Surgical and Adjuvant Treatment of Clear Cell Ovarian Carcinoma:

Current Approach

Prof. Dr. Aydın Özsaran
Subtypes of epithelial ovarian carcinomas;

- High-grade serous (HGSC; 70 to 80 percent)
- Endometrioid (10 percent)
- Clear cell (CCCO; ~10 percent)
- Mucinous (3 percent)
- Low-grade serous (LGSC; <5 percent)
Clear cell carcinoma of ovary (CCCO)

• Second most common histologic subtype after high grade serous carcinoma
• The incidence of CCCO is different by ethnicity
• Incidence rates were 4.8% in whites, 3.1% in blacks, and 11.1% in Asians
• Most commonly in perimenopausal women in their late 40s or 50s
• Endometriosis was associated with increased risk of ovarian cancer especially with endometrioid and clear cell histologic type
• Thromboembolic events (independent prognostic factor??)
• Hypercalcemia
Gross and microscopic pathology

- A large mass with an average size of 15 cm
  - A thick-walled uni or multilocular cyst with yellowish
  - Fleshy nodules protruding into the lumen of the cyst
  - Watery, mucinous or brownish “chocolatecolored” fluid with in the cyst
- Different architecture, characterized by papillary structures,
  - Solid components with desmoplastic and hyalinized stroma and high-grade nuclear atypia
  - Hobnail cells
Immunohistochemistry

- **Negative** for estrogen/ progesterone receptor and Wilms tumor suppressor 1 (WT1)
- CK7 (+) and CK20 (-)
- Typically express
  - hypoxia-inducible factor 1 α (HIF-1 α)
  - glypican-3
  - hepatocyte nuclear factor 1- β (HNF-1 β)
- **HNF-1β : sensitive and specific marker of CCCO (~82-100 %)**
Molecular biology

- Usually **negative** for p53, BRCA1, and BRCA2 mutations

- **Positive** for ARID1A and PIK3CA mutations
  - (although p53, KRAS and PTEN mutations are frequently observed in ovarian cancers in general)

- ARID1A mutations are seen in 40% to 60% of CCCO; but not in HGS carcinomas.

- Lynch syndrome is associated with CCCO
The new classifications of ovarian, fallopian tube, and primary peritoneal cancer and their clinical implications.

Author information

Abstract
The roles of histologic characterization and staging are to provide reproducible metrics for cancer classification with which to direct the most appropriate clinical care and to yield the most stable reliable system to allow both prospective and retrospective data analysis. Both the histologic and staging classifications of malignant ovarian/tubal/peritoneal cancers have recently changed. The World Health Organization sponsored a review and reclassification of the pathology of the cancers of the ovaries, fallopian tubes, and peritoneum, and published these updates in 2014. In so doing, they codified the two-tiered grading system that has been in use in serous ovarian cancers for nearly a decade. In parallel, FIGO reviewed and updated the surgical staging system, applied to all histotypes of ovarian, tubal, and peritoneal cancers, also published in 2014. In both cases, the changes made are meant to encompass a better understanding of disease, but both have important merits and drawbacks. Changes in staging complicate analysis of retrospective data against current data. Though in some aspects controversial, the changes overall are meant to represent a better biologic understanding of disease that we hope will lead to an improvement in patient care and directed therapy.

<table>
<thead>
<tr>
<th>Type</th>
<th>% of total</th>
<th>Molecular characteristics</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGSOC</td>
<td>70</td>
<td>TP53(^{\text{mut}}), genomic instability</td>
<td>STIC precursor, no BOT</td>
</tr>
<tr>
<td>LGSOC</td>
<td>3.5</td>
<td>KRAS(^{\text{mut}}), BRAF(^{\text{mut}})</td>
<td>Mutations more common in SBOT</td>
</tr>
<tr>
<td>CCC</td>
<td>10</td>
<td>ARID1(^{\text{a,b,c}}), PIK3CA(^{\text{b,c}}), PIK3CA(^{\text{d}})</td>
<td>15%–30% with endometriosis</td>
</tr>
<tr>
<td>ENDO Igr</td>
<td>10</td>
<td>ARID1(^{\text{a,b,c}}), PIK3CA(^{\text{b,c}}), PTEN LOH, (\beta) catenin(^{\text{mut}})</td>
<td>EBOT frequency of mutations similar to invasive, 15%–30% associated with endometriosis</td>
</tr>
<tr>
<td>ENDO hgr</td>
<td>10</td>
<td>TP53(^{\text{mut}})</td>
<td>Recategorized as HGSOC</td>
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<tr>
<td>Mucinous</td>
<td>3.6</td>
<td>80%(^{+}) KRAS(^{\text{mut}})</td>
<td>Intestinal type only</td>
</tr>
</tbody>
</table>

Igr, low grade; hgr, high grade.
Demographic, Clinical, and Prognostic Factors of Ovarian Clear Cell Adenocarcinomas According to Endometriosis Status.

Schnack TH¹, Hegdall E, Thomsen LN, Høgdall C.

Author information

Abstract

OBJECTIVES: Women with endometriosis carry an increased risk for ovarian clear cell adenocarcinomas (CCCs). Clear cell adenocarcinoma may develop from endometriosis lesions. Few studies have compared clinical and prognostic factors and overall survival in patients diagnosed as having CCC according to endometriosis status.

➢ 179 patient, in the period from 2005 to 2013.

➢ The CCCO patients were divided into 3 groups:
  • Patients with concomitant ovarian endometriosis (n = 46),
  • CCCO with pelvic endometriosis including the 46 CCCO patients with concomitant ovarian endometriosis (n = 80),
  • Patients with no concomitant endometriosis (n=95).
➢ A significantly higher proportion of patients with ovarian endometriosis had pure CCCOs (97.8% vs 82.1%; P = 0.001) as compared with patients without endometriosis.

➢ Overall survival was poorer among CCCO patients with concomitant ovarian endometriosis.

<table>
<thead>
<tr>
<th></th>
<th>CCC + Pelvic Endometriosis</th>
<th>CCC + Ovarian Endometriosis</th>
<th>CCC No Endometriosis</th>
<th>Pelvic vs No Endometriosis, P value</th>
<th>Ovarian vs No Endometriosis, P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>80</td>
<td>46</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology of adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure clear cell</td>
<td>78 (97.5)</td>
<td>45 (97.8)</td>
<td>78 (82.1)</td>
<td>0.001</td>
<td>0.025</td>
</tr>
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<td>Clear cell/serous</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (10.5)</td>
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<td></td>
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<tr>
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<td>2 (2.5)</td>
<td>1 (2.2)</td>
<td>0 (0)</td>
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<td></td>
</tr>
<tr>
<td>Clear cell/mucinous</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>48 (57.9)</td>
<td>31 (67.4)</td>
<td>55 (60.0)</td>
<td>0.39</td>
<td>0.34</td>
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<tr>
<td>Stage II</td>
<td>10 (12.5)</td>
<td>5 (10.9)</td>
<td>7 (7.4)</td>
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<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>17 (21.3)</td>
<td>8 (17.4)</td>
<td>21 (22.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>5 (6.3)</td>
<td>2 (4.3)</td>
<td>12 (12.6)</td>
<td></td>
<td></td>
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<tr>
<td>Endometriosis location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic endometriosis*</td>
<td>80</td>
<td>46</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Pelvic other than ovarian</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Ovarian contralateral</td>
<td>13</td>
<td>13</td>
<td>0</td>
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<tr>
<td>Ovarian ipsilateral</td>
<td>33</td>
<td>33</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomyosis only</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
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</tr>
</tbody>
</table>

Ovarian endometriosis was defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis. Pelvic endometriosis was defined as endometriosis in the pelvis including ovarian endometriosis.

*Including ovarian endometriosis and adenomyosis.
Prognostic factors

- Age
- Tumor diameter
- Tumor origin (of endometriosis or not)
- Residual disease
- Lymph node status
- Stage
- Optimal cytoreduction
- Chemotherapy cycles and sensitivity
Prognosis

• Up to 60% of the patients with CCCO receive their diagnosis in stage I.
• Poor prognosis.
• In Stage I disease, clear cell cancer recurs more frequently, up to 50% of the cases, with a 5-year survival varying from 50% to 73%.
• In advanced disease, it has been reported that the activity of chemotherapy is lower in this cancer hystotypes.
28118 incident epithelial ovarian cancer cases diagnosed in 2004–2014

With in two years after diagnosis, localized/regional-stage carcinosarcoma and distant-stage mucinous, clear cell, and carcinosarcoma had a higher risk of mortality compared with high-grade serous, with the most pronounced association for localized/regional carcinosarcoma and distant-stage mucinous.

Both localized/regional and distant-stage low-grade serous and endometrioid carcinomas had the most favorable outcomes.
Figure 1. Kaplan-Meier survival curves of invasive epithelial ovarian cancer survival by stage and histotype, 2004–2014, SEER 18 registries. A) Localized and regional stage disease. B) Distant-stage disease. Malignant Brenner tumors were excluded due to small sample size.
Primary treatment

✓ The standard surgical treatment is the same as for other epithelial ovarian cancers;
   - Hysterectomy
   - Bilateral salpingo-oophorectomy
   - Omentectomy
   - Pelvic and paraaortic lymphadenectomy
   - Cytoreductive surgery

✓ Cytoreductive surgery should be performed for patients with stage II, III, IV
NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/
Primary Peritoneal Cancer

CLINICAL PRESENTATION
- Suspicious⁹ palpable pelvic mass on abdominal/pelvic exam and/or ascites, abdominal distention
- Symptoms without source of malignancy (ie, bloating, pelvic/abdominal pain, difficulty eating or feeling full quickly, urinary symptoms [urgency or frequency])¹⁰

WORKUP
- Abdominal/pelvic exam
- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated¹¹
- Chest CT or chest x-ray as clinically indicated¹²
- Complete blood count, chemistry profile, liver function test (LFT)
- CA-125 or other tumor markers as clinically indicated⁹
- Evaluate nutritional status
- GI evaluation as clinically indicated
- Obtain family history
- Refer to gynecologic oncologist for clinically suspicious lesions

CLINICAL STAGE¹³
- IA (fertility desired)
- IB (fertility desired)
- IA-IV, surgical candidate (fertility not desired)

PRIMARY TREATMENT¹⁴
- Unilateral salpingo-oophorectomy (USO) + comprehensive surgical staging
- Bilateral salpingo-oophorectomy (BSO) + comprehensive surgical staging
- Total abdominal hysterectomy (TAH)/BSO + comprehensive staging and debulking as needed

Diagnosis by previous surgery or tissue biopsy (cytopathology)

See Workup, Findings and Primary Treatment (OV-2)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

¹⁰See NCCN Guidelines for Genital/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genital/Familial High-Risk Assessment: Colorectal.
¹¹Primary treatment should not be delayed for a genetic counseling referral.
¹²PET/CT or MRI may be indicated for indeterminate lesions if results will alter management.
¹³Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and CA 19-9. See Discussion for usefulness of diagnostic tests.
¹⁴Evaluation by a gynecologic oncologist is recommended for:
- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant chemotherapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas.
- Prior to surgery for ovarian cancer, all women should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration. NCI Clinical Announcement.
See Principles of Surgery (OV-1).
See Principles of Chemotherapy (OV-8) and Management of Drug Reactions (OV-10).
Carcinomas, clear cell, mucinous, low-grade serous, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.
• Lymphadenectomy has been shown to improve survival

• The staging system for high grade serous ovarian and primary peritoneal cancer is also used for CCCO.

• Fertility–sparing surgery is not recommended for stage IA to C clear cell carcinomas.
ESGO- Ovarian Cancer Surgery Guidelines

Algorithm 1 for Epithelial Ovarian Cancer Surgery

- Metastatic disease and non-epithelial tumours have been ruled out
- Epithelial ovarian cancer
- Surgical skills Available?

- Yes
  - Send patient to a multidisciplinary unit with surgery meeting the ESGO quality indicators.
  - Do not abuse neoadjuvant therapy
  - Stage IIA
  - TAH and ESGO + Comprehensive surgical staging **

- No
  - Stage IIB-IV
  - Algorithm 2

Algorithm 2 for Epithelial Ovarian Cancer Surgery

- Stage IIB-IIIb
  - Upfront debulking surgery aiming at complete resection*
  - Tumour extension compatible with primary debulking?

- Yes
  - Algorithm 3

- No
  - Pathological assessment
  - Noreadjuvant chemotherrapy or palliation

* Consider fertility preservation in selected young patients.
** With exceptions for retrospective planning (see specific recommendations on surgery of early-stage ovarian cancer).

*With exceptions for IIIb (e.g., poor patient condition or very extensive pelvic disease where neoadjuvant might be preferable).
ALGORITHM 3 FOR EPITHELIAL OVARIAN CANCER SURGERY

Neoadjuvant chemotherapy x 3 courses

Progressive Disease

No Progressive Disease

NO SURGERY

Patient still not fit for surgery or persistence of tumour spread incompatible with complete resection

Patient fit for major surgery and tumour spread compatible with complete resection

Later reassessment after additional courses

SURGERY (INDIVIDUAL EVALUATION)

INTERVAL DEBULKING SURGERY
Multicenter Italian Trials in Ovarian Cancer (MITO)

9 retrospective studies, in Italy, in the years 1991-2007

A total of 240 patient with ovarian cancer (hystological subtypes; pure clear cell: 62.9%, mixed: 34.5%)

45% of patient had stage I disease

Lymphadenectomy was performed in 47.9% of the patient
### TABLE 2. Univariate and multivariate analyses for DFS and OS

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Events/Patients</th>
<th>Median DFS (Months)</th>
<th>5-year DFS (%)</th>
<th>Univariate $P$</th>
<th>HR</th>
<th>95% CI</th>
<th>Multivariate $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ($\leq$70 vs &gt;70)</td>
<td>63/189 vs 12/33</td>
<td>105.5 vs 58.4</td>
<td>57 vs 41</td>
<td>0.49</td>
<td>0.68</td>
<td>0.28–1.65</td>
<td>0.40</td>
</tr>
<tr>
<td>Histology (pure vs mixed)</td>
<td>48/145 vs 18/42</td>
<td>105.5 vs 46.0</td>
<td>54 vs 40</td>
<td>0.82</td>
<td>0.60</td>
<td>0.29–1.23</td>
<td>0.16</td>
</tr>
<tr>
<td>Front-line chemotherapy (+ vs – taxanes)</td>
<td>23/86 vs 50/117</td>
<td>45.2 vs NR</td>
<td>46 vs 63</td>
<td>0.02</td>
<td>1.06</td>
<td>0.56–1.99</td>
<td>0.84</td>
</tr>
<tr>
<td>LA (not done vs done)</td>
<td>55/120 vs 29/112</td>
<td>20.9 vs NR</td>
<td>39 vs 69</td>
<td>0.0001</td>
<td>0.30</td>
<td>0.15–0.59</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

| Stage (I and II vs III and IV)                  | 18/106; 9/50 vs 50/8; 6/13 | NR; NR vs 18.4; 4.8 | 81; 55 vs 16; 0 | 0.0001 | 2.20 | 1.38–5.50 | 0.0009 |
| Residual disease after surgery (absent vs present) | 27/135 vs 56/92 | NR vs 18.9          | 74 vs 19       | 0.0001 | 1.88 | 1.16–3.05 | 0.01  |

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Events/Patients</th>
<th>Median OS (months)</th>
<th>5-year OS (%)</th>
<th>Univariate $P$</th>
<th>HR</th>
<th>95% CI</th>
<th>Multivariate $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ($\leq$70 vs &gt;70)</td>
<td>25/186 vs 2/32</td>
<td>NR vs NR</td>
<td>80 vs 82</td>
<td>0.53</td>
<td>0.60</td>
<td>0.06–5.27</td>
<td>0.64</td>
</tr>
<tr>
<td>Histology (pure vs mixed)</td>
<td>21/141 vs 5/42</td>
<td>NR vs NR</td>
<td>77 vs 87</td>
<td>0.20</td>
<td>0.43</td>
<td>0.11–1.73</td>
<td>0.24</td>
</tr>
<tr>
<td>Front-line chemotherapy (+ vs – taxanes)</td>
<td>4/82 vs 28/117</td>
<td>83.2 vs NR</td>
<td>66 vs 91</td>
<td>0.0004</td>
<td>2.17</td>
<td>0.63–7.45</td>
<td>0.22</td>
</tr>
<tr>
<td>LA (not done vs done)</td>
<td>24/116 vs 9/112</td>
<td>NR vs NR</td>
<td>63 vs 87</td>
<td>0.0012</td>
<td>0.15</td>
<td>0.04–0.54</td>
<td>0.004</td>
</tr>
</tbody>
</table>

| Stage (I and II vs III and IV)                  | 5/107; 5/27 vs 20/76; 3/13 | NR; NR vs 86.1; 21.9 | 95; 68 vs 49; 0 | 0.0001 | 2.29 | 1.08–4.85 | 0.030 |
| Residual disease after surgery (absent vs present) | 2/143 vs 31/85 | NR vs NR          | 91 vs 59      | 0.0001       | 1.42| 0.64–3.18     | 0.38             |

LA, Lymphadenectomy; NR, not reached.
FIGURE 1. Prognostic role of stage in patients with clear cell ovarian cancer (A, DFS; B, OS).
FIGURE 2. Prognostic role of lymphadenectomy (DFS) in all patients (A), stage I and stage II patients (B), and in advanced stages III and IV (C).

FIGURE 3. Prognostic role of lymphadenectomy (OS) in all patients (A), stage I and stage II patients (B), and in advanced stages III and IV (C).
➢ Primary surgery and lymphadenectomy have a prognostic role in patients with CCOO.

➢ Lymphadenectomy was independently associated with DFS and OS, whereas the addition of paclitaxel to platinum-based chemotherapy had no effect on the outcome.

➢ The recurrence rate of early stages is higher, and the presence of clear cell in stage I ovarian cancer is considered a cancer specific feature that suggests the use of adjuvant chemotherapy.

➢ Advanced clear cell disease has been associated with a poorer survival compared to the other histological subgroups.
Between 1988 and 2013

21,537 cases of stage I–II epithelial ovarian cancer (serous (n=7,466), clear cell (n=6,903), mucinous (n=4,066), and endometrioid (n=3,102) histology)

On multivariable analysis, adequate lymphadenectomy was independently associated with improved cause-specific survival compared to inadequate lymphadenectomy: GOG criteria, CGR criteria and Mayo criteria

Compared to inadequate lymphadenectomy, adequate lymphadenectomy was significantly associated with improved cause-specific survival for serous, endometrioid, and clear cell types but not in mucinous type.
Table 5. Histology type-specific cause-specific survival based on lymphadenectomy performance

<table>
<thead>
<tr>
<th>Histology type</th>
<th>Nodal extent</th>
<th>10-yr (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>10-yr (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>10-yr (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>Inadequate</td>
<td>68.5</td>
<td>1.00</td>
<td></td>
<td>71.4</td>
<td>1.00</td>
<td></td>
<td>73.5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate</td>
<td>76.4</td>
<td>0.67 (0.58-0.78)</td>
<td>&lt;0.001</td>
<td>76.5</td>
<td>0.73 (0.63-0.85)</td>
<td>&lt;0.001</td>
<td>73.9</td>
<td>0.86 (0.70-1.06)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Unstaged</td>
<td>56.5</td>
<td>1.69 (1.50-1.90)</td>
<td>&lt;0.001</td>
<td>56.5</td>
<td>1.86 (1.67-2.07)</td>
<td>&lt;0.001</td>
<td>56.5</td>
<td>2.06 (1.87-2.27)</td>
<td>&lt;0.001</td>
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<tr>
<td>Endometrioid</td>
<td>Inadequate</td>
<td>75.3</td>
<td>1.00</td>
<td></td>
<td>76.4</td>
<td>1.00</td>
<td></td>
<td>79.6</td>
<td>1.00</td>
<td></td>
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<tr>
<td></td>
<td>Adequate</td>
<td>83.2</td>
<td>0.61 (0.49-0.76)</td>
<td>&lt;0.001</td>
<td>84.9</td>
<td>0.59 (0.47-0.73)</td>
<td>&lt;0.001</td>
<td>84.2</td>
<td>0.76 (0.56-1.02)</td>
<td>0.07</td>
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<tr>
<td></td>
<td>Unstaged</td>
<td>72.5</td>
<td>1.11 (0.90-1.38)</td>
<td>0.33</td>
<td>72.5</td>
<td>1.11 (0.98-1.45)</td>
<td>0.08</td>
<td>72.5</td>
<td>1.43 (1.19-1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Inadequate</td>
<td>85.6</td>
<td>1.00</td>
<td></td>
<td>85.8</td>
<td>1.00</td>
<td></td>
<td>86.8</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate</td>
<td>88.5</td>
<td>0.73 (0.60-0.88)</td>
<td>&lt;0.001</td>
<td>89.3</td>
<td>0.71 (0.58-0.86)</td>
<td>&lt;0.001</td>
<td>90.5</td>
<td>0.66 (0.50-0.88)</td>
<td>&lt;0.004</td>
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<tr>
<td></td>
<td>Unstaged</td>
<td>79.8</td>
<td>1.45 (1.22-1.74)</td>
<td>&lt;0.001</td>
<td>79.8</td>
<td>1.52 (1.29-1.78)</td>
<td>&lt;0.001</td>
<td>79.8</td>
<td>1.65 (1.43-1.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Inadequate</td>
<td>88.6</td>
<td>1.00</td>
<td></td>
<td>88.6</td>
<td>1.00</td>
<td></td>
<td>89.8</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate</td>
<td>88.7</td>
<td>0.91 (0.69-1.20)</td>
<td>0.51</td>
<td>88.8</td>
<td>0.90 (0.68-1.19)</td>
<td>0.46</td>
<td>83.6</td>
<td>0.80 (0.53-1.22)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Unstaged</td>
<td>82.5</td>
<td>1.54 (1.21-1.96)</td>
<td>&lt;0.001</td>
<td>82.5</td>
<td>1.56 (1.26-1.93)</td>
<td>&lt;0.001</td>
<td>82.5</td>
<td>1.58 (1.30-1.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unadjusted Cox proportional hazard regression test for p-values. Significant p-values are emboldened.

CGR, Collaborative Group Report criteria for bladder cancer; CI, confidence interval; GOG, Gynecologic Oncology Group; HR, hazard ratio; 10-yr (%), 10-year cause-specific survival rate.
Adjuvant therapy

CCCa

• For patient with intravenous taxane – carboplatin stage IA to IC disease recommended postoperative treatment is the standard regimens (with paclitaxel or doxetaxel) used for high grade serous ovarian cancer.

• For patients with stage II to IV clear cell carcinoma, postoperative treatment is standard regimens used for epithelial ovarian cancer (eg. intravenous carboplatin with paclitaxel, docetaxel or liposomal doxorubicin)

• Data suggest that 6 or 3 cycles equivalent of postoperative chemotheraphy are for patients with clear cell carcinoma.
NCCN Guidelines Version 2.2018
Clear Cell Carcinoma of the Ovary

PATHOLOGIC DIAGNOSIS

Clear cell carcinoma of the ovary

Stage IA-C

Stage II-IV

Borderline

ADJUVANT TREATMENT

IV platinum-based therapy x 3–6 cycles
[see primary regimens for stage I disease (OV-B, 3 of 10)]

Chemotherapy as per epithelial ovarian cancer
[See Primary Chemotherapy/Primary Adjuvant Therapy on OV-3]

MONITORING/FOLLOW-UP

See Monitoring/ Follow-Up (OV-S)

See LCOH-6

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Sugiyama T1, Okamoto A2, Enomoto T3, Hamano T4, Aotani E5, Itoh Y6, Suzuki N7, Miwa M8, Yamasaki N8, Kato K7, Yoshikawa H7, Yokoyama Y9, Tanabe H9, Nishino K10, Nomura H7, Kim JW11, Kim BG12, Pignata S1, Alexandre J13, Green J1, Isonishi S1, Terauchi F14, Fujikawa K15, Aoki D1.

• 619 patient with stage I to IV CCCO,
• Randomly, irinotecan 60 mg/m2 on days 1, 8, and 15 plus cisplatin 60 mg/m2 on day 1 (CPT-P group) every 4 weeks for six cycles or paclitaxel 175 mg/m2 plus carboplatin area under the curve 6.0 mg/mL/min on day 1 every 3 weeks for six cycles (TC group).
• With a median follow-up of 44.3 months, 2-year PFS rates were 73.0% in the CPT-P group and 77.6% in TC group; which was not significantly different
• Two-year OS rates were 85.5% with CPT-P and 87.4% with TC.
Three versus six cycles of adjuvant platinum-based chemotherapy in early stage clear cell ovarian carcinoma - A multi-institutional cohort.


- 210 patients, all cases of stage I and II CCCO, 116 of whom underwent full surgical staging, in the years 1994-2011
- Patients were divided into 2 groups: those who received 3 versus 6 cycles of adjuvant chemotherapy.
- The majority of patients were Caucasian (83.8%).
- All patients received adjuvant chemotherapy with 90% receiving carboplatin and paclitaxel.
- Thirty-eight (18.1%) patients received 3 cycles, and 172 (81.9%) patients received 6 cycles of adjuvant treatment.
- Recurrence rate was comparable between groups (18.4% vs. 27.3% for 3 vs. 6 cycles, p=0.4). There was no impact of 3 versus 6 cycles of chemotherapy on PFS.
- There was no benefit to more chemotherapy in stratified analysis by stage nor on multivariate analysis adjusting for the impact of stage. Subgroup analysis of surgically staged patients also showed no difference in survival between 3 versus 6 cycles of chemotherapy.
All patients had one or two prior regimens with measurable disease. Tumors were at least 50% clear cell histomorphology and negative for WT-1 antigen and estrogen receptor expression by immunohistochemistry.

Sunitinib 50 mg per day for 4 weeks was administered in repeated 6-week cycles until disease progression or prohibitive toxicity. Primary end points were progression-free survival (PFS) at 6 months and clinical response.

Of 35 patients enrolled, 30 were treated and eligible (median age: 51, range: 27–73). Five (16.7%) patients had PFS ≥6 months (90% CI: 6.8%–31.9%). Two (6.7%) patients had a partial or complete response (90% CI: 1.2%–19.5%). The median PFS was 2.7 months. The median overall survival was 12.8 months.

Sunitinib demonstrated minimal activity in the second- and third-line treatment of persistent or recurrent clear cell ovarian carcinoma.
We investigated the clinicopathologic and prognostic relevance of ARID1B in OCCC by immunohistochemical analysis of 53 OCCC patient samples and loss-of-function experiments in OCCC cell lines.

We also examined whether ARID1B could be a therapeutic target or prognostic biomarker in OCCC.

In the immunohistochemical analyses, low ARID1B level was frequent in samples lacking ARID1A and was associated with shorter progression-free survival. This is the first report demonstrating that a low ARID1B level could be a marker of poor prognosis in OCCC.

The correlation between the loss of ARID1A immunoreactivity and reduced ARID1B levels indicates that ARID1B could be an attractive target for anti-cancer therapy.
Figure 5. Kaplan-Meier survival analysis of 53 OCCC patients. (a) Low ARID1B level (black line, n = 8) in OCCC patients is associated with shorter progression-free survival as compared to high expression (blue line, n = 45) (p = 0.044, log-rank test); (b) Low (black line, n = 8) and high (blue line, n = 45) ARID1B expression had no influence on the overall survival of OCCC patients (p = 0.7096, log-rank test).
Sequencing studies revealed that ARID1A is mutated in over 50% of ovarian clear cell carcinomas.

We show here that BRD2 inhibition is predominantly lethal in ARID1A mutated ovarian clear cell cancer cells.

Small molecule inhibitors of the BET (bromodomain and extra terminal domain) family of proteins, to which BRD2 belongs, specifically inhibit proliferation of ARID1A mutated cell lines, both in vitro and in ovarian clear cell cancer xenografts and patient-derived xenograft models.

BET inhibitors cause a reduction in the expression of multiple SWI/SNF members including ARID1B, providing a potential explanation for the observed lethal interaction with ARID1A loss.

Our data indicate that BET inhibition may represent a novel treatment strategy for a subset of ARID1A mutated ovarian clear cell carcinomas.
A cohort of patients diagnosed between 2004 and 2015 with OCCC was drawn from the National Cancer Database. Those with stage I disease who had primary surgery and underwent systematic lymphadenectomy (defined as at least 10 lymph nodes removed) were selected for further analysis. A total of 2325 patients met the inclusion criteria. Median age was 55 years. Adjuvant chemotherapy was administered to 1839 (79.1%) patients. Hospital type and location, patient age, disease sub-stage, and year of diagnosis were independently associated with the administration of chemotherapy.

Patients who received adjuvant chemotherapy (n = 1629) had better OS than those who did not (n = 443), (5-year OS rates 89.2% vs 82.6%, p < 0.001).

Adjuvant chemotherapy could be associated with a survival benefit for patients with stage I OCCC.
Fig. 1. Overall survival of women with stage I ovarian clear cell carcinoma who did (n = 1629) and did not (n = 443) receive adjuvant chemotherapy, p = 0.001 from log-rank test.

Fig. 2. Overall survival of women with sub-stage IA or IB ovarian clear cell carcinoma who did (n = 873) and did not (n = 290) receive adjuvant chemotherapy, p < 0.001 from log-rank test.

Fig. 3. Overall survival of women with sub-stage IC ovarian clear cell carcinoma who did (n = 744) and did not (n = 145) receive adjuvant chemotherapy, p = 0.116 from log-rank test.
241 patients, in the years 1984-2008

- 5 and 10 year DFS rates were 84% and 70% for stage IA/B; 67% and 57% for stage IC; and 49% and 44% for stage II. Five and 10 year DFS rates for those with stage IC disease based purely on rupture were similar to rates for patients with stage IA/B, at 92% and 71%, respectively. The remaining patients with stage IC had 48% 5- and 10-year DFS.

- Multivariate analysis using a decision tree identified positive cytology as the most important factor (72% relapse rate if positive and 27% if negative or unknown). If, in addition, the capsule surface was involved, then the relapse rate was 93%. **Irradiation had no discernible survival benefit for patients with stage IA and IC (rupture alone), whereas for the remainder of patients with stage IC and stage II, it improved DFS by 20% at 5 years; the benefit was most evident in the cytologically negative/unknown group.**
Radiation Therapy for Recurrent Clear-Cell Cancer of the Ovary.

Westhoff GL, Fuhr KC, Longacre TA, McNally JL, Hsu IC, Kapp DS, Teng N, Chen LM.

- 53 patients, in the years 1994-2012
- Fifty-three patients had recurrent CCCO, and 24 (45.3%) of these patients received RT.
- There were no significant differences in age, stage, optimal cytoreduction, platinum response, or the percentage of patients that received more than 3 regimens of chemotherapy between the 2 groups.
- Patients who received RT for recurrent CCC were more likely to have had a focal recurrence (62.5% vs 10.3%, \( P \leq 0.001 \)) and to have undergone secondary cytoreduction (70.8% vs 10.3%, \( P \leq 0.001 \)). Of patients who received RT, 73.9% underwent surgery with or before their treatment.
- Five-year survival after recurrence was significantly higher in the group that received RT, 62.9% versus 18.8% (\( P = 0.002 \)).
- In a multivariate analysis, platinum-sensitive disease and RT were associated with improved survival from recurrence.

**FIGURE 1.** Survival from recurrence. Five-year survival from recurrence was significantly improved with the use of radiation; RT = 62.9% (n = 24) versus no RT = 18.8% (n = 29), \( P = 0.002 \).
Summary

• Endometriosis was associated with increased risk of ovarian cancer especially with endometrioid and clear cell histologic type
• Up to 60% of the patients with CCCO receive their diagnosis in Stage I
• Poor prognosis
• In Stage I disease, clear cell cancer recurs more frequently, up to 50% of the cases, with a 5-year survival varying from 50% to 73%
✓ The standard surgical treatment is the same as for other epithelial ovarian cancers;
• Lymphadenectomy has been shown to improve survival
• The staging system for high grade serous ovarian and primary peritoneal cancer is also used for CCCO.
• Fertility–sparing surgery is not recommended for stage IA to C clear cell carcinomas.
• intravenous taxane – carboplatin stage IA to IC disease recommended postoperative treatment is the standard (3-6 cycles)
• There are new studies of targeted drugs but not promising yet)
THANKS FOR YOUR ATTENTION..