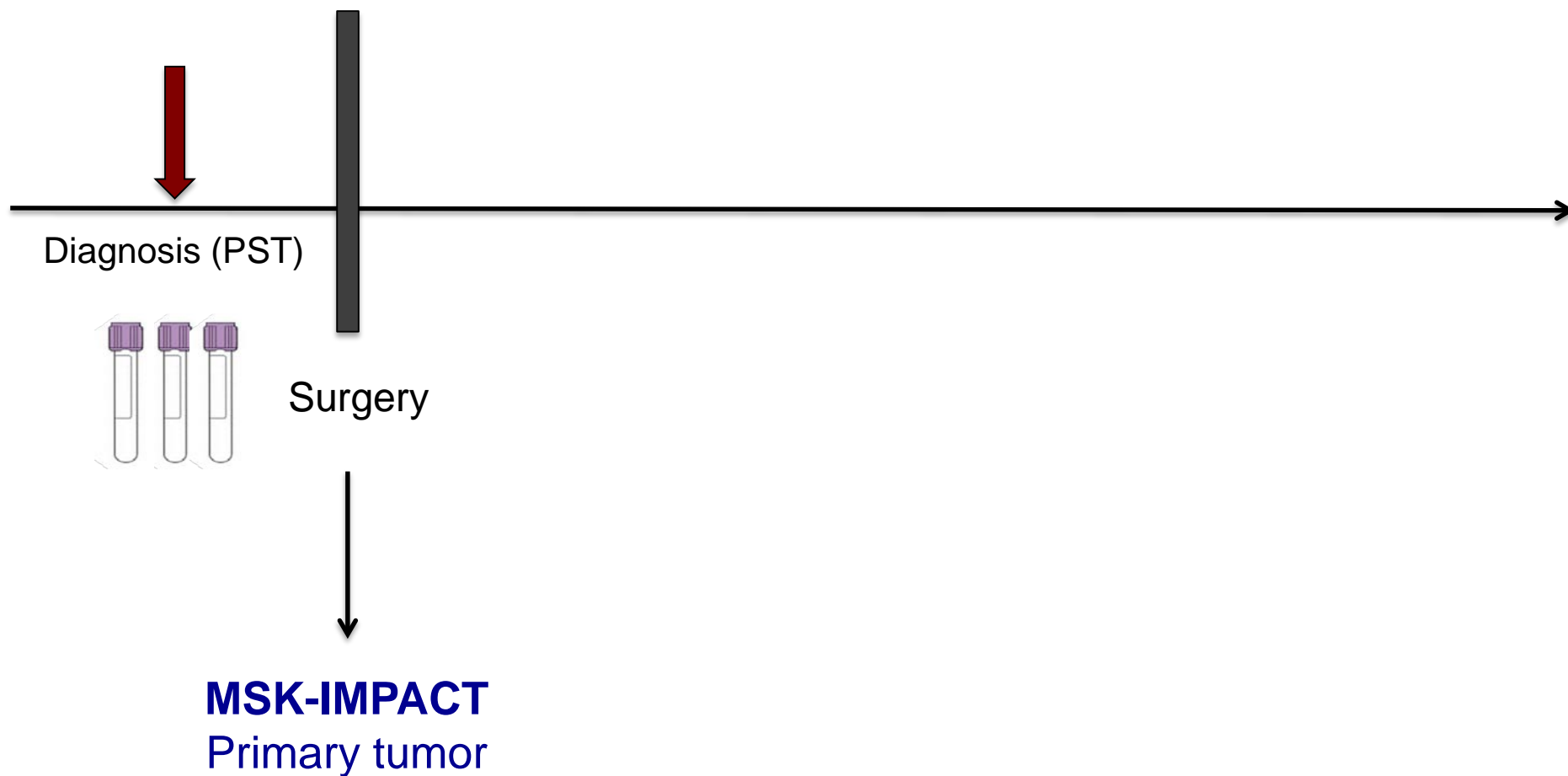


cfDNA
analysis

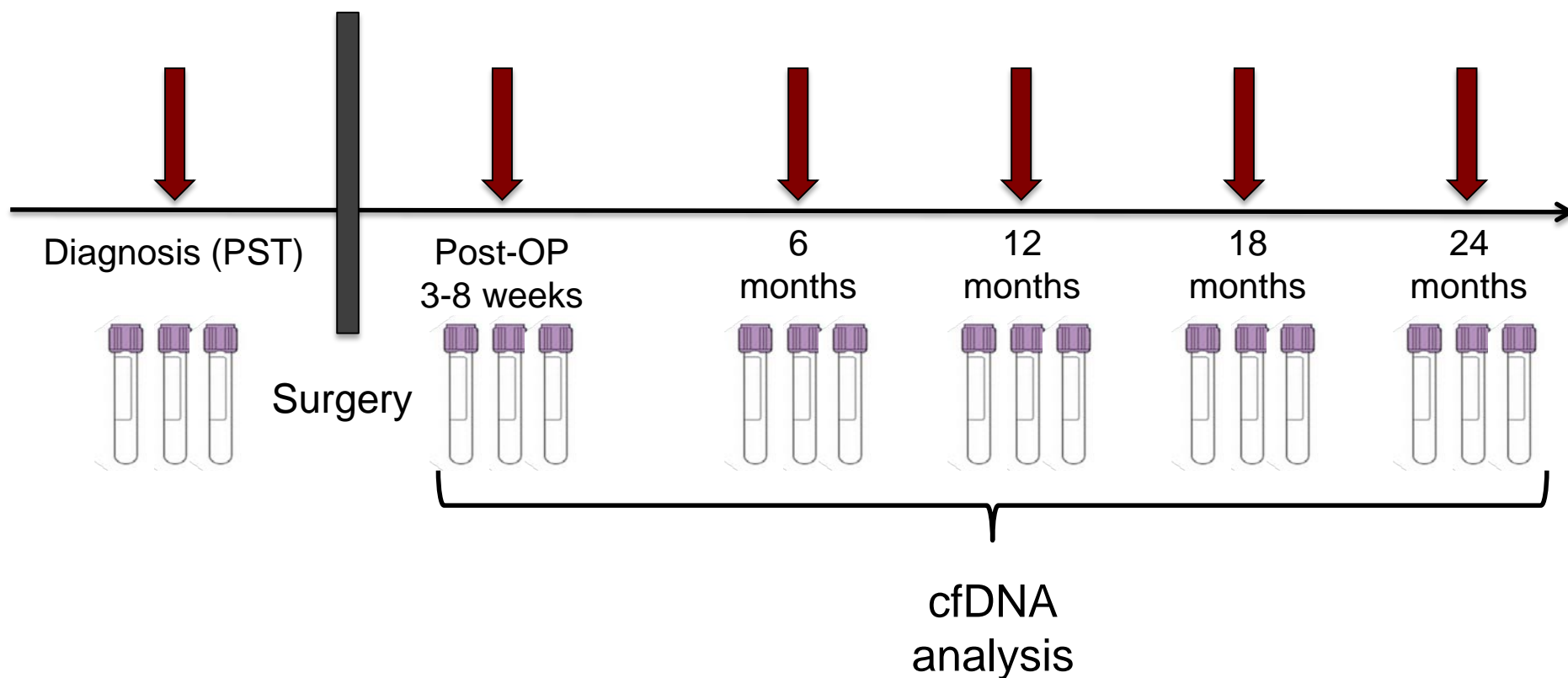
To define the amount of ctDNA present in endometrial cancer patients according to stage and histologic type.



ConFiDenT Study Design



ConFiDenTStudy Design



To determine whether mutation detection in cfDNA can be used to monitor disease in patients with endometrial cancer.



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