

# **EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER**

Effective Date: April 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

### KEY POINTS

1. Completely staged, early epithelial ovarian, fallopian tube, and primary peritoneal cancers are highly curable. As such, patients should be referred to a gynecologic oncologist for adequate staging; including sampling of para-aortic and pelvic lymph nodes, infracolic omentectomy, possible appendectomy and biopsy of suspicious peritoneal lesions, in addition to a thorough inspection and palpation of all peritoneal surfaces, and peritoneal washings
2. Advanced epithelial ovarian, fallopian tube, and primary peritoneal cancers are best treated with optimal debulking surgery in conjunction with adjuvant therapy. As such, patients should be referred to a gynecologic oncologist

### BACKGROUND

Epithelial ovarian, fallopian tube and primary peritoneal cancer present, behave, and respond to current treatment similarly. Collectively, they represent the second most common cancer of the female genital tract (eighth most common cancer overall, among women) and, account for more than 25% of all new gynecologic cancers (3.1% of all cancers) in women. It is the second leading cause of death due to gynecologic cancers (fifth leading cause of death due to all cancers) in women.<sup>1</sup> Statistics Canada estimates that there will be 2,500 new cases in Canada this year, with 1,750 deaths. The five-year survival rate for epithelial ovarian, fallopian tube and primary peritoneal cancer is about 46%,<sup>3</sup> as 80% of cases are advanced stage.<sup>2</sup> About 50% of cases occur in women over the age of 65 years.

There are several histological types of epithelial ovarian cancer, including serous, mucinous, endometrioid, clear cell, unclassified tumours, and other malignant tumours. Fallopian tube and primary peritoneal cancers are, in general, histologically serous. Staging of this cancer is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).<sup>4</sup> The last update to the classification system was in 1989. A detailed description of this staging system can be found in the Appendix.

### GUIDELINE QUESTIONS

1. What is considered optimal debulking for advanced stage disease?
2. What is the optimal adjuvant chemotherapy (if any) for early-stage disease?
3. What should be chosen for first line chemotherapy for the treatment of advanced stage disease?
4. What role (if any) does intraperitoneal chemotherapy play in adjuvant treatment for patients with advanced stage disease? If so, who should receive this treatment and what regimen(s) should be used?
5. What role (if any) does neoadjuvant chemotherapy play for patients with advanced stage disease? Which treatment regimen(s) should be used?
6. What is considered optimal timing/regimen for interval debulking surgery and adjuvant chemotherapy afterwards?
7. What is (are) the best choice(s) of second-line treatment(s) for recurrent disease?
8. What is the role of secondary cytoreduction after a recurrence?

9. What additional therapy can be administered for recurrent disease after failure of second and third-line treatment?
10. What is the optimal treatment for disease that recurs between 6 and 12 months of treatment?
11. What is the optimal monitoring regimen (if any) during treatment to measure response?
12. What is the optimal surveillance for cancer recurrence following treatment and clinical remission?
13. How should clear cell carcinoma be managed?
14. What are the indications for docetaxel to be administered and what is the optimal treatment regimen?

## DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

## SEARCH STRATEGY

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: (ovary AND cancer or neoplasm AND epithelial OR epithelial ovarian cancer) AND chemotherapy or adjuvant chemotherapy or intraperitoneal chemotherapy or taxotere or platinum chemotherapy or optimal debulking or second line treatment or second line chemotherapy or salvage treatment or salvage therapy or third line treatment or third line chemotherapy or chemotherapy resistant, with limits of human studies in females only in the English language.

Guidelines reviewed include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2010)<sup>5</sup> the European Society for Medical Oncology (ESMO) guidelines (2009),<sup>6</sup> the BC Cancer Agency (BCCA) guidelines (2006),<sup>7</sup> Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines (2004-2009)<sup>8-10</sup> and the National Health and Medical Research Council (Australia)<sup>11</sup> and the Tom Baker Cancer Centre guidelines.<sup>12</sup>

The guideline was originally developed in 2011 and then updated in 2012 and 2013. The literature was reviewed prior to each update, using the search strategy described above. The 2012 and 2013 reviews included a total of 35 studies and eight studies, respectively. Following a review of the evidence by the Alberta Gynecologic Oncology Team, no major changes were made to the recommendations, with the exception of classifying dose-dense and intraperitoneal chemotherapy as preferred options for chemotherapy. The guideline was otherwise reaffirmed.

## TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with epithelial ovarian cancer. Different principles may apply to pediatric patients.

## RECOMMENDATIONS

### Staging

- The gold standard for adequate staging includes inspection and palpation of all peritoneal surfaces, peritoneal washings, pelvic and para-aortic lymph node sampling, infracolic omentectomy, possible appendectomy, and biopsy of suspicious lesions and resection of adhesions adjacent to the primary tumor
- Staging should be ideally performed by a gynecologic oncologist

### Early Stage: Stage I / IIA

Options include:

- Young patient: fertility preserving staging
- Older patient: total hysterectomy, bilateral salpingoophorectomy and staging
  - Stage IA / IB, Grade 1: Observation
  - Stage IA / IB, Grade 2
    - Observation depending on histologic type and individual case selection.
    - Chemotherapy depending on histologic type and individual case selection.
  - Stage IC / IIA, Grades 1-3
    - Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles dependent on histological type, grade, and individual case selection
  - Clear cell carcinoma: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles
  - Papillary serous carcinoma:
    - Grade 1: Observation
    - Grade 2/3: Chemotherapy with carboplatin and paclitaxel × 6 cycles
  - Endometrioid tumours:
    - Grade 1/2: Observation
    - Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles
  - Mucinous tumours:
    - Grade 1/2: Observation
    - Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 cycles
  - Undifferentiated tumors: Chemotherapy with carboplatin and paclitaxel X 6 cycles
  - If incomplete staging, consider:
    - Completion of surgical staging if medically fit patient +/- chemotherapy as indicated
    - OR chemotherapy

### Intermediate Stage: Stage IIB / IIC

Options include:

- Medically unfit patients and/or patients who cannot be optimally debulked:
  - Chemotherapy × 6 cycles
  - OR chemotherapy × 3 to 6 cycles depending on individual case selection followed by interval debulking surgery (IDS);
    - If microscopic residual disease at IDS, then chemotherapy × 3 cycles
    - If macroscopic residual disease at IDS, then chemotherapy × 3 to 6 cycles
    - Note: total chemotherapy would not normally exceed 9 cycles

- Patients undergoing primary debulking surgery:
  - Optimal debulking is ideally defined as microscopic residual disease or, at most, macroscopic residual disease <1 cm
  - Debulking would include total hysterectomy, bilateral salpingoophorectomy,, infracolic omentectomy and maximum reduction of pelvic tumor
  - Debulking is typically followed by chemotherapy x 6 cycles depending on individual case selection
- If incomplete primary debulking surgery, consider:
  - Completion of surgical debulking if medically fit patient +/- chemotherapy as indicated
  - OR chemotherapy

### **Advanced Stage: Stage III / IV**

Options include:

- Medically unfit patients and/or patients who cannot be optimally debulked:
  - Chemotherapy x 6 cycles
  - OR chemotherapy x 3 to 6 cycles depending on individual case selection followed by interval debulking surgery (IDS);
    - If microscopic residual disease at IDS, then chemotherapy x 3 cycles
    - If macroscopic residual disease at IDS, then chemotherapy x 3 to 6 cycles
    - Note: total chemotherapy would not normally exceed 9 cycles
- Patients undergoing primary debulking surgery:
  - Optimal debulking is ideally defined as microscopic residual disease or, at most, macroscopic residual disease <1 cm
  - Debulking would include total hysterectomy, bilateral salpingoophorectomy, omentectomy and maximum reduction of pelvic tumor +/- upper abdominal tumor, including possible resection of involved bowel, lymph nodes, retroperitoneal masses, spleen etc.
  - Debulking is typically followed by chemotherapy x 6 cycles depending on individual case selection.
- If incomplete primary debulking surgery, consider:
  - Completion of surgical debulking if medically fit patient +/- chemotherapy as indicated
  - OR chemotherapy

### **Chemotherapy**

*Preferred options include:*

- Dose dense IV chemotherapy regimen: carboplatin (AUC 5 to 6 IV on day 1) + paclitaxel (80 mg/m<sup>2</sup> IV on days 1, 8, 15), q 3 weeks x 6 cycles
- Intraperitoneal (IP) chemotherapy regimen: day 1: cisplatin (75 mg/m<sup>2</sup> IP) + paclitaxel (135 mg/m<sup>2</sup> IV); day 8: paclitaxel (60 mg/m<sup>2</sup> IP), q 3 weeks x 6 cycles
- Clinical trials

*Other option:*

- Intravenous (IV) chemotherapy regimen: Carboplatin (AUC 5 to 6 IV) + paclitaxel (175 mg/m<sup>2</sup> IV), q 3 weeks x 6 cycles

*Modifications:*

- If hypersensitivity to paclitaxel, substitute with docetaxel (75 mg/m<sup>2</sup> IV)
- If significant toxicity develops, or in medically unfit patients, consider single agent carboplatin (AUC 5 or 6 IV) and/or dose reduction at the discretion of the oncologist

- If hypersensitivity to platinum, consider desensitization protocol
- Note: The use of abraxane (nab-paclitaxel) in this setting is not funded in Alberta at the present time.

### Radiotherapy

Consider in select cases to improve local control, at the discretion of the radiation oncologist.

### Recurrent Disease

Options include:

- Clinical trials
- Carboplatin +/- paclitaxel
- Carboplatin / liposomal doxorubicin
- Liposomal doxorubicin
- Topotecan
- Cisplatin +/- liposomal doxorubicin
- Also consider: docetaxel, etoposide (oral), gemcitabine, paclitaxel, tamoxifen, or melphalan
- Consider cytoreductive surgery if clinically low volume of focal recurrence followed by clinical trial or platinum-based chemotherapy (below)

Recurrence >12 months: consider cytoreductive surgery followed typically by carboplatin / paclitaxel chemotherapy

### Follow Up and Surveillance

Follow-up should include a complete history and a pelvic examination as follows:

- Years 1 and 2: q 3 to 6 months
- Years 3 through 5: q 6 to 12 months

CA-125 blood tests and radiographic scanning has not been proven to be beneficial and is therefore not recommended for routine follow-up.

## DISCUSSION

Up front debulking is the standard of care for patients with epithelial ovarian, fallopian tube, and primary peritoneal cancer. In young patients, efforts should be made to preserve fertility when possible. In older patients with stage I/II disease, total hysterectomy, bilateral salpingo-oophorectomy, and staging should be performed. Following surgery, observation is an acceptable option for grade 1 and grade 2 tumours (except grade 2 papillary serous and stages IC and IIA). For grade 3 tumours, as well as stages IC and IIA (all grades), adjuvant platinum-based chemotherapy with a taxane should be considered.<sup>5</sup>

Three cycles of chemotherapy may be sufficient for some early stage tumours, including endometrioid tumours and mucinous tumours, whereas six cycles could be recommended for more aggressive type tumours, including all clear cell carcinomas,<sup>11</sup> grade 2 papillary serous carcinomas,<sup>13-15</sup> and early stage grade 3 tumours. An acceptable intravenous (IV) regimen includes carboplatin (AUC 5 to 6) plus paclitaxel (175 mg/m<sup>2</sup>) or docetaxel (75 mg/m<sup>2</sup>)<sup>5,16</sup> every three weeks for six cycles.<sup>5,6,8,11,12,16</sup> There are no recent trials comparing the efficacy of different platinum agents in combination with taxane therapy, but current

evidence suggests that paclitaxel plus carboplatin or cisplatin is equivalent to docetaxel or paclitaxel plus carboplatin.<sup>5</sup>

In medically fit patients with stage III/IV disease where there is extension beyond the ovaries, optimal debulking (defined as residual disease no more than 1 cm),<sup>5,17,18</sup> includes total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy for maximal tumour reduction, with or without lymphadenectomy, with or without bowel resection if indicated. Adjuvant chemotherapy with carboplatin and paclitaxel × 6 cycles should be administered. An acceptable alternative could include an intraperitoneal (IP) regimen of cisplatin (75 mg/m<sup>2</sup>) plus IV paclitaxel (135 mg/m<sup>2</sup>) or docetaxel (75 mg/m<sup>2</sup>)<sup>5,16</sup> on day 1, followed by IP paclitaxel (60 mg/m<sup>2</sup>) on day 8, every three weeks for six cycles.<sup>5,8,11,12,19-21</sup> A dose-dense regimen is also acceptable for this group and includes IV paclitaxel (80 mg/m<sup>2</sup> on days 1, 8, and 15) plus carboplatin (AUC 5 to 6 on day 1) every three weeks for six cycles.<sup>22</sup> Recent phase III data has shown a survival advantage with the addition of bevacizumab to carboplatin and paclitaxel in patients with newly diagnosed high risk disease;<sup>23</sup> however, more trials are needed before this regimen can be adopted into practice.

Although there is currently no evidence of benefit with neoadjuvant chemotherapy followed by interval cytoreductive surgery for medically fit patients,<sup>5,24</sup> in patients with conditions unfavorable for primary surgery, neoadjuvant chemotherapy may lower the risk for suboptimal cytoreduction.<sup>25</sup> However, more trials are needed to establish the role of neoadjuvant chemotherapy in this setting. Published data are pending for two clinical trials: the NCIC OV.13 Trial and the Japan Clinical Oncology Group (JCOG) 0602 Trial. Data presented at the International Gynecologic Cancer Society Meeting in 2008 from the NCIC OV.13 trial, comparing upfront debulking with neoadjuvant chemotherapy in stage IIIc/IV disease, showed that both treatments were similar in terms of overall survival and progression-free survival; however neoadjuvant chemotherapy was associated with lower morbidity.<sup>26</sup> Preliminary data from the JCOG 0602 Trial, comparing neoadjuvant chemotherapy (carboplatin plus paclitaxel × 4 cycles) followed by interval debulking plus post-surgical chemotherapy (× 4 cycles) with primary debulking plus post-surgical chemotherapy (× 8 cycles) with or without interval debulking in stage III/IV disease, showed that the neoadjuvant chemotherapy group achieved complete clinical remission in 22 patients (42%) with median overall and progression-free survival times of 45 and 14 months, respectively.<sup>27</sup>

Optimal treatment for recurrent disease has not yet been established. High risk patients (i.e. those with a recurrence within the first six months of finishing chemotherapy) are best suited for enrolment in a clinical trial or may benefit from six cycles of either liposomal doxorubicin or topotecan.<sup>12,28</sup> Pegylated liposomal doxorubicin (50 mg/m<sup>2</sup> every four weeks) was shown to be equivalent to topotecan (1.5 mg/m<sup>2</sup> for five consecutive days every three weeks) in terms of overall survival (60 weeks vs. 56.7 weeks); however, in platinum-sensitive patients, liposomal doxorubicin showed superior progression-free survival (median 28.9 weeks vs. 23.3 weeks; p=.037) and overall survival (median 108 weeks vs. 71.1 weeks; p=.008).<sup>29</sup>

The majority (approximately 75%) of recurrences will present after the first six months post-chemotherapy. Intermediate risk patients (i.e. those with relapse at six to twelve months) could be considered for secondary cytoreductive surgery followed by enrolment in a clinical trial or combination platinum-based chemotherapy (preferred for the first recurrence) or supportive care.<sup>5</sup> The CALYPSO Study, a multicenter phase III trial, showed that carboplatin (AUC 5) plus pegylated liposomal doxorubicin (30 mg/m<sup>2</sup>, IV) every four weeks was superior to carboplatin (AUC 5) plus paclitaxel (175 mg/m<sup>2</sup>, IV) every three weeks (≥ 6 cycles), in terms of median progression-free survival (11.3 months vs. 9.4 months; P=.005) with less grade 3/4 neutropenia (35% vs. 46%) and grade 3/4 non-hematologic toxicity (28% vs. 37%).<sup>30</sup> A phase III randomized controlled trial comparing patupilone (10 mg/m<sup>2</sup> IV q 3 weeks with pegylated liposomal doxorubicin (PLD; 50 mg/m<sup>2</sup> IV q 4 weeks) in 829 patients with platinum-refractory or

-resistant disease, and 3 or fewer prior regimens demonstrated no additional benefit. The median overall survival time was 13.2 months for patupilone versus 12.7 months for PLD (HR 0.93; 95% CI 0.79-1.09;  $p=0.195$ ) and median progression-free survival was 3.7 months for both arms. The most common adverse events were diarrhea (85.3%) and peripheral neuropathy (39.3%) for patupilone and mucositis/stomatitis (43%) and hand-foot syndrome (41.8%) for PLD.<sup>31</sup>

There are limited phase III trials comparing treatment regimens as third-line or higher treatment of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. Recent work has focused on canfosamide, an apoptotic glutathione analogue (ASSIST-1 Study Group),<sup>32</sup> gemcitabine,<sup>33</sup> whole body hyperthermia plus carboplatinum,<sup>34</sup> pemetrexed,<sup>35</sup> and capecitabine.<sup>36</sup> Canfosamide and gemcitabine were shown to be less and equally efficacious, respectively, as compared to liposomal doxorubicin and, although whole body hyperthermia and pemetrexed achieved overall response rates of 45% and 21%, respectively, the studies were small and did not include comparison groups. Despite these potentially beneficial findings, more work is needed to determine best treatment options for this group.

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of AHS, Cancer Care.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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## APPENDIX

Staging of epithelial ovarian cancer of the based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) 2010:

Stage I: Tumour confined to the ovaries

- IA: Tumour limited to one ovary, capsule intact T1a; no tumour on ovarian surface; no malignant cells in the ascites or peritoneal washings
- IB: Tumour limited to both ovaries, capsules intact T1b; no tumour on ovarian surface; no malignant cells in the ascites or peritoneal washings
- IC: Tumour limited to one or both ovaries, T1c; with any of the following: capsule ruptured, tumour on ovarian surface, positive malignant cells in the ascites or positive peritoneal washings

Stage II: Tumour involves one or both ovaries with pelvic extension T2.

- IIA: Extension and/ or implants in uterus and/or tubes T2a; no malignant cells in the ascites or peritoneal washings.
- IIB: Extension to other pelvic organ T2b; no malignant cells in the ascites or peritoneal washings.
- IIC: IIA/B with positive malignant cells in the ascites or positive peritoneal washings T2c.

Stage III: Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis T3 and/or N1

- IIIA: Microscopic peritoneal metastasis beyond the pelvis T3a.
- IIIB: Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension T3b.
- IIIC: Peritoneal metastasis beyond pelvis more than 2cm in greatest dimension and/or regional lymph nodes metastasis T3c and/or N1.

Stage IV: Distant metastases beyond the peritoneal cavity.