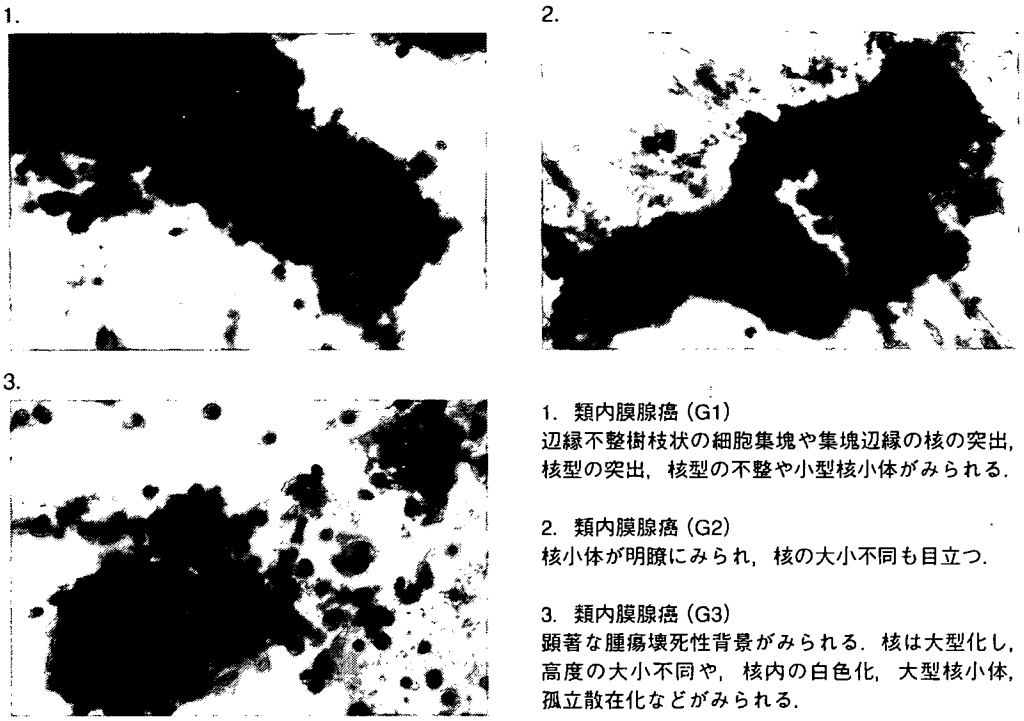


1. 類内膜腺癌 (G1)
辺縁不整樹枝状の細胞集塊や集塊辺縁の核の突出，核型の突出，核型の不整や小型核小体がみられる．

2. 類内膜腺癌 (G2)
核小体が明瞭にみられ，核の大小不同も目立つ．

3. 類内膜腺癌 (G3)
顕著な腫瘍壊死性背景がみられる．核は大型化し，高度の大小不同や，核内の白色化，大型核小体，孤立散在化などがみられる．

図3　類内膜腺癌の細胞像

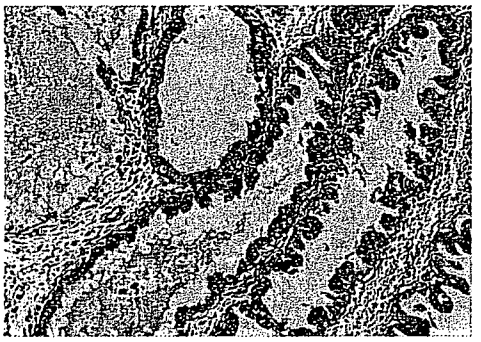
表2　子宮体癌および上皮性関連病変の組織分類

1) 子宮内膜増殖症　endometrial hyperplasia
   a) 単純型子宮内膜増殖症　endometrial hyperplasia, simple
   b) 複雑型子宮内膜増殖症　endometrial hyperplasia, complex
2) 子宮内膜異型増殖症　atypical endometrial hyperplasia
   a) 単純型子宮内膜異型増殖症　atypical endometrial hyperplasia, simple
   b) 複雑型子宮内膜異型増殖症　atypical endometrial hyperplasia, complex
3) 子宮内膜ポリープ　endometrial polyp
   a) 類内膜癌　endometrioid carcinoma
      (1) 類内膜腺癌　endometrioid adenocarcinoma
         (a) 分泌型類内膜腺癌　endometrioid adenocarcinoma, secretory variant
         (b) 綿毛細胞型類内膜腫癌　endometrioid adenocarcinoma, ciliated cell variant
      (2) 扁平上皮への分化を伴う類内膜腺癌　endometrioid adenocarcinoma with squamous differentiation (腺扁平上皮癌adenosquamous carcinoma ; 腺棘細胞癌adenoacanthoma)
   b) 漿液性腺癌　serous adenocarcinoma
   c) 明細胞腺癌　clear cell adenocarcinoma
   d) 粘液性腺癌　mucinous adenocarcinoma
   e) 扁平上皮癌　squamous cell carcinoma
   f) 混合癌　mixed carcinoma
   g) 未分化癌　undifferentiated carcinoma

すべての類内膜癌は腺癌成分の形態によりGrade 1・2・3に分類される
Grade1 : 充実性増殖の占める割合が腺癌成分の5％以下であるもの
Grade2 : 充実性増殖の占める割合が腺癌成分の6～50％のもの．あるいは充実性増殖の割合が5％以下でも細胞異型の著しく強いもの
Grade3 : 充実性増殖の占める割合が腺癌成分の50％を超えるもの．あるいは充実性増殖の割合が6～50％でも細胞異型の著しく強いもの

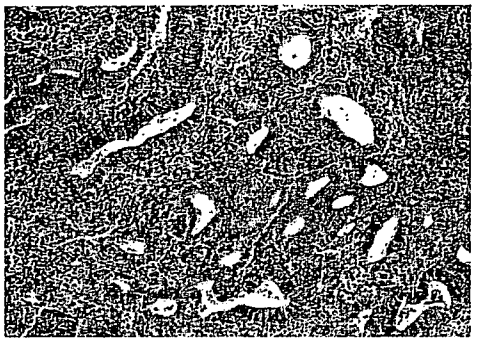
[細胞学的分化度に関する注意]
①漿液性腺癌，明細胞腺癌，扁平上皮腺癌は核異型によりGradeを判定する．
②扁平上皮への分化を伴う腺癌のGradeは腺癌成分によって判定する．

1. 複雑型子宮内膜増殖症



細胞異型を伴わない内膜線の過剰増殖から成り，腺は増殖期内膜に類似する．
腺の拡張を伴うことが多い．

2. 複雑型子宮異型内膜増殖症

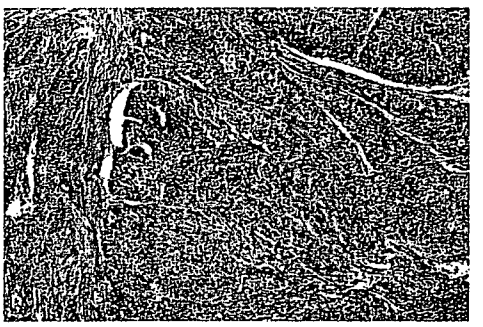


腺構造の異常と細胞異型を伴う内膜腺の過剰増殖がみられる．

3. 子宮類内膜腺癌（G1）

内膜腺に類似した構造を示す腺癌で，充実性増殖の占める割合が腺癌成分の5％以下．
間質への浸潤がみられ，腺の不規則な突出像，癒合した腺構造，乳頭状増生像をみる．

4. 子宮類内膜腺癌（G3）



腫瘍細胞は充実性増殖を示し，扁平上皮化生部分を含まない充実性部分は50％を占める．

図4　子宮内膜増殖症/子宮類内膜癌の組織像

片を採取する．診断のためのひとかき掻爬では採取された組織片に病変部が含まれず，誤診につながることもある．したがって，最終診断や治療のためには全面掻爬が理想的ではあるが，少なくとも時計回りに0時，3時，6時，9時の4方向から内膜組織を採取する必要がある．子宮内膜掻爬は，頸管拡張を要する場合もあるが，閉経前患者の場合には不要のことが多い．子宮腟部前唇をミューゾー鉗子にて把持・索引し，あらかじめ双合診・超音波により子宮腔の方向・長さ・形状を確認後に行う．頸管拡張を必要とする場合は，ヘガール型頸管拡張器を用いたり，術数時間前よりラミセルを1本挿入しておくのも便利である．

2. 子宮鏡を用いた子宮内膜狙い組織診

われわれは子宮鏡を併用した内膜狙い組織診を施行することによる，さらなる正診率の向上を目指している．不正出血を主訴とする症例すべてに対し麻酔下の全面掻爬を施行すれば，もちろん内膜細胞診の正診率を上げることは可能であろう．しかしながら，内膜細胞診を参考にしつつ症例を選択して子宮鏡下の狙い組織診を施行することは，いたずらに患者の侵襲を広げることなく高頻度に予後良好な初期体癌を発見し得る有効な手段と思われる．

3. 子宮内膜組織型

表2にかかげる組織型が存在する．また，子宮内膜増殖症および類内膜腺癌の代表的な像を示す

(図4).

おわりに

子宮体癌は増加しており，今後もこの傾向は変わらないであろう．臨床医としては細胞診の有用性と限界を理解し，症例を選択しつつ子宮鏡下の狙い組織診が必要となる．また，超音波やそのほかの画像検査も駆使して早期発見に努める必要があると思われる．

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国際連携事業報告

GCIG 委員会

GCIG委員会

委員 紀川 純三　委員長 寒河江 悟

寒河江委員長が海外出張のため，代理でお話しさせていただきます．

Gynecologic Cancer Intergroup (GCIG)は，世界の婦人科腫瘍の研究グループのインターグループです．ドイツのAGOとか，アメリカのGOG，われわれのJGOGもこのグループに入って活動を行っているということです（図1）．

ちょうど2003年からJGOGがこのGCIGに参加しました．初めは，GOG Japanの委員会がGCIG委員会を担当していたのですが，やはり組織改組になり，GCIG国内委員として，寒河江先生を委員長としてこのメンバーで実際の活動を行っております（表1）．GCIG委員会の構成につきましては，お手元の資料を参照していただければと思います．

2005年のGCIG活動は，まず電話会議が行われ，

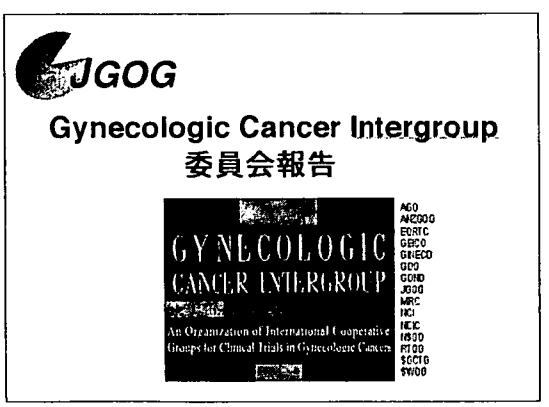

図1

表1

● GCIG国内委員
寒河江　悟（札幌鉄道病院）委員長
青谷恵利子（北里研究所）
紀川　純三（鳥取大学）
高橋　史朗（北里研究所）
波多江正紀（鹿児島市立病院）
藤原　恵一（川崎医科大学）

● GCIG委員会細則
理事会　運営委員会　承認すみ

表2　GCIG 2005

1. Teleconferences
Executive Board (Jan 18)
Endometrial Cancer Working group (Feb 17, Apr 14)

2. GCIG　Annual Spring Meeting
Pre ASCO May 12&13, 2005　Orlando, Florida

3. GCIG　Annual Fall Meeting
After ECCO13 Nov 3&4, Paris

その後，ASCOの前にオーランドでGCIGの年次総会，これは春と秋にミーティングがあるのですけれども，春の総会がありました．現在パリで，ちょうど11月3，4日にJGOG総会とダブるのですが，ECCOのあとに秋の総会を行っております．寒河江委員長が，現在その会議に出席されておりますので，代わりに私がお話をさせていただいております（表2）．

電話会議の内容としては，イタリア，インド，オーストリア，中国と韓国のグループが，GCIGの新会員としてノミネートされており，さらに，

表3 Teleconferences

1) Executive Board meeting
Membership: Italian, Chinese, Austrian, Korean groups nominate
Finances: $42,847 Cdn.
Statutes : honorary membership
provisional memb. Criteria
Chair-elect nominations
Website Report: 134,000 visitors in 2004
Working groups: endometrial, Radiotherapy
HNPCC protocol(GOG)
Sentinel nodes/vulvar cancer by Levenback
Ovarian consensus workshop update
2) Endometrial cancer working group
Taxol/Carbo vs Taxol/Carbo/CCI-779
For advanced or recurrent endometrial cancer

表4 GCIG Annual Spring Meeting 2005 Orlando, Florida

May 12
- 11 Working groups
- Executive Board
- Social evening

May 13
- General Assembly

表5 11 Working groups

Harmonization	Aotani, Sugiyama, Fujiwara
Cervix Cancer	Hatae
Translational Research	Kigawa
Rare tumours	Fujiwara, Hatae
Symptom Benefit	Sugiyama
Classifications	
Screening HNPCC	
Sentinel Nodes vulvar cancer	
Endometrial Cancer	Sagae, Sugiyama
TJ vs TJ+target	
Response/Progression	Sagae, Sugiyama
1st line response criteria	
Early Ovary	Sagae
Proteomic evaluation	

表6 Executive Board

- Membership : NCI-US (and GOG,RTOG) request reject by vote
- Statutes : membership
Austria OK, Itary and India OK,
but Korea and Chinese were NO.
- Website : concept form, webtrends, Q & A, bibliography(include JGOG)/Trials format
- Working groups :
Endometrial cancer consensus conference 2006
- OVCC update BMS germany X Annal Oncol? IJGC? Gyn Oncol?

表7 General Assembly

- Executive board report
- Chair-elect nominations MRC or NCIC NCICanada winner
- FIGO staging review up to July
- Ovarian cancer
1st line, recur, Clear cell, small cell etc
intraperitoneal therapy clinical announce by NCI-US in July
- Endometrial cancer Taxol/Carbo ± Target
- Cervix Cancer CCR ± C225(Cetuximab)
- Vulvar Cancer sentinel nodes
- Other Gyne disease sites vagina GTD
- Working group reports

表8 GCIG Annual Fall Meeting
Nov 3&4, 2005 Paris, France

- Attendance ; Sagae, Takahashi, Isonishi
Schedule
Nov 3
- Executive Board
- 11 Working groups
- Social evening
- Nov 4
- General Assembly
JGOG3017CCC protocol

GCIGが4万2,000ドルほどの予算で行われているということぐらいです.

この会議の後，2005年5月にオーランドで年次総会の春季総会が行われました（表4）．その会議では，前日に11種類のワーキンググループの会議，理事会，さらに懇親会です（表5）．翌日には全体会議が行われ，日本から参加したのは，委員長のほか，北里データセンターの青谷さん，杉山徹先生が明細胞腺がんのプロトコール関連で参加していただきましたし，藤原恵一，波多江正紀の両先生が各委員会に参加しております．

決定事項は，GCIG新会員として，オーストリア，イタリア，インドは認可されましたが，P3臨床試験が未実施であることから，韓国と中国は，

表9 Next meeting of GCIG

- 2006 Teleconference January
- 2006 Spring meeting
  June preASCO, Atlanta
- 2006 Fall meeting
  October preIGCS, Santa Monica

残念ながら今回GCIGのメンバーには入れなかったということです．さらに，GCIGの議長選挙があり，今回はイギリスとカナダとの投票になりまして，結局カナダのグループが議長国になったということです．

現在，パリで寒河江先生と北里データセンターの高橋さん，卵巣がん委員会から磯西先生が，このGCIG秋季会議に出席されております．また来年2006年の予定ですが，1月電話会議，来年6月のASCOアトランタで春季総会が行われ，どちらもアメリカになりますが10月IGCSの後に秋季総会が予定されております（表9）．

● 原 著 ●

進行子宮体癌に対する術後 Doxorubicin/Cisplatin (AP) 併用化学療法の認容性の検討

西尾 真 勝俣 範之 田部 宏 松本 光史 米盛 勧
河野 勤 清水千佳子 安藤 正志 藤原 康弘*

〔*Jpn J Cancer Chemother* 33(11): 1589-1593, *November*, 2006〕

A Feasibility Study of Doxorubicin/Cisplatin (AP) for Postoperative Chemotherapy in Patients with Advanced Endometrial Cancer: Shin Nishio, Noriyuki Katsumata, Hiroshi Tanabe, Koji Matsumoto, Kan Yonemori, Tsutomu Kouno, Chikako Shimizu, Masashi Ando and Yasuhiro Fujiwara (*Division of Medical Oncology, National Cancer Center Hospital*)

Summary

Objective: We evaluated the feasibility of doxorubicin/cisplatin (AP) for postoperative chemotherapy in patients with advanced endometrial cancer.

Methods: Patients with newly diagnosed advanced endometrial cancer received AP (doxorubicin 60 mg/m², cisplatin 50 mg/m²) every 3 weeks. Treatment was continued until disease progression or completion of 6 courses. Toxicities were evaluated every cycle according to NCI-CTCAE Ver. 3.0.

Results: Fifteen patients were enrolled from April 2004 through December 2005. All patients successfully completed therapy. There were two patients who needed dose reduction and nine patients with prolongation of treatment interval. Patients with over Grade 3/4 toxicity were observed to have leucopenia (47%), neutropenia (67%), anemia (26%), and vomiting (13%). No grade 3/4 cardiac and renal failure were observed.

Conclusions: The doxorubicin/cisplatin (AP) regimen is tolerated and can be safely given without severe toxicity.

Key words: Endometrial cancer, Postoperative chemotherapy, Doxorubicin/cisplatin (*Received Apr. 3 2006/ Accepted May 23, 2006*)

要旨 目的: 進行子宮体癌に対する術後 doxorubicin (DXR)/cisplatin (CDDP) (AP) 療法の認容性について検討した。方法: 進行子宮体癌で初回に標準手術を施行し，年齢 20～80 歳，PS 0～2，十分な骨髄，肝，腎，心機能をもつ患者を対象とした。DXR 60 mg/m² と CDDP 50 mg/m² をそれぞれ day 1 に投与し，21 日ごとに病状の進行や重篤な有害事象がみられない限り 6 コース施行した。有害事象は NCI-CTC Ver. 3 により判定した。結果: 2004 年 4 月から 2005 年 12 月まで 15 例に施行した。投与中止症例はなかった。2 例に減量を要し 9 例に投与遅延を認めた。grade 3 以上の有害事象を白血球減少 7 例 (47%)，好中球減少 10 例 (67%)，貧血 4 例 (26%)，嘔吐 1 例 (13%) に認めたが，いずれも可逆性であった。6 コース終了後腎障害，心障害は認めなかった。結論: 進行子宮体癌に対する術後 DXR/CDDP (AP) 療法は推奨用量の DXR 60 mg/m² と CDDP 50 mg/m² で投与可能であり，有害事象も管理可能である。

はじめに

ライフスタイルの変化などに伴い，本邦における子宮体癌の子宮癌に占める割合は年々増加傾向にある[1]。

子宮体癌の初回治療は手術であり，進行症例をはじめ術後の病理学的な予後不良因子を有する再発高危険群には，再発制御と生存率改善を目的に術後 (補助) 療法が行われている[2]。

この術後療法について，欧米では放射線療法を用いることが多く，本邦では多くの施設で化学療法が行われてきた[3]。アメリカの Gynecologic Oncology Group (GOG) は III/IV 期の optimal 切除例を対象とした術後補助療法について，全腹部外照射と AP 療法を比較した大規模ランダム化比較試験を行い，AP 療法が生存期間において優越であることを証明した (GOG 122)[4]。

子宮体癌に対する化学療法としては，doxorubicin (DXR) と cisplatin (CDDP) が長い間 key drug とみなされており，その併用による AP 療法は第III相試験での

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0385-0684/06/¥500/論文/JCLS

生存期間に関する成績[5-7]も多く，毒性も許容範囲内とみなされていた。それを術後補助療法に用いた前述のGOG 122の成果は，化学療法による術後補助療法の有用性を示し，それによるさらなる予後改善の可能性を示した。

これらの結果を踏まえて，厚生労働省「抗がん剤併用療法に関する検討委員会」は，子宮体癌に対するAP療法を審議し，CDDP 50 mg/m²とDXR 60 mg/m²の併用療法（3週間隔）について，2005年2月からの子宮体癌に対する保険の適応拡大を承認するに至った[6]。しかし，このレジメンの本邦での使用経験は十分とはいえず，また安全に施行できるという保証はない。さらに，前述のGOG 122でも放射線療法と比較した白血球減少，消化器症状増強などに伴う毒性中止の多さ(17%)，治療完遂率の低さ（63.4%），治療関連死割合の高さ（4.1%）がみられ，有害事象増強に伴うfeasibility低下が問題とされた[4]。

よって，今回われわれはAP療法の実施可能性を検証することは重要と思われ，認容性を検討することとした。

I．対　象

2004年4月から2005年12月まで当科にて診断，治療を行った症例を対象とした。以下の適格基準をすべて満たす患者を適格例とした。

①組織学的に上皮性子宮体部悪性腫瘍と診断されているもの。

②手術以外の前治療歴がない。

③手術進行期IIIa期以上。

④手術から2週間以上経過している。

⑤20歳以上80歳以下。

⑥Eastern Clinical Oncology Group（ECOG）のperformance status（PS）が0～2のいずれか。

⑦骨髄，肝，腎，心機能が保たれている。

II．方　法

プライマリー・エンドポイントは治療完遂率，治療関連死割合とし，セカンダリー・エンドポイントは有害事象発生割合とした。また，有害事象の評価にはCTCAE Ver. 3.0日本語訳JCOG/JSCO版を用いた[8]。治療中止・終了後に増悪した後の後治療は規定しなかった。

1．治療レジメン

1）AP療法

DXR 60 mg/m² 15分で点滴静注day 1，CDDP 50 mg/m² 2時間で点滴静注day 1を3週1コースとし，病変増悪，重篤な有害事象がみられない限り6コース施行した。

支持療法はASCOのガイドラインに沿って施行した。day 1には急性悪心・嘔吐対策としてdexamethasone 20 mgと5-HT_3製剤投与，遅発性悪心・嘔吐対策としてday 2，3にはdexamethasone 12 mgを投与した。予期性悪心・嘔吐対策としてベンゾジアゼピン製剤を積極的に使用した。またCDDPによる腎障害予防のためにday 1には十分な点滴による水分負荷を施行し，day 2，3も飲水の状況に応じて点滴による水分負荷を施行した。day 4の状態で十分な飲水が可能であれば退院とした。全症例当科で作成したクリティカルパスに遵守した（図1）。

1コース退院時には感染対策として抗生剤（ciprofloxacin hydrochloride），解熱剤（acetaminophen）を処方した。来院も3週間に一度とし，頻繁な採血による血液毒性の確認，予防的G-CSF製剤の投与は行わなかった。

2．治療中止基準

以下いずれかの場合，治療を中止した。

①治療開始後に病変の増悪が認められた場合。

②重篤な有害事象により治療が継続できない場合。

・grade 4の非血液毒性

・grade 2～3の血清クレアチニンの上昇

・grade 3の末梢神経障害

・grade 2～3の聴力障害

・grade 2～3の左室収縮機能不全，伝導障害

③後述の減量規定により用量レベルを下げた後にも，再び減量規定に抵触した場合。

④担当医が治療中止を必要と判断した場合。

3．コース開始基準

第2コース以降，コース開始2日以内に以下の条件をすべて満たしていることを確認し開始とした。これらの条件を満たさない場合，次コースは延期とした。

①好中球数≥1,500/mm²。

②血小板数≥75×10^3 mm²。

③PS 2以下。

④血清クレアチニンの上昇grade 1以下。

⑤脱毛，末梢神経障害以外の非血液毒性がgrade 1以下。

⑥末梢神経障害grade 2以下。

4．減量規定

1）Doxorubicin

コース中，以下の有害事象のいずれか一つ以上が認められた場合，次コースからはDXRを45 mg/m²に減量することとした。また，有害事象が消失・軽減しても再度用量レベルを上げることはしなかった。

①血小板数≦50×10^3 mm²。

②grade 3の嘔吐・口内炎・下痢。

患者氏名＿＿＿＿＿＿＿＿ ID＿＿＿＿＿＿＿＿
在院日数: 5日

年月日	/	/	/	/
病日	day 1	day 2	day 3	day 4
達成目標	嘔気・嘔吐がGrade 1以下である 尿量が1,500 m*l* 以上確保されている	嘔気・嘔吐がGrade 1以下である 尿量が1,500 m*l* 以上確保されている	嘔気・嘔吐がGrade 1以下である 尿量が1,500 m*l* 以上確保されている	コップ1杯の水を飲むことができる
薬剤	9：00 ①ソルデム1 1,000 m*l* 3時間 12：00 ②生食50 m*l* デキサート24 mg カイトリル1A 15分 12：15 ③アドリアシン＿＿＿＿mg 生食50 m*l* 15分 12：30 ④シスプラチン＿＿＿＿mg 生食500 m*l* 2時間 ※合わせて計500 m*l* とする 14：30 ⑤生食500 m*l* 2時間 16：30 ⑥ラシックス10 mg ワンショット静注 16：30 ⑦ソルデム1 1,000 m*l* 3時間	9：00 ①生食50 m*l* デキサート12 mg 15分 9：15 ②ソルデム3A 2,000 m*l* 8時間	9：00 ①生食50 m*l* デキサート12 mg 15分 9：15 ②ソルデム3A 1,500 m*l* 6時間	
	悪心・嘔吐時（①から④の順番に） ①プリンペラン5 mg 1錠（1日3回まで，経口不能時②へ） ②ナウゼリン坐薬60 mg 1個 ③生食50 m*l*＋プリンペラン10 mg 1A/30分 ④ソラナックス0.4 mg 1錠（1日3回まで）	便秘時 カマ，マグミット，プルゼニド，ラキソベロン内服可 GE，レシカルボン坐薬使用可 （各薬剤の投与量，タイミングは状態にて調節可） 発熱時（38.0°C以上） ①カロナール200 mg 2錠内服 ②カロナール内服でも解熱しなければDr call	不眠時 アモバン 7.5 mg 1錠 （追加1錠まで可）	

図1 当科のクリティカルパス（抜粋）

表1 患者背景

年齢（歳）	
中央値（範囲）	57（42～80）
Performance status	
0/1	13/2
進行期	
IIIa	10
IIIc	2
IVb	3
病理組織型	
類内膜腺癌	8
漿液性腺癌	6
低分化腺癌	1

表2 血液毒性

Toxicity	grade				grade
	1	2	3	4	3～4
白血球減少	0	3	7	0	47%
好中球減少	0	0	4	6	67%
血小板減少	2	0	0	0	0%
好中球減少性発熱	0	0	2*	0	13%
貧血	4	3	2	2	26%

*: 1名にG-CSF使用

2）Cisplatin

血清クレアチニンgrade 1の時は24時間クレアチニン・クリアランスを施行し，60 m*l*/min以上は減量なし，60～50 m*l*/minの場合はCDDPを40 mg/m²に減量した。また，有害事象が消失・軽減しても再度用量レベルを上げることはしなかった。

III. 結 果

2004年4月から2005年12月まで15例を登録した。表1に患者背景を示す。年齢中央値は57歳であった。performance status (PS) は0，1のみで2は認めなかった。進行期はIIIa期10例，IIIc期2例，IVb期3例であった。IVb期はいずれも横隔膜下に播種性の転移を認めただけで，他の臓器に転移は認めなかった。全症例，初回手術で腫瘍は完全切除されており，明らかな肉眼的残存は認めなかった。病理組織では類内膜腺癌が8例と最も多く，漿液性腺癌も6例と多く認められた。血液毒性は表2に示すごとくで，grade 3以上の白血球減少症7例（47%），好中球減少症10例（67%）を高率に認めた。好中球減少性発熱を2例（13%）に認めたが，G-CSF製剤を使用したのは1例であった。grade 3以上の貧血を4例（26%）に認め，2例に濃厚赤血球の輸血を要した。

非血液毒性を表3に示す。grade 3以上の毒性は嘔吐の1例（13%）のみであった。grade 2の脱毛を9例（60%）と高頻度に認めた。その他は支持療法にて管理可能であった。

治療は15例全症例に投与中止なしで完遂できた。次コース延期は15例中9例（60%）に認めた。好中球減少症での投与延期が7例でgrade 3の感染による延期を2

表 3 非血液毒性

Toxicity	grade				grade
	1	2	3	4	2～4
食欲不振	11	2	0	0	13%
嘔気	10	3	0	0	20%
嘔吐	9	1	1	0	13%
体重減少	0	0	0	0	0%
疲労	4	0	0	0	0%
粘膜炎・口内炎	3	0	0	0	0%
脱毛	4	9	—	—	60%
血清クレアチニン上昇	6	1	0	0	6.5%

名に認めた。投与量の減量を2例に要した。1例はgrade 3の嘔吐でDXRを45 mg/m²に減量し，1例はgrade 2の血清クレアチニンの上昇でCDDPを減量規定に従って40 mg/m²に減量した。治療関連死は認めなかった。1例を除き入院日数は5日間以内であった。2日目以降の点滴を省略できたのが2例あり，これら症例では，2コース目以降は入院日数は3日間で管理可能であった。

IV. 考 察

進行子宮体癌に対する化学療法は，いくつかのrandomized controlled trial（RCT）の結果evidenceとして培われてきた。GOGで行われたRCTが代表的なものであるが，DXR単独(60 mg/m²)とcyclophosphamide (CPA)/DXR（CA）療法（CPA 500 mg/m²+DXR 60 mg/m²）のRCTでは奏効率で24% vs 32%，無増悪期間の中央値で3.2か月vs 3.9か月，生存期間の中央値でそれぞれ6.7か月vs 7.3か月であり，奏効率では有意差は認められず，生存期間でわずかにCA群が優れていた[5]。

一方，DXR単独(60 mg/m²)とAP療法(DXR 60 mg/m²+CDDP 50 mg/m²)のRCTでは奏効率で25% vs 42%とAP療法が優れていたが，生存期間の中央値は9.2か月vs 9.0か月と差が認められなかったものの，毒性も許容範囲内であった[6]。以上よりGOGは進行・再発子宮体癌においてDXR単剤と並んでAP療法も標準治療とし，GOGのRCTではAP療法を標準治療群と定めるようになった。これらの結果を受けてGOGはAP療法を進行・再発子宮体癌の標準的治療とするに至った。さらにEuropean Organization for Research and Treatment of Cancer（EORTC）でも化学療法の既往がない177例の進行・再発子宮体癌にDXR単剤87例(DXR 60 mg/m²)とDXR 60 mg/m²+CDDP 50 mg/m² 90例の無作為化比較試験を行った[7]。DXR+CDDPでは43%が奏効し，DXR単剤（17%）に比べ有意に良好であった。生存期間中央値はDXR+CDDPが9か月で，DXR単剤の7か月に比して有意差には至らなかったものの良好であり，GOG 107と同様な結果が示された。以上の結果より，欧米ではAP療法は進行・再発子宮体癌の標準的化学療法と考えられるようになった。

術後補助療法としての化学療法は再発のハイリスク例（骨盤または傍大動脈リンパ節転移のある症例や，筋層浸潤が深い症例など）が対象となると考えられるが，これまで術後化学療法の有用性は確認されなかった。しかし，GOG 122[4]の結果より子宮体癌において初めて術後補助療法としての化学療法の有用性が示され，標準的治療として推奨されるに至ったと考えられる。

本邦においても2005年2月に承認取得された経緯となった[9]。しかし，GOG 122の問題として治療完遂率の低さ（63.4%）と治療関連死割合の多さ（4.1%）があげられる。原因として考えられるのは，GOG 122においてAP療法が6コースではなく8コース（実際はAP療法は7コースで，8コース目は心毒性の観点からCDDPだけ投与されている）だったこと，70歳以上の症例が2割も登録されていたことが考えられる。以上の観点から承認取得となったもののすぐに実地臨床での実施は難しいと考えられ，認容性試験が必須と考えられ今回の試験を行った。

今回の検討では症例数が15例と少ないものの，治療完遂割合は100%であり，重篤な有害事象もなく治療関連死も認めなかった。GOG 122に比して高い完遂割合であったのは，症例数が少ないことはもちろん考えられるが，PSがすべて0または1だったことや55歳以下の症例が多く登録されていたことも考えられる。喜多川らもAP療法の治療完遂割合は，PSと関連すると指摘している[10]。また，当科ではAP療法を4泊5日のクリティカルパスに遵守して施行しており，十分な支持療法がすべての症例で施行されたのも高い治療完遂割合に寄与したものと考えられる。さらに，消化管毒性（悪心・嘔吐，食思不振）が許容される症例に関しては2日目以降の点滴の省略も可能であり，短期（1泊2日や2泊3日）での入退院が可能であった。退院後は3週間に1回の経過観察であったが，退院時に抗生剤を処方することにより，grade 3の感染を2例認めるにとどまった。また，DXRの心毒性については，総投与量450 mg/m²を超えなければ重篤な心毒性の発生頻度は低いとされている[11]。実際のAP療法では6コース終了時点での総投与量は360 mg/m²であることから，本検討でも重篤な心毒性が生じたものはなかった。AP療法は安全に行えるレジメンと考えられる。

子宮体癌の化学療法の今後の展開として，taxane製剤が期待されている。AP療法にpaclitaxel(TXL)を追加

したTAP療法[12]や，TC(TXL/carboplatin(CBDCA))療法[13]などの有用性が期待されているが，まだ確固たるevidenceが証明されているわけではない。わが国でも第II相試験が終了し，2005年5月，8月にTXL[14]，docetaxel (TXT)[15]がそれぞれ子宮体癌に適応承認されている。Japanese Gynecologic Oncology Group (JGOG) でも，taxane製剤を含んだ化学療法 (TXT/CDDP，TXT/CBDCA，TXL/CBDCA) の無作為化第II相試験が行われ，その結果の解析が待たれるところである。

しかし，現時点で進行子宮体癌に対するtaxane/platinum療法は第II相試験のevidenceであり，標準治療であるAP療法を第III相試験で凌駕したデータがない今，術後補助療法として安易な認容性の観点から，taxane/platinum療法を行うべきではない。まず，現段階ではAP療法をしっかり施行することが肝要であろう。今後この点に関してはGOGでもRCTが進行中であり(GOG 209: TAP vs TC)，本邦においてもJGOGが標準治療をAP療法として試験治療群にtaxane/platinum製剤とした第III相試験を計画している。そのためにも各施設においてAP療法を安全に行えることは必須だと考える。

今回，推奨用量であるDXR 60 mg/m²とCDDP 50 mg/m²は十分な支持療法の下で重篤な有害事象なく管理可能であった。単施設のデータであるが，十分に認容性は保たれており，施行可能なレジメンだと考えられた。

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Status of surgical treatment procedures for endometrial cancer in Japan: Results of a Japanese Gynecologic Oncology Group Survey

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Abstract

Objective. We investigated the current status of surgical procedures for endometrial carcinoma in Japan by surveying members of the Japan Gynecologic Oncology Group (JGOG).

Methods. A mail survey focusing on hysterectomy procedures, indications for radical hysterectomy, methods for detecting pelvic (PEN) and para-aortic lymph node (PAN) status, and indications for PAN dissection/biopsy, was sent to all 215 authorized JGOG member institutions.

Results. A total of 139 (57.2%) members responded to the survey. Abdominal total hysterectomy (TAH) was utilized by 35.3% of institutions and Piver class II extended hysterectomy by 30.2%. In 35.5% of institutions, hysterectomy procedures were selectively employed based on tumor-related factors. Radical hysterectomy (RH) was utilized by 29.5% of institutions; TAH was used significantly more frequently by specialist hospitals while RH was significantly less commonly utilized by specialist hospitals compared with university hospitals and general hospitals. PEN dissection was routinely utilized by 97.8% of institutions. In 93.5% of institutions, PAN dissection/biopsy was used either routinely (12.2%) or selectively based on tumor-related factors (81.2%). In 6.5% of institutions, PAN dissection/biopsy has never been employed.

Conclusion. The status of surgical procedures for the treatment of endometrial cancer is still not standardized. However, TAH, bilateral salpingo-oophorectomy, PEN dissection, and PAN dissection/biopsy in selected cases are recent surgical procedures used for the treatment of endometrial cancer in Japan. Clinical trials to determine the survival benefit of the different surgical procedures should be developed to determine the standard surgical procedures to be used for the treatment of endometrial cancer.

Keywords: Endometrial cancer; Surgical procedure; JGOG; Survey

Introduction

Surgical treatment of endometrial cancer has been employed for two major purposes: removal of the tumor burden as far as is possible and obtaining pathological information to determine International Federation of Obstetrics and Gynecology (FIGO) surgical stage. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [1] have recommended the following surgical treatment procedures for endometrial cancer: when disease is limited to the uterus, abdominal total hysterectomy (TAH), bilateral salpingo-

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oophorectomy (BSO), and pelvic/para-aortic lymph node dissection; TAH, BSO, pelvic/para-aortic lymph node dissection and omentectomy are recommended for patients with suspected extra-uterine disease. Furthermore, radical hysterectomy (RH), BSO, and pelvic/para-aortic lymph node dissection are recommended for patients with cervical stromal involvement. However, there is a significant variety in the actual surgical procedures employed in the treatment of patients with endometrial cancer in Japan because although extensive surgical staging is recommended by some investigators, there is some concern regarding possible post-operative morbidity. Furthermore, differences in surgical treatment may influence the results of clinical trials of adjuvant therapy for endometrial cancer. Therefore, to determine the actual status of surgical treatment for endometrial cancer in Japan, we surveyed members of the Japan Gynecologic Oncology Group (JGOG) by mail.

Materials and methods

A mail survey regarding surgical procedures for endometrial cancer was sent to 243 JGOG authorized institutions. It included questions on standard hysterectomy procedures, performance of pelvic lymph node (PEN) dissection, performance of para-aortic lymph node (PAN) dissection or biopsy, and criteria for PAN dissection or biopsy procedures performed between December 2004 and February 2005. The nomenclature of the retroperitoneal lymph nodes was determined according to the General Rules for Clinical and Pathological Management of Uterine Corpus Cancer edited by the Japan Society of Obstetrics and Gynecology (1996). PEN dissection was defined as removal of the common iliac, external iliac, internal iliac, obturator, suprainguinal, and the sacral lymph node while PAN was defined as the region inferior to the inferior mesenteric artery and/or up to the renal artery. Although it is not a standard definition, PAN dissection was tentatively defined as the removal of 4 or more nodes, while PAN biopsy was defined as the removal of 3 or fewer nodes (the minimum value of the range of numbers of resected PANs in domestic reports was 2 [2,3]). Member institutions were temporarily classified into the following types in order to determine if there were any differences between them: university hospital, specialist hospital (such as a cancer center or a medical center that only treats gynecologic diseases), and general hospital (such as a public or private hospital that treats both gynecologic and obstetric diseases). All hospitals were JGOG membership committee-authorized as institutions active in the treatment of gynecologic cancer. All replies were returned by FAX. We used the Chi-square Test and a p-value of less than 0.05 was considered to be significant.

Results

A total of 139 institutions (57.2%) responded to the survey; respondents answered all of the questions. Table 1 shows routinely indicated hysterectomy procedures, indications for RH, and treatments for PEN and PAN endometrial cancer in JGOG member institutions.

Status of hysterectomy procedures

Forty-nine (35.3%) institutions used only TAH, 42 (30.2%) employed only Piver class II [4] extended hysterectomy (Class II), and the remaining 48 (34.5%) selected TAH, Class II, or RH based on tumor-related factors. RH was performed in 41 (29.5%) institutions (one institution routinely used RH and another 40 institutions performed RH based on tumor-related factors). Criteria for indication of RH were cervical involvement, non-endometrioid histologic subtypes, or > 1/2 myometrial invasion. Regarding the depth of myometrial invasion, this was comprehensively determined by all members based on preoperative findings from magnetic resonance imaging and macroscopic findings from the resected uterus.

Table 1
Surgical procedures for endometrial cancer

Total number of responder	139
Hysterectomy procedure	
TAH only (%)	49 (35.3)
Class II only (%)	42 (30.2)
Alternates based on clinicopathologic conditions (%)	48 (34.5)
Radical hysterectomy	
Routinely performed (%)	1 (0.7)
Performed based on clinicopathologic conditions (%)	40 (28.8)
Never performed (%)	98 (70.5)
Pelvic lymph node dissection	
Routinely performed (%)	136 (97.8)
Performed based on clinicopathologic conditions (%)	1 (0.7)
Never performed (%)	2 (1.5)
Para-aortic lymph node treatment	
Routinely performed dissection (%)	12 (8.6)
Routinely performed biopsy (%)	5 (3.6)
Performed dissection based on clinicopathologic conditions (%)	90 (64.7)
Performed biopsy based on clinicopathologic conditions (%)	23 (16.5)
Never performed (%)	9 (6.6)

TAH: abdominal simple total hysterectomy, Class II: extended hysterectomy (Piver), para-aortic lymph node biopsy: removal of 3 or fewer lymph nodes, para-aortic lymph node dissection: removal of 4 or more lymph nodes.

Status of surgical treatment of the pelvic lymph node

Almost all institutions (136; 97.8%) used PEN dissection for all patients. One institute used PEN dissection based on tumor-related factors (histologic grade 3 or > 1/2 myometrial invasion), and two institutions never used PEN dissection. No institution used selective lymph node biopsy as part of the PEN surgical procedure.

Status of surgical treatment of para-aortic lymph node

Regarding the surgical treatment of PAN, a total of 130 (93.5%) institutions used PAN dissection or biopsy, including 12 (8.6%) institutions that routinely utilized PAN dissection, 5 (3.6%) that routinely utilized PAN biopsy, 90 (64.7%) that utilized PAN dissection based on tumor-related factors, 23 (16.5%) that utilized PAN biopsy based on tumor-related factors, and 9 (6.5%) that never performed any type of surgical procedures to determine PAN status. Moreover, > 1/2 myometrial invasion (23.3%), PAN enlargement (22.0%) either by preoperative computer tomography, magnetic resonance imaging, or intraoperative direct palpitation, and histological grade 3 tumor (21.6%) were frequently identified as indication criteria for PAN treatment (Table 2). Furthermore, 62 (47.7%) institutions determined the necessity of PAN treatment by direct palpitation of lymph nodes.

Table 2
Clinicopathologic conditions to perform para-aortic lymph node treatment

Total number of respondents	130
Total number of valid answers [a]	236
Clinicopathologic condition to perform para-aortic lymph node treatment (%)	
Evidence of para-aortic lymph node(s) swelling	52 (22.0)
Evidence of pelvic lymph node(s) swelling	21 (8.9)
Non-endometrioid histologic subtypes	25 (10.6)
Cervical involvement	7 (3.0)
Myometrial invasion	
Any depth	24 (10.2)
>1/3	2 (0.8)
>1/2	55 (23.3)
Histologic grade	
≥Grade 2	16 (6.8)
Grade 3 only	51 (21.6)

[a] Multiple answers were permitted to the question concerning para-aortic lymph node disposition.

Differences in surgical treatment procedures by hospital type

Table 3 shows differences in selected surgical treatment procedures by hospital type. TAH was more frequently used in specialist hospitals than in university hospitals and general hospitals ($p<0.05$) while RH was selected significantly less often in specialist hospitals than in university hospitals ($p<0.01$). However, there were no significant differences between the types of hospitals and the selection of surgical treatment procedures for PEN and PAN.

Discussion

The most recent annual report of the Japan Society of Obstetrics and Gynecology (JSGO) indicated that approximately 4046 cases of endometrial cancer (including 324 cases of stage 0 endometrial cancer) were treated between 1 January 2003 and 31 December 2003 in Japan. Surgery is the treatment of choice for endometrial cancer in Japan as 3575 (96.1%) of 3722 patients with stage I–IV disease underwent surgical treatment in this country [5]. However, although the International Federation of Gynecology and Obstetrics (FIGO) adopted surgical staging in 1988, and NCCN also recommended standard surgical procedures based on clinical stage, the actual status of surgical treatment procedures for patients with endometrial cancer is still not standardized in Japan. Moreover, standard surgical procedures for endometrial cancer also vary in other countries. Crawford et al. [6] retrospectively studied the staging quality of 703 cases of endometrial cancer in Scotland during 1996 and 1997 and reported that FIGO stage was defined in the case record by the surgeon and/or pathologist in only 36.4% of cases, the extent of invasion and tumor grade was noted in 88.6% of cases, and peritoneal cytology was examined only in 46.6% of cases. They concluded that documentation of FIGO stage by proper surgery was one of the independent prognostic factors in endometrial cancer. Maggino et al. [7] also analyzed the management of endometrial cancer by 48 respondents in North America and found that pelvic lymphadenectomy was routinely utilized by 54.2% centers; 43.5% of the centers utilized the procedure based on the selective clinical–pathological condition of the patient, whereas only one center never performed pelvic lymphadenectomy. Furthermore, according to their study, the standard hysterectomy procedure in North America can be considered to be TAH as they reported that Class II or III extended hysterectomy was routinely utilized by only one center and 29.2% of centers never performed Class II or III extended hysterectomy for the treatment of endometrial cancer. On the other hand, Amadori et al. [8] studied the status of lymphadenectomy for patients with endometrial cancer in Northern Italy and reported that no case of para-aortic lymphadenectomy was observed while pelvic lymphadenectomy was performed in 86 (31.0%) of 276 eligible cases. Compared with these surveys, the present JGOG survey suggests that although TAH has similarly been indicated as a common hysterectomy procedure, PEN or PAN are more aggressively examined and treated in patients with endometrial cancer in Japan. Furthermore, the present survey has also revealed that the type of hysterectomy procedure selected for the treatment of endometrial cancer differs depending on the type of hospital in which the procedure is performed. RH was utilized in 25 (38.4%) university hospitals and 15 (26.8%) general hospitals while only 1 (5.6%) specialist hospital indicated RH for the treatment of endometrial cancer. The utilization rate of RH was significantly higher in the university hospitals and tended to occur more often in the general hospitals

Table 3
Differences of selected surgical procedures between hospital types

	University hospital	Specialist hospital	General hospital
Total number (%)	65 (46.8)	18 (12.9)	56 (40.3)
Hysterectomy procedures			
TAH only (%)	21 (32.3)	11 (61.1)*	17 (30.4)
Class II only (%)	19 (29.2)	3 (16.7)	19 (33.9)
Alternates based on clinicopathologic conditions (%)	24 (36.9)	4 (22.2)	20 (35.7)
Radical hysterectomy			
Routinely performed (%)	1 (1.5)	0 (0.0)	0 (0.0)
Performed based on clinicopathologic conditions (%)	24 (36.9)**	1 (5.6)	15 (26.8)
Never performed (%)	40 (61.6)	17 (94.4)**	41 (73.2)
Pelvic lymph node dissection			
Routinely performed (%)	65 (100)	17 (94.4)	54 (96.2)
Performed based on clinicopathologic conditions (%)	0 (0.0)	1 (5.6)	0 (0.0)
Never performed (%)	0 (0.0)	0 (0.0)	2 (3.8)
Para-aortic lymph node			
Routinely performed dissection (%)	8 (12.3)	1 (5.6)	3 (5.4)
Routinely performed biopsy (%)	3 (4.6)	1 (5.6)	1 (1.8)
Dissection based on clinicopathologic conditions (%)	43 (66.2)	15 (83.2)	33 (58.9)
Biopsy based on clinicopathologic conditions (%)	8 (12.3)	1 (5.6)	13 (23.2)
Never performed (%)	3 (4.6)	0 (0.0)	6 (10.7)

TAH: abdominal simple total hysterectomy, Class II: extended hysterectomy (Piver), para-aortic lymph node biopsy: removal of 3 or fewer lymph nodes, para-aortic lymph node dissection: removal of 4 or more lymph nodes.
* $p<0.05$.
** $p<0.01$.

than in the specialist hospitals. The General Rules for Clinical and Pathological Management of Uterine Corpus Cancer by JSGO (1995) [9] originally adopted parametrial spread as a factor for determination of surgical stage IIIc. However, the present survey shows that recent Japanese gynecologic oncologists, especially members belonging to the specialist hospitals (including cancer and specialist medical centers) think that TAH is a more suitable hysterectomy procedure for endometrial cancer. Regarding the survival benefit of RH, Sartoli et al. [10] studied the treatment outcome of 203 stage II endometrial cancers and reported that the survival of patients treated with RH was significantly higher than that of patients treated with TAH. However, Ayhan et al. [11] studied 48 patients with stage II endometrial cancer and reported that the initial surgical staging procedure consisting of RH achieved excellent survival, although there was no significant difference in survival between patients treated with RH only and those treated with TAH plus adjuvant radiation therapy. Therefore, it is still not known whether RH can improve the survival of patients with endometrial cancer. Moreover, 30.2% of institutions performed Class II hysterectomies despite there being no reliable clinical evidence as to whether Class II hysterectomy is suitable for endometrial cancer. Furthermore, the present survey revealed that even though no comparative study has been performed to determine whether systematic PAN dissection can improve survival of patients with endometrial cancer, 47.7% of institutions determined the need for PAN dissection/biopsy by intraoperative palpation. However, Eltabbakh [12] studied 178 consecutive women undergoing a lymphadenectomy and concluded that although systemic intraoperative clinical evaluation of lymph nodes by a trained surgeon has a high overall accuracy and correlates well with the final histopathologic diagnosis, it also has a high false-negative rate and cannot be considered a substitute for histopathologic examination. Therefore, the outcome of a discussion of not only whether PAN dissection or biopsy is required but also whether determination of a PAN is warranted should be decided based on a detailed analysis of the individual clinical condition of patients with endometrial cancer. Although the results of the present survey were limited in order to clarify how treatment procedures were dependent on the individual clinical condition of patients with endometrial cancer, they still suggest that surgical treatment procedures vary in each Japanese institution. Furthermore, the results of the present survey also suggest that although it may be difficult to conduct a comparative phase III clinical trial to determine the survival effects of the different surgical procedures, an accurate meta-analysis based on international reports of survival benefit by surgical procedure is needed to establish standard surgical treatment procedures and to conduct accurate clinical trials (such as a comparison of survival in patients who have undergone a Class II hysterectomy versus RH or a PAN biopsy versus systematic PAN dissection) to improve the survival of patients with endometrial cancer. Moreover, a standard surgical manual for endometrial cancer is needed to improve the precision of clinical trials and to educate JGOG members as to the most suitable treatment procedures for endometrial cancer.

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The CD-DST can be used to test chemosensitivity to anticancer agents using a small number of cells in a three-dimensional culture, and can be analyzed by cultured cells and specimens in the same system. This method has also been reported to show a strong correlation with clinical response in gynecological tumors (14). Therefore, the aberrant hypermethylation of the *CHFR* gene may be useful for a molecular marker for selection of therapy for cervical cancer. Furthermore, transfection of siRNA for *CHFR* increased the sensitivity of cervical squamous carcinoma to taxanes without affecting the sensitivity to other anticancer agents. This approach may be applicable to preoperative chemotherapy for stage Ib and IIb patients, and may offer a new therapeutic strategy for cervical cancer.

Acknowledgments

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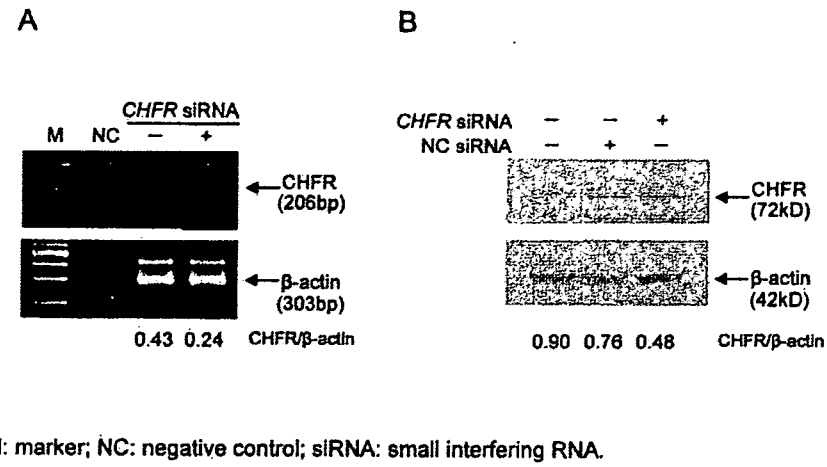

Figure 5. siRNA-induced suppression of CHFR expression in SKG-IIIa cells. (A) RT-PCR, (B) Western blotting. siRNA suppressed expression of mRNA and protein to approximately 50% of control levels.

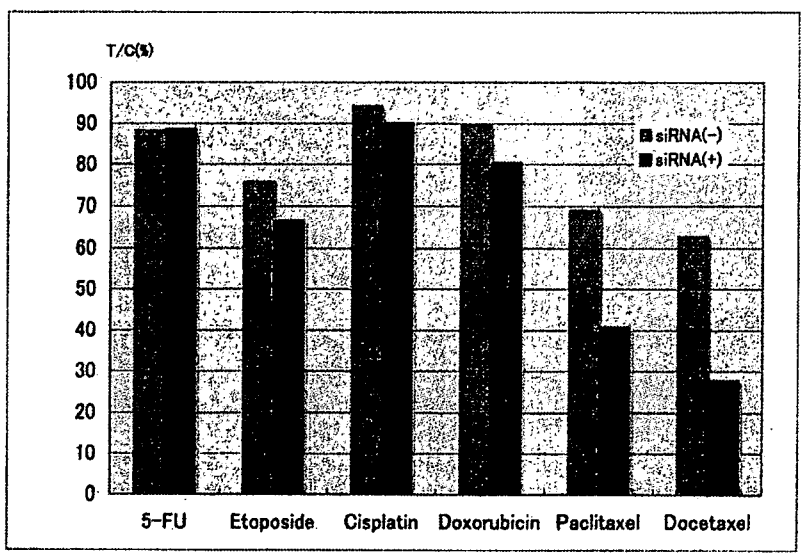

Figure 6. siRNA-induced changes in sensitivity (T/C ratio) of SKG-IIIa cells to various anticancer agents. After suppression of *CHFR* expression, the sensitivity to taxanes alone was increased.

support the hypothesis that when tumor cells are treated with taxane, cells with normal *CHFR* expression undergo arrest in G2 phase to repair damaged DNA and are resistant to taxane, whereas cells with an inactivated *CHFR* gene due to aberrant hypermethylation cannot detect DNA damage and proceed to mitosis, thereby showing high sensitivity to taxane. This mechanism was apparent in cells with inactivated *CHFR* genes following paclitaxel treatment, which caused an increase in Sub-G1 cells, rather than G2/M cells, indicating progression to mitosis and subsequent cell death due to the mitotic catastrophe.

In CD-DST analysis of the sensitivity of HeLa cells to anticancer agents, demethylation significantly reduced the sensitivity to taxanes. Treatment with 5-aza-dC is likely to demethylate various genes, in addition to *CHFR*. However, we also confirmed that suppression of *CHFR* in siRNA-transfected SKG-IIIa cells did not alter sensitivity to cisplatin and doxorubicin, but specifically to taxanes (paclitaxel and docetaxel). This result suggests that epigenetic inactivation of the *CHFR* gene specifically contributed to taxane sensitivity. Therefore, aberrant hypermethylation of *CHFR* may be a molecular marker for prediction of the sensitivity of cervical cancer (and especially cervical adenocarcinoma) to taxane therapy. As discussed above, cervical adenocarcinoma is more refractory and shows a poorer response to anticancer agents compared with squamous carcinoma. Clinical responses of cervical adenocarcinoma are 20% with cisplatin, 14% with 5-fluorouracil, and 12% with etoposide, which are slightly lower than those for squamous carcinoma (28). However, in cervical adenocarcinoma with higher epigenetic inactivation of CHFR gene compared to squamous carcinoma, the clinical response to paclitaxel alone is 31%, 17% higher than with any other agent (29), and these findings are consistent with our results.

Table IV. Changes in sensitivity (T/C ratio) of cervical cancer-derived cells to various anticancer agents by treatment with a demethylation agent.

Cell line	*CHFR*	5-FU (%)		Etoposide (%)		Cisplatin (%)		Doxorubicin (%)		Paclitaxel (%)		Docetaxel (%)	
		5aza (-)	5aza (+)	5aza (-)	5aza (+)	5aza (-)	5aza (+)	5aza (-)	5aza (+)	5aza (-)	5aza (+)	5aza (-)	5aza (+)
SKG IIIa	U	88.5	83.2	76.0	84.2	94.5	80.7	90.1	98.6	69.2	87.0	63.1	88.5
HeLa	M/U	71.4	84.6	46.3	55.9	75.2	70.9	79.1	81.2	9.8	51.4	9.7	57.1

5aza, 5-aza-dc; M, methylated; U, unmethylated.

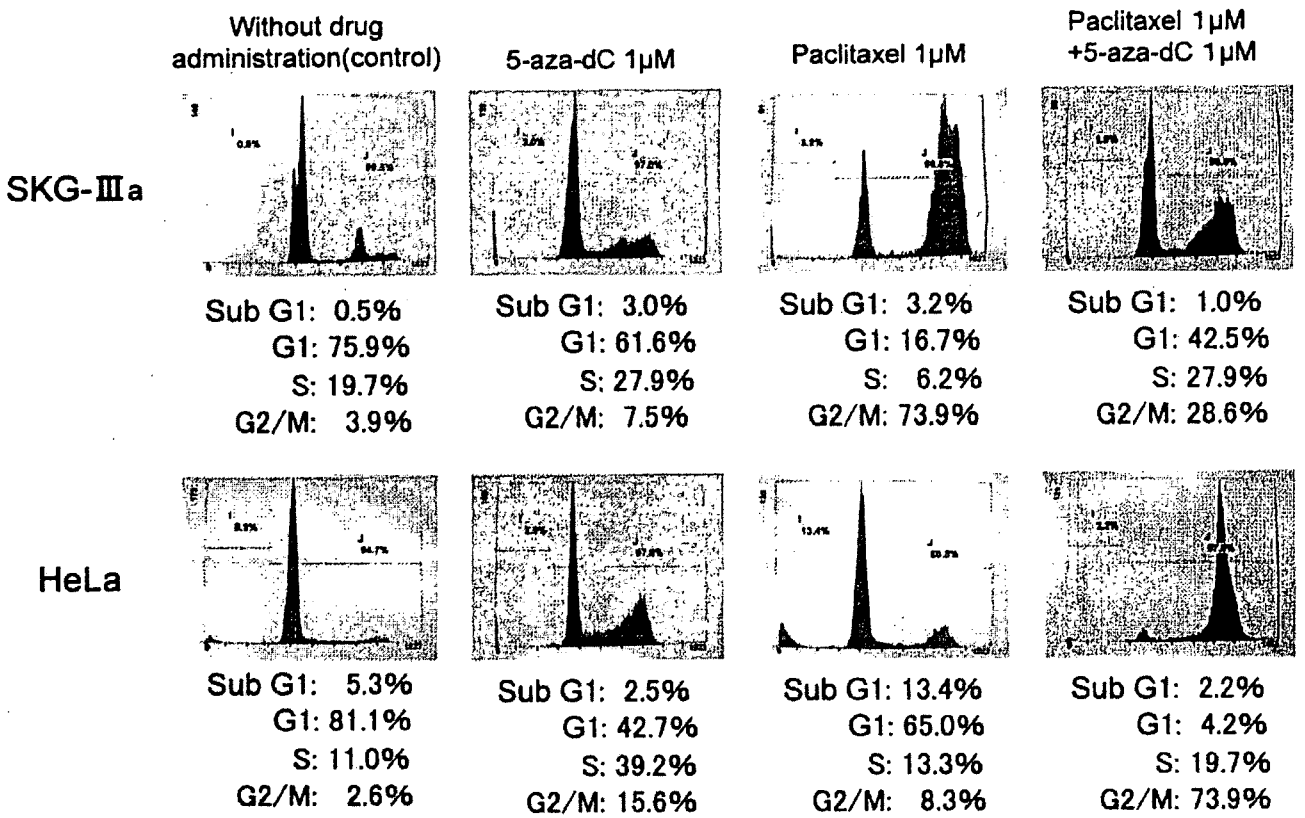

Figure 4. Cell-cycle analysis of SKG-IIIa and HeLa cells using flow cytometry. In SKG-IIIa cells after treatment with paclitaxel alone, the percentage of cells in the G2/M phase was high and that of cells in the Sub-G1 phase did not change markedly. In HeLa cells with paclitaxel alone, the percentage of cells in the G2/M phase was low and that of cells in the Sub-G1 phase increased. In contrast, after treatment with a combination of paclitaxel and 5-aza-dC, cells in the G2/M phase markedly increased and those in the Sub-G1 phase decreased to a level similar to that of the control.

inactivation of *CHFR* has also been observed in endometrial cancer cells, suggesting that aberrant hypermethylation may play an important role in development of uterine cancer, and specifically in adenocarcinoma. There has been a recent increase in cases of cervical cancer, especially in women aged up to 35 years (18-20), and cervical adenocarcinoma has markedly different biological characteristics from squamous cell carcinoma; these characteristics include high nodal metastasis, a refractory nature, poor outcome, and severe malignancy (21-23). The *CHFR* gene negatively regulates the *Aurora-A* gene, a mitotic kinase; hence, suppression of *CHFR* expression increases Aurora-A expression (24). Aurora-A overexpression is reported to induce chromosomal instability (CI) and lead to a poor prognosis in ovarian, breast and bladder cancers (25-27), and a similar mechanism might underlie the characteristics of cervical adenocarcinoma.

Cell-cycle analysis of cervical cancer-derived cells using flow cytometry showed an increase in G2/M cells after paclitaxel treatment in cells with a normal *CHFR* gene. In cells with *CHFR* inactivated epigenetically by aberrant hypermethylation, paclitaxel treatment alone resulted in only a small number of G2/M cells, whereas treatment with a combination of paclitaxel and a demethylation agent caused a marked increase in G2/M cells. These results strongly

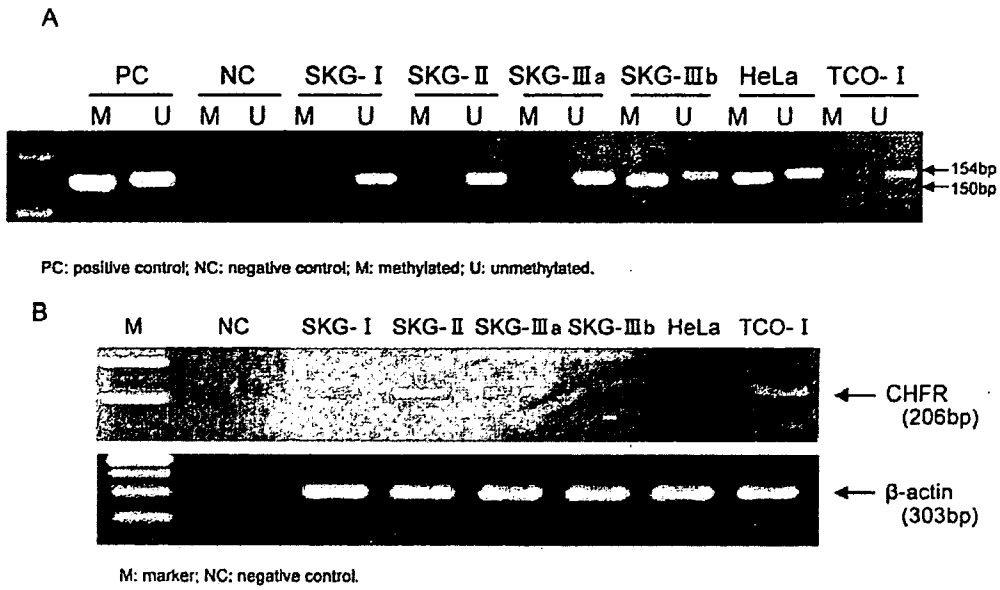

Figure 2. (A) MSP analysis of the *CHFR* gene in cervical cancer-derived cell lines. Aberrant hypermethylation of the *CHFR* gene was observed in SKG-IIIb and HeLa cells. (B) Analysis of *CHFR* expression in cervical cancer-derived cell lines using RT-PCR. CHFR expression was decreased in SKG-IIIb and HeLa cells, which had aberrant hypermethylation of the *CHFR* gene.

Table III. Sensitivity (T/C ratio) of cervical cancer-derived cells to various anticancer agents, assessed using the CD-DST.

Cell line	*CHFR*	Cisplatin (%)	Doxorubicin (%)	Paclitaxel (%)	Docetaxel (%)
SKG-I	U	75.9	89.6	39.5	41.3
SKG-II	U	97.8	91.6	55.5	49.6
SKG-IIIa	U	94.5	90.1	69.2	63.1
SKG-IIIb	M/U	93.2	77.2	14.0	14.0
HeLa	M/U	75.2	79.1	9.8	9.7
TCO-I	U	96.9	66.7	33.2	35.1

M, methylated; U, unmethylated.

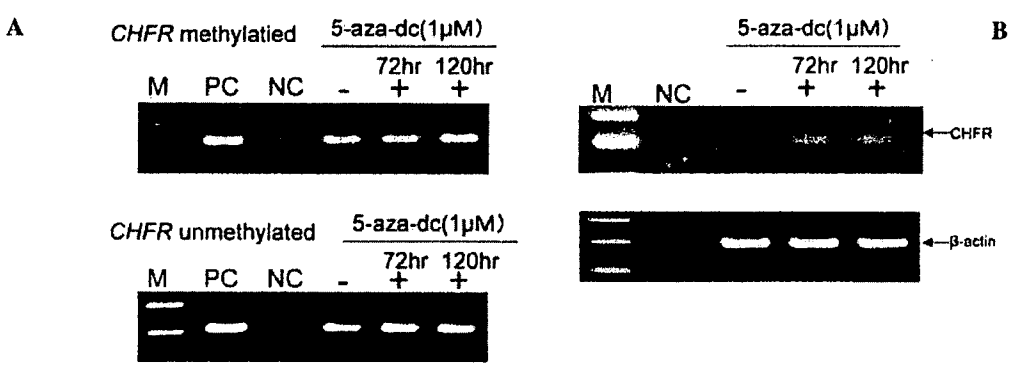

Figure 3. Demethylation analysis of the *CHFR* gene in HeLa cells. (A) MSP analysis after 5-aza-dC treatment. (B) *CHFR* expression recovered 72 h after 5-aza-dC retreatment (RT-PCR).

cancer, including sensitivity to taxanes, is unclear. In this study, aberrant hypermethylation of *CHFR* was observed in adenocarcinoma cells at a rate of 14.3%, but not in normal cervical cells and squamous cell carcinoma cells. Epigenetic

Table I. Aberrant methylation of the *CHFR* gene in cervical cancer cytologic specimens.

No.	Tissue type	Stage	*CHFR*
CC1	SCC	Ib1	U
CC2	SCC	Ib1	U
CC3	SCC	Ib1	U
CC4	SCC	Ib1	U
CC5	SCC	IIa	U
CC6	SCC	IIa	U
CC7	SCC	Ib2	U
CC8	SCC	IIb	U
CC9	SCC	Ib1	U
CC10	SCC	Ib1	U
CC11	SCC	Ib1	U
CC12	SCC	Ib2	U
CC13	SCC	Ib1	U
CC14	SCC	Ib1	U
CC15	SCC	Ib1	U
CC16	SCC	IIa	U
CC17	SCC	Ib2	U
CC18	SCC	Ib2	U
CC19	SCC	Ib1	U
CC20	SCC	Ib2	U
CC21	SCC	Ib1	U
CC22	SCC	Ib1	U
CC23	SCC	Ib2	U
CC24	SCC	Ib1	U
CC25	SCC	Ib1	U
CC26	SCC	IIb	U
CC27	MAD	Ib1	U
CC28	MAD	IIa	M
CC29	MAD	Ib1	U
CC30	MAD	Ib1	U
CC31	MAD	Ib1	U
CC32	MAD	Ib1	M
CC33	MAD	IIa	U
CC34	MAD	Ib1	U
CC35	MAD	Ib1	U
CC36	MAD	Ib1	U
CC37	MAD	Ib2	U
CC38	MAD	Ib1	U
CC39	MAD	Ib1	U
CC40	MAD	IIb	U

CC, cervical cancer; SCC, squamous cell carcinoma; MAD, mucinous adenocarcinoma (endocervical type).

Table II. Aberrant methylation frequency of the *CHFR* gene in cervical cancer cytologic specimens.

	CHFR	
	M (%)	U (%)
NCE	0 (0)	20 (100)
SCC	0 (0)	26 (100)
MAD	2 (14.3)	12 (85.7)

NCE, normal cervical epithelium; SCC, squamous cell carcinoma; MAD, mucinous adenocarcinoma (endocervical type); M, methylated; U, unmethylated.

higher high sensitivity to these agents, compared to other cells (Table III).

Recovery of *CHFR* expression by treatment with 5-aza-dC was examined in HeLa cells (which showed aberrant *CHFR* hypermethylation), and increased CHFR expression following 5-aza-dC treatment was confirmed by RT-PCR (Fig. 3). Changes in the sensitivity of HeLa cells and SKG-IIIa cells (which did not show aberrant CHFR hypermethylation) to 6 anticancer agents were determined before and after 5-aza-dC addition, using the CD-DST. Anticancer agents other than taxanes (5-fluorouracil, etoposide, cisplatin and doxorubicin) showed almost no change in the T/C ratio before and after 5-aza-dC addition and regardless of aberrant *CHFR* hypermethylation. In contrast, the T/C ratios of HeLa cells treated with paclitaxel and docetaxel increased significantly after 5-aza-dC addition, indicating a significant decrease in sensitivity (Table IV).

Changes in cell cycle were determined using flow cytometry in SKG-IIIa and HeLa cells treated with paclitaxel alone or a combination of paclitaxel and 5-aza-dC. In SKG-IIIa cells (no aberrant *CHFR* methylation), cells in G2/M phase markedly increased to 73.9% after paclitaxel treatment and G2 arrest was observed. In contrast, in HeLa cells (aberrant *CHFR* hypermethylation), the percentage of G2/M cells remained low (8.3%) after paclitaxel treatment and Sub-G1 cells increased to 13.4%, higher than that of controls, suggesting that paclitaxel treatment induced apoptosis. However, combined treatment with paclitaxel and 5-aza-dC resulted in 73.9% of cells in the G2/M phase and a marked decrease in Sub-G1 cells to 2.2%, showing a similar pattern to paclitaxel treatment of SKG-IIIa cells (Fig. 4).

SKG-IIIa cells were transfected with siRNA for *CHFR* and the expression levels of *CHFR* mRNA and protein decreased to approximately half of the control levels (Fig. 5). Under these conditions, changes in sensitivity to anticancer agents were determined using the CD-DST. The T/C ratios for paclitaxel and docetaxel were significantly decreased compared with those for non-taxane anticancer agents, indicating that reduction of CHFR expression specifically increases sensitivity to taxanes (Fig. 6).

Discussion

Aberrant hypermethylation of the *CHFR* gene has been reported in endometrial, gastrointestinal and lung cancers (12,15-17). A similar effect has not been studied in cervical cancer, and the relationship between aberrant *CHFR* hypermethylation and the biological characteristics of cervical