

表1 子宮頸癌 (Odicino F &amp; Pecorelli S)

---

Stage 0 前がん病変につき削除  
 Stage I A1 切片の多少が予後に影響はない  
 Stage II A II A1 と II A2 腫瘍の size と volume が重要  
 Stage II B/III B 一側か両側浸潤での細分類? 臨床的治療方針に差異はなし

NOTES:  
 1 子宮頸癌は依然臨床進行期分類を使用する。早期がんで MRI/CT が実施可能な施設は腫瘍径などの所見を FIGO 登録に含め AR に含めること。尿管侵襲は記録のみ。多発浸潤病巣は upstage せず記録。微小浸潤腺癌は扁平上皮癌と同様に扱う。  
 2 微小浸潤や多発浸潤の定義は依然議論が絶えず、この問題は Tampa での会議でも熱心に議論されたことを明記する。

---

参考文献: *Int J Gynecol Obstet* 105: 103-104, 107-108, 2009. 訂正 Oct 12, 2009.

表2 子宮体癌 (Creasman W, Mariani A, Podratz K)

---

Stage I A/ I B 旧 Stage I A と I B での予後の違いはない GOG33, vol. 24-26 of AR  
 Stage II 頸管間質浸潤  
 Stage III A 細胞診 賛否両論のなかで upstage しない  
 Stage III C III C1 骨盤のみ III C2 PAN を含む GOG33, Boronow

NOTES:  
 1 細胞診に関しては相反するデータはあるが、分類は勧めるが記録は常に行うこと。  
 2 この分類は MMMT (carcinosarcoma) にも適応すること。大網切除は、MMMT, papillary serous, clear cell, grade 3 endometrial cancer では行うこと  
 3 リンパ節郭清 low risk: 疑いのある骨盤リノパ節のみ生検  
 high risk: 系統的骨盤リノパ節郭清+疑いのある傍大動脈リノパ節の生検

---

参考文献: *Int J Gynecol Obstet* 105: 109, 2009 Podratz K. *Int J Gynecol Obstet* 105: 110-111, 2009.

表3 子宮肉腫 (Prat J &amp; D'Angelo E) 子宮肉腫では、今回新たに進行期分類を制定

- 
- 全体としてI期は子宮に限局,  
 II期は子宮を超えるが骨盤内まで,  
 III期は腹腔内進展,  
 IV期は膀胱・直腸浸潤あるいは遠隔転移と分類された。
  - 組織型別のI期細分類  
 平滑筋肉腫と内膜間質肉腫: I期を腫瘍径5cmで分類し, I A期とI B期  
 腺肉腫: 粘膜内, 筋層浸潤1/2で分類し, I A期, I B期, I C期  
 に細分類された。
- 

参考文献: *Int J Obstet Gynecol* 104: 177-178, 179, 2009. 訂正文あり  
 D'Angelo E. & Prat J. *Gynecol Oncol* 116: 131-139, 2010.

表4 外陰癌 (Hacker N)

---

Stage 0 前癌病変につき分類しない  
 Stage I 外陰に限局 size 2 cm, Stromal Invasion 1.0 mm, n (-)  
 Stage I B SEER のデータ 腫瘍径8cm以上でも n (-) で予後良好  
 Stage III stage II との違い = n (+) の数, 形態  
 Stage III A 5 mm と 1-2 個の問題  
 Stage III B 5 mm と 2-3 個の問題  
 Stage III C 被膜外進展  
 Stage IV 治療法に違いが生ずる 手術と放射線療法どちらか

---

Notes: micrometastasis か macrometastasis かの境界を 5 mm とした

---

参考文献: *Int J Gynecol Obstet* 105: 105-106, 2009.

## 文 献

- 1) Petru E, Luck H-J, Stuart G, et al: Gynecologic Cancer Intergroup (GCIg) proposals for changes of the current FIGO staging system. *Eur J Obstet Gynecol Reprod Biol* 143: 69-74, 2009.
- 2) FIGO committee on Gynecologic Oncology Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obstet* 105: 103-104, 2009.
- 3) Pecorelli S, Zigliani L and Odicino F: Revised FIGO staging for carcinoma of the cervix. 107-108, 2009. (訂正 Oct 12, 2009)
- 4) Creasman W: Revised FIGO staging for carcinoma of the endometrium. *Int J Gynecol Obstet* 105: 109, 2009.
- 5) Mariani A, Dowdy SC and Podratz KC: New surgical staging of endometrial cancer: 20 years later. *Int J Gynecol Obstet* 105: 110-111, 2009.
- 6) FIGO staging for uterine sarcomas. *Int J Obstet Gynecol* 104: 177-179, 2009. (訂正文あり)
- 7) Hacker NF: Revised FIGO staging for carcinoma of the vulva. *Int J Gynecol Obstet* 105: 105-106, 2009.
- 8) 寒河江悟: FIGO 婦人科がん進行期分類改訂の最新情報. 日本臨床細胞学会誌 48: Suppl 1, 151, 2009.
- 9) 寒河江悟: 1) 婦人科癌進行期分類の改訂 クリニカルカンファランス 9 婦人科癌進行期分類の問題点. 日産婦誌 62(9): N-211-N-216, 2010.
- 10) 寒河江悟: 1. 新 FIGO 進行期分類改訂の経緯 新 FIGO 進行期分類について. 日本婦人科腫瘍学会 28(3): 280, 2010.

Gynecologic Cancer Intergroup だより

Homepage: <http://www.gcig.igcs.org/>

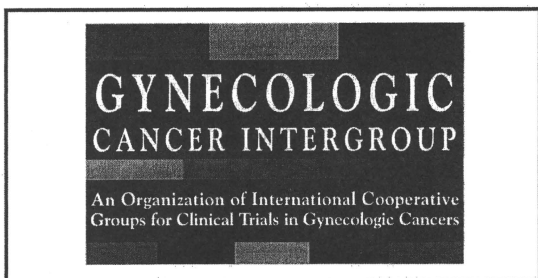
第6号 2010年総集号

JGOG GCIG委員会 編集

寒河江 悟 委員長

委員: 青谷恵利子、岡本愛光、竹内正弘、進 伸幸、藤原恵一

(2011,2,1)



## GCIG 委員会 2010年活動報告書

1.平成 22 年 1 月 11 日 EXECUTIVE BOARD TELECONFERENCE Membership: ICORG が暫定加入, 予定は GICOM, TRSGO. 新規申請 SGOG 上海, Brazil, Thai/Lithuania/Romania など。Governance & Statutes: 参加基準の改定が必要。総会での教育 topic は Spring 2010 ... pharmacogenomics、Autumn 2010 ... Neo-adjuvant therapy (trial designs and resources) とする。論文: Uncommon Histologies (IJGC), Cervix Ca SOTs 2007, Ovarian Ca CTPM (June 2009), Cervix Ca SOTs (June 2009), Cervix Cancer Research Network 参加基準確認。4<sup>th</sup> Ovarian Cancer Consensus Conference 6 月予定。Principles of Independence 討論中。New Business: Incorporation 議論中。

2. GCIG 春季総会報告書 2010 年 6 月 3-4 日シカゴ開催。参加者: 寒河江、藤原、進、岡本、青谷、濱野 計 6 名  
GCIG Executive Board Meeting: Michelle Powers が web 担当、本会に 125 名以上が登録。Membership: 今後参加 group に GCP 下臨床試験実施を証明する宣誓書の提出を要求。毎回最低一人は Harmonization Comm. に参加すること。Ireland, Mexico, COGI が暫定会員に承認。Turkey, Shanghai, India, Georgia, Lithuania, Romania などから打診。次回総会 topic はバンクーバーでの Ovarian Cancer Consensus Conference。GCIG の体制: 現在 GCIG は任意団体で運営だが、参加団体数や賛助企業の増加に伴い、財務体質の強化が望まれ、法人格の取得が望ましい。GCIG 単独で法人格を取得するか、IGCS などの既存法人に所属するなどの選択肢があり、出来るだけ早い段階で方針を決定へ。GCIG Cervix Com: 進行中の臨床試験 ①S-1+CCDDP vs CDDP Phase3 study in Cervical cancer (VB/Rec) は 254/360 症例登録があり順調。②GOG 240 : Cisplatin + Paclitaxel vs Topotecan + Paclitaxel +/- Bevacizumab 450 例を目標に進行。③GOG 263 : Pelvic RT vs CCRT in Early Stage Cx Ca 480 例を目標に開始。④RTOG-0724 (GOG): ChemoRT ± adjuvant chemotherapy in high risk cervix cancer after hysterectomy 現在進行中。立案中の試験 the OUTBACK trial : A Phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone CCRT+/-CT CCRT のみでは成績ははまだ不十分、CT として Carbo/Taxol を 3 週毎 4 サイクルの追加の有用性を検証する、780 例対象で QOL の評価も行う。現在最終案を作成中。the SHAPE trial: Simple Hysterectomy And Pelvic node dissection in Early cervix cancer 低リスク子宮頸がんに広汎+PLN vs 単純全摘+PLN の RCT で予後と QOL の比較で術後療法も規定し、欧米を中心に行う非劣性比較試験。neoadjuvant Phase 3 trial in LACC を対象に weeklyTC+CCRT vs CCRT。CCRT 不十分なので RT の前に CT を行う試験を考案、Ib2-Iva 期 CxCa を対象に 730 例を目標。以上の他に RCT of Weekly vs 3-Weekly CCRT in LACC ( CDDP 40mg/m<sup>2</sup> wk, CDDP 75mg/m<sup>2</sup> 3wks 500 例) , Neoadjuvant Chemotherapy followed by Exenteration in Cervical Cancer. ACRI6671-GOG0233 LACC & EmCa への CCRT 前に LN 転移発見に対する PET/CT の有用性を検証する試験などが議論された。

Endometrial Cancer Com 提案: LYTEC : LYmphadenectomy Trial in EMCA 再発ハイリスク症例 (組織型 (G3Em, S, C) 、筋層浸潤 1/2 超、頸部間質浸潤) を対象に TAH&BSO を行い、LN するかで無作為化を行う。その後再発 RF の存在で observation or brachytherapy や GOG249 (RT vs brachy+chemo)、GOG258 (chemoRT + chemo vs chemo)、After 4 trial (chemo + RT vs chemo)、ENGOT EN2 EGCG Trial (chemo vs obs)などに振り分けられ、それぞれの群で予後を比較検討。各 arm 360 例ずつ 720 例で 4 年で登録完了し 4 年の F/U。GOG-0238 RCT of Pelvic Irradiation with or without Concurrent Weekly Cisplatin in Patients with Pelvic-only Recurrence of EMCA 22/164 登録、GOG-0248 RCT II of Temsirolimus vs Hormone+ Tem. in Advanced, Persistent, or Recurrent EMCA 43/84、GOG-0249 RCT of Pelvic RT vs Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin CT in Patients with High Risk, Early EMCA 112/562、GOG-0258 RCT of cisplatin and tumor directed RT followed by TC vs TC for optimally debulked advanced endometrial cancer 67/804、GOG-0261 RCT of Pacli/Carbo versus Ifosfamide Plus Paclitaxel in Chemotherapy-Naive Patients with Newly Diagnosed Stage I-IV, Persistent or Recurrent Carcinosarcoma 47/424、PORTEC3/EN7 RT 群 pelvic radiation(48.6Gy) vs CMT (combined modality treatment) 群(CCRT(cisplatin 50mg/m<sup>2</sup>, 2 cycles)+CT pacli175+carboAUC5 4 cycles 179/500、After 4 CT (pacli175 3hr +carboplatin AUC 5-6) 4 cycles その後に RT (44Gy 以上) vs CT (pacli/carbo) 2 cycles 追加の比較検討。Ovarian Cancer Com. Closed trials : Surgery : EORTC55971 Upfront Surgery vs Neoadjuvant Chemotherapy は NEJM に採用が決定。AGO-OVAR-OP.2 DESKTOP II は 412 例登録し終了。分子標的: Tarceva Trial EORTC 55041 は 835 例登録。GOG218 は ASCO2010PL#1 で発表され、同時にさらに維持療法の arm で予後改善。ICON7 は 1520 例登録、ESMO/IGCS で発表予定。再発: CARYPSO 試験は JCO に発刊、AGO-OVAR-9 (Carbo Paclitaxel +/- Gemcitabine) は JCO 採用、SCOTROC4 論文作成中、HECTOR 550 例登録終了。Ongoing Trials : 手術: AGO - OVAR OP.3 (LION), LYmphadenectomy In Ovarian Neoplasms) は 184/640 例登録、AGO-OVAR-OP.4 DESKTOP III Cytoreductive surgery vs No surgery in platinum-sensitive recurrent EOC 目標 385 例今年 6 月開始、CHORUS (Chemotherapy or Upfront Surgery) A randomised trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma あと 15 例で 550 例目標達成、初回: dose-dense ICON8 : An international three-stage randomised

trial of dose-fractionated chemotherapy compared to standard three-weekly chemotherapy, following immediate primary surgery or as part of delayed primary surgery, for women with newly diagnosed epithelial ovarian cancer. 3年で1485例目標。MITO7 dd vs 3wks CT (QOL) 227/400例で順調、intraperitoneal JGOG iP trial : A Randomized Phase II/III Trial of 3 Weekly Intraperitoneal versus Intravenous Carboplatin in Combination with Intravenous Weekly Dose-Dense Paclitaxel for Newly Diagnosed Ovarian, Fallopian Tube and Primary Peritoneal Cancer。NCIG CTG OV21 : Do EOC patients who have received neoadjuvant chemotherapy benefit from IP therapy? NAC3-4サイクル後に手術を行い、IVvsIPの比較を行う。GOG252登録中。Histology-specific JGOG3017 明細胞癌試験は541/652例で韓、英、仏、伊が参加、mEOC/GOG241: A multicentre randomised factorial trial comparing oxaliplatin + capecitabine, bevacizumab and carboplatin + paclitaxel in patients with previously untreated mucinous Epithelial Ovarian Cancer 目標332例開始間近。分子標的 : AGO-OVAR-12 Carbo Paclitaxel +/- BIBF 1120 (Vargatef) は146 / 1300 (2:1 random)で現在進行中、AGO-252 16 Pazopanibの維持療法 752/900例で終了まじか、AURELIA: Bevacizumab plus chemotherapy vs chemotherapy alone in patients with platinum-resistant EOC 110/332例登録、ICON6 : A Randomised Trial of Concurrent Cediranib (with Platinum-based Chemotherapy) and Maintenance Cediranib in Women with Platinum-Sensitive Relapsed Ovarian Cancer 150/2000例、再発 MITO8 LipDox vs CT cross-over in 6-12 m platinum-free interval OVCA 46/253例登録、OVATyON試験 : Relapsed ovarian cancer with platinum-free interval (PFI) of 6-12 monthsを対象に、PLD 30 mg/m2 + Carboplatin AUC 5 q4weeks 6 cycles と PLD 30 mg/m2 + Trabectedin 1.1 mg/m2 q3weeks 6 cycles のRCTで588例が目標、PARPi in BRCA relapsed ovarian cancer : International randomised phase III study of a PARP inhibitor versus liposomal doxorubicin or topotecan for ovarian cancer patients relapsing following previous platinum therapy and carrying a deleterious germline *BRCA1* or *BRCA2* mutation PARPi と PLDH or topotecan と比較検討。

**Translational Research WG 1. 粘液性がん (mEOC/GOG241) の GCIG trial :** TR に関した検体材料の収集法の重要性が話し合われ、SOP (Standard Operating Procedures) についてのより細かな検討が必要である。trial では angiogenesis marker を検討する。また他にゲノム解析も予定している。各グループがどのように組織検体にアプローチできるのか、さらなる検討が必要である。**2. TR レビュー委員会 :** TR レビュー委員会という小委員会の設立について検討している。これは異なったメンバーからなる委員会、特に GCIG trial からの検体リクエストのレビューを行う。PI と参加グループとの連携をとって行う委員会である。**3. 進行中の clear cell trial :** これは GCIG/3017 の TR trial ではないが、Clear cell の TR は順調に行っている一つの例である。150 の frozen sample より DNA, RNA を抽出し、CGH array, cDNA array が行われ、化学療法感受性 vs 耐性、進行期別 (stage Ic vs IIIc)、子宮内腺症合併 vs 合併なし、さらには日本人 vs 他の人種を検討予定である。他の国からの clear cell の frozen tissue の提供が可能なら協力していただきたい。**4. 子宮頸がん trial :** 2番目の GCIG trial であり既保存された material を用いて、Hypoxia/angiogenesis markers を調べる予定である。異なる患者背景の RTG cervical cancer trial で、既に保管された material を用いて、予後に関する Expression profile を調べる予定である。**5. TR に対する GCIG group の取り組み :** TR が含まれている Clinical trial (PIII) の comprehensive list の作成を行い、委員間で情報をシェアする。リストを website に掲載するかは検討中。余剰なサイエンティフィックなディスカッションはカットし、お互いのグループが協力し合い、相乗作用を期待する。**6. GCIG バイオマーカーラボラトリー :** Trial に必須のバイオマーカーとして PARP, PI3 kinase などがあげられる。International な trial にジェノミック/プロテインバイオマーカーを組み入れるのは難しい。今後の GCIG 関連バイオマーカー研究の将来性について具体的に明らかにする必要がある。

**RARE tumor wg Ongoing Trial :** GOG187: 第2相試験 paclitaxel for ovarian stromal tumors : 11/2000 から 26/37 pts, Paclitaxel 175 mg/m2 IV q 21d 再発測定可能病変あり、GOG239: 第2相試験 AZD6244 in women with recurrent low-grade serous carcinoma of Ovary/peritoneum : 12/2007 から 1st stage 27例で終了、2nd stage 5/26/09 から 11/09 に終了、解析待ち。AZD6244 を再発 で再発測定可能病変あり low-grade serous が対象、GOG251: 第2相試験 Bevacizumab for recurrent sex-cord-stromal tumors of the ovary : 9/08 から 1st stage 終了 37例 Bevacizumab 15 mg/kg IV q 21d、GOG254: 第2相試験 SU 11248 (sunitinib malate) in the treatment of persistent or recurrent clear cell ovarian carcinoma : 36-43 pts が目標、4/10 から Sunitinib 50 mg QD、GOG264: 第2相試験 paclitaxel and carboplatin vs. bleomycin, etoposide, and cisplatin for newly diagnosed advanced stage and recurrent chemo-naive sex cord-stromal tumors of the ovary : 80-128 例対象で 2-10 から TC vs BEP 提案試験として、GOG241/mEOC trial、RTM0905: 第2相試験 Dasatinib (Sprycel) in the treatment of vulvovaginal melanoma harboring somatic alterations of c-kit : EOC trial が進行中で Dasatinib 70mg bid、GOG268: 第2相試験 temsirolimus (CCI-779) in combination with carboplatin and paclitaxel followed by temsirolimus (CCI-779) consolidation as first-line therapy in the treatment of stage III-IV clear cell carcinoma of the ovary その他の国際試験として ANZGOG: 第2相試験 Aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic Gynaecologic Neoplasms (PARAGoN)、JGOG 3017 など

**GCIG Harmonization WG :** ハーモナイゼーション・グループでは、各国の法規及び異なるグループポリシーに関する互いの理解を深め、国際共同試験を円滑に行うために必要となる「調整」を行っている。特に今回のトピック : Group

**Contacts & Summaries** 全ての参加グループの試験実施体制や運営上の取り決めについて、CGICのHPに公開して Update が義務。今回より、オランダの試験グループが加入。**Translational research Checklist** 各国のTR用説明同意書に記載されなければならない必須項目の“チェックリスト”について紹介された。**Informing Participants the Study Results** ヘルシンキ宣言の2008年ソウル改訂33項に“At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.”という記載があり、各国の対応が確認された。どこまで、どのような方法で試験結果を患者に伝えるかは、MRCのレターを例として引き続き検討することになった。**Sensitive Data** NSGO については sensitive data の取り扱いが法の規制されている。したがって、例えば SAE 報告書は病院や担当医師名、患者の診療情報を含んでいるので、情報の安全管理が担保された方法でなければ送付できない。FAX では許容されず、ユーザーとアクセス管理が徹底している WEB サイト、パスワードロックされたEメールなどが使用されなければならない。**Common Data Elements (CDEs)** NCI によって開発された、各領域独自の臨床試験用語についてまとめた標準言語(CDEs)について説明があった。これにより用語の定義を明確にし、データ収集を統一した定義で行えるようにしている。また、CRF標準化とメタアナリシスへの活用が期待される。CaDSR (Cancer Data Standards Repository) のWEBページよりダウンロード可能である。**CTC-AE Version 4.0** 4.0バージョンについて解説があった。申請資料に使用するMeDRA対応となった790用語は、WEB状で3.0バージョンとマッピングすることも可能である。米国では、たゞ version3.0で開始した試験であっても version4.0に途中から変更することをNCIが求めており、GOGを含む臨床試験グループは大反対をしている。**Group Specific Appendix** 他国の臨床試験に参加しようとする、自国の現状に合わない記載部分がある。その場合は、Group Specific Appendix を作成して対応している。この内容について、Table of Contents として各国の状況をまとめることになった。**Survey of Group Policies** 今後の調査対象は、クエリ/の作成/回答方法、逸脱の取り扱い、モニタリングの方法と決定した。**Current CGIC Studies** 各グループで現在実施しているCGIC試験について、その進捗状況が報告された。JGOGからは、JGOG3017およびAGO-OV16の進捗状況について青谷より報告された。今回のミーティングより、各グループ少なくとも1名のメンバーがハーモナイゼーションWGに参加することが必須とされた。これは国際共同試験を実施する上で、実務的な調整を重視したうえでの決定であった。

**Harmonization Committee -- Statistical Section:** 2010年6月3日、統計に関するCGIC協議会議が米国シカゴで実施された。CGIC所属団体の統計家が統計関連の話題について意見交換を行った。本会議では以下の話題について議論がなされた。**盲検化の可能性および方法について:** 婦人科腫瘍関連の臨床試験における盲検下の可能性および方法について意見交換がなされた。GOG218試験が二重盲検下で実施されたことも本トピックの選定に関連していると思われる。各団体において盲検試験の経験についてヒアリングが実施された。現時点では盲検を実施した経験のある団体は少なかった。また、抗がん剤特有の毒性によって盲検が破れる可能性や、試験の状況によって適用可能性が異なる、等の意見が聞かれた。**主要評価変数としての PFS と OS の選択について:** 主要評価変数として PFS と OS のどちらを選択すべきかについて意見交換がなされた。各団体から PFS と OS の選択について様々な意見が出された。本議題は6月24-28日にカナダで実施されるCGIC 4th Ovarian Cancer Consensus Conference において細密に検討される予定である。**上皮性卵巣がんの first-line 試験における標準的なベースライン変数の選定:** 上皮性卵巣がんに関する first-line 試験において重要となる、標準的なベースライン変数について議論が行われた。年齢やPS等の代表的な変数についてリストによる確認がなされるとともに、特にCA125を当該リストに含めるか否かで議論が交わされた。**今後の検討課題について:** 今後、本セッションにおいて議論する検討課題について議論が交わされた。Rare tumor or biomarker の問題を次回の主な検討課題とするという議論がなされ、また QOL の解析など本トピックについて提案がなされた。

### 3. Clear Cell Carcinoma-Challenge & Change 6月24日2010年 バンクーバー

1. Epidemiology 岡本が疫学に関して静岡コホート研究、JGOG3014, CGIC/JGOG3017 などについて説明した。アメリカに移住した日本人のCCCが9%であるのになぜ日本人は25%と高いのか、子宮内膜症の頻度は決して高くはないのに、なぜCCCの頻度が高くなるのかなど質問が数多くあった。私見では1)子宮内膜症(卵巣チョコレート嚢腫)の治療に関し、欧米・韓国では小さくても早期に腹腔鏡で核出術を行う傾向があるが、日本ではまずホルモン療法などで保存的に観察し、症状・サイズ増大により手術に踏み切る傾向がある。そのため40歳以上でサイズがある程度大きいチョコレート嚢腫患者が多く、結果的にCCCの頻度が高くなる。2)長期間低用量ピルを内服する患者は欧米に比較して少ない。3)未婚・晩婚・高齢出産の増加になどによりエストロゲンの暴露量が多くなり、結果的に子宮内膜症・CCC頻度が高くなる。4)遺伝的背景の違いといった回答をした。2. Surgery (Michael Quinn) 結果論文を多く引用し、complete surgery を目指す重要性を説明した。Stage I にも systemic LNX を行う必要があるのか、妊孕性温存手術はこれまで可能ななどの質問があった。JCO の佐藤論文を岡本が説明した。Ia, Ib は温存が可能であることが皆に浸透した印象。3. Pathology (Blake Gilks) IHC で CCC は HNF1 $\alpha$ , ER $\beta$ , WT1 $\beta$  で serous はそのパターンがまったく逆である。Mixed CCC は Mixed SC, SC とパターンが似ている。SC や EA が実は CCC であった事例を出し、Central review をすることで CCC の頻度がもう少し上がる可能性を説明している。morphology を重視するのか IHC を重視するのかという質問があった。4. Systemic oncology (Paul Hoskins) 目新しいことなし。Radiation Oncology

(Gillian) 化学療法耐性症例は必ずしも放射線に耐性でないことを説明していた。5. Genomic studies (David Bowtell) 日本人の特異的な変化は 20q の amplification であった。c-Met, HGF, STT3 pathway, IL6→pSTAT→JAK2→STAT3→HIF の重要性、pThrR, hypercalcemia との関係、また sunitinib が分子標的薬として候補であることを説明していた。6. Molecular Pathology (Ie Ming Shih) スライドのみ。HNF-1beta, CDKN1A, HIF-1alpha, IL-6, STAT が重要。PIK3CA→AKT mTOR inhibitor が効果的かも ZNF217, CCC は type I tumor である。7. CCC at base pair resolution (David Huntsman) ARID1a の mutation study が進んでいる。8. Model systems & new opportunity (Michael Birrer) FLT1, HIF1 alpha pathway, SDH gene GOG では clear cell を外して行う方がよい。Sutent の in vitro, in vivo のデータを出し、候補であることを強調した。9. Testing new agents in subtypes of subtypes (Ted Trimble NCI) CCC も分子標的治療薬で行うべきだ。新しい protocol 作成、薬の使い方、Astrazenca が多くのサポートをしてくれているなどの話して具体的な話はなし。10. Abstract of Presentation SA with CCC は pure CCC とは違う。environment factor は何なのか? stage I は chemo をしなくてよいのか→Ia, Ib はよいが、Ic は慎重にいく。IL-6 と endometriosis, VEGF と immuno-response、CCC の診断基準を明確にする。CCC のガイドライン作り、CCC の重要な pathway。

#### 4. 平成 22 年 6 月 卵巢がんの consensus meeting (カナダ・バンクーバーにて開催)

**A1-1: What are the appropriate endpoints for different trials: (maintenance, upfront chemotherapy trials including molecular drugs)?**

Appropriate endpoints for clinical trials should reflect the achievement of clinical benefit which is defined as improvement of one or more of the following subjective and objective endpoints: **toxicity, time without symptoms, patient reported outcomes (PRO), PFS, OS**. In addition, **cost effectiveness** should be evaluated when feasible.

**A1-2: What are the appropriate endpoints for different trials: (maintenance, upfront chemotherapy trials including molecular drugs)?**

The recommended **primary** endpoints for future front line/maintenance clinical trials in ovarian cancer are:

**Phase II Screening for activity** PFS, PFS at defined time point, or Response.

**Phase III Early ovarian cancer** - Recurrence free survival (note: recurrence = recurrent disease + deaths from any cause). **Advanced ovarian cancer** - Both PFS and OS are important endpoints to understand the full impact of any new treatment. Although overall survival is an important endpoint, progression free survival is most often the preferred primary endpoint for trials because of the confounding effect of the post-recurrence/progression therapy on overall survival. Each protocol should specify if PFS or OS is the preferred endpoint. Regardless of which is selected, the study should be designed and powered for both PFS and OS when feasible. **Maintenance trials**: These criteria should be applied to trials that include maintenance therapy.

**A2: Are there any subgroups defined by tumor biology who need specific treatment options/trials?**

Histopathology remains the gold standard to classify epithelial ovarian cancer subgroups; however, there is emerging evidence to show different genetic and molecular profiles. Since there are different clinical behaviour patterns for some of the histopathological subgroups, it is advised that separate trials are developed for the subgroups listed below: Clear cell carcinoma, Mucinous carcinoma, Low grade serous cancer. When trials for the above are not available patients within these subgroups should be entered into ongoing phase III studies.

**A3: In the 2004 GCG recommend standard comparator arm still valid?**

The standard arm must contain a taxane and a platinum agent administered for six cycles. The recommended regimen is paclitaxel (175mg/m<sup>2</sup>) and carboplatin (AUC 5-6) intravenously every 3 weeks. Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum.

**A4: What is the role of modifying dose schedule, and delivery of chemotherapy?**

Optimizing dose, schedule, and route of delivery of available agents is under ongoing study. The results of these studies should clarify the eventual role of these approaches. Two specific approaches, the alteration of dose/schedule and the use of intraperitoneal therapy, have been shown to be superior in at least one trial\*. **Dose-dense weekly paclitaxel plus every three week carboplatin (JGOG 3016), Intraperitoneal chemotherapy as given in GOG 172**

**A5: What role does surgery play today?**

Surgical staging should be mandatory and should be performed by a gynecologic oncologist.

The ultimate goal is cytoreduction to microscopic disease. There is evidence that reduction to  $\leq 1$  cm macroscopic disease is associated with some benefit. The term "optimal" cytoreduction should be reserved for those with no

macroscopic residual disease. Documentation must be provided as to the level of cytoreduction (at least microscopic vs. macroscopic). Delayed primary surgery following neoadjuvant chemotherapy is an option for selected patients with stage IIIC and IV ovarian cancer as included in EORTC 55971.

#### **B1 Molecular Prognostic and Predictive Factors: What should be the standards for clinical trials?**

Current prognostic and predictive markers are not adequately validated or useful. Histotype specific biomarkers are useful for subtype classification and should be included in histotype-specific clinical trials. Central pathology review should be encouraged for these trials. The design of clinical trials should include the collection of biological specimens to address important translational research questions. The collection of biological specimens at the time of relapse and subsequent progression should be encouraged in order to allow comparison with primary samples.

#### **B-2 What are the promising targets for future therapeutic approaches?**

The most promising targets in clinical trials are angiogenesis and homologous recombination deficiency. To select patients for trials investigating these targets, predictive biomarkers are required. Understanding mechanisms of resistance is a priority. Other promising targets currently being studied based on ovarian cancer biology include: **PI3-Kinase and Ras/Raf pathways, Folate receptor, Immune targets/cytokines, Notch/hedgehog, IGF merit further investigation.** Targeted agents should be studied both as single agents and in combination based on appropriate preclinical data.

#### **B-3 Do We have Appropriate Methods for Evaluating Targeted Therapies?**

Currently there is no other validated method than the standard methods for evaluating targeted therapies. In order to evaluate targeted therapies, it is important to demonstrate an appropriate effect on the target in early phase studies. Patient selection for clinical trials should be based on the known biology of target action and appropriately validated. Criteria other than response (RECIST) are relevant and assessment of patient reported outcomes, quality of life, and measurement of the duration of stable disease may provide valuable information about efficacy. New trial designs such as randomised feasibility studies, or trials using a patient as their own control should be used to evaluate novel agents. Ca-125 and functional imaging should be validated for use with targeted agents.

#### **B-4 Which Targeted Therapies could be regarded as part of a Control arm in Ovarian Cancer Clinical Trials?**

Bevacizumab could be incorporated in the control arm of a randomised trial, as a consequence of the results of a trial with bevacizumab that met its primary endpoint.

Future trials of targeted agents must include measures that better characterize meaningful outcomes for patients. Eg. cost effectiveness, clinical benefit which includes toxicity and quality of life.

(Note: Further discussion on this point will occur in October 2010)

#### **C1: What is the role of cytoreductive surgery for recurrent ovarian cancer?**

Surgery may be appropriate in selected patients. As yet there is no level I evidence which demonstrates a survival advantage associated with surgical cytoreduction for women with recurrent ovarian cancer. Randomised phase III trials evaluating the role of surgery in recurrent ovarian cancer are a priority. Cytoreductive surgery for women with recurrent ovarian cancer may be beneficial if it results in optimal cytoreduction as defined in A4.

#### **C2: How to Define Distinct Patient Populations in need of specific therapeutic approaches?**

Distinct patient populations for clinical trial enrolment may be considered by interval from last platinum therapy. Each trial will need to specify how they define the date of progression (Ca-125 alone, radiological, symptomatic).

The following subgroups should be considered:

Progression while receiving last line of platinum based therapy or within 4 weeks of last platinum dose

Progression-free interval since last line of platinum of < 6 months

Progression-free interval since last line of platinum of 6-12 months

Progression-free interval since last line of platinum of > 12months\*

The PFI is defined from the last date of platinum dose until PD

Note: (Document whether patient had maintenance/ consolidation therapy – which agent and for how long.)

(Document histological type, molecular markers (such as BRCA), and surgery for recurrent disease.)

\* For this group, a platinum-based combination therapy should be the control arm for randomized trials.

#### **C3: Should endpoints for trials with recurrent disease vary from those of first-line trials?**

Phase III trials for patients with recurrent epithelial ovarian cancer (progression-free interval since last line of platinum of >6 months from the last day of platinum dose until PD) should be large enough to detect clinically



meaningful differences in both PFS and OS. Trial design should consider scheduled interim analyses to monitor for fertility. In phase II trials for recurrent disease standard endpoints such as response rate (RECIST or GCIg-defined CA 125 response) and PFS are appropriate. Additional endpoints may include symptom benefit and clinical benefit. The choice of the primary endpoint needs to be fully justified with appropriate power calculations Symptom control/ Quality of life (for early relapse) and overall survival (for late relapse) may be the preferred primary endpoints although PFS should still be used in the assessment of new treatments. Future research should include the development and validation of primary and secondary endpoints such as clinical benefit which includes health-related quality of life, patient-reported outcomes of symptoms, time without symptoms or toxicity, and additionally cost-effectiveness. Note: Early relapse = progression-free interval since last line of platinum of <6 months from the last day of platinum dose until PD. Late relapse = progression-free interval since last line of platinum of >6 months from the last day of platinum dose until PD.

#### C4: Is CA 125 progression alone sufficient for entry/eligibility into clinical trials?

Asymptomatic patients who meet GCIg definition of CA125 progression (without radiological or clinical evidence of recurrence) could be eligible for specific clinical trials. There is evidence that treating patients with asymptomatic CA-125 increase does not improve overall survival.

5. GCIg 秋季総会報告書 2010 年 10 月 21-22 日 チェコ・プラハ開催。参加：寒河江、藤原、進、岡本、青谷、高野 計 6 名

**Executive Board Meeting** M. Quinn が司会で開始。Membership Com 23 groups + 2 observer (TRSGO & SGOG) Chairs and Co-Chairs は各グループから独立して参加 (6 per group)。参加者・企業 9 社合計 120 名 **Strategic Planning** : Governance & Statutes 改訂中。Cervix Cancer Research Network では OUTBACK, SHAPE, Interlace, and KGOG/Thai trial が対象。Incorporation 協議中。**Ongoing Business**: GA topic: June 2011 – Neo-adjuvant therapy debate (trial designs and resources)—other : HRQOL; benchmarks in clinical trials; chemo-radiation in cervix cancer studies; Gyne cancer in the Elderly. 論文: 9 papers under preparation. GCIg Highlights: IGCS oct.26,2010 (Quinn); SGO 2011 (Trimble); ESGO 2011 (action Quinn w Colombo) **New Business**: 5<sup>th</sup> OCCO は討論の結果 2015 年に日本で開催が決定。Scheduling: January 2011 – teleconf. June 2 & 3, 2011, Chicago Sept. 8 & 9, 2011, Milan . January 2012 – teleconf. May 31 & June 1, 2012, Chicago Oct. 11 & 12, 2012, Vancouver (IGCS Oct13-16, 2012)。

**GCIg Cervix Committee**: 発表論文 1) Kitchener HC ら。The Development of Priority Cervical Cancer Trials: A Gynecologic Cancer InterGroup Report. Int J Gyn Cancer, 20(6):1092-1100, August 2010.2)Viswanathan, AN ら Brachytherapy Practice Patterns in the Gynecologic Cancer InterGroup. In Press, Int J Radiol Oncol Biol Phys, 2010. 登録中試験: S-1+CDDP vs single agent CDDP Phase3 study in Cervical cancer (IVB/Rec) 登録順調で 2011.01 には終了。GOG240 (GOG 204 Replacement) 2 x 2 Factorial Design First randomization: Winner of GOG 204 (Cisplatin +Paclitaxel) vs Topotecan + Paclitaxel Second Randomization: Bevacizumab vs No Bevacizumab OS の比較で 30%以上 HR 減少が目標、450 例登録目標、GOG 263 RCT of Adjuvant Radiation vs Chemoradiation In Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy Ryu, SY. RTOG-0724 (GOG): ChemoRT with and without adjuvant chemotherapy in high risk cervix cancer after hysterectomy. 計画・討論試験: THE OUTBACK TRIAL A Phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone 2010 年中には開始予定、参加希望多数。the SHAPE Trial: Simple Hysterectomy And Pelvic node dissection in Early cervix cancer Comparing radical hysterectomy and pelvic node dissection against simple hysterectomy and pelvic node dissection in patients with low risk cervical cancer 実質的議論進展、参加希望多数。統計学的に両群の比較が問題? INTERLACE : INduction ChemoThERapy in Locally Advanced CERvical Cancer-for the NCR I Gynaecological Clinical Studies Group 内容は RT 前に 6 週間毎週の ddCT 後に CCRT か CCRT のみの RCT 今年中の完成をめざし来春から登録開始へ。参加興味多数。TAKO trial: A phase III trial comparing efficacy and cost-effectiveness between Weekly and Three-Weekly cisplatin Chemotherapy for Chemoradiation in Cervical Cancer 韓国とタイからの提案で CCRT での CT を 3 週毎と毎週の比較 PI は Dr. Wilailak S & Dr. Ryu SY. 最後に Proposal for GCIg Cervix Cancer Network of Trial Centres in non-GCIg Countries 途上国からの参加を上記の trials で行い、global なレベルアップを目指す。世界の 4 か所が中心施設として選定。Endometrial Cancer WG : 提案試験(1)Staging LYTEC : LYmphadenectomy Trial in Endometrial Cancer 再発ハイリスク症例をリスク毎にフローチャートを作成し種々の臨床試験へ割り振りをする。まず治療として: 子宮全摘+両側付属器切除 (FIGO stage2009)を行い、リンパ節廓清を行うか行わないかで大きく無作為化し、No nodal

dissection 群では IB, G1orG2 ではリスク因子により observation or brachytherapy または GOG249 (RT vs brachy+chemo) に登録する。G3, st, II, occ III/IV ではリスク因子により GOG249 (RT vs brachy+chemo), GOG258 (chemoRT + chemo vs chemo) または After 4 trial (chemo 4 + RT vs chemo 6) に登録する。一方 PLN+PAN (腎静脈下まで) dissection 群では、リンパ節転移陰性の場合は st IB, G1orG2 では observation or brachytherapy, G3 st II では ENGOT EN2 DGCG (chemo vs obs) に登録する。リンパ節転移陽性すなわち occ III/IV では GOG258 (chemoRT + chemo vs chemo) か After 4 trial (chemo 4 + RT vs chemo 6) に登録する。Primary endpoint は系統的骨盤+傍大動脈リンパ節郭清が DFS を改善するかどうかであり、統計解析: 各 arm 360 例ずつ 4 年で登録完了 4 年の F/U。多くの参加希望あり。(2)ENGOT-NESTEC: Network Study in Endometrial Cancer under the ENGOT umbrella and in cooperation with the Mayo clinic. 対象 1: Clinically presumed: FIGO IB-II any histo type, FIGO IA G3 endometrioid, FIGO IA/B histo type II などに対し、No bulky LN の場合術中 R1 で LN 郭清を行い転移なしでは R2 として経過観察か化学療法 TC を行う。転移ありでは R3 として化学療法 TC か化学療法+放射線療法を行う。LN 郭清なしはこのまま経過観察する。Bulky LN の場合 LN 郭清を行い転移なしか否かの判断後に登録へ。進行がんで R4 として TC+placebo か TC+mTOR 阻害剤に参加する。(3)ENGOT-EN2-DGCGA phase III trial of postoperative chemotherapy or no further treatment for patients with node negative stage I-II intermediate or high risk endometrial cancer: リンパ節転移なし群に術後化学療法を行うか否かの臨床試験 (4)AFTER 4 NSGO Trial phase III intergroup trial of adjuvant therapy in radically operated endometrial cancer patients with high risk for micro-metastatic disease: 4 courses of adjuvant CT followed by RT versus 2 more courses of CT 進行・再発癌での試験: GOG-0238 A randomized trial of pelvic irradiation with or without concurrent weekly cisplatin in patients with pelvic-only recurrence of carcinoma of the uterine corpus 25/164 : 再発子宮体癌 (骨盤・腔に限局)

**Ovarian Committee WG:** GCG Ovarian Trials の Update. 終了した試験: EORTC66971: NEJM に論文掲載。EORTC56041: TC 後に Tarceva の Maintenance Therapy 2 年間追加の有無を問う試験。データ成熟待ち。ICON-7 が発表され、TC+Bevacizumab followed by Bev Maintenance 群が、有意の PFS 改善を示した。同様の結果を示した GOG218 試験 (ASCO 2010 で公表) 結果も発表された。また、Bevacizumab を用いた現在進行形の試験、GOG252, OCEANS, GOG213 試験の紹介があった。CALYPSO 試験、AGO-OVAR-9 試験は JCO に論文掲載。SCOTROC4, HECTOR, AGO DESKTOP, AGO-OVAR16 各試験の登録は終了。進行中の試験: AGO-OVAR-12, AGO LION,, JGOG3017, JGOG3019, MITO-7, MITO-8, DESKTOP III, mEOC, NCIC CTG OV21 各試験。計画中の試験: OVATYON, ICON6, ICON8 各試験

**Translational Research WG : Interleukin-6 as a target in ovarian cancer** Co-chair の Dr. Iain McNeish より platinum 耐性再発卵巣癌 18 症例を対象に IL-6 抗体である CNT0328 の phase II study の報告があった。この study の結果は、①18 例中 8 例が SD/PR であった、②SD/PR 群は投与開始 6 週以内に CA125 の低下または不変が認められた、③すべての SD/PR 群は CRP の低下が認められた、④SD/PR 群において CRP, B2 microglobulin, TNF- $\alpha$ , IL-8, VEGF は有意に低下した、⑤SD/PR 群の腫瘍組織において投与開始 6 週で cytokine の濃度が不変または減少し、M30 (アポトーシスのマーカー) は上昇した。⑥SD/PR 群の腫瘍組織において CCL2(chemokine ligand 2) は 6 ヶ月後に有意に低下した、⑦SD/PR 群の腫瘍組織において 3 ヶ月・6 ヶ月において gp130(IL-6 受容体)の濃度は上昇した。以上の結果より、①IL6 阻害剤は卵巣癌において治療効果が期待できる、②SD/PR 群の血清 cytokine は低下し、腫瘍内 IL6/gp130 は上昇するという矛盾した結果が得られた、③血清 IL-6 高値症例は予後が不良である。Update on the clear cell study JGOG の岡本が clear cell TR study の報告を行った。日本人・オーストラリア人・ドイツ人・韓国 人計 162 例の clear cell 症例検体より DNA, RNA を抽出し、Array CGH/cDNA microarray を行い、人種差・化学療法耐性・予後・子宮内膜症共存の有無に關する遺伝子を解析中である。現在まで OS/PFS/化学療法耐性に關する領域として染色体 16q loss が関与し、約 20 の候補遺伝子に絞り込まれている。NCI pharmacogenomics study NCI, GOG から次の Pharmacogenomics 研究が提案されている。卵巣癌において個人や人種による遺伝的背景が第一次化学療法の奏効率・有害事象・QOL・予後に影響するのではないかと仮定の下、卵巣癌のジェノミック DNA と臨床データから検討する研究で、数千の卵巣癌検体を用いる国際的な pharmacogenomics study である。今後の Clinical trial に末梢血検体採取を組み入れ、検体を供与していただきたいと JGOG にも協力が求められている。今後約 5 年間で約 1000 検体を収集することを最初の目標にしている。Update on TCGA data in high grade serous ovarian cancer ゲノムプロジェクトである The Cancer Genome Atlas (TCGA) や International Genomics Consortium (IGC) project について報告があった。約 300 例のハイグレード漿液性腺癌を用い、シークエンシング、Array CGH、メチレーション解析を行い、データ解析中である。P53, BRCA1 遺伝子変異以外のランダムなゲノムの変化に規則性はないかなどを中心に探索している。Genome-wide transcriptomics study and international collaboration 世界中で Array CGH やシークエンシングが行われているが、各専門家が国際的に協力し、問題点を解決していくべきであり、その意味では 4 の Pharmacogenomics study はいい機会となる。今後は Rare tumor も含め、データを持ち合って国際的に協力する重要性を確認した。

**Harmonization WG :** この WG では、各国の法規及び異なるグループポリシーに関する互いの理解を深め、国際共同試験を円滑に行うために必要となる「調整」を行っている。今回のトピックス: **Harmonization Chair** からの報告事

項 GCIG study reference page をアップデートするために、Web 管理者の Michele へ Lead group として実施した試験名と臨床試験登録番号を送付する (JGOG では、JGOG3017 と S-1 治験が対象となる)。各グループは年 2 回の GCIG ミーティングの際、Harmonization WG に少なくとも 1 名参加させなければならないことが、GCIG Executive Board で決定された。Nursing studies MITO 7 は看護師主導の GCIG 試験として実施されており、目標症例数 400 例のうち 175 例の登録があり進捗は順調であることが報告された。ASNZ 主導の Symptom Benefit 試験も、カナダでは看護研究者主導で実施し、Phase A を終了した。Phase B (英語圏以外のグループへ拡大)においても、看護研究者の参加を歓迎するとのことであった。今後は、さまざまな GCIG 試験において看護師の関与を推進していく方向性が示された。Common Data Elements (CDEs)CDE とは、NCI によって開発された、各領域独自の臨床試験用語についてまとめた標準言語である。これにより用語の定義を明確にし、CRF 標準化と meta-analysis への活用が期待されている。CaDSR (Cancer Data Standards Repository) の WEB ページよりダウンロード可能。各国の検査法ならびに単位の違いが問題になる可能性について討論した。Remote Data Capture Archiving 国際共同試験を実施するにあたり、各グループがどのような EDC システムを使用しているのかを調査した結果、Phase Forward (Inform), Medidata (Rave), Macron あるいは自前のシステムが多かった。NCI Cooperative groups, NCI-Canada, JGOG は Medidata (Rave)を導入。すべてのグループが同じ EDC システムを導入することは不可能だが、利点/欠点や運用上の注意などの情報共有を継続。Secure Emails and Digital Protection of Sensitive Data 何を sensitive data とするのか、定義が各国で異なる。患者情報や試験情報をやりとりする場合は Web-base でパスワード管理されていることが望ましい。Email でやりとりする場合には、パスワード保護と Encryption 保護をかけることが必要である。Survey of Group Policies 各グループのクエリ・の作成/回答方法、逸脱の取り扱い、モニタリングの方法について、NCIC が中心となって調査を実施することが決定。Current GCIG Studies 各グループで現在実施している GCIG 試験について、その進捗状況が報告された。JGOG からは、JGOG3017、S-1 治験、AGO-OV16、GOG3019 への参加グループ募集について報告された。

#### Gynecologic Cancer Intergroup (GCIG) 2010 Autumn meeting に参加して 防衛医大病院 産科婦人科 高野政志

このたびは JGOG 卵巣癌委員の代表として Gynecologic cancer intergroup (GCIG) 2010 Autumn meeting に参加する機会を頂きました。IGCS2010 が行われた Prague Congress Centre の道路を隔てた向かい側にあるプラハでもっとも高層ビルディングとされる Corinthia Hotel で平成 22 年 10 月 21 日、22 日の 2 日間にわたって開催されました。春は ASCO 開催前に Spring meeting を、秋は IGCS あるいは ESGO の開催前に Autumn meeting と年 2 回、定期的に会議を行っています。GCIG は米国 GOG を始めとして全世界の婦人科がん臨床研究グループの総括を行っている組織といえます。Full member として参加しているグループを記すると、「ACRIN, AGO - Au, AGO - De, ANZGOG, DDOG, EORTC - GCG, GEICO, GINECO, GOG, JGOG, KGOG, MaNGO, MITO, MRC/NCRI, NCIC CTG, NSGO, RTOG, SGCTG, SWOG」と婦人科腫瘍の主だった研究を行っているグループのほとんど全てが参加していることがわかります。2 日間にわたり各分野別に行われている臨床試験の進捗具合、今後予定されている試験の紹介等が行われます。初日のメイン会場では一日かけて Translational research, Ovarian cancer, Endometrial cancer, Cervical cancer の各委員会からの発表、そして討論がありました。他にも 2 会場において、Rare tumor や QOL の研究、その他が討議されました。2 日目の午前中に各委員会で討議された内容の総まとめが発表されました。Cervical cancer 委員会のまとめは寒河江先生が発表されましたが、大変コンパクトで、かつ正確、そしてフレンドリーに発表されていたので感嘆しました。午後には Trial-specific meeting として種々の臨床試験グループが試験の紹介、進捗具合、そして試験に参加するよう宣伝も行われました。2 日間にわたって世界における婦人科腫瘍の臨床試験のながれ、今後の方向性をみることができます。各臨床グループとも抗がん剤の試験はハードルが低いもの、手術を組み込んだ臨床試験はなかなか実施が困難である実情があるようです。JGOG の研究についても積極的議論として協議されました。中でも、卵巣癌に対する IP 療法 (JGOG3019) に対して興味をしめすグループがいくつかあり、今後国際的共同研究として発展していくことを期待します。

今回はじめて参加させて頂いたわけですが、最初にびっくりしたのは世界的に名の知れた先生方が全員 First name でよびあっているのです。Michael A Bookman 先生は「マイケル」Ignace Vergote 先生は「イグナス」です。JGOG の先生方も当然、First name で呼ばれます。JR 札幌病院の寒河江先生は「サトル」、埼玉医大の藤原先生は「ケイイチ」です。定期的に議論を交わっていますし、臨床試験で相互に協力しあう間柄ですから当然、このような関係が築かれているでしょう。我々、日本人は引っ込み思案と言われがちですが、とどろき GCIG meeting のようなところに出て行きアピールする必要性を感じました。2 つ目の驚きは GCIG meeting に集まってくる研究者の知名度の高さです。各臨床試験グループからそうそうたる研究者が集まり、米国 GOG を例にとっても各 Disease committee の委員長クラスが全員参加しておりました。そして各グループの臨床試験を宣伝し積極的に参加するように勧誘も行っていきます。JGOG の各 Disease committee においても、今後は世界的な臨床試験の動向をみつめ、他の臨床グループから症例登録をしてもらい早期に集積・解析できるような魅力ある臨床試験を提唱していく必要を強く感じました。

今回、このような期間を与えてくださった JGOG の関係者の皆様には心から深謝いたします。ここで得たことを今後の JGOG の活動に生かしていけるよう努力する所存であります。本当にありがとうございました。

# Evaluation of Parametrial Spread in Endometrial Carcinoma

Yoh Watanabe, MD, PhD, Takao Satou, MD, PhD, Hidekatsu Nakai, MD, PhD, Tomomaro Etoh, MD, Kensaku Dote, MD, PhD, Nahoko Fujinami, PhD, and Hiroshi Hoshiai, MD, PhD

**OBJECTIVE:** To evaluate the detailed clinicopathologic characteristics of parametrial spread in uterine endometrial cancer.

**METHODS:** We retrospectively identified 334 individuals with uterine endometrial cancer who had undergone radical hysterectomy between 1988 and 2007. Parametrial spread was determined by histopathological analysis of surgically resected specimens.

**RESULTS:** Twenty-eight (8.4%) individuals had histopathologically confirmed parametrial spread, and lymphatic or blood vessel invasion (22 cases) was the most frequently observed type of parametrial spread; direct invasion to parametrial connective tissue (five cases) or cardinal lymph node metastasis (four cases) were less frequently observed. Parametrial spread occurred not only in individuals with cervical involvement but also in individuals with more than half myometrial invasion, retroperitoneal (pelvic, paraaortic, or both), lymph node metastasis, ovarian metastasis, positive peritoneal cytology results, and lymphovascular space invasion. Twenty-six individuals (92.9%) with parametrial spread showed more than one of these histopathological factors (median number of factors 3, range 1–6); the other two individuals had lymphovascular space invasion alone. In 10 individuals with parametrial spread (35.7%), the condition recurred during the median follow-up period of 49 months,

and initial recurrence was observed in the lung in six individuals (60.0%). Although the long-term prognosis for those with parametrial spread was significantly poorer than that of those without parametrial spread, both among all individuals ( $P < .001$ ) and among individuals with International Federation of Gynecology and Obstetrics stage III ( $P < .05$ ), multivariate analysis showed that parametrial spread was not an independent prognostic factor for uterine endometrial cancer.

**CONCLUSION:** Parametrial spread cannot be predicted by cervical involvement alone but may be predicted by various lymphovascular space invasion-related histopathologic factors. Further, parametrial spread may not be an independent prognostic factor in individuals with uterine endometrial cancer.

(*Obstet Gynecol* 2010;116:1027–34)

**LEVEL OF EVIDENCE:** III

Parametrial spread in uterine endometrial cancer has been thought to be predicted by cervical involvement; therefore, both the National Comprehensive Cancer Network Practice Guidelines in Oncology (version 2, 2009)<sup>1</sup> and the Endometrial Cancer Treatment Guidelines of Japan Society of Gynecologic Oncology<sup>2</sup> recommend radical hysterectomy when the individuals show uterine endometrial cancer with cervical involvement. However, a recent survey among members of the Japanese Gynecologic Oncology Group regarding the status of surgical treatment procedures for endometrial cancer<sup>3</sup> has revealed that 35.5% of the member institutions of the Japanese Gynecologic Oncology Group performed only simple total hysterectomy, and 70.5% never performed radical hysterectomy in the cases of endometrial cancer. Although detailed investigation of the clinicopathologic characteristics of parametrial spread in uterine endometrial cancer should be performed to safely omit radical hysterectomy, only four studies on parametrial spread in uterine endometrial cancer have been found in the English literature.<sup>4–7</sup> More-

See related editorial on page 1016 and related articles on pages 1095 and 1141.

From the Departments of Obstetrics and Gynecology and Pathology, Kinki University School of Medicine, Osaka, Japan.

The authors thank Dr. K. Noda, honorary president of Japanese Gynecologic Oncology Group, honorary president of Kinki University, for his suggestions on the histopathologic characteristics of parametrial spread.

Corresponding author: Yoh Watanabe, MD, PhD, Department of Obstetrics and Gynecology, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-sayama, Osaka 589-8511, Japan; e-mail: watanabe@med.kindai.ac.jp.

#### Financial Disclosure

The authors did not report any potential conflicts of interest.

© 2010 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.

ISSN: 0029-7844/10

over, the actual incidence and detailed clinicopathologic characteristics of uterine endometrial cancer with parametrial spread are still unknown, because the previous studies had assessed only individuals with International Federation of Gynecology and Obstetrics (FIGO) stage II disease or included individuals who were treated using modified radical hysterectomy. Therefore, although recent studies have reported that minimally invasive surgeries, such as laparoscopic surgery, can be safely performed in gynecologic malignancies, especially in individuals with uterine endometrial cancers,<sup>8-11</sup> radical hysterectomy should still be performed as a standard surgery in individuals with uterine endometrial cancer with cervical involvement.

In this regard, we were able to examine the detailed characteristics of parametrial spread in individuals with uterine endometrial cancer because we have been routinely performing pelvic nerve-sparing radical hysterectomy<sup>12,13</sup> as a standard surgical procedure for individuals with endometrial cancer, except those with endometrioid adenocarcinoma without myometrial invasion,

aged older than 80 years, uncontrollable complications such as diabetes mellitus or cardiac disease, peritoneal macroscopic tumor spread, or stage IV disease. We performed a retrospective study to evaluate the clinicopathologic characteristics and histopathological predictive factors of parametrial spread in individuals with uterine endometrial cancer who were treated using radical hysterectomy.

## MATERIALS AND METHODS

We used clinical records to retrospectively review 334 individuals with endometrial cancer who were treated by pelvic nerve-sparing radical hysterectomy at Kinki University Hospital from January 1988 to December 2007. Further, histopathologic specimens of surgically resected tissues were independently rediagnosed by two pathologists who were completely blinded to the clinical information of the individuals. For accurate diagnosis, we had obtained routine histopathologic specimens of parametrial spread by performing the following procedures when the individuals underwent radical hysterectomy: bilateral parametrial tissues were removed immediately after radical hysterectomy

**Table 1. Clinicopathologic Characteristics of Patients (N=334)**

Characteristic	Patients
Age (y)	57 (27-81)
No. of pregnancies	2 (0-12)
No. of deliveries	2 (0-7)
Histologic subtypes	
Endometrioid adenocarcinoma	308 (92.2)
Adenoacinar carcinoma	12 (3.6)
Adenoacanthoma	9 (2.7)
Serous or mucinous adenocarcinoma	5 (1.5)
Histologic grade	
Grade 1	226 (67.1)
Grade 2	72 (21.6)
Grade 3	36 (10.7)
FIGO (1989) stage	
Stage 1	224 (67.1)
1A	10
1B	155
1C	59
Stage 2	16 (4.8)
Stage 3	94 (28.1)
3A	41
3B	2
3C	51
Adjuvant therapy	
None	161 (48.2)
Chemotherapy	140 (41.9)
Radiation therapy	23 (6.9)
Chemotherapy plus radiation therapy	10 (3.0)

FIGO, International Federation of Gynecology and Obstetrics. Data are median (range), n (%), or n.

**Table 2. Histopathologic Characteristics of Patients**

Characteristic	Patients
Parametrial spread	
Negative	306 (91.6)
Positive	28 (8.4)
Depth of myometrial invasion	
None	9 (2.7)
50% or more	206 (61.7)
Less than 50%	119 (35.6)
Pelvic lymph node metastasis	
Negative	291 (87.1)
Positive	43 (12.9)
Paraaortic lymph node metastasis	
Negative	154 (46.1)
Positive	16 (4.8)
Not performed	164 (49.1)
Ovarian metastasis	
Negative	317 (94.9)
Positive	16 (4.8)
Not performed	1 (0.3)
Cervical involvement	
Negative	285 (85.3)
Positive	49 (14.7)
Peritoneal cytology	
Negative	278 (83.2)
Positive	56 (16.8)
Lymphovascular space invasion	
Negative	217 (65.0)
Positive	117 (35.0)

Data are n (%).

and fixed separately; and paraffin-embedded specimens of the surgically resected parametrial tissues were used to prepare three to five serial histopathological sections stained with hematoxylin and eosin.

Pelvic lymph node dissection was performed in all cases, and the pelvic lymph node dissection included the common iliac, external iliac, internal iliac, obturator, supra-inguinal, sacral, and cardinal lymph nodes. Para-aortic lymph node (para-aortic lymph node) dissection was selectively performed in the cases in which preoperative magnetic resonance imaging or intraoperative macroscopic findings indicated more than 50% myometrial invasion and the cases in which pelvic lymph node or para-aortic lymph node swelling was diagnosed by preoperative computed tomography, magnetic resonance imaging, or intraoperative direct palpation. Para-aortic lymph node dissection was performed in the region inferior to the inferior mesenteric artery, up to the renal artery, or both of these.

Furthermore, postoperative adjuvant therapy was indicated in the individuals, except for those with International Federation of Gynecology and Obstetrics (1988) stage Ia disease or stage Ib disease without lymphovascular space invasion.

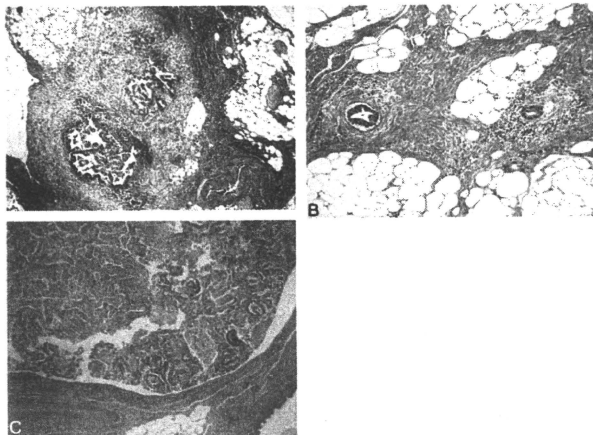
A standardized computer software package was used for statistical analysis. We used  $\chi^2$  test and considered  $P < .05$  as statistically significant. Further, we used the logistic regression test (stepwise, backward selection, conditional method) for multivariate analysis. This study was approved as a retrospective

study by Ethical Committee of Kinki University Faculty of Medicine.

## RESULTS

The clinicopathologic characteristics of the 334 individuals are shown in Table 1. All individuals underwent pelvic nerve-sparing radical hysterectomy, pelvic lymph node dissection, and analysis of peritoneal cytology. Para-aortic lymph node dissection was performed in 170 (50.9%) individuals, and one individual did not undergo oophorectomy. The histological subtype, histological grade, depth of myometrial invasion, presence of cervical involvement, parametrial spread, and lymphovascular space invasion were determined in all the individuals. On the basis of the histopathological analysis, 308 (92.2%) individuals had endometrioid adenocarcinoma diagnosed; among these, 226 (67.7%) cases were grade 1, 72 were grade 2, and 36 were grade 3. On the basis of FIGO surgical staging, 224 cases (67.1%) were stage 1, 16 were stage 2, and 94 were stage 3. Postoperative adjuvant therapies were performed in 173 (51.8%) cases, and adjuvant chemotherapy was the most frequently performed treatment.

Table 2 shows the histopathologic characteristics of the patients. Parametrial spread was observed in 28 (8.4%) individuals. Further, myometrial invasion, pelvic lymph node metastasis, ovarian metastasis, cervical involvement, positive peritoneal cytology results, and lymphovascular space invasion were observed in 317 (94.9%), 40 (12.0%), 21 (6.4%), 46 (14.1%), 54



**Fig. 1.** Histopathologic form of parametrial spread. **A.** Lymphovascular invasion. Adenocarcinoma cells are seen in lymphovascular space of parametrial tissue. Hematoxylin and eosin (H&E) stain (original magnification  $\times 50$ ). **B.** Direct invasion to parametrial connective tissue. Adenocarcinoma cells are seen in parametrial connective tissue (H&E stain, original magnification  $\times 50$ ). **C.** Metastasis to cardinal lymph node. Metastatic adenocarcinoma cells are seen in lymph node of parametrial tissue (H&E stain, original magnification  $\times 50$ ).

Watanabe. Parametrial Spread in Endometrial Cancer. *Obstet Gynecol* 2010.

(16.6%), and 110 (33.7%) individuals, respectively. Although paraaortic lymph node dissection was performed in 170 individuals, paraaortic lymph node metastasis was observed in only 16 (4.8%) individuals.

On the basis of histopathological assessments, parametrial spread was classified into lymphatic and blood vessel involvement (Fig. 1A), direct invasion to parametrial connective tissue (Fig. 1B), and cardinal lymph node metastasis (Fig. 1C), and these forms of parametrial spread were observed in 22 cases (78.6%), five cases, and four cases, respectively.

Table 3 shows the correlation between histopathologic factors and parametrial spread in the 28 individuals with parametrial spread. Parametrial spread was significantly correlated with FIGO stage III, more than 50% myometrial invasion, retroperitoneal lymph node metastasis, ovarian metastasis, cervical involvement, positive peritoneal cytology results, and lymphovascular space invasion, whereas

parametrial spread did not show any significant correlation with the histologic grade.

Figure 2 shows the detailed histopathologic characteristics of individuals with parametrial spread. The frequencies of each histopathologic factor in individuals with parametrial spread were as follows: tumor with grade 2 or higher, 35.7% (13 cases); more than 50% myometrial invasion, 67.9% (19 cases); pelvic lymph node or paraaortic lymph node metastasis, 50.0% (14 cases); ovarian metastasis, 17.9% (five cases); cervical involvement, 39.3% (11 cases); positive peritoneal cytology, 39.3% (11 cases); and lymphovascular space invasion, 100% (28 cases). Twenty-six individuals (92.9%) had multiple histopathologic factors; the median number of histopathologic factors was three (range 1–6). Two individuals (cases 4 and 26) had only lymphovascular space invasion. One individual (case 17) showed direct invasion to parametrial tissue and cardinal lymph node metastasis and one individual (case 25) showed direct invasion to parametrial tissue, cardinal lymph node metastasis, and lymphatic and blood vessel involvement. We observed seven parametrial spread-positive cases even among individuals with stage I. Although four cases had more than 50% myometrial invasion and lymphovascular space invasion, the other three cases showed only lymphovascular space invasion. Furthermore, in the histopathological analysis, none of the individuals with stage I showed the direct-invasion form of parametrial spread.

The outcomes are as follows: 26 individuals died because of disease progression, 13 died because of another cause, and four were alive with recurrent disease. The outcomes of patients with parametrial spread during the median follow-up period of 49 months (range 6–216 months) are shown in Table 4. All the individuals with parametrial spread received postoperative adjuvant therapy and 10 (35.7%) individuals showed recurrence. The most frequent site of recurrence was the lung (six individuals), and the median time to progression was 7 months (range 2–42 months). Long-term prognosis of parametrial spread by Kaplan-Meier analysis is shown in Figure 3. Individuals with parametrial spread had significantly poorer prognoses, among both all individuals (Fig. 3A;  $P < .001$ ) and individuals with FIGO stage III (Fig. 3B,  $P < .05$ ). However, multivariate analysis showed that, although individual age and pelvic lymph node metastasis predicted outcome, parametrial spread was not an independent prognostic factor in individuals with uterine endometrial cancer who had undergone radical hysterectomy (Table 5).

**Table 3. Clinicopathologic Characteristics of Patients With Parametrial Spread**

Characteristic	Patients
FIGO (1988) stage (%)	
Stage I	8/224 (3.6)
Stage II	0/16 (0.0)
Stage III	20/94 (21.3)*
Histologic grade	
Grade 1	15/226 (6.6)
Grade 2	9/72 (12.5)
Grade 3	4/36 (11.1)
Depth of myometrial invasion	
None	0/9 (0.0)
50% or less	9/206 (4.4)
More than 50%	19/119 (16.0)†
Pelvic lymph node metastasis	
Negative	14/291 (4.8)
Positive	14/43 (32.6)*
Paraaortic lymph node metastasis	
Negative	18/154 (11.7)
Positive	5/16 (31.3)*
Ovarian metastasis	
Negative	22/317 (6.9)
Positive	6/16 (37.5)*
Cervical involvement	
Negative	18/285 (6.3)
Positive	10/49 (20.4)†
Peritoneal cytology	
Negative	15/278 (5.4)
Positive	13/56 (23.2)*
Lymphovascular space invasion	
Negative	0/217 (0.0)
Positive	28/117 (23.9)*

FIGO, International Federation of Gynecology and Obstetrics.

Data are n (%).

\*  $P < .001$ .

†  $P < .01$ .

Case number	Histopathologic factors					Histopathologic type of parametrial spread					
	Histologic grade 2 or 3	Myometrial invasion of more than 1/2 the endometrium	Lymph node metastasis	Ovarian metastasis	Cervical involvement	Peritoneal cytology	Lymphovascular space invasion	Direct invasion of parametrial connective tissue	Lymphovascular space invasion	Cardinal lymph node metastasis	
1	○	●	○	○	○	○	●	○	●	○	
2	○	●	○	○	○	○	●	○	●	○	
3	○	●	○	○	○	○	●	○	●	○	
4	○	○	○	○	○	○	○	○	●	○	
5	○	○	●	○	○	○	●	○	●	○	
6	●	○	●	○	○	○	●	○	●	○	
7	●	○	○	●	○	○	○	○	●	○	
8	○	●	○	○	●	○	●	○	●	○	
9	●	●	●	○	●	○	●	○	○	●	
10	●	○	○	○	○	○	○	○	○	○	
11	○	●	●	○	○	●	●	○	●	○	
12	○	○	●	○	○	●	●	○	●	○	
13	●	●	○	○	●	○	○	○	○	○	
14	○	○	○	○	●	●	●	●	○	○	
15	○	●	●	○	●	●	●	●	○	○	
16	●	●	●	○	●	●	○	○	○	○	
17	○	●	○	○	●	○	●	○	○	●	
18	●	●	○	○	○	○	○	○	●	○	
19	●	●	●	○	●	○	○	○	○	○	
20	●	○	○	○	○	○	○	○	○	●	
21	○	○	●	○	○	○	○	○	○	○	
22	●	●	●	●	●	○	●	○	○	○	
23	●	●	○	○	○	○	○	○	○	○	
24	●	●	●	○	○	●	●	○	●	○	
25	○	●	●	●	●	●	●	●	●	●	
26	○	○	○	○	○	○	○	○	○	○	
27	●	●	●	○	○	○	●	○	●	○	
28	○	○	●	●	●	●	○	○	●	○	

Fig. 2. Detailed characteristics of individuals with parametrial spread. Filled circles, present; open circles, absent. Watanabe. Parametrial Spread in Endometrial Cancer. Obstet Gynecol 2010.

## DISCUSSION

Individuals with uterine endometrial cancer with cervical involvement have been undergoing radical hysterectomy for sufficient excision of the vaginal wall and the effective cardinal ligament to prevent vaginal stump and parametrial recurrences.<sup>14-17</sup> Furthermore, several studies<sup>18-22</sup> have reported the superiority of radical hysterectomy in the treatment of FIGO stage II uterine endometrial cancer with cervical involvement. However, the detailed clinicopathologic features of parametrial spread in uterine endometrial

cancer were still unknown. Parametrial spread was predicted only by cervical involvement, and radical hysterectomy should be performed only for uterine endometrial cancer with cervical involvement. On the basis of the results of these previous studies, the understanding of parametrial spread in uterine endometrial cancer can be summarized. First, parametrial spread in uterine endometrial cancer occurs as a result of causes similar to those of uterine cervical adenocarcinoma with endometrial invasion. Second, radical hysterectomy should be performed only for



**Table 4. Outcomes of Patients with Parametrial Spread (N=28)**

Characteristic	Patients
Follow-up period (mo)	49 (6–216)
Adjuvant therapy	
Chemotherapy	24
Radiation therapy	3
Chemotherapy and radiation therapy	5
Disease status	
Recurrent	10
Disease-free	18
Recurrent site	
Pelvic cavity	3
Abdominal cavity	1
Lung	6
Outcome	
Disease-free survival	18
Alive with disease	0
Died by disease progression	10
Time to progression (mo)	7 (2–42)

Data are median (range) or n.

FIGO stage II because parametrial spread is predicted by cervical involvement. Third, parametrial spread is not observed in individuals with FIGO stage I disease. However, our present study has revealed that although parametrial spread was associated with cervical involvement in 21.3% of the individuals, none of the individuals with stage II had parametrial spread. Furthermore, although parametrial spread occurred even in stage I, histopathologic assessments in these

**Table 5. Prognostic Factors of Subjected Cases**

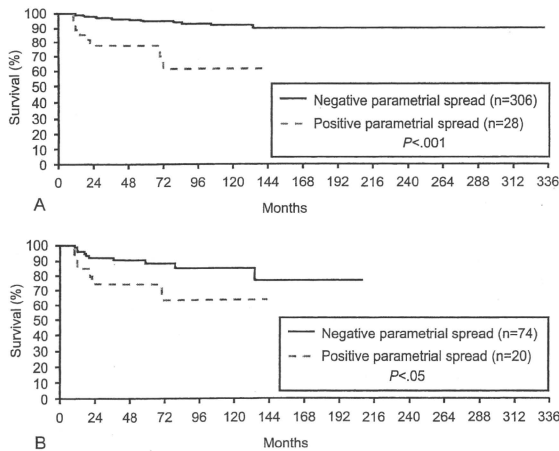
Clinicopathologic Factors	P	Odds Ratio	95% Confidence Interval
Age (older than 65 compared with 65 or younger)	.032	6.231	1.171–33.165
Pelvic lymph node metastasis	.033	3.736	1.109–12.589
Peritoneal cytology	.148	2.469	0.726–8.396
Ovarian metastasis	.067	3.739	0.912–15.336
PRMS	.233	2.177	0.607–7.808

PRMS, parametrial spread.

Value was calculated by logistic regression test.

individuals revealed lymphovascular space invasion or cardinal lymph node metastasis.

Table 6 summarizes the results of four previous retrospective studies,<sup>4–7</sup> including our present study on parametrial spread in uterine endometrial cancer. Interestingly, although the reported frequency of cervical involvement ranged from 39.3% to 75.0%, the dominant histopathologic type of parametrial spread was not direct invasion but lymphatic involvement or lymph node metastasis. Moreover, Gadducci et al<sup>23</sup> studied individuals with FIGO stage I–II endometrioid type of uterine endometrial cancer and showed that lymphovascular space invasion and outer one-third myometrial invasion were independent predictive variables for the risk of distant hematogenous failure.



**Fig. 3.** Long-term prognosis for individuals with parametrial spread. **A.** Prognosis in all individuals. **B.** Prognosis of individuals with Intentional Federation of Gynecology and Obstetrics (FIGO) stage III disease.

Watanabe. Parametrial Spread in Endometrial Cancer. *Obstet Gynecol* 2010.

**Table 6. Characteristics of Parametrial Spread in Endometrial Cancer**

No. of Patients Studied	Subjected Patient	Surgical Procedures	Frequency of PRMS	Frequency of Clinical Stage I in PRMS Patients	Histopathologic Type of PRMS	
91	Clinical stage I, II	MRH RH	12/91 (13.2%)	9/12 (75.0%)	Direct invasion LVS1	5 (41.7%) 7 (58.3%)
24	Clinical stage II	RH	2/24 (8.3%)	2/2 (100%)	Direct invasion	2 (100%)
268	Clinical stage I-III	MRH RH	16/269 (5.9%)	10/16 (62.5%)	Direct invasion LVS1 CLNM	13 (81.3%)* 7 (43.8%) 3 (18.8%)
133	Clinical stage II	RH	10/71 (14.1%)	0/41 (0.0%)	Not described	
334 <sup>†</sup>	Clinical stage I-III	RH	28/334 (8.4%)	11/28 (39.3%)	Direct invasion LVS1 CLNM	5 (17.9%)* 22 (78.6%) 4 (14.3%)

MRH, modified radical hysterectomy; RH, radical hysterectomy; LVS1, lymphovascular space invasion; CLNM, cardinal lymph node metastasis.

\* Five cases of LVS1 and two cases of CLNM.

<sup>†</sup> One case of both LVS1 and CLNM and one case of CLNM.

<sup>‡</sup> Our present study.

These results suggest that parametrial spread in uterine endometrial cancer may occur because of different processes associated with uterine cervical cancer. These results also elucidated why parametrial spread was a prognostic factor in univariate analysis but did not show any significant correlation in multivariable analysis. Moreover, radical hysterectomy for stage II uterine endometrial cancer may not improve individual prognosis if parametrial spread in uterine endometrial cancer is a type of multiple spread caused by disease progression. Therefore, parametrial spread in uterine endometrial cancer would be predicted not by cervical involvement but by clinical factors related to lymphovascular space invasion, which is known as a predictive factor of tumor spread and prognosis for uterine endometrial cancer,<sup>24-27</sup> such as deep myometrial invasion. Furthermore, parametrial spread was observed only in endometrioid histology in the present study. In this regard, additional studies are required to determine the correlation between histologic subtypes and parametrial spread in uterine endometrial cancer, because only 7.8% of the individuals showed nonendometrioid histology in our study. However, previous studies have reported that the histological type is not a significant predictive factor of parametrial spread<sup>4</sup> in uterine endometrial cancer.

Although several previous studies<sup>28-31</sup> have reported that radical hysterectomy improved the prognosis for uterine endometrial cancer with positive parametrial spread (surgical stage II), the accuracy of preoperative examination to determine cervical involvement has remained within 29.6%<sup>32</sup> to 4.5%.<sup>33</sup>

Therefore, the majority of individuals with clinical stage II uterine endometrial cancer have undergone surgical overtreatment.

Our results imply that radical hysterectomy should not be performed for individuals with cervical involvement alone, except when the preoperative inner pelvic examination shows obvious parametrial invasion. However, parametrial lymph node dissection should be considered if parametrial lymph node swelling or deep myometrial invasion is suspected by preoperative magnetic resonance imaging findings.

## REFERENCES

1. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. [http://www.nccn.org/professionals/physician\\_gls/PDF/uterine.pdf](http://www.nccn.org/professionals/physician_gls/PDF/uterine.pdf). Retrieved June, 09 2010.
2. Endometrial cancer treatment guidelines 2006 [Japanese]. Japan Society of Gynecologic Oncology. Tokyo [Japan]: Kanehara-Syuppan; 2006.
3. Watanabe Y, Aoki D, Kitagawa R, Takeuchi S, Sagae S, Sakuragi N, et al. Status of surgical treatment procedures for endometrial cancer in Japan: results of a Japanese Gynecologic Oncology Group survey. *Gynecol Oncol* 2007;105:325-8.
4. Yura Y, Tauchi K, Koshiyama M, Konishi I, Yura S, Mori T, et al. Parametrial involvement in endometrial carcinomas: Its incidence and correlation with other histological parameters. *Gynecol Oncol* 1996;63:114-9.
5. Tamussino KF, Reich O, Gucer F, Moser F, Zivkovic F, Lang PF, et al. Parametrial spread in patients with endometrial carcinoma undergoing radical hysterectomy. *Int J Gynecol Cancer* 2000;10:313-7.
6. Sato R, Jobo T, Kuramoto H. Parametrial spread is a prognostic factor in endometrial carcinoma. *Eur J Gynecol Oncol* 2003;24:241-5.
7. Lee TS, Kim JW, Kim DY, Kim YT, Lee KH, Kim BG, et al. Necessity of radical hysterectomy for endometrial cancer

- patients with cervical invasion. *J Korean Med Sci* 2010;25:552-6.
8. Malur S, Possover M, Michels W, Schneider A. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. *Gynecol Oncol* 2001;80:239-44.
  9. Fram KM. Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. *Int J Gynecol Cancer* 2002;12:57-61.
  10. Palomba S, Falbo A, Mocciano R, Russo T, Zullo F. Laparoscopic treatment for endometrial cancer: a meta-analysis of randomized control trials (RCTs). *Gynecol Oncol* 2009;112:415-21.
  11. Zullo F, Palomba S, Falbo A, Russo T, Mocciano R, Tartaglia E, et al. Laparoscopic surgery vs laparotomy for early stage endometrial cancer: long-term data of a randomized control trial. *Am J Obstet Gynecol* 2009;200:296.e1-9.
  12. Sasaki H, Yoshida T, Noda K, Yachiku S, Minami K, Kaneko S. Urethral pressure profiles following radical hysterectomy. *Obstet Gynecol* 1982;59:101-4.
  13. Noda K. Presevation of function and radicality in radical operation of cancer of the uterine cervix. *Gan To Kagaku Ryoho* 1988;15:1150-3.
  14. Rutledge F. The role of radical hysterectomy in adenocarcinoma of the endometrium. *Gynecol Oncol* 1974;2:331-47.
  15. Roberts DWT. Carcinoma of the body of the uterus at Chelsea Hospital for Women, 1943-1953. *J Obstet Gynaecol Br Commonw* 1961;68:132-8.
  16. Parsons L, Cesare F. Wertheim hysterectomy in the treatment of endometrial carcinoma. *Surg Gynecol Obstet* 1959;108:582-90.
  17. Lefevre H. Node dissection in cancer of the endometrium. *Surg Gynecol Obstet* 1956;102:649-56.
  18. Boothby RA, Carlson JA, Neiman W, Rubin MM, Morgan MA, Schults D, et al. Treatment of stage II endometrial carcinoma. *Gynecol Oncol* 1989;33:204-8.
  19. Boente MP, Yordan EL Jr, McIntosh DG, Grendys EC Jr, Orandi YA, Davies S, et al. Prognostic factors and long-term survival in endometrial adenocarcinoma with cervical involvement. *Gynecol Oncol* 1993;51:316-22.
  20. Boente MP, Orandi YA, Yordan EL, Miller A, Graham JE, Kirshner C, et al. Recurrence patterns and complications in endometrial adenocarcinoma with cervical involvement. *Ann Surg Oncol* 1995;2:138-44.
  21. Sartori E, Gadducci A, Landoni F, Lissoni A, Maggino T, Zola P, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. *Int J Gynecol Cancer* 2001;11:430-7.
  22. Ayhan A, Taskiran C, Celik C, Yuce K. The long-term survival of women with surgical stage II endometrioid type endometrial cancer. *Gynecol Oncol* 2004;93:9-13.
  23. Gadducci A, Cavazzana A, Cosio S, Di Cristofano C, Tana R, Fanucchi A, et al. Lymph-vascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogenous failures in patient with stage I-II endometrioid-type endometrial cancer. *Anticancer Res* 2009;29:1715-20.
  24. Inoue Y, Obata K, Abe K, Ohmura G, Doh K, et al. The prognostic significance of vascular invasion by endometrial carcinoma. *Cancer* 1996;78:1447-51.
  25. Watari H, Todo Y, Takeda M, Ebina Y, Yamamoto R, Sakuragi N. Lymph-vascular space invasion and number of positive para-aortic node groups predict survival in node-positive patients with endometrial cancer. *Gynecol Oncol* 2005;96:651-7.
  26. Briet JM, Hollema H, Reesink N, Aalders JG, Mourits MJ, ten Hoor KA, et al. Lymphovascular space involvement: an independent prognostic factor in endometrial cancer. *Gynecol Oncol* 2005;96:799-804.
  27. Gemer O, Arie AB, Levy T, Gdalevich M, Lorian M, Barak F, et al. Lymphovascular space involvement compromises the survival of patients with stage I endometrial cancer: results of a multicenter study. *Eur J Surg Oncol* 2005;33:644-7.
  28. Sartori E, Gadducci A, Landoni F, Lissoni A, Maggino T, Zola P, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. *Int J Gynecol Cancer* 2001;11:430-7.
  29. Mariani A, Webb MJ, Keeney GL, Calori G, Podratz KC. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. *Gynecol Oncol* 2001;83:72-80.
  30. Cornelson TL, Trimble EL, Kosary CL. SEER data, corpus uteri cancer: treatment trends versus survival for FIGO stage II, 1988-1994. *Gynecol Oncol* 1999;74:350-5.
  31. Cohn DE, Woeste EM, Cacchio S, Zanagnolo VL, Havrilesky IJ, Mariani A, et al. Clinical and pathologic correlates in surgical stage II endometrial carcinoma. *Obstet Gynecol* 2007;109:1062-7.
  32. Pete I, Godeny M, Toth E, Rado J, Pete B, Pulay T. Prediction of cervical infiltration in Stage II endometrial cancer by different preoperative evaluation techniques (D&C, US, CT, MRI). *Eur J Gynaecol Oncol* 2003;24:517-22.
  33. Creasman WT, DeGeest K, DiSaia PJ, Zaino RJ. Significance of true surgical pathologic staging: a Gynecologic Oncology Group Study. *Am J Obstet Gynecol* 1999;181:31-4.

## Outcomes of Fertility-Sparing Surgery for Stage I Epithelial Ovarian Cancer: A Proposal for Patient Selection

Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi, Toshiharu Kamura, Ikuo Konishi, and Hiroyuki Yoshikawa

### ABSTRACT

From the Department of Obstetrics and Gynecology, University of Tsukuba, Tsukuba; Department of Obstetrics and Gynecology, Kagoshima City Hospital, Kagoshima; Department of Obstetrics and Gynecology, Tohoku University, Sendai; Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine; Department of Obstetrics and Gynecology, Osaka City General Hospital, Osaka; Department of Gynecology, Niigata Cancer Center Hospital, Niigata; Department of Gynecologic Oncology, Hyogo Cancer Center, Akashi; Department of Obstetrics and Gynecology, The Jikei University School of Medicine; Department of Obstetrics and Gynecology, Juntenno University School of Medicine; Department of Obstetrics and Gynecology, University of Tsukuba, Tsukuba; Department of Obstetrics and Gynecology, National Defense Medical College, Saitama; Department of Gynecology, Saitama Cancer Center, Ina; Department of Obstetrics and Gynecology, National Hospital Organization Kure Medical Center/Chugoku Cancer Center, Kure; Department of Gynecology and Obstetrics, Kyushu University, Fukuoka; Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Matsumoto; Department of Gynecology, Aichi Cancer Center Hospital, Nagoya; Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume; Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Submitted July 2, 2009; accepted November 20, 2009; published online ahead of print at [www.jco.org](http://www.jco.org) on March 1, 2010.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Toyomi Satoh, MD, PhD, Department of Obstetrics and Gynecology, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan; e-mail: [toyomi@md.tsukuba.ac.jp](mailto:toyomi@md.tsukuba.ac.jp).

© 2010 by American Society of Clinical Oncology  
0732-183X/10/2810-1727/\$20.00  
DOI: 10.1200/JCO.2009.24.8617

### Purpose

The objective of this study was to assess clinical outcomes and fertility in patients treated conservatively for unilateral stage I invasive epithelial ovarian cancer (EOC).

### Patients and Methods

A multi-institutional retrospective investigation was undertaken to identify patients with unilateral stage I EOC treated with fertility-sparing surgery. Favorable histology was defined as grade 1 or grade 2 adenocarcinoma, excluding clear cell histology.

### Results

A total of 211 patients (stage IA,  $n = 126$ ; stage IC,  $n = 85$ ) were identified from 30 institutions. Median duration of follow-up was 78 months. Five-year overall survival and recurrence-free survival were 100% and 97.8% for stage IA and favorable histology ( $n = 108$ ), 100% and 100% for stage IA and clear cell histology ( $n = 15$ ), 100% and 33.3% for stage IA and grade 3 ( $n = 3$ ), 96.9% and 92.1% for stage IC and favorable histology ( $n = 67$ ), 93.3% and 66.0% for stage IC and clear cell histology ( $n = 15$ ), and 66.7% and 66.7% for stage IC and grade 3 ( $n = 3$ ). Forty-five (53.6%) of 84 patients who were nulliparous at fertility-sparing surgery and married at the time of investigation gave birth to 56 healthy children.

### Conclusion

Our data confirm that fertility-sparing surgery is a safe treatment for stage IA patients with favorable histology and suggest that stage IA patients with clear cell histology and stage IC patients with favorable histology can be candidates for fertility-sparing surgery followed by adjuvant chemotherapy.

*J Clin Oncol* 28:1727-1732. © 2010 by American Society of Clinical Oncology

### INTRODUCTION

The standard surgical treatment for early-stage epithelial ovarian cancer (EOC) is total hysterectomy plus bilateral salpingo-oophorectomy with peritoneal and lymph-node sampling. Fertility-sparing surgery that includes unilateral salpingo-oophorectomy and optimal surgical staging is an option available to young women with stage I EOC. However, the recommended indications for such treatment remain controversial.

Fertility-sparing surgery for reproductive-age patients with invasive EOC has been adopted for stage IA and non-clear cell histology grade 1 (G1)/grade 2 (G2) according to the 2007 guidelines of the American College of Obstetrics and Gynecology (ACOG)<sup>1</sup> and for unilateral stage I tumor without dense adhesions showing favorable histology (ie, non-clear cell histology G1/2) according to the 2008

guidelines of the European Society for Medical Oncology (ESMO).<sup>2</sup> In Japan, fertility-sparing surgery has been recommended for patients with stage IA tumor or unilateral stage IC tumor on the basis of intraoperative capsule rupture [IC(b)] and favorable histology, according to the 2004 guidelines<sup>3</sup> and the 2007 guidelines<sup>4</sup> of the Japan Society of Gynecologic Oncology (JSGO). EOC with clear cell or grade 3 (G3) histology and with bilateral ovarian involvement has been excluded from indications for fertility-sparing surgery in all three guidelines. The recommendations regarding fertility-sparing surgery for unilateral and stage IC EOC differ widely among these guidelines, although those for unilateral and stage IA EOC with favorable histology are common to all three guidelines.

The number of published studies concerning fertility-sparing surgery in young EOC patients who wish to preserve the possibility of pregnancy is