CT Imaging and Staging of Ovarian Cancer

Priya Bhosale MD
Professor of Radiology
Ovarian Cancer

- Introduction
- Staging
- Restaging
- Radiology Report/Summary
Ovarian Cancer

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Ovarian Cancer

serous tubal intraepithelial carcinoma (STIC)
Ovarian Cancer

- 2nd common gynecologic malignancy in the US
- Leading cause of mortality in women with malignancy of the reproductive tract
- Incidence 1 in 70 women
Ovarian Cancer

90% - Sporadic

10% - Breast-ovarian cancer syndrome- linked
BRCA1 and BRCA2 (15-20% risk)
Site-specific ovarian cancer syndrome
Lynch syndrome II
Ovarian Cancer

- 75% are diagnosed at stage (III/IV), 5-year survival is 18%
- Early detection may extend life expectancy
Ovarian Cancer

• Currently the methods used for diagnosis of ovarian cancer are physical exam

• TVUS

• Tumor marker - CA125
Ovarian Cancer

- Only a minority of the frequently encountered adnexal masses in clinical practice are malignant.

- 5% - 10% of women undergo surgery and only 13% - 21% have ovarian carcinoma.

NIH Consensus Conference. Ovarian cancer. Screening, treatment, and follow-up. NIH Consensus Development Panel on Ovarian Cancer JAMA 1995
Ovarian Cancer

56 year old female with right ovarian mass, CA125 of 200
Risk Malignancy Index (RMI)

RMI was developed in 1990, by Jacobs

- Product of serum CA 125 level (U/ml)
- Ultrasound scan result (0-3)
- Menopausal status (1 if premenopausal and 3 if postmenopausal)
## Ovarian Cancer (RMI) For Detection

<table>
<thead>
<tr>
<th>Article</th>
<th>RMI Cutoff Values</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs et al\textsuperscript{6}</td>
<td>200</td>
<td>85</td>
<td>97</td>
</tr>
<tr>
<td>Prys Davies et al\textsuperscript{7}</td>
<td>200</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Tingulstad et al\textsuperscript{8}</td>
<td>200</td>
<td>80</td>
<td>92</td>
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<tr>
<td>Tingulstad et al\textsuperscript{9}</td>
<td>200</td>
<td>71</td>
<td>92</td>
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<tr>
<td>Torres et al\textsuperscript{10}</td>
<td>150</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Andersen et al\textsuperscript{11}</td>
<td>&gt;200</td>
<td>70.6</td>
<td>89.3</td>
</tr>
<tr>
<td>Bailey et al\textsuperscript{12}</td>
<td>&gt;200</td>
<td>87.4</td>
<td></td>
</tr>
</tbody>
</table>

Mansour G.2009, Int J Gynecol Cancer
Ovarian Mass Characterization

42 year old female with history of low back pain and CA125 of 625
Ovarian Mass Characterization

42 year old female with history of low back pain and CA125 of 625
Ovarian Cancer

Internal architecture of the tumor is better seen on the lower keV images, and thus can help better assess adnexal lesions.
Types of ovarian cancer

- **Type I**: low-grade serous, low-grade endometrioid, mucinous and clear cell carcinomas have mutation in **BRAF** and **KRAS** genes.

- **Type II**: high-grade serous, high-grade endometrioid, undifferentiated carcinomas and malignant mixed mesodermal tumors have **TP53** gene mutation.

Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm.

Robert J. Kurman, Ie-Ming Shih 2011
Spread of Ovarian Cancer
Spread of Ovarian Cancer

- Lymphatic
- Peritoneal
- Hematogenous
Spread of Ovarian Cancer

Lymphatic Spread

Gonadal vessels- Retroperitoneal adenopathy

Broad ligament- Internal iliac, obturator, and external iliac adenopathy

Round ligament- Superficial and deep inguinal Nodes

Lymphatic obstruction- Ascites
Lymphatic Spread

- **Supradiaphragmatic** lymph node metastasis is commonly seen in patients who have ascites at the time of diagnosis.

- **Axillary** lymph node metastasis are rare but may be seen when metastasis to the parasternal, cardiophrenic, or mediastinal region is present.

FDG PET/CT in staging of advanced epithelial ovarian cancer: Frequency of supradiaphragmatic lymph node metastasis challenges the traditional pattern of disease spread. Johanna Hynninen Gynecologic oncology 2012
Peritoneal Spread

- Liver
- Spleen
- Stomach
- Phrenicocolic Ligament
- Ascending Colon
- Ascites
- Uterus
- Liver
- Stomach Pancreas
- Colon
- Root of Mesentery
- Uterus
- Rectum
- Bladder
Ligamentous Spread
Ovarian cancer

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Ovarian Cancer Staging

Currently Ovarian cancer is staged surgically according to Federation of Obstetricians and Gynecologists (FIGO)

Radiological Sub-Commission of the Cancer Commission of the Health Organization of the League of Nations in 1928

History of the FIGO cancer staging system  Franco Odicino 2008
# Ovarian Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Limited to ovaries</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>Involves ovaries with pelvic extension</td>
<td>70%</td>
</tr>
<tr>
<td>III</td>
<td>Involves ovaries with mets outside pelvis/ lymphadenopathy</td>
<td>39%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>17%</td>
</tr>
</tbody>
</table>

SEER data last revised 2/2016
## Summary change in FIGO

<table>
<thead>
<tr>
<th>Previous</th>
<th>Recent (2014)</th>
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</thead>
<tbody>
<tr>
<td>IA &amp; IB</td>
<td>IA &amp; IB</td>
</tr>
<tr>
<td>IC</td>
<td>IC1, IC2, IC3</td>
</tr>
<tr>
<td>IIIA &amp; IIIB</td>
<td>IIIA &amp; IIIB, IIC eliminated</td>
</tr>
<tr>
<td>IIIA</td>
<td>IIIA1, IIIA2</td>
</tr>
<tr>
<td>IIIB</td>
<td>IIIB &lt;2cm retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>IIIC</td>
<td>IIIC &gt;2cm retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>IVA, IVB</td>
</tr>
</tbody>
</table>
Patterns and Prognostic Importance of Hepatic Involvement in Patients with Serous Ovarian Cancer: A Single-Institution Experience with 244 Patients. O'Neill AC

N=244

OS with LPI 83 months vs hematogenous 63 months

Ovarian Cancer Staging
Stage IV

- Left-sided moderate or large pleural effusion and presence of ascites were significantly associated with solid pleural metastasis (26/44)

- Moderate or large right-sided pleural effusion was malignant

Thoracic metastasis in advanced ovarian cancer: comparison between computed tomography and video-assisted thoracic surgery  Oleg Mironov J Gynecol Oncol 2011

N=44
Ovarian Cancer Staging

Modalities used are

- CT
- MRI
- PET/CT
Staging

Recommedation 1.2

A primary clinical evaluation should include a CT of the abdomen and pelvis with oral and intravenous contrast and chest imaging (CT preferred) to evaluate the extent of disease and the feasibility of surgical resection. The use of other tools to refine this assessment may include laparoscopic evaluation or additional radiographic imaging (eg, FDG-PET scan or diffusion-weighted MRI).

(Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)
Ovarian Cancer Staging

CT is the primary modality used for staging ovarian cancer as it is readily available.

Peritoneal metastases - Sensitivity of 92%
Specificity of 82%

Tempany et al. Radiology 2000
Ovarian Cancer Staging

Courtesy of DR Charles Levenback MD
Suboptimal Cytoreduction and Survival

No macroscopic residual disease - median survival is 106 months

Residual < 0.5 cm disease - median overall survival of 66 months
< 1 cm disease – 48 months

N= 465

Chi et al, What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol (2006)
Sub diaphragmatic implant is better seen on lower keV images, and on the iodine (-water) images. The lesion does not contain calcium, which would have been conspicuous on water(-iodine) images and on calcium (-iodine) images—in a patient with high grade ovarian cancer.
Ovarian Cancer Staging

Note the calcified implants are better seen on the water only and the calcium only images in this patient with low grade serous cancer. Contrast may obscure calcified implants.
Predictors of suboptimal cytoreduction

- Diaphragmatic involvement
- **Serosal** involvement of large and small bowel
- Infiltrative **mesenteric** implants
- Hepatic metastases/liver surface disease
- Involvement of the supracolic omentum and stomach

MD Anderson criteria
Predictors of suboptimal cytoreduction
Predictors of suboptimal cytoreduction
Survival of patients who undergo debulking with no residual tumor is longer than that of patients who undergo debulking with residual tumor ($P = 0.0001$). (lived 7.8 months longer)
Neoadjuvant Therapy

3/14/2012  5/29/2012
Prediction of Response to Neoadjuvant Chemotherapy by Sequential F-18-Fluorodeoxyglucose Positron Emission Tomography in Patients With Advanced-Stage Ovarian Cancer  JCO Avril 2005
Ovarian Cancer

• Introduction

• Staging

• Restaging for recurrence

• Radiology Report/Summary
Restaging

- CT scans are obtained 3 months post surgery for 1st year and then every 6 months after that.
- CA-125 done with every scan.
- Elevation of CA-125 suggests recurrent disease.
Restaging

“There is no survival benefit from early treatment based on a raised serum marker level alone unless there is radiological or clinical evidence of disease, such as the patient being symptomatic”

N=1442

Rustin GJ. Should clinicians give second line chemotherapy after detecting elevated CA-125 levels ASCO. Chicago 2009
Recurrent disease

• About 80% of patients with advanced disease will relapse after first-line chemotherapy
Recurrent disease

Explicit mathematical form for computing the risk score for TTP based on the image features. The authors caution against using this predictor in clinical practice without a larger study confirming its performance.

<table>
<thead>
<tr>
<th>Component</th>
<th>Formula/Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.0082 × number of locations with peritoneal disease</td>
</tr>
<tr>
<td>Peritoneal disease present in paracolic gutters</td>
<td>Add 0.022</td>
</tr>
<tr>
<td>Peritoneal disease present in liver/right upper quadrant</td>
<td>Add 0.112</td>
</tr>
<tr>
<td>Supradiaphragmatic adenopathy</td>
<td>Add 0.078</td>
</tr>
</tbody>
</table>

Risk score: sum of above components

Unpublished data from TCGA radiology group – accepted in Radiology 2016
53-year-old woman with a history of low-grade recurrent serous carcinoma of the ovary with gradual elevation of CA-125
Recurrent Disease
Recurrent Disease

55 year old women with ovarian cancer CT/MRI performed for surgical evaluation
Recurrent Disease

60 year old women with ovarian cancer
MRI performed for surgical evaluation
Recurrent Disease

CA 125, PET alone, PET–CT, CT and MRI in diagnosing recurrent ovarian carcinoma: A systematic review and meta-analysis  Ping Gu  2009 European Radiology

<table>
<thead>
<tr>
<th></th>
<th>Pooled-sensitivity (95% CI)</th>
<th>Pooled-specificity (95% CI)</th>
<th>AUC</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125</td>
<td>0.69 (0.65–0.72)</td>
<td>0.93 (0.89–0.95)</td>
<td>0.9219</td>
<td>0.145</td>
</tr>
<tr>
<td>CT</td>
<td>0.79 (0.74–0.84)</td>
<td>0.84 (0.76–0.90)</td>
<td>0.8845</td>
<td>0.146</td>
</tr>
<tr>
<td>MRI</td>
<td>0.75 (0.69–0.80)</td>
<td>0.78 (0.70–0.85)</td>
<td>0.7955</td>
<td>0.300</td>
</tr>
<tr>
<td>PET alone</td>
<td>0.88 (0.84–0.92)</td>
<td>0.89 (0.83–0.94)</td>
<td>0.9297</td>
<td>0.229</td>
</tr>
<tr>
<td>PET–CT</td>
<td>0.91 (0.88–0.94)</td>
<td>0.88 (0.81–0.93)</td>
<td>0.9555</td>
<td>0.109</td>
</tr>
</tbody>
</table>
Recurrent Disease

In the setting of rising CA-125 levels with negative or questionable conventional imaging findings, FDG-PET/CT may detect recurrence.

54-year-old female with a recurrent low-grade serous carcinoma of the ovary with rising CA-125
Recurrent Disease

55 year old female post resection of mucinous ovarian cancer
Recurrent Disease

PET can help detect disease in symptomatic patients with normal CA125

N=66

Bhosale et al 2010 Int Journal of Gynecologic Cancer
Recurrent Disease

74 year old female with ovarian cancer with normal CA-125 of 8 and low back pain
51 year old female with serous borderline tumor with recurrence currently on letrozole CA125-23 stable
Ovarian Cancer

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• Subdiaphragmatic, supracolic omentum, hepatic metastases, small bowel mesenteric involvement, serosal involvement

If adenopathy present should mention if lymph nodes are seen above the renal hila

The utility of computed tomography scans in predicting suboptimal cytoreductive surgery in women with advanced ovarian carcinoma. 2004 Gynecology Oncology
Radiology Report

- For recurrent disease the exact location is to be reported

- Abutment of important vascular structures and organs is to be mention so as to assist surgical planning
Summary

• PET /CT can identify distant disease that can affect optimal debulking

• CT and MRI can localize recurrent disease and can be used to plan optimal therapy for recurrent disease

• PET/CT can identify disease in symptomatic patients, in whom CT is negative or equivocal
The End
To investigate associations between radiophenotypic features observed on preoperative CT, CLOVAR gene signatures, and survival in women with high-grade serous ovarian cancer (HGS-OvCa), this study was conducted.

Notch receptors participate in signal transduction by localizing a receptor tyrosine kinase domain to the nucleus, where they activate an array of downstream effectors that play important roles in cell proliferation and survival. The association of genetic changes in Notch and human cancer has been recently established in lung carcinoma. Translocation of t(15;19) was identified in non-small-cell lung cancer cell lines and the breakpoint has been mapped to 50 bp upstream of the Notch locus. The translocation of chromosome 19p was found to correlate with overexpression of Notch3 full-length mRNA. Our data provide new evidence that demonstrates that translocation, gene amplification, and alternative splicing may contribute to Notch3 expression.

**Functional analysis of Notch3 expression:** To determine if Notch3 is essential for cell growth and survival in cell lines that overexpress Notch3, we used γ-secretase inhibitor 1, which prevents the activation of Notch by inhibiting the proteolysis and translocation of Notch3 to the nucleus. This compound has been shown to be a potent and specific inhibitor of Notch pathway (19, 20). γ-secretase inhibitor was applied to the culture medium in nine cell lines, including three cancer cell lines with Notch3 overexpression (OVCA3, A2780, and MCF7), an immortalized OSE cell line (OSE 29), and five cancer cell lines (MCF-7, TOV-21G, and Si-2) without Notch3 expression (Fig. 5A). We first determined the concentration of γ-secretase inhibitor to be used and found that the IC50 was lowest in OVCA3 (1 μmol/L). Therefore, we treated different cell lines with 1 μmol/L in culture and found that there was a substantial reduction in cell number of OVCA3, A2780, and MCF7 cells compared with Notch3 compared with control cells that did not have Notch3 overexpression (Fig. 5B, P < 0.001, Student’s t test). To assess the mechanisms underlying the growth inhibition by the γ-secretase inhibitor in OVCA3, A2780, and MCF7 cells, we measured the percentage of BrdUrd-labeled cells for cellular proliferation and Annexin V-labeled cells for apoptosis (Fig. 5C and D). We found that γ-secretase inhibitor significantly reduced cellular proliferation and induced apoptosis in all three cell lines with Notch3 overexpression compared with the DMSO controls (P < 0.001, Student’s t test). siRNA was used to knock down the expression of Notch3 in the same nine cell lines used for the γ-secretase inhibitor assay. The knockdown effect of siRNA was shown by Western blot (Fig. 6A). siRNA treatment significantly reduced the Notch3 protein expression compared with the mock or control siRNA-treated groups. Similar to the effects of γ-secretase inhibitor, Notch3 siRNA reduced cell number most significantly in OVCA3, A2780, and MCF7 cells, which overexpressed Notch3 compared with the other cell lines (Fig. 6B, P < 0.001, Student’s t test). The BrdUrd-positive cells decreased and the Annexin V-labeled cells increased in Notch3 siRNA-treated cells compared with control siRNA-treated cells (Figs. 6C and D, P < 0.001, Student’s t test).

In vitro data to indicate Notch3 by γ-secretase inhibitor and siRNA may have clinical implications for ovarian cancer patients and suggest that Notch3 can be a candidate therapeutic target. γ-Secretase inhibitors have been studied in the past several years as a potential therapeutic intervention in Alzheimer’s disease. Very recently, γ-secretase inhibitors have been shown to inhibit the Notch pathway and block cell differentiation in intestinal adenomas Apcmin (min) mice (20). Furthermore, γ-secretase was shown to be able to inhibit the growth of Kaposi sarcoma cells in mouse tumor model (19). Therefore, with the promising effects at both in vitro and in vivo systems, γ-secretase inhibitors can be used as a new target-based therapy for those tumors with Notch3 activation.

The current study suggests that Notch3 is a strong candidate oncogene among the genes within the ch1p33.312 amplicon in ovarian carcinomas. This is because Notch3 gene shows a high level of gene amplification and overexpression and is functionally essential for tumor growth and survival. Although the above represents our preferred interpretation, other alternative interpretations should be pointed out. For example, Notch3 may not be the only gene with high correlation of DNA copy number and gene expression level after analyzing a large series of amplified and nonamplified tumors. It is possible that other coamplified gene(s) within the Notch3 amplicon also plays a role in tumorigenesis and may cooperate with Notch3 in propelling tumor progression.

In conclusion, we have identified Notch3 as a candidate amplified oncogene that overexpressed in 66% of ovarian serous carcinomas. Our findings suggest that Notch3 amplification may play an important role in the development and progression of ovarian carcinomas; moreover, these findings provide a rationale for future development of Notch3-based therapy for ovarian cancer.

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**References**