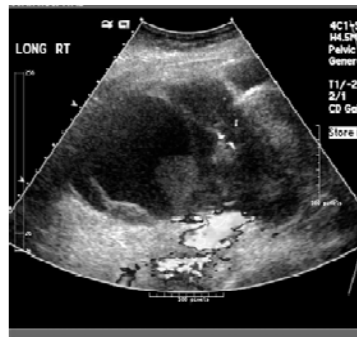# Ovarian Cancer

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General Division of Obstetrics and Gynecology
The Ohio State University Wexner Medical Center

Objectives

- **Define symptoms and risk factors for ovarian cancer**
- **Review the evaluation for an adnexal mass**
- **Discuss the diagnosis and management of ovarian cancer**

Initial Presentation

- **50 y/o presents with pelvic pressure and PCP ordered CT scan revealing a 15cm pelvic mass with solid and cystic components**
- **43 y/o presents with pelvic pain and ultrasound shows 4cm complex adnexal mass**
- **65 y/o had MRI for back pain, found to have a 9cm cystic lesion in the right adnexa**

Differential diagnoses

Benign
Functional cyst
Endometriosis/Endometrioma
Benign neoplasm
    Teratoma
    Cystadenoma
    Leiomyoma
Pregnancy related conditions
    Ectopic pregnancy
    Theca-Lutein cysts
Embryological remnants
    Paratubal cyst
    Paraovarian cyst
 Tubal processes
    Tubo-ovarian abscess
    Hydrosalpinx/Pyosalpinx

Differential Diagnoses

Malignant
Ovarian cancer
- Epithelial ovarian cancers
- Germ cell tumors
- Borderline ovarian tumors
- Sex cord-stromal tumors

Fallopian tube cancers
Primary peritoneal cancer
Uterine cancer

Differential diagnoses

Non-gynecologic causes

Gastrointestinal conditions
- Diverticular disease
- Appendiceal abscess/mucocele
- Meckel's diverticulum
- Small bowel tumors
  - Colorectal cancer

Urinary tract conditions
- Ureteral diverticulum
- Bladder diverticulum
- Pelvic kidney

Other
- Retroperitoneal tumors
- Retroperitoneal sarcomas
- Desmoid tumors
- Schwannomas
- Metastatic disease to adnexa
  - Bowel
  - Breast
  - Lymphoma

When to worry about cancer

- **Symptoms**
- **Risk Factors**
- **Exam**
- **Labs**
- **Imaging**

Symptoms

- **Asymptomatic**
- **Pelvic pain**
- **Weight loss, early satiety, bloating**
- **Vaginal bleeding, breast tenderness, precocious puberty**
- **Hirsutism, deepening of the voice**
- **Flushing, diarrhea, hyperthyroid symptoms**

Risk factors

- **Incessant ovulation**
  - **Aberrant repair process of the epithelium**
  - **Nulliparity/infertility**
  - **Early menarche/late menopause**
- **Inflammation**
  - **Endometriosis**
- **Genetic predisposition**
  - **BRCA 1 and 2**
  - **Hereditary NonPolyposis Colorectal Cancer (Lynch syndrome)**

Genetic predisposition

- **BRCA 1**
  - **90% lifetime risk for breast cancer**
  - **40% lifetime risk for ovarian cancer**
- **BRCA2**
  - **20% lifetime risk for ovarian cancer**
- **HNPCC (Lynch Family II)**
  - **Endometrial, colon and ovarian cancers**

Risk-reducing surgery

- **Genetic predisposition**
  - **Risk reducing bilateral salpingo-oophorectomy**
    - **Recommended by age 35 or after completion of childbearing**
    - **Occult cancer in ~8%**
    - **Risk of primary peritoneal cancer ~4%**
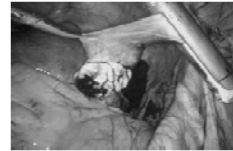
Physical Examination

- **General examination: cachexia, virilization, breast tenderness, lymphadenopathy, fever**
- **Abdominal exam: masses, pain, ascites**

Physical Examination

- Pelvic/speculum exam: clitoromegaly, bleeding, cervical displacement
- Mass characteristics: contour, firmness, mobility
- RV exam: tenderness, nodularity, stool guaiac.

Biomarkers

- May aid in determining the malignant potential and histology of an adnexal mass
- CA-125 is most commonly used biomarker
  - May be elevated in benign conditions
  - Ordered selectively
    - Age
    - Presentation of symptoms
    - Findings on physical examination
    - Imaging

Biomarkers

- **Cancer antigen (CA) 125**
  - **Epithelial ovarian cancer (serous)**
  - **Benign processes**

- **Alpha Fetoprotein (AFP)**
  - **Endodermal sinus tumors**
  - **Hepatocellular carcinoma**

- **Human chorionic gonadotrophin (hCG)**
  - **Choriocarcinoma, embryonal carcinoma**
  - **Pregnancy**
  - **Gestational trophoblastic disease**

- **Lactate dehydrogenase (LDH)**
  - **Dysgerminomas**
  - **Lymphomas**

- **Inhibin A and B**
  - **Granulosa cell tumors**

- **Cancer antigen (CA) 19-9**
  - **Pancreas and biliary tract**
  - **Mucinous tumors of the ovary**

- **Carcinoembryonic antigen (CEA)**
  - **Colorectal cancer**

Biomarkers

Age	Tumor Markers
≤30 years	AFP, hCG, LDH, Inhibin A, Inhibin B
30-50 years	Inhibin A, Inhibin B, +/- CA-125 (family history)
≥50 years	CA-125, CA 19-9, +/- Inhibin A & B (if symptoms), +/- CEA

OVA1 ™

- **Combines five immunoassays into a single numerical result**
  - **CA-125**
  - **Transthyretin (prealbumin)**
  - **Apolipoprotein A1**
  - **ß2-microglobulin**
  - **Transferrin**

OVA1 ™ Scoring

OvaCalc software uses assay results and calculates ovarian cancer risk index score

- Premenopausal
  - less than 5 = low risk
  - 5 or greater = high risk
- Postmenopausal
  - less than 4.4 = low risk
 - 4.4 or greater = high risk

HE4 and CA-125

- **Study of 531 patients with pelvic mass**
  - **Low risk: 352 cases**
    - **Benign ovarian tumors**
  - **High risk: 179 cases**
    - **Epithelial ovarian cancers (n=129)**
    - **22 borderline tumors/6 non-epithelial ovarian cancers**
    - **22 non ovarian cancers**

	Sensitivity	Specificity
Postmenopausal	92.3%	75.0%
Premenopausal	76.5%	74.8%

Moore RG, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2009 Jan;112(1):40-6.

Radiographic imaging

- **Ultrasound**
  - **Size, location, locularity, echogenicity, blood flow, septations, presence of ascites**
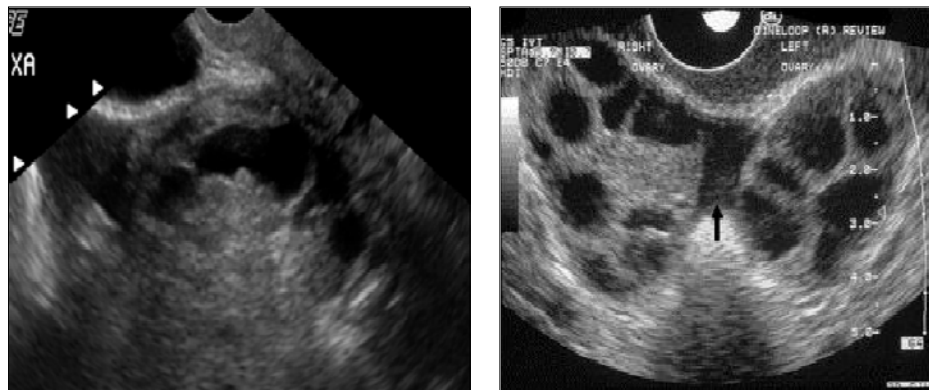
# Radiographic imaging

- **MRI**
  - **May be helpful in further assessing those masses that have an indeterminate malignant potential on ultrasound**
  - **Expensive, but may prevent patients from undergoing an unnecessary surgical procedure.**
- **CT scan**
  - **Ovarian cancer pre-operative and post-operative treatment planning**

Concerning for Malignancy

- **Complex or solid mass**
- **Ascites**
- **Presence of blood flow within papillary projection**
- **Diameter >10cm**
- **Bilateral tumors**
- **Septation >3mm in width**
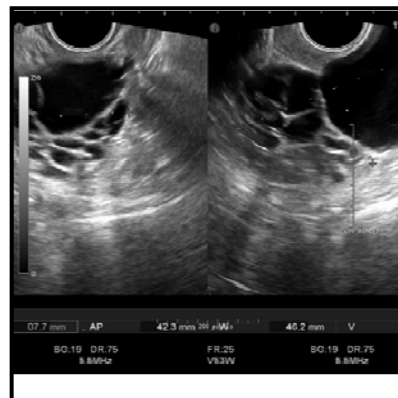
Referral Guidelines

SGO AND ACOG REFERRAL GUIDELINES FOR A
NEWLY DIAGNOSED PELVIC MASS

PREMENOPAUSAL (< 50 YEARS OLD)
CA-125 > 200 U/mL
  Ascites
  Evidence of abdominal or distant metastasis
  (by exam or imaging study)
  Family history of breast or ovarian cancer (in a
  first-degree relative)

POSTMENOPAUSAL (≥ 50 YEARS OLD)
CA-125 > 35 U/mL
  Ascites
  Nodular or fixed pelvic mass
  Evidence of abdominal or distant metastasis (by
  exam or imaging study)
  Family history of breast or ovarian cancer (in a
  first degree relative)

Only one criterion from the list is required to recommend referral

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Ovarian Cancer

Ritu Salani, MD, M.B.A.
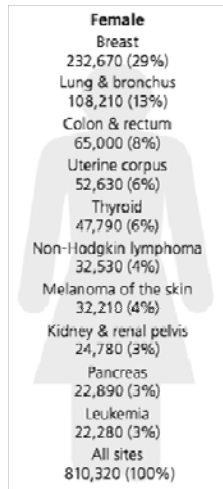**Assistant Professor**
Division of Gynecology Oncology
The Ohio State University Comprehensive Cancer Center
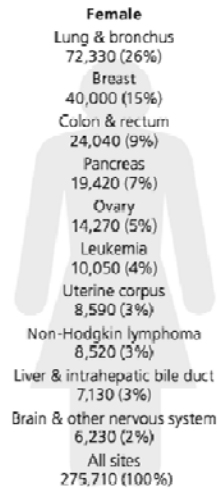**Arthur G. James Cancer Hospital and**
Richard J. Solove Research Institute

Cancer statistics 2014

Estimated new cases

Female
Breast
232,670 (29%)
Lung & bronchus
108,210 (13%)
Colon & rectum
65,000 (8%)
Uterine corpus
52,630 (6%)
Thyroid
47,790 (6%)
Non-Hodgkin lymphoma
32,530 (4%)
Melanoma of the skin
32,210 (4%)
Kidney & renal pelvis
24,780 (3%)
Pancreas
22,890 (3%)
Leukemia
22,280 (3%)
All sites
810,320 (100%)

Estimated deaths

Female
Lung & bronchus
72,330 (26%)
Breast
40,000 (15%)
Colon & rectum
24,040 (9%)
Pancreas
19,420 (7%)
Ovary
14,270 (5%)
Leukemia
10,050 (4%)
Uterine corpus
8,590 (3%)
Non-Hodgkin lymphoma
8,520 (3%)
Liver & intrahepatic bile duct
7,130 (3%)
Brain & other nervous system
6,230 (2%)
All sites
275,710 (100%)

American Cancer Society®

# Types of ovarian cancer

- **Epithelial cancer (85%)**
  - **Serous**
  - **Mucinous**
  - **Clear cell**
  - **Endometrioid**
  - **Transitional cell (Brenner)**
- **Non-epithelial cancer**
  - **Germ cell tumors**
  - **Sex cord stromal tumors**

|	Ovarian cancer staging	Incidence	Survival
Stage I	Confined to the Ovary	20%	85%
I$_A$	Growth limited to one ovary.		
I$_B$	Same as I$_A$ but involves both ovaries		
I$_C$	Above with positive washings or ruptured capsule		
Stage II	Extends to True Pelvis	5%	60%
II$_A$	Involves fallopian tube or uterus		
II$_B$	Extension to other pelvic tissues		
Stage III	Extends Beyond the True Pelvis	58%	26%
III$_{A1}$	Positive retroperitoneal nodes only		
III$_{A2}$	Microscopic positive biopsy outside the pelvis		
III$_B$	Abdominal implants up to 2 cm		
III$_C$	Positive lymph nodes or abdominal implants > 2 cm		
Stage IV	Distant Disease	17%	12%
IV$_A$	Pleural effusion with positive cytology		
IV$_B$	Parenchymal and extra-abdominal metastases		

Diagnosis

- **Examination**
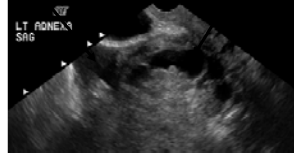- **Imaging**
- **CA-125 level**
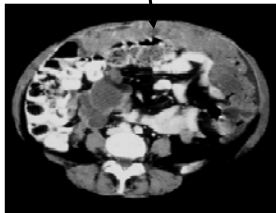
Septation   Excrescences
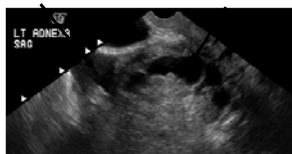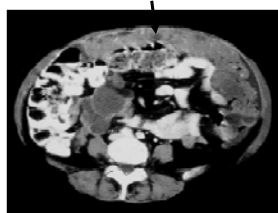
Omental Cake

Diagnosis

- **Examination**
- **Imaging**
- **CA-125 level**

Septation **Excrescences**


Omental Cake

SURGERY

Role for surgery

- **Establish diagnosis (surgery)**
  - **Laparotomy versus laparoscopy**
  - **Cytology only if unable to operate**

- **Surgical goals**
  - **Determine extent of disease (staging)**
  - **Cytoreduction (debulking)**
  - **Restore/preserve anatomy**

Surgical staging

- **Cytology**
- **Assessment/biopsies of peritoneal surfaces**
- **Hysterectomy and salpingo-oophorectomy**
- **Pelvic and para-aortic lymph nodes**
- **Appendectomy**
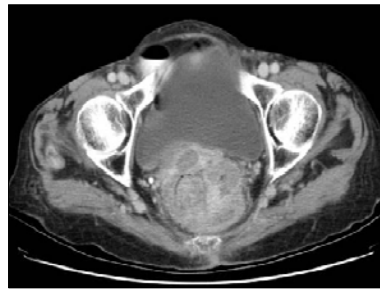
Importance of surgical staging

- **Clinically early stage**
  - **Completion staging upstages 31%**
- **Therapeutic**
  - **Resection of metastatic deposits**
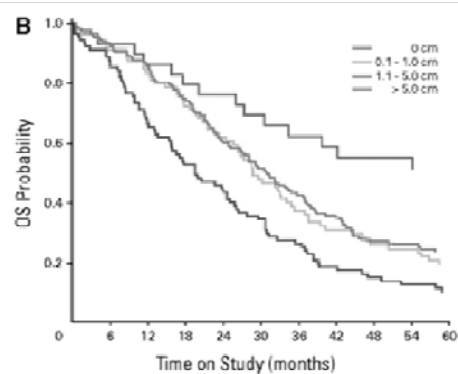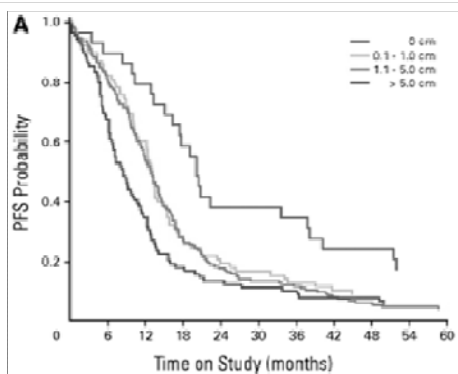 - **Assign appropriate adjuvant treatment**
  - **Maximizes survival**

Cytoreductive Surgery

- **Goal is elimination of all tumor**
  - **No gross residual (microscopic)**
  - **Optimal (≤1 cm)**
  - **Suboptimal (>1 cm)**
- **Operative Technique**
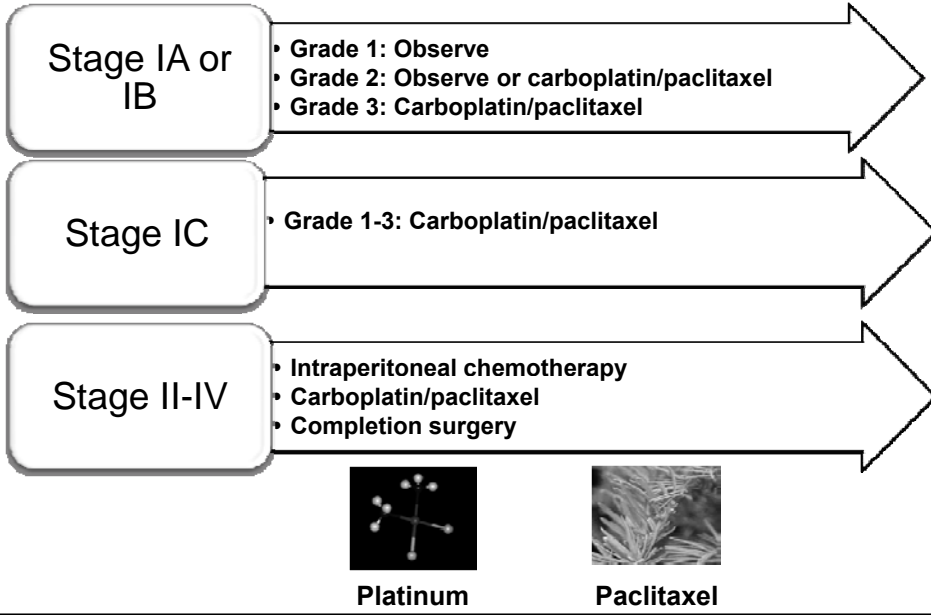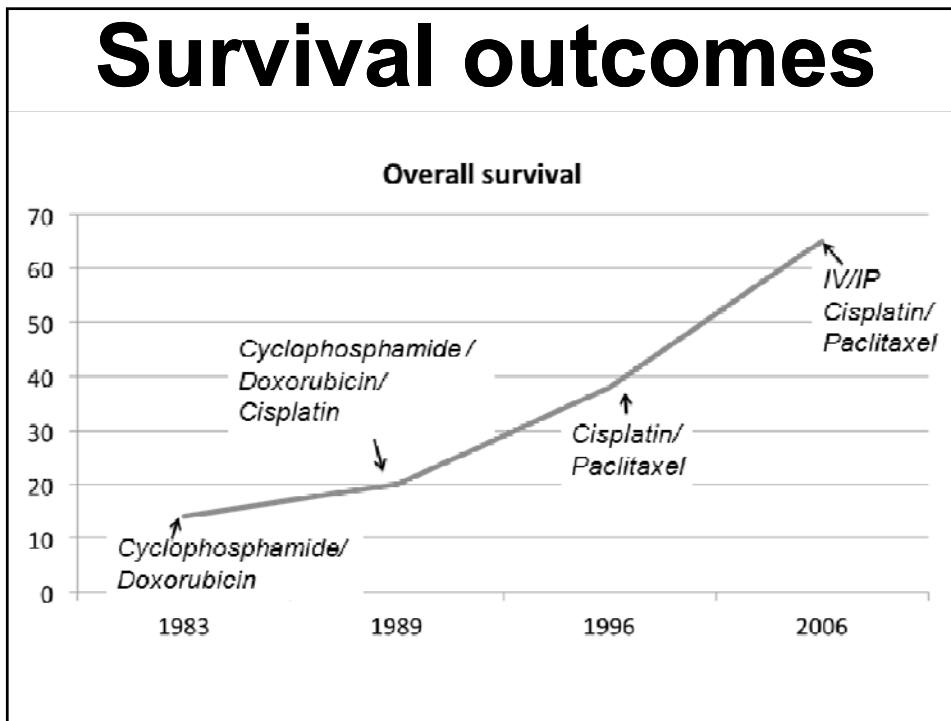 - **Radical resection**
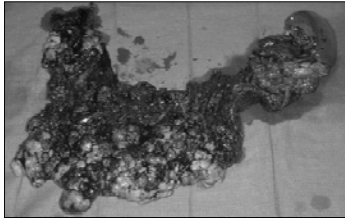
Importance of surgical debulking

Resection of all visible disease should be the goal

Winters et al. J Clin Oncol 2008; 26(1): 83-89

Chemotherapy

Stage IA or IB
- Grade 1: Observe
- Grade 2: Observe or carboplatin/paclitaxel
- Grade 3: Carboplatin/paclitaxel

Stage IC
- Grade 1-3: Carboplatin/paclitaxel

Stage II-IV
- Intraperitoneal chemotherapy
- Carboplatin/paclitaxel
- Completion surgery

Platinum   Paclitaxel

Survival outcomes

Overall survival

Cyclophosphamide/
Doxorubicin/
Cisplatin

Cisplatin/
Paclitaxel

IV/IP
Cisplatin/
Paclitaxel

Cyclophosphamide/
Doxorubicin

1983   1989   1996   2006

Surgery and chemotherapy

- **Goals of Treatment**
  - **Prolong survival**
  - **Delay time to progression**
  - **Control disease-related symptoms**
  - **Minimize treatment-related adverse events**
  - **Maintain or improve quality of life**

Neoadjuvant chemotherapy

- **Utilized when patients are not likely to undergo complete surgical resection**

- **Disease factors**
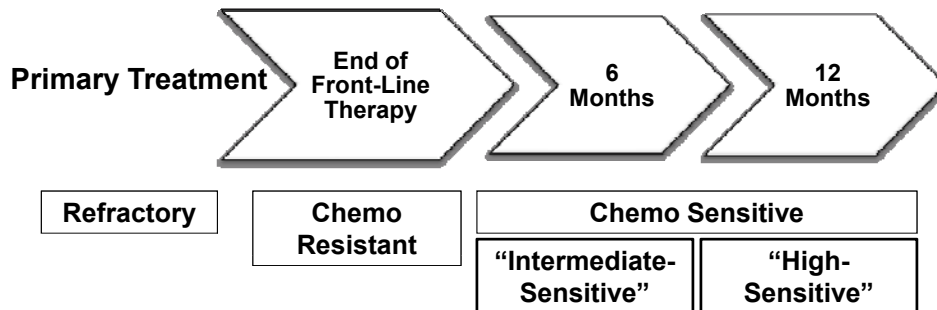- **Patient factors**
- **Surgeon factors**

Recurrent Ovarian Cancer

Stage	CR	Recurrence
Stage I	~ 100%	20-25%
Stage II	~100%	50%
Optimal stage III	> 90%	75%
Suboptimal stage III / IV	50%	> 90%

- **Most patients will have disease recur within 5 years**
- **Retreatment challenges**
  - **Low response rates**
  - **Shortened PFS**

Chemotherapy Sensitivity

Primary Treatment → End of Front-Line Therapy → 6 Months → 12 Months

Refractory	Chemo Resistant	Chemo Sensitive	
		"Intermediate-Sensitive"	"High-Sensitive"

Future opportunities and directions

- **Screening**
  - **New tumor markers/Better imaging**
- **Referral to gynecologic oncology**
  - **Majority of women do not receive standard care**
- **Prolonging recurrence free interval**
  - **The role of maintenance therapy**
- **Improving second line therapies**
  - **Role of biologics**

Screening

- **Ultrasound**

- **CA-125**

  - **High rate of false positives**

  - **Often not abnormal until advanced stages**

Ovarian cancer screening

- **Randomization of ~78,000 low risk women to screening or routine care**
  - **Women aged 55 to 74 years randomized**
  - **Screening: annual CA-125 (cut-off ≥ 35) and ultrasound**
- **Results**
  - **False-positive rate ~10%**
  - **No improvement in mortality rates**
  - **High rate of serious complications**

Screening – US and CA 125

National Health Institutes:
"…there is no evidence available yet that the current screening modalities of CA 125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer…"

Screening – US and CA 125

National Health Institutes:

"... ROUTINE OVARIAN CANCER SCREENING IS NOT RECOMMENDED
tha   s of
CA
ult
us
reduce mortality from ovarian cancer…"

Future opportunities and directions

- **Screening**
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