Current Organ Topics:

Gynecologic Cancer
婦人科 癌

Ⅲ. 子宮体癌における化学療法

寒河江 悟，杉村 政樹（札幌鉄道病院産婦人科）

〔*Jpn J Cancer Chemother* 35(2): 218-223, *February*, 2008〕

はじめに

2006年11月28，29日英国のマンチェスターにて子宮体癌に関する国際会議が開催され，分子メカニズム，治療法，今後の臨床試験のあり方について，早期がん，進行がん，稀な組織型（明細胞，漿液性腺癌など）の治療，translational research などを対象に討議された[1]。これは英国の NCRI，米国の NCI-US，さらに国際的臨床試験グループである GCIG の共同開催であり，その内容から現在世界の専門家はどのような理解のもとに今後の臨床研究を考えているのかを整理し，特に化学療法に焦点を当てて解説してみたい。

1．原則は手術療法

子宮体癌の治療は，あくまで手術療法の役割が中心である。そこで術後の再発危険因子を理解することが最も重要であり，子宮体癌の術後管理をいかに正確に行うかに直結する課題である。再発危険因子は子宮内因子と子宮外因子に分けられ[2]，表1のごとく多くの因子が存在し，それぞれが FIGO の進行期分類で反映されている[3]。

表1 子宮体癌の予後因子

Uterine Factors	Extrauterine Factors
Histology	Adnexal Metastases
Grade	Intraperitoneal Spread
Myometrial Invasion	Peritoneal Cytology
Cervical-Isthmus Extension	Pelvic Node Metastases
Lymph-Vascular Invasion	Paraortic Node Metastases

昨今はこれらの危険因子を危険度の程度別に，low，intermediate，high risk などとグループ分けされ詳細に検討されている（図1）。そしてこれらが種々の治療法の選択に欠かせない指針となっている。従って，正確な術後進行期の決定がその症例の予後を語るもっとも正確な手段であることは議論の余地がない。

こと手術に関しては，単純子宮全摘術とは異なり，広汎子宮全摘術を子宮体癌で行うことが骨盤内や腟断端への再発を減らすとされ，リンパ節への再発転移をも低くするものとされてきたが，早期であるⅠ期症例への広汎子宮全摘術を支持する証拠は何もない。この手術は明らかな頸管浸潤を伴ったⅡb期症例に限られるべきである[4]。リンパ節郭清の効用は疾患の進行期を決め，そうすることで予後を推測し術後療法の必要性を決めることである。しかしリンパ節を摘出すること自体が治療的意義があるか否かは今日もっとも議論のあるところである[5]。2007年米国での ASCO 総会にて ASTEC 試験の報告[6]があり，二段階の無作為化試験により TAH & BSO 後にリンパ節郭清を行うかどうかと，病理学的に再発高危険群であるが肉眼的に完全に摘出された症例には，放射線の外照射を行うか否かにより，生存期間が比較された（図2）。全生存期間は治療法で差はなかったが，無再発期間はリンパ節郭清のない群で，行った群より優っていた。彼らは多数の症例での成績であり骨盤リンパ節郭清は特に術後療法の存在下では生存期間を延長するものではないと結論した。リンパ節郭清群には無再

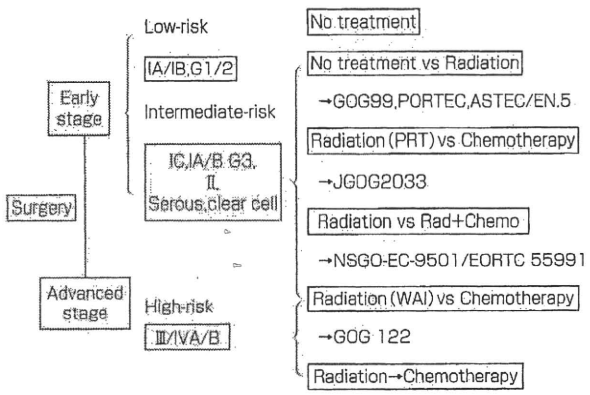

図1 リスク別術後療法のシェーマ

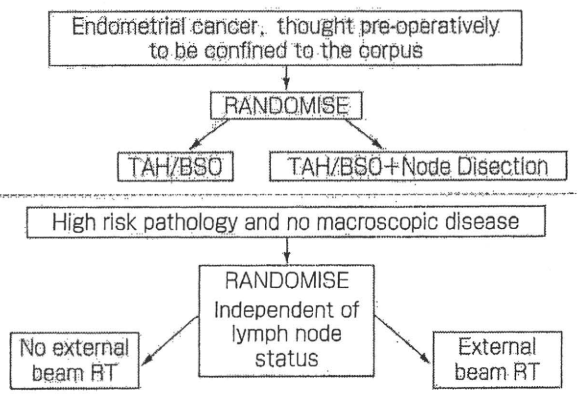

図2 ASTEC 臨床試験 ASCO2007

表 2　Radiotherapy versus Chemotherapy in endometrial cancers JGOG2033[11], Italian Study[12] and GOG122[13]

	JGOG2033* (Susumu N, 2007)	Italian Study (Maggi R, 2006)	GOG 122 (Randall ME, 2006)
Regimen RT	Pelvic	Pelvic±PA	WAI
CT	CAP	CAP	AP
Number of Patients	385	340	396
Disease Stage	Ⅰc, 61%; Ⅱ, 14% Ⅲ, 25%	Ⅰ, 26.5%; Ⅱ, 9% Ⅲ, 64.5%	Ⅲ, 73%; Ⅳ, 27%
5-year PFS RT	84	63	38
CT	82	63	50**
5-year OS RT	86	69	42
CT	87	66	55**

*In press　**Adjusted for stage, $p<0.01$

発期間の短い傾向が確認され，さらに術後の放射線治療によるリンパ浮腫の増大という危険性もあると強調した。日本の婦人科がん化学療法研究機構 JGOG は子宮体癌に関するアンケート調査[7]を行い，子宮の摘出方法やリンパ節郭清には国内的に種々の方法が用いられていることを報告し，子宮摘出法は単純と Piver Ⅱ型（いわゆる準広汎）が 1/3 ずつで，あとは進行期を考慮して子宮を摘出するというものであった。さらなる広汎手術を行うか否かの質問では，30%のみが行うと回答し，決して子宮を広範囲に摘出することが予後改善につながるとは考えていない。また傍大動脈リンパ節郭清については，いつも行うのが 13%しかなく，81%は腫瘍関連因子の存在で選択的に行っていたし，6%の施設では全然行っていなかった。この場合の腫瘍関連因子は傍大動脈リンパ節転移，分化度 3，筋層浸潤 1/2 以上，組織型が漿液性・明細胞，骨盤リンパ節転移などが 20%以上の因子であった。結論としては子宮体癌の手術術式はいまだ標準化されておらず，子宮全摘術，両側付属器摘出術，骨盤リンパ節郭清，選択的傍大動脈リンパ節郭清が日本で行われている子宮体癌の今日的術式であることが判明した。子宮体癌における手術に関する三大問題点は，子宮の摘出術式すなわち単純か広汎か，リンパ節郭清か生検か，傍大動脈リンパ節の扱いである。これらの種々の術式の治療的意義を決定づける臨床試験を大々的に行うことは，子宮体癌における術式の標準化に最も寄与するであろうと結論つけられた。

2．術後療法

次に骨盤放射線療法，すなわち外照射と腔内照射は，これまで何十年も広く子宮体癌治療の基本であった。特に進行期不明な症例の術後療法の場合や intermediate や high リスク症例やリンパ節転移症例など，さらに摘出不能な骨盤内進展症例などには放射線療法が標準であった。Intermediate リスク症例に対する放射線療法は三つの無作為化臨床試験が存在し，the Norwegian trial[8]，PORTEC Ⅰ[9]，GOG99[10]である。これらはすべて骨盤内再発の減少には寄与するが，最終生存には寄与しなかった。さらに GOG 試験ではリンパ節郭清後の骨盤照射群に合併症の明らかな増加を認めた。

術後療法としての放射線療法と化学療法を直接比較した日本の臨床試験は 2005 年に ASCO で報告されたが，Ⅰc 期からⅢ期までの 385 例が登録され，CAP 療法と骨盤放射線療法が比較された[11]が，これまでに放射線療法と化学療法の直接比較は三つの臨床試験（表 2）しか存在せず，JGOG2033[11]，Italian Study[12]，GOG122[13]である。これらを比較すると，JGOG2033 では完全手術で筋層浸潤 1/2 以上症例でⅠcからⅢc 期まで登録され，類内膜腺癌 385 例が放射線療法と CAP 化学療法の無作為化比較試験で検討された。一次評価項目は全生存期間であり，二次的には無再発期間と副作用であった。両群は年齢，閉経，合併症，術式，進行期などに有意な差はなく，Ⅰc 期 61%，Ⅱ期 14%，Ⅲa 期 13%，Ⅲc 期 12%であった。約 74%がⅠcからⅡb 期までであった。結論としては 385 例での両群の比較では無再発や全生存期間には全く差はなく，サブ解析で intermediate リスクでもさらに再発危険度の低い群 190 例では両群に予後の差はないが再発危険度の高い群（Ⅱ期からⅢa 期など）では放射線治療群より有意に化学療法群で予後良好であった[11]。

Italian Study の high リスク子宮体癌症例に対する放射線療法と化学療法 CAP 療法の比較であり，Ⅰc/Ⅱ期 G3 とⅢ期症例 345 例が登録され，化学療法は cisplatin（CDDP）50 mg/m^2，doxorubicin（DXR）45 mg/m^2，cyclophosphamide（CPA）600 mg/m^{2}を 4 週毎に 5 サイクルであり，放射線療法は外照射（45～50 Gy 週 5 日治療）であった。両群で全生存期間に差はなかったが放射線療法は骨盤内再発を遅らせ，化学療法は遠隔転移を遅らせた[12]。

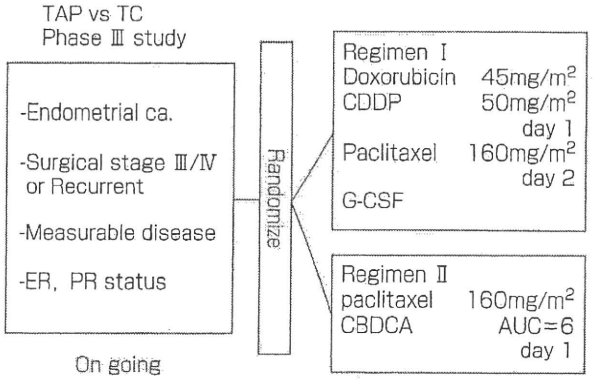

図 3 GOG209[15]

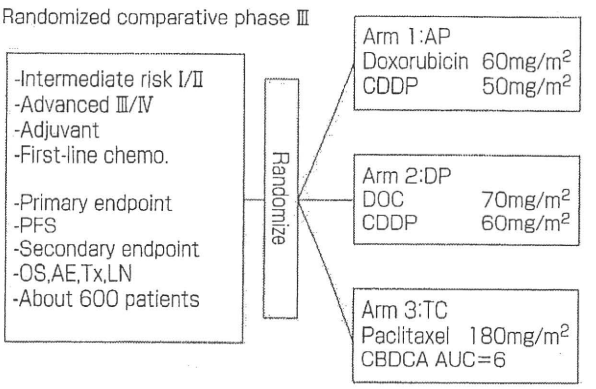

図 4 Ongoing Phase Ⅲ JGOG2043[18]

進行子宮体癌での放射線療法と化学療法の比較はGOG122研究があり2004年にASCOで報告され2006年に論文化された。全腹腔内照射とAP化学療法の比較であり，396例のⅢ期Ⅳ期症例が登録され，予後の比較では神経障害や心毒性がより強く出たが，明らかに放射線療法より化学療法が良好であった。この研究結果はその後の治療法に多大なインパクトを与え，標準であった放射線療法から選択肢としての「化学療法」の時代へのあけぼののようであった[13]。

3．子宮体癌における化学療法

それまでの化学療法は進行・再発子宮体癌症例の中でも肥満症例や前回放射線療法症例，高齢者などに限られていた。化学療法の既往なし症例では20%程度の効果が期待できた。たとえばDXR/epirubicin（EPI），paclitaxel（PTX）/docetaxel（DOC），さらにCDDP/carboplatin（CBDCA）などの併用療法である。AP療法は長い間唯一の標準化学療法であったが，GOGがAP対AP+PTX（TAP）の比較試験GOG177を行った[14]。既往の化学療法なしで測定可能病変がある進行・再発子宮体癌症例を対象に，AP療法とAP+PTX（G-CSF補助）療法の比較を行った。結果としてTAP療法が生存率の優越性を認めたが副作用が重症であり死亡症例も認められた。そこで現在より副作用の少ないPTX/CBDCA療法が第Ⅱ相試験で検討され60%を越える奏効率が得られている。そこで現在GOGではTAP療法vsTC療法の比較をⅡ期からⅣ期子宮体癌症例を対象に登録を進めている（GOG209）（図3）。本試験にはJGOGの中のGOG Japanを通じて日本人女性も登録が行われており，今後の研究成果が期待されている。

これらの状況の中，JGOGは最近さらに子宮体癌における化学療法のアンケート調査を行い，国内的にもPTX/Platinum（CBDCA）が最も汎用されている化学療法であることが示されている[15]。JGOGでは数年前からTaxane系薬剤とプラチナ系薬剤の併用の中で最も有効な薬剤の検討も始めており，JGOG2041では，DOC/CDDP，DOC/CBDCA，PTX/CBDCAの3種類の併用療法を30例ずつ登録し，2004年に登録終了し現在予後解析を待っているところである。中間解析ではPTX/CDDPが最も神経毒性が強かった[16]。3併用療法の中で副作用の出現頻度は異なり，DOC/CDDPでは消化器毒性がより強く発現し，DOC/CBDCAやPTX/CBDCAでは貧血や血小板減少がより高頻度であった。さらに1年経過での奏効率はDOC/CDDPで51.7%であり，PTX/CBDCAは60.0%であったが，DOC/CBDCAでは48.3%とやや低かった。

このJGOG2041に引き続き，現在国内では臨床第Ⅲ相試験JGOG2043（図4）が進行中である[17]。Ⅰc期，G2/G3，Ⅱ/Ⅲ期子宮体癌の術後治療として3種類の併用化学療法が無作為化され，登録が進んでいる。化学療法の内容はJGOG2041で評価されたDOC/CDDPとPTX/CBDCAであり，対照治療がこれまでの基本であるAP療法の3治療法である。現在各群200例の目標に対しやや登録が遅れているがすでに計100例以上の登録がなされており，今後の登録を期待しつつ最終成績に注目しているところである。一次評価項目は無再発期間であり，二次評価項目は全生存期間，副作用，治療内容，リンパ節転移などである。本研究は，GOG209と並んで，子宮体癌に対するTaxane系薬剤とプラチナ系薬剤の併用療法のなかで何が最も効果的なのかを決定することにもなり極めて重要である。

4．ホルモン療法

ホルモン療法は過去40年以上にわたって進行・再発子宮体癌症例に効果があるとされてきた。単剤プロゲステロン製剤（GOG48やGOG81[18]）ではPR陽性腫瘍やG1腫瘍に20%の奏効率があるとされた。またプロゲステロン製剤とタモキシフェンの併用療法（GOG119 and GOG153[19]）は30%内外の臨床効果があるとされた。さらに昨今ではaromatase inhibitors，anastrozoleやle-

trozoleなどの臨床効果が検討されたが極めて限定的であった。またホルモン剤のこれまでの臨床試験を総合的に判定したMeta-analysisでは，プロゲステロン製剤は初回治療の補助療法としての臨床効果は有効でないと結論されている[20]。それでも子宮体癌症例に対する保存的治療法への応用も本邦では検討され，早期子宮体癌や内膜増殖症の症例にMPAを投与する第Ⅱ相試験がこのほど発表された[21]。40歳未満のⅠa期子宮体癌症例28例と異型内膜増殖症17例の合計45例が登録され，MPA 600 mgを低用量アスピリンとともに26週間連続投与された。病理学的CRは子宮体癌症例の55%，異型増殖症の82%で観察され，全体でpCR率は67%にのぼった。これらの症例群では経過観察3年間で12例にその後妊娠が確認され，7例で無事出産にこぎつけている。従って子宮体癌や異型増殖症に対する妊孕能温存高用量MPA療法の有用性はこの前方視的研究により証明された。しかし有効例においても実質的再発率の高さから厳重な経過観察が必要であることが結論つけられた。

5．分子標的療法

現在，生物学的治療法が種々の分子標的に対して多くの臨床試験が実施されている。子宮体癌においても同様であり，大きな流れとして二つの方向性が現存する。すなわちひとつは子宮体癌で43%に発現しているPTENに対する治療法である。PTEN機能の欠損がAKTを増加させ，mTORを増加させる。原発腫瘍ではmTORが70%で増加しており，再発腫瘍でも50%で増加しており，このmTOR抑制剤は治療に極めて重要である，たとえばRAD001[22]，CCI-779（NCIC）などが報告されており，CCI-779は16例中5例のPRが得られ31%の奏効率を報告している[23]。もうひとつはEGFRに対する治療法である。EGFRは子宮体癌の60～80%（とくに漿液性）に発現しており，EGFR標的治療はこれまで多くの薬剤が開発され，たとえばIressa（GOG 229-C），Herceptin（GOG 181b），and Erlotinibなどであり，OSI-774（NCIC）では7%の奏効率が報告されている。

6．ASCO2007におけるNSGO/EORTC臨床試験

以上のごとく，子宮体癌に対する化学療法にも種々の薬剤の試みが現在進行中である。そのような状況の中，本年のASCOで子宮体癌の治療法に関して極めて重要な報告がなされた。それはNSGO/EORTCの共同研究であり，早期highリスク子宮体癌症例の術後療法として，放射線単独療法か，それに化学療法を併用するか否かの無作為化臨床試験（図5）である[24]。登録の基準は，子宮全摘術と両側付属器摘出術の後に手術進行期Ⅰ期とⅡ期，さらに腹腔内細胞診陽性のⅢa期，骨盤リンパ節転移要請のⅢc期を対象にしており，さらに漿液性，明

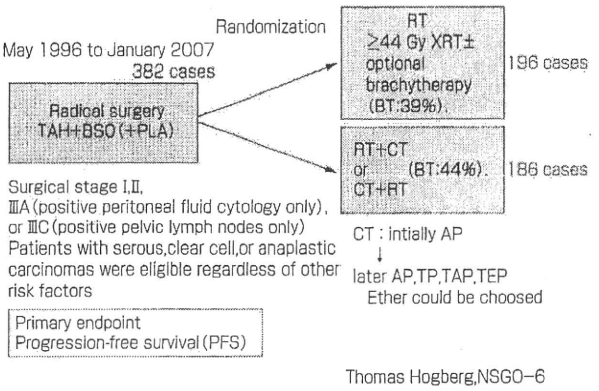

図5　NSGO and EORTC at ASCO 2007.[31]

細胞，未分化癌などは他のリスク因子の有無にかかわらず登録対象としている。症例は放射線療法群と放射線療法と化学療法の併用群に無作為に分けられ，化学療法はこれまで有効とされたAP，TP，TAP，またはTEP療法などが含まれている。一次評価項目は無再発期間であり，90%の症例が進行期Ⅰ期に属したが，67%は類内膜腺癌G3，明細胞，漿液性がんであった。これまでの試験の結果は無再発期間で両群間に明らかに差があり，放射線療法に化学療法が併用された群で有意に予後良好であった。演者らはこれらのデータより，併用群に割り振られた症例の27%が化学療法を受けなかったり，一部しか受けなかったにもかかわらず，両治療法の併用が早期子宮体癌で微小転移を認めるhighリスクの症例には術後療法として両治療法の併用が放射線療法単独より有用であると結論した。NSGO/EORTCでは現在今後の臨床試験としてまずは術後に化学療法を行い，その後に放射線療法を行うか否かの臨床試験を企画中である。ということは，NSGO/EORTCでは早期子宮体癌の術後療法の標準は化学療法であり，高intermediateリスク症例である微小転移を認める可能性がある症例がまさに適応であると伝えている。

最後に，2006年英国で開催された子宮体癌に関するコンセンサス国際会議のまとめとして，

A）今後早期子宮体癌に対する術後療法としては化学療法の重要性を十分に認識しておかなければならない。今後将来の方向性として注目される臨床試験は以下のごとくである。

1）現在登録中のPORTEC Ⅲ臨床試験

これは骨盤放射線療法と化学療法併用放射線療法＋地固め化学療法の比較である。対象はⅠb期Ⅰc期G3，Ⅱ期G3，ⅢaまたはⅡc期の類内膜腺癌，さらにⅠb期からⅢc期までの明細胞か漿液性癌である。化学療法併用放射線療法は7日目と22日目にCDDP 50 mg/m^{2}を併用し，地固めにPTX/CBDCA（175/AUC5）を3週毎

に4サイクル行うものである。800例の登録を予定している。

2）骨盤放射線療法と化学療法＋腔内照射の比較をリンパ節転移陰性の子宮体癌に行う無作為化比較試験

3）手術進行期を決定してリンパ節転移があった症例に化学療法を追加する群と手術なしに骨盤照射と化学療法の併用を行う群の無作為化比較試験

B）さらに進行子宮体癌への治療としてⅢ期症例の術後地固め療法として，NSGO/EORTCの今回の発表の延長として全身化学療法に放射線療法の有無による無作為化比較試験も期待される。

C）そして最後に再発子宮体癌症例に対する治療としては，孤立性の骨盤内再発にはGOG238すなわち放射線療法単独かCDDP併用放射線療法の比較試験が現在進行中である。さらにⅣ期または再発子宮体癌の治療としてPTXはGOG209，TAP vs TCにおいて標準治療の一部として汎用されているし，欧州でのAPとCBDCA/Doxil（liposomal DXR）の比較試験も進行中である。さらには分子標的薬剤CCI-779に化学療法やホルモン療法を併用する臨床試験がGCIGを中心に展開されている。

以上が今後期待される臨床試験としてまとめられた。

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ANTICANCER RESEARCH *28*: 2385-2388 (2008)

Feasibility Study of Docetaxel and Nedaplatin for Recurrent Squamous Cell Carcinoma of the Uterine Cervix

YOH WATANABE, HIDEKATSU NAKAI, TOMOMARO ETOH, KAZUMI KANEMURA, ISAO TSUJI, AYAKO ISHIZU and HIROSHI HOSHIAI

Department of Obstetrics and Gynecology, Kinki University School of Medicine, 377-2 Ohno-Higashi Osakasayama Osaka 589-8511, Japan

Abstract. *Background: To determine a new taxane plus platinum treatment regimen for squamous cell carcinoma of the uterine cervix (CSCC), a phase I feasibility study of docetaxel (DTX) plus nedaplatin (CDGP) combination therapy was conducted. Patients and Methods: Twenty consecutive patients were enrolled into the study. The starting dose of DTX/CDGP was 60 mg/m^2 / 80 mg/m^2, every 4 weeks for at least three courses and the dose was escalated to 70 mg/m^2 / 100 mg/m^2. DTX 60 mg/m^2 / CDGP 100 mg/m^2 was also evaluated as an extra dose level. Results: Dose-limiting toxicity was granulocytopenia and the maximum tolerated dose was determined as 70 mg/m^2 / 100 mg/m^2. All 20 patients had measurable disease and a partial response was achieved in 8 (40.0%) patients. Conclusion: DTX/CDGP therapy appears to be a tolerable regimen for cervical squamous cell carcinoma, even in patients previously treated by cisplatin concurrent chemoradiotherapy. The recommended doses of DTX and CDGP were determined to be 60 mg/m^2 and 100 mg/m^2, respectively.*

Previous phase III studies of chemotherapy for recurrent or advanced squamous cell carcinoma of the uterine cervix (CSCC) (1-4) have revealed that cisplatin is the key chemotherapeutic drug; the addition of bleomycin did not improve patient survival and combined treatment with paclitaxel or topotecan plus cisplatin yielded superior survival to that with cisplatin alone. Combined paclitaxel and cisplatin (TP) therapy is thought to be an effective regimen, because the Gynecologic Oncology Group (GOG) 169 trial (3) reported an overall response rate of 46% even among patients with recurrent CSCC with a history of having undergone radiation therapy. However, TP therapy includes several problems such as the inconvenience of 24 hour administration of paclitaxel and the high incidence of neurotoxicity. Since *in vitro* (5) and *in vivo* (6) studies have reported the efficacy of *cis*-diammine (glycolato) platinum (CDGP; Nedaplatin), especially in cases of squamous cell carcinoma, the effects of CDGP-based combination chemotherapy have been studied in carcinoma of the uterine cervix (7), esophagus (8) and head and neck (9). Moreover, a recent phase I/II study of irinotecan plus CDGP therapy reported an overall response rate of 68%, including 2 complete responses in 27 patients with advanced or recurrent CSCC (7). Docetaxel (DTX) had a significantly lower neurotoxicity than and comparable activity with paclitaxel combined with carboplatin for ovarian cancer (10). In patients with advanced or recurrent CSCC, single agent docetaxel demonstrated tumor activity with a response rate of 13% (11). Therefore, to determine the feasibility of DTX/CDGP as an optional regimen for patients with CSCC, a phase I study was conducted in patients with recurrent CSCC.

Patients and Methods

The present study was conducted as a phase I dose escalation study. The protocol was approved by the Institutional Review Committee of Kinki University School of Medicine, and full informed consent was obtained from all the patients prior to their enrollment in the study. The eligibility criteria for inclusion in the study are shown in Table I. The criteria for starting the next treatment course are shown in Table II. DTX/CDGP treatment was planned for 4-weekly administration, beginning at an initial dose of DTX 60 mg/m^2 and CDGP 80 mg/m^2, with the dose escalated to 70 mg/m^2 / 80 mg/m^2, 70 mg/m^2 / 90 mg/m^2 and 70 mg/m^2 / 100 mg/m^2. However, since the highest dose level was considered to be the maximum tolerated dose (MTD) and at the second highest dose level disease progression was observed (see Results), an additional dose level (60 mg/m^2 / 100 mg/m^2) was evaluated. CDGP (Aqupla; Shionogi & Co. Ltd, Osaka, Japan) was administered intravenously over 90 minutes, followed by intravenous administration of DTX (Taxotere; Sanofi-Aventis K.K., Tokyo, Japan) over 90 minutes. Premedication prior to the administration of DTX consisted of the intravenous administration of dexamethasone (8 mg)

Correspondence to: Yoh Watanabe, MD, Ph.D., Department of Obstetrics and Gynecology, Kinki University School of Medicine, 377-2 Ohno-Higashi Osakasayama Osaka 589-8511, Japan. Tel: +81 72366 0221, Fax: +81 72368 3745, e-mail: watanabe@med.kindai.ac.jp

Key Words: Feasibility, cervical cancer, docetaxel, nedaplatin, chemotherapy.

0250-7005/2008 $2.00+.40

Table I. *Eligibility criteria.*

1.	Recurrent uterine cervical squamous cell carcinoma
2.	Measurable region to determine direct effects of chemotherapy
3.	Performance status ≤ ECOG 2
4.	Normal ECG
5.	No active infectious diseases or active inflammatory diseases
6.	Leukocyte count ≥4,000/mm^3 and <12,000/mm^3
7.	Granulocyte count ≥2,000/mm^3
8.	Platelet count ≥100,000/mm^3
9.	Hemoglobin level ≥9.0 g/dl
10.	Serum total bilirubin ≤1.5 mg / dl
11.	Normal serum creatinine
12.	GOT, GPT within 2 x normal value
13.	Full informed consent from patient obtained

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase.

Table II. *Criteria for starting next treatment course.*

1.	Leukocyte count ≥3,000/mm^3 and <12,000/mm^3
2.	Granulocyte count ≥1,500/mm^3
3.	Hemoglobin level ≥8.0 g/dl
4.	Platelet count ≥50,000/mm^3
5.	Performance status ≤ECOG 2
6.	Normal ECG
7.	GOT, GPT within 2.5 x normal value
8.	Serum creatinine within normal limit
9.	Fever <38.0°C
10.	Non-hematological toxicity* CTCAE ≤ Grade 1
11.	No progressive disease

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase; CTCAE: Common Terminology Criteria for Adverse Events, 2003. *Not including nausea, vomiting, and alopecia.

and granisetron (3 mg) over 30 minutes and hydration with a total intravenous fluid volume of 2000 ml. Granulocyte-colony stimulating factor (G-CSF) support was only employed for those patients who exhibited Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia or febrile neutropenia and none of the patients received prophylactic G-CSF supplementation. The dose-limiting toxicities (DLTs) were defined as grade 4 granulocytopenia lasting for over 5 days, grade 4 thrombocytopenia, febrile neutropenia (granulocytopenia ≤,1000/mm^3 and body temperature ≥38.5°C, grade 3/4 non-hematological toxicity excluding nausea, vomiting, and alopecia or treatment delay of more than 6 weeks due to toxicity. Toxicity was graded by the National Cancer Institute Common Toxicity Criteria, version 2.0. Three patients were entered at the initial dose level and monitored for DLT. If no DLT was observed, three additional patients were treated at the next higher dose level until DLT was observed or the maximum dose level was reached in the absence of DLT. If one of the three patients developed DLT at any level, the cohort was expanded to three additional patients, and if no DLT was observed in the three additional cases, the treatment dose was escalated to the next level. Maximum tolerated dose (MTD) was determined as the dose level at which no more than one out of six patients experienced a DLT. The direct antitumor effects were determined based on the criteria proposed in the new guidelines to evaluate the response to treatment in solid tumors (12).

Table III. *Characteristics of patients.*

Number of patients	20
Mean age (range)	52.4±8.0 years (28-66)
PS	
0	8
1	10
2	2
Prior treatment	
CCRT alone	7
RT alone	2
RH alone	2
RH + adjuvant CCRT	6
RH + adjuvant RT	3
Recurrent site	
Prior irradiation area	9
Extra irradiation area	7
Both	2
No prior irradiation	2
Median no. of treatment courses (range)	5.5 (1-11)

PS: Performance status determined by Eastern Cooperative Oncology Group Criteria; CCRT: cisplatin concurrent chemoradiotherapy; RT: radiation; RH: radical hysterectomy.

Results

Between August 2004 and November 2006, a total of 20 patients were enrolled into the study. The clinicopathological characteristics of the patients are listed in Table III. Table IV shows results of the present phase I dose escalation study. Among the patients receiving the DTX/CDGP therapy, 1 out of the 6 patients developed DLT (neutropenia) at level 3 (DTX 70 mg/m^2 / CDGP 90 mg/m^2), and 2 out of the 5 patients developed DLT (neutropenia with a delay of planned treatment by over 2 weeks and febrile neutropenia) at level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2). Six out of the 17 patients (35.3%) given dose levels 1-4 showed a partial response. At dose levels 1 and 3, disease progression was observed. Three patients given the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT. Two out of the 3 patients at this dose level showed a partial response. Disease progression was not observed at this dose level. Two patients had received no radiation therapy, four patients had disease within the irradiation field and two patients had disease outside the irradiation field among the patients who responded to DTX/CDGP.

Leukopenia (75.0%) and granulocytopenia (85.0%) were the most frequently observed CTCAE grade 3/4 hematological toxicities, and 12 patients (60.0%) needed G-CSF support. Other grade 3 toxicities observed were

Table IV. *Summary for each dose level.*

Dose level	DTX CDGP	Number of patients	Prior therapy	Total treatment courses	DLT	Best response
1	60 mg/m^2	3	CCRT	6		SD
	80 mg/m^2		CCRT	3		PD
			RT	7		SD
2	70 mg/m^2	3	RH+RT	6		SD
	80 mg/m^2		RH+RT	6		PR
			CCRT	6		SD
3	70 mg/m^2	6	CCRT	11		SD
	90 mg/m^2		CCRT	3		PR
			RH+CCRT	2	NEU	PD
			RH	8		PR
			RH	6		PR
			RH+CCRT	4		PD
4	70 mg/m^2	5	RH+RT	5		PR
	100 mg/m^2		CCRT	2	FN	SD
			RH+CCRT	4		SD
			RH+CCRT	3		PR
			CCRT	1	NEU	SD
EX	60 mg/m^2	3	RH+CCRT	7		PR
	100 mg/m^2		RT	11		PR
			RH+CCRT	3		SD

DTX: Docetaxel; CDGP: nedaplatin; CCRT: cisplatin concurrent chemoradiation; RT: radiation therapy; RH: radical hysterectomy; DLT: dose limiting toxicity; NEU: neutropenia; FN: febrile neutropenia; SD: stable disease; PR: partial response; PD: progressive disease; EX: extra dose level.

anemia (2 patients), thrombocytopenia (1 patient), nausea (5 patients), and vomiting (1 patient). Two patients exhibited a grade 1 allergic reaction soon after the start of DTX administration. None of the patients exhibited neurotoxicity. All of the patients with adverse effects, including those with DLTs, recovered within 3 weeks and no treatment-related deaths were observed.

Discussion

Dose level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2) was determined as the MTD for DTX/CDGP, and three patients at level 1 and 3 had disease progression. In contrast, the three patients at the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT and two of these patients responded to the DTX/CDGP. Therefore the recommended treatment dose for a subsequent phase II study was determined as the extra dose level, DTX 60 mg/m^2 / CDGP 100 mg/m^2, administered every 4 weeks. While the effects of platinum-based combination chemotherapy alone for recurrent CSCC have been unsatisfactory, survival benefit of CCRT both as a primary therapy (13-16) and an adjuvant therapy (17) has been shown in patients with CSCC. CCRT has been widely used as the standard treatment for patients with CSCC. However, the treatment options for recurrent CSCC after CCRT are limited because the overall response rate to platinum-based chemotherapy in cases of recurrent CSCC has been reported to be around 20% (18) in chemotherapy-naive patients, and 5.3% (19) in patients with recurrent disease within the previously irradiated field. Therefore, the establishment of an effective chemotherapeutic regimen for CCRT-treated patients with recurrent CSCC is urgently needed to improve the long-term prognosis of such patients. Based on the results of our present study, CDGP-based chemotherapy may be effective even for cases with disease within the previous irradiation field, although the treatment results remain unsatisfactory.

The efficacy (9-13% for overall response) of DTX alone was limited for patients with advanced or recurrent CSCC who had received previous chemotherapy (11, 20). Subsequent studies should be planned carefully to observe the efficacy of DTX/CGDP. Large-scale phase II studies of DTX/CDGP and the combination of CDGP and paclitaxel as another taxane for a calibration may be needed to discover a therapy improving the long-term prognosis of patients with recurrent CSCC previously treated by CCRT or radiation therapy.

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Received March 6, 2008
Revised May 16, 2008
Accepted May 19, 2008

Reduced risk of endometrial cancer from alcohol drinking in Japanese

Satoyo Hosono,[1,2] Keitaro Matsuo,[2,3,7] Hiroaki Kajiyama,[1] Kaoru Hirose,[4] Takeshi Suzuki,[1] Akio Hiraki,[1] Takakazu Kawase,[1] Kumiko Kidokoro,[1,2] Toru Nakanishi,[5] Nobuyuki Hamajima,[6] Fumitaka Kikkawa,[1] Kazuo Tajima[3,7] and Hideo Tanaka[2]

[1]Deparment of Gynecology and Obstetrics, Nagoya University Graduate School of Medicine; [2]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute; [3]Department of Epidemiology, Nagoya University Graduate School of Medicine; [4]Department of Planning and Information, Aichi Prefectural Institute of Public Health; [5]Department of Gynecologic Oncology, Aichi Cancer Center Hospital; [6]Department of Preventive Medicine, Biostatistics and Medical Decision-making, Nagoya University Graduate School of Medicine

(Received December 17, 2007/Revised February 6, 2008/Accepted February 11, 2008/Online publication April 14, 2008)

The role of alcohol consumption in the etiology of endometrial cancer has not been clarified. To examine the association between alcohol consumption and endometrial cancer risk, we conducted a case-control study with 148 histologically diagnosed incident endometrial cancer cases and 1468 matched non-cancer controls. Median consumption of alcohol was only 19.3 g/week among cases who drank and 28.2 g/week among controls who drank. These values are lower than in Western countries. Relative risk was analyzed in subjects classified into four groups according to weekly alcohol consumption (non-drinkers, 1–24 g/week, 25–175 g/week, and >175 g/week). Confounder-adjusted odds ratios for those consuming alcohol at <25 g/week, 25–175 g/week, and >175 g/week compared to non-drinkers were 0.79 (95% confidence interval (CI), 0.49–1.28), 0.42 (95% CI, 0.23–0.79), and 0.47 (95% CI, 0.14–1.58), respectively. Further analysis was conducted concerning self-reported physical reaction to alcohol. Among women without flushing after drinking, a significant inverse association between risk and alcohol intake was seen (trend $P = 0.001$). In contrast, no protective effect of alcohol was seen among women who experience flushing after drinking. These results suggest the presence of an inverse association between alcohol drinking and endometrial cancer risk among Japanese women, and that this association is evident among those without flushing. Further investigation of these findings is warranted. (*Cancer Sci* 2008; 99: 1195–1201)

Endometrial cancer is a common gynecologic cancer in Japan, and its incidence is increasing, possibly due to the recent Westernization of the Japanese lifestyle.[1] The development of endometrial cancer has been related to exposure to unopposed estrogens.[2–4] Several studies have shown a positive association between alcohol intake and estrogen level in postmenopausal women.[5,6] Although alcohol intake could therefore be expected to increase the risk of endometrial cancer by elevating estrogen levels, epidemiologic studies of this association have been inconsistent. Most previous studies have indicated that alcohol consumption is either weakly or not associated with the risk of endometrial cancer.[7–11] However, several others have shown an increased risk in heavy drinkers[12,13] while a case-control study by Swanson *et al.* suggested an inverse association between moderate alcohol consumption and endometrial cancer risk among young women (<55 years).[14] These inconsistent findings, as well as uncertainties regarding the etiology of endometrial cancer, hamper any coherent understanding of this association.

Here, we conducted a hospital-based case-control study to examine the association between alcohol consumption and endometrial cancer risk among Japanese women, considering other predisposing characteristics, such as body mass index and a history of hormone replacement therapy. In addition, given recent findings that a genetic polymorphism in *aldehyde dehydrogenase2 (ALDH2)*, which has a strong impact on alcohol metabolism, was associated with several cancer risks,[15–17] we also analyzed this risk using self-reported reactions after drinking as a surrogate for *ALDH2* genotyping.

Materials and Methods

Subjects. The subjects were 148 patients newly and histologically diagnosed with endometrial carcinoma between January 2001 and June 2005 at Aichi Cancer Center Hospital (ACCH) in Japan. The distribution of histological subtypes among 148 cases was 93 type I tumor (low-grade endometrioid adenocarcinoma) (62.8%), and 55 type II tumor (high-grade endometrioid adenocarcinoma and other adenocarcinomas) (37.2%). Mixed epithelial and mesenchymal tumors were excluded due to the paucity of knowledge on their etiology. Controls ($n = 1476$) were randomly selected and matched by age (± 3 years) and menopausal status (premenopause or postmenopause) to cases with a 1:10 case-control ratio from 11 814 women who were diagnosed as cancer-free (four cases were matched with nine controls). All subjects were recruited in the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere.[18,19] In brief, information on lifestyle factors was collected using a self-administered questionnaire for all first-visit outpatients at Aichi Cancer Center Hospital aged 20–79 who were enrolled in HERPACC between January 2001 and November 2005. Patients were also asked about lifestyle when healthy or before the current symptoms developed. Responses were checked by a trained interviewer. Approximately 90% of eligible subjects completed the questionnaire. Outpatients were also asked to provide blood samples. Our previous study showed that the lifestyle patterns of first-visit outpatients accorded with those in a randomly selected sample of the general population of Nagoya City.[20] The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update the data on cancer incidence. All participants gave written informed consent and the study was approved by Institutional Ethical Committee of Aichi Cancer Center.

Assessment of alcohol intake and alcohol reaction. All subjects were asked about their average frequency, beverage type, and amount of drinking per day during the 1-year period before onset of the present disease or before being interviewed. Usual alcohol intake was first reported as frequency of consumption in the five categories of non-drinker, <1 day/week, 1–2 days/week, 3–4 days/week, and 5 or more days per week. Consumption of each type of beverage (Japanese sake, beer, shochu, whiskey,

[7]To whom correspondence should be addressed. E-mail: kmatsuo@aichi-cc.jp

doi: 10.1111/j.1349-7006.2008.00801.x

Table 1. Characteristics of subjects

Characteristic	Cases		Controls		*P*-values
Number	148		1476		
Age (median, [min–max])	56.0 (26–79)		56.0 (23–80)		0.846
≤39 (%)	22	(14.9)	223	(15.1)	0.986
40–49 (%)	13	(8.8)	136	(9.2)	
50–59 (%)	64	(43.2)	610	(41.3)	
60–69 (%)	36	(24.3)	385	(26.1)	
≥70 (%)	13	(8.8)	122	(8.3)	
Smoking status					
Ever (%)	24	(16.2)	244	(16.5)	0.942
Never (%)	123	(83.1)	1225	(83.0)	
Unknown (%)	1	(0.7)	7	(0.5)	
Body mass index (median, [min–max])	23.2 (13.4–40.9)		21.9 (13.2–42.7)		<0.001
<25 kg/m² (%)	104	(70.3)	1211	(82.1)	<0.001
≥25 kg/m² (%)	40	(27.0)	257	(17.4)	
Unknown (%)	4	(2.7)	8	(0.5)	
Regular exercise					
No (%)	46	(31.1)	388	(26.3)	0.252
Yes (%)	101	(68.2)	1057	(71.6)	
Unknown (%)	1	(0.7)	31	(2.1)	
Menstrual status					
Premenopausal (%)	51	(34.5)	506	(34.3)	0.965
Postmenopausal (%)	97	(65.5)	970	(65.7)	
Age at menarche (median, [min–max])	14.0 (10–20)		14.0 (10–21)		0.963
≤12 (%)	38	(25.7)	379	(25.7)	0.729
13–14 (%)	75	(50.7)	701	(47.5)	
≥15 (%)	31	(21.0)	365	(24.7)	
Unknown (%)	4	(2.7)	31	(2.1)	
Duration of menstration (median, [min–max])	37.0 (0–49)		36.0 (11–43)		0.390
≤32 (%)	38	(25.7)	395	(26.8)	0.822
33–36 (%)	33	(22.3)	367	(24.9)	
37–39 (%)	38	(25.7)	388	(26.3)	
≥40 (%)	34	(23.0)	284	(19.2)	
Unknown (%)	5	(3.4)	42	(2.9)	
Parity (median, [min–max])	2 (0–4)		2 (0–6)		<0.001
0 (%)	41	(27.7)	207	(14.0)	<0.001
1–2 (%)	82	(55.4)	911	(61.7)	
≥3 (%)	24	(16.2)	348	(23.6)	
Unknown (%)	1	(0.7)	10	(0.7)	
Diabetes history					
No (%)	137	(92.6)	1416	(95.9)	0.056
Yes (%)	11	(7.4)	60	(4.1)	
Hypertension history					
No (%)	121	(81.8)	1273	(86.3)	0.135
Yes (%)	27	(18.2)	203	(13.8)	
Contraceptive usage history					
No (%)	138	(93.2)	1377	(93.3)	0.934
Yes (%)	8	(5.4)	74	(5.0)	
Unknown (%)	2	(1.4)	25	(1.7)	
Hormone replacement therapy history					
No (%)	132	(89.2)	1355	(91.8)	0.247
Yes (%)	15	(10.1)	100	(6.8)	
Unknown (%)	1	(0.7)	21	(1.4)	

and wine) was determined by the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. One Japanese drink equates to one 'go' (180 mL) of Japanese sake, which contains 23g of ethanol, equivalent to one large bottle (633 mL) of beer, two shots (57 mL) of whiskey, or 2.5 glasses of wine (200 mL). One drink of shochu (distilled spirit), which contains 25% ethanol, was rated as 108 mL. Total alcohol consumption was estimated as the summed amount of pure alcohol consumption (g/drink) of Japanese sake, beer, shochu, whiskey, and wine among current regular drinkers. Weekly ethanol consumption was calculated by combining the amount of ethanol per day and frequency per week. In this study, we used self-reported flushing (yes/no) after a small amount of drinking (a glass of beer) as a stratification factor in the examination of alcohol impact.

Statistical analysis. To assess the strength of associations between alcohol consumption and risk of endometrial cancer, odd ratios (OR) with 95% confidence intervals (CI) were estimated using unconditional logistic models adjusted for potential confounders. For subgroup analysis, subjects were classified by

doi: 10.1111/j.1349-7006.2008.00801.x

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer according to frequency and quantitiy of alcohol intake

Category	Cases (n = 148)	Controls (n = 1476)	Age-adjusted OR (95% CI)	Multivariate OR (95% CI)†
Frequency of alcohol intake				
None	108	929	1.00 (Reference)	1.00 (Reference)
<1/week	14	166	0.72 (0.40–1.29)	0.71 (0.39–1.29)
1–2/week	11	119	0.79 (0.41–1.52)	0.77 (0.40–1.50)
3–4/week	8	99	0.69 (0.33–1.46)	0.67 (0.31–1.43)
5-/week	7	154	0.39 (0.18–0.85)	0.37 (0.17–0.82)
unknown	0	9		
***P*-trends**			0.011	0.009
Amount of alcohol consumption				
None	109	933	1.00 (Reference)	1.00 (Reference)
<25 g/week	23	246	0.79 (0.49–1.27)	0.79 (0.49–1.28)
(median, range) (eta g/week)	(8.6, 2.9–24.2)	(8.6, 1.7–24.2)		
25–175 g/week	12	232	0.44 (0.24–0.81)	0.42 (0.23–0.79)
(median, range) (eta g/week)	(54.3, 25.9–96.6)	(69, 25.3–172.5)		
>175 g/week	3	47	0.54 (0.16–1.76)	0.47 (0.14–1.58)
(median, range) (eta g/week)	(201.3, 179.4–552)	(276, 177.1–805)		
unknown	1	18		
***P*-trends**			0.006	0.005

†Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, hormone replacement therapy, and flushing after drinking.

alcohol intake into the four groups of non-drinkers, and weekly ethanol intake of 1–24, 25–175, and >175 g. Among controls, median weekly intake in current drinkers was 25 g. Potential confounders considered in the multivariate analyses were age, smoking habit (never smokers or ever smokers), body mass index (BMI; <25 or ≥25 kg/m^2 based upon our previous study),[21] regular exercise (yes or no), menstrual status (premenopausal or postmenopausal), age at menarche (≤ 12, 13–14, or ≥ 15), duration of menstruation (years, quartiles), parity (0, 1–2, ≥ 3), diabetes history (yes or no), hypertension history (yes or no), contraceptive usage history (yes or no), hormone replacement therapy history (yes or no), flushing after drinking (yes or no), and histological subtype (type I or type II). Missing values for any covariate were treated as a dummy variable in the logistic model. Differences in categorized demographic variables between the cases and controls were tested by the χ^2-test. Age, age at menarche, duration of menstruation, BMI, and parity between cases and controls were compared by the Mann–Whitney test. Stratification analysis was used to estimate risk for subgroups by drinking habit. P-values less than 0.05 were considered statistically significant. All analyses were conducted using STATA version 9 (Stata, College Station, TX, USA).

Results

Baseline characteristics of the 148 endometrial cancer patients and 1476 controls are shown in Table 1. Median age was 56 years for both patients and controls. Smoking status did not differ between the two groups. Prevalence of ever smokers was 16.2% and 16.5% in case and controls, respectively. BMI was higher among cases than controls ($P < 0.001$). Regarding reproductive factors, only parity showed a significant difference between two groups. Low experience of delivery was more prevalent among cases than controls ($P < 0.001$). A history of diabetes was more common in cases, although with only marginal statistical significance. Although contraceptive usage did not differ, hormone replacement therapy was more prevalent in cases.

Median consumption of alcohol among cases and controls who drank was only 19.3 and 28.2 g/week, respectively. Table 2 shows the impact of drinking habit on endometrial cancer risk. Frequent drinkers showed a reduced risk: compared with non-drinkers, the age-adjusted OR of those who drank 5 or more days per week was 0.39 (95% CI, 0.18–0.85). Although without significance, all groups except non-drinkers showed OR below unity and their point estimates decreased as frequency increased (P-trend = 0.011). This trend was consistently observed in the multivariate model. Similarly, with regard to the amount of alcohol consumed, those who consumed less than 25 g per week, those who consumed 25–175 g per week, and those who consumed 175 g or more per week showed a lower risk of endometrial cancer than non-drinkers, with OR of 0.79 (95% CI, 0.49–1.27), 0.44 (95% CI, 0.24–0.81), and 0.54 (95% CI, 0.16–1.76), respectively. The multivariate model again showed consistent results.

Table 3 shows a stratified analysis according to potential confounders designed to examine the consistency of association and to explore the possible interaction with weekly alcohol consumption. The inverse association between endometrial cancer risk and alcohol intake persisted after stratification by BMI, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, and type I tumor. In contrast, no associations were seen for ever smokers, oral contraceptive users, hormone replacement therapy users, and type II tumor. Regarding BMI, obese women (BMI ≥ 25) showed a stronger protective effect by alcohol than leaner women (BMI < 25). Among postmenopausal women, the OR for weekly drinking of less than 25, 25–175, and 175 g or more for EC were 0.83 (95% CI, 0.46–1.52), 0.46 (95% CI, 0.21–1.02), and 0.72 (95% CI, 0.17–3.15), respectively, but the P-trend was marginally significant ($P = 0.069$). Generally, endometrial cancer risk was lowest among women with weekly consumption of 25–175 g.

Table 4 shows a stratified analysis according to self-reported reaction to alcohol. Flushing after drinking depends mainly on the activity of aldehyde dehydrogenase, particularly ALDH2, and might therefore reflect lower ALDH2 activity. Among women who did not experience flushing after drinking, an inverse association was seen between endometrial cancer risk and alcohol intake. The age-adjusted OR for weekly drinking of less than 25, 25–175, and 175 g or more for endometrial cancer were 0.51 (95% CI, 0.26–0.98), 0.24 (95% CI, 0.11–0.56), and 0.49 (95% CI, 0.14–1.69), respectively, and the P-trend was statistically significant ($P = 0.001$). By contrast, the protective

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer stratified according to weekly alcohol consumption and lifestyle factors

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Total (case/control)†	109/933	23/246	12/232	3/47	
OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.27)	0.44 (0.24–0.81)	0.54 (0.16–1.76)	0.006
Smoking					
Never (case/control)	98/829	18/213	5/157	1/16	
OR (95% CI)	1.00 (Reference)	0.70 (0.41–1.18)	0.26 (0.11–0.66)	0.51 (0.07–3.87)	0.002
Ever (case/cotrol)	11/98	4/33	7/75	2/31	
OR (95% CI)	1.00 (Reference)	1.25 (0.36–4.40)	0.89 (0.33–2.46)	0.63 (0.13–3.04)	0.586
Unknown (case/cotrol)	0/6	1/0	0/0	0/0	
Body mass index					
<25 kg/m² (case/control)	73/757	17/197	11/202	2/40	
OR (95% CI)	1.00 (Reference)	0.92 (0.53–1.61)	0.58 (0.30–1.12)	0.54 (0.13–2.31)	0.090
≥25 kg/m² (case/control)	32/168	6/49	1/30	1/7	
OR (95% CI)	1.00 (Reference)	0.55 (0.21–1.43)	0.15 (0.02–1.13)	0.48 (0.05–4.34)	0.035
Unknown (case/control)	4/8	0/0	0/0	0/0	
Regular exercise					
No (case/control)	36/257	7/40	2/63	1/22	
OR (95% CI)	1.00 (Reference)	1.27 (0.53–3.05)	0.23 (0.05–0.97)	0.34 (0.04–2.57)	0.047
Yes (case/control)	72/654	16/201	10/167	2/25	
OR (95% CI)	1.00 (Reference)	0.70 (0.40–1.24)	0.53 (0.27–1.05)	0.69 (0.16–3.00)	0.053
Unknown (case/control)	1/22	0/5	0/2	0/0	
Menstrual status					
Premenopausal (case/control)	35/280	9/99	5/98	1/23	
OR (95% CI)	1.00 (Reference)	0.72 (0.34–1.57)	0.41 (0.15–1.07)	0.35 (0.05–2.65)	0.038
Postmenopausal (case/control)	74/653	14/147	7/134	2/24	
OR (95% CI)	1.00 (Reference)	0.83 (0.46–1.52)	0.46 (0.21–1.02)	0.72 (0.17–3.15)	0.069
Age at menarche					
≤12 (case/control)	28/236	8/61	1/64	1/13	
OR (95% CI)	1.00 (Reference)	1.04 (0.45–2.40)	0.12 (0.02–0.92)	0.56 (0.07–4.49)	0.053
13–14 (case/control)	53/428	11/127	9/114	1/22	
OR (95% CI)	1.00 (Reference)	0.72 (0.36–1.42)	0.65 (0.31–1.37)	0.38 (0.05–2.90)	0.120
≥15 (case/control)	26/249	2/54	2/48	1/11	
OR (95% CI)	1.00 (Reference)	0.39 (0.09–1.73)	0.44 (0.10–1.91)	1.07 (0.13–8.88)	0.260
Unknown (case/control)	2/20	2/4	0/6	1/0	
Duration of menstruation					
≤32 years (case/control)	27/219	7/77	4/71	0/22	
OR (95% CI)	1.00 (Reference)	0.69 (0.28–1.67)	0.43 (0.15–1.29)	NE	0.029
33–36 years (case/control)	27/246	5/51	1/54	0/9	
OR (95% CI)	1.00 (Reference)	0.93 (0.34–2.55)	0.18 (0.02–1.35)	NE	0.063
37–39 years (case/control)	29/249	3/71	4/57	1/8	
OR (95% CI)	1.00 (Reference)	0.36 (0.11–1.23)	0.60 (0.20–1.78)	1.07 (0.13–8.88)	0.249
≥40 years (case/control)	23/189	6/43	3/43	2/7	
OR (95% CI)	1.00 (Reference)	1.13 (0.43–2.95)	0.56 (0.16–1.95)	2.23 (0.43–11.49)	0.932
Unknown (case/control)	3/30	2/4	0/7	0/1	
Parity					
0 (case/control)	30/115	6/36	4/42	1/10	
OR (95% CI)	1.00 (Reference)	0.63 (0.24–1.65)	0.36 (0.12–1.09)	0.38 (0.05–3.10)	0.046
1–2 (case/control)	58/599	15/147	6/129	2/25	
OR (95% CI)	1.00 (Reference)	1.12 (0.61–2.05)	0.50 (0.21–1.20)	0.90 (0.21–3.93)	0.271
≥3 (case/control)	21/213	2/61	1/59	0/12	
OR (95% CI)	1.00 (Reference)	0.37 (0.08–1.64)	0.19 (0.02–1.43)	NE	0.035
Unknown (case/control)	0/6	0/2	1/2	0/0	
Diabetes history					
No (case/control)	99/894	22/237	12/224	3/45	
OR (95% CI)	1.00 (Reference)	0.81 (0.50–132)	0.47 (0.25–0.87)	0.57 (0.17–1.89)	0.015
Yes (case/control)	10/39	1/9	0/8	0/2	
OR (95% CI)	1.00 (Reference)	0.48 (0.05–4.33)	NE	NE	0.212
Hypertension history					
No (case/control)	87/797	21/225	10/200	2/38	
OR (95% CI)	1.00 (Reference)	0.85 (0.51–1.40)	0.45 (0.23–0.89)	0.47 (0.11–2.00)	0.016
Yes (case/control)	22/136	2/21	2/32	1/9	
OR (95% CI)	1.00 (Reference)	0.54 (0.12–2.47)	0.36 (0.08–1.62)	0.64 (0.08–5.32)	0.178

doi: 10.1111/j.1349-7006.2008.00801.x

Table 3 (*Continued.*)

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Contraceptive usage history					
No (case/control)	101/871	23/231	12/216	1/43	
OR (95% CI)	1.00 (Reference)	0.85 (0.53–1.38)	0.47 (0.26–0.88)	0.20 (0.03–1.45)	0.005
Yes (case/control)	6/44	0/11	0/15	2/4	
OR (95% CI)	1.00 (Reference)	NE	NE	3.63 (0.53–24.92)	0.892
Unknown (case/control)	2/18	0/4	0/1	0/0	
Hormone replacement therapy history					
No (case/control)	101/860	18/227	10/212	2/40	
OR (95% CI)	1.00 (Reference)	0.66 (0.39–1.12)	0.39 (0.20–0.77)	0.41 (0.10–1.72)	0.002
Yes (case/control)	7/59	5/15	2/19	1/7	
OR (95% CI)	1.00 (Reference)	2.79 (0.78–10.05)	0.89 (0.17–4.64)	1.21 (0.13–11.31)	0.826
Unknown (case/control)	1/14	0/4	0/1	0/0	
Histological subtype					
Type I (case/control)	68/933	17/246	6/232	1/47	
OR (95% CI)	1.00 (Reference)	0.71 (0.51–1.57)	0.34 (0.14–0.79)	0.27 (0.04–1.97)	0.007
Type II (case/control)	41/933	6/246	6/246	2/47	
OR (95% CI)	1.00 (Reference)	0.60 (0.25–1.43)	0.63 (0.26–1.50)	1.09 (0.25–4.69)	0.323

†One case and 18 controls were excluded from analyses due to lack of information on alcohol drinking.
NE, not estimated because of no case in this category.

Table 4. Impact of alcohol consumption according to self-reported reaction to alcohol

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Total (case/control)†	109/933	23/246	12/232	3/47	
Age-adjusted OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.27)	0.44 (0.24–0.82)	0.54 (0.16–1.76)	0.006
Multivariate OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.28)	0.42 (0.23–0.79)	0.47 (0.14–1.58)	0.005
Flushing after drinking					
No (case/control)	44/292	13/157	7/175	3/36	
Age-adjusted OR (95% CI)	1.00 (Reference)	0.51 (0.26–0.98)	0.24 (0.11–0.56)	0.49 (0.14–1.69)	0.001
Multivariate OR (95% CI)	1.00 (Reference)	0.53 (0.27–1.05)	0.25 (0.11–0.59)	0.48 (0.14–1.67)	0.002
Yes (case/control)	61/574	9/86	5/55	0/10	
Age-adjusted OR (95% CI)	1.00 (Reference)	1.03 (0.49–2.15)	0.89 (0.34–2.30)	NE	0.560
Multivariate OR (95% CI)‡	1.00 (Reference)	1.07 (0.51–2.27)	0.97 (0.37–2.57)	NE	0.677
Unknown (case/control)	4/67	1/3	0/2	0/1	

†One case and 18 controls were excluded from analyzes due to lack of information on alcohol drinking.
‡Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, and hormone replacement therapy.
CI, confidence interval; NE, not estimated because of no case in this category; OR, odds ratio.

effect of alcohol was not observed among women who had flushing after drinking (age-adjusted *P*-trend = 0.560). The multivariate model again showed consistent results.

Discussion

In this study, we found that a small amount of alcohol consumption was protective against endometrial cancer among Japanese women. This association was consistently observed regardless of potential confounders. OR were lowest among those who consumed 25–175 g per week. In addition, the protective effect of alcohol drinking decreased among women who reported flushing after drinking.

Results to date regarding the relationship between alcohol intake and endometrial cancer risk are inconsistent. Although most previous studies have indicated a null association,[7–9,11,22–25] three have shown a protective effect of alcohol,[10,14,26] while three others have reported that alcohol intake was a risk factor of endometrial cancer.[12,13,27] Newcomb *et al.* suggested a significant inverse association in premenopausal women consuming one drink per day or more (RR = 0.20; 95% CI, 0.06–0.71)[10] while Swanson *et al.* showed an inverse association between moderate consumption and endometrial cancer risk among young women (<55 years), with relative risks for three levels of drinking (<1, 1–4, >4 drinks per week) from lowest to highest of 0.78, 0.64, and 0.41 compared to non-drinkers.[14] Webster *et al.* showed that non-drinkers aged 20–54 years had a higher relative risk (RR = 1.83; 95% CI, 1.11–3.01) than women who consumed an average of 150 g or more of alcohol per week.[26] These results may indicate that light alcohol consumption decreases endometrial cancer risk in younger women. In contrast, Setiawan *et al.* suggested that alcohol consumption equivalent to two or more drinks per day increased the risk of endometrial cancer in postmenopausal women.[12] The other two case-control studies showed similar positive associations between increased alcohol consumption and risk.[13,27]

Here, our study has added to the evidence for a protective effect of alcohol on endometrial cancer. The degree of consumption

may be an important consideration in determining the impact of alcohol. Average consumption in our study was very low compared with previous studies. Relatively high consumption (≥175 g/week) was seen in only three cases and 99 controls, who showed a protective effect compared with non-drinkers (multivariate OR = 0.47; 95% CI, 0.14–1.58). The provision of stable estimates for this subgroup is hampered by their small sample size.

One possible explanation for these results is that a small amount of drinking might be protective against cancer, as suggested in several prospective cohort studies.[28–32] The biological mechanism of this protective effect for cancer among light-moderate drinkers is not clear. Tsugane *et al.* considered the background characteristics of moderate drinkers to be healthier than those of either non-drinkers or heavy drinkers.[32] It has been reported that alcohol intake increases endogenous serum levels of estrogen in postmenopausal women,[5,6] but it is unclear whether this is due to either a decrease in metabolic clearance or an increase in production.[33] It has thus been hypothesized that alcohol drinking might lead to an increased risk of endometrial cancer risk due via the increased mitotic proliferation of endometrial cells, resulting in increased DNA replication errors and somatic mutations.[34] Our findings here contradict this hypothesized mechanism; nevertheless, we assume that the amount of drinking may differentiate the impact of alcohol on endometrial cancer risk, as stated above.

Of interest was the combined effect of the amount of consumption and physical reaction to alcohol.[19] Subjects who reported flushing did not show the protective effect observed in the non-flushing group. It has been suspected that the oxidative metabolite of ethanol, acetaldehyde, is carcinogenic for humans due to its binding to cellular proteins and DNA, thus leading to carcinogenesis.[35,36] Further, in individuals with ALDH2 encoded by *ALDH2* Glu/Lys, the blood acetaldehyde level after drinking is approximately six-fold that in individuals with active ALDH2.[37] Taking results from our previous study demonstrating sensitivity and specificity of self-reported flushing for ALDH2 genotype as 83.5% and 87.8%,[38] our findings may have resulted from a decrease in the protective effect of alcohol owing to exposure to high levels of acetaldehyde.

Several potential limitations of our study warrant consideration. First, because it was a hospital-based case-control study, the threat of inadequate comparability between cases and controls rested on whether the control population was the source population from which cases arose. In the ACCH, it is assumed that those who are diagnosed as not having cancer at a particular period of time will visit the ACCH in the event that they do develop malignant disease. Our source of controls is therefore assumed to be appropriate for the drawing of causal inferences. Second, as with other case-control studies, this study may have suffered from recall bias. Although the questionnaires, including that on alcohol intake, were completed before diagnosis in our hospital, some case patients referred to the hospital might have known their diagnosis. The fact that alcohol intake is not a well-accepted risk factor for endometrial cancer among the public might preclude this possibility of information bias regarding alcohol Third, our study had a modest sample size, and replication in other studies is required.

In conclusion, our case-control study suggested that alcohol drinking decreases the risk of endometrial cancer among Japanese women who consume small amounts. Further, a similar association was observed after stratification by potential confounders. However, this protective effect of alcohol was modified in those who experienced a flushed reaction to it after drinking. Further investigation of these findings is warranted.

Acknowledgments

The authors are grateful to the assistant staff at Division of Epidemiology and Prevention at Aichi Cancer Center Research Institute for their support for this study. This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture, and Technology of Japan and by a Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan.

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子宮体癌治療後の経過観察に関する考察

Follow-up after primary treatment for malignancy of uterine body

中西　透　丹羽慶光
Toru NAKANISHI　Yoshimitsu NIWA
水野美香　伊藤則雄
Mika MIZUNO　Norio ITO

愛知県がんセンター中央病院婦人科
Department of Gynecologic Oncology, Aichi Cancer Center Hospital

Key Words: *endometrial cancer, uterine sarcoma, follow-up*

[**概要**] 悪性腫瘍の取り扱いは、診断・治療・経過観察の3要素から成り立っている。治療・診断に関する研究や報告は多数あるものの、経過観察に関する報告は非常に少ない。2006年に発行された婦人科腫瘍学会ガイドラインでは1～3年目は1～3ヶ月毎、4～5年目では6ヶ月毎、6年目以降では1年毎の経過観察を推奨しており、2001年に発行されたAmerican Cancer Society's Clinical Oncologyでは1～3年目は3～6ヶ月毎、4年目以降は6ヶ月毎の経過観察を推奨している。これらの根拠は子宮体癌の経過観察に関する後方視的な報告で、主に再発例の初回治療後から再発までの期間と再発時の状況、その治療成績、経過観察時の検査などからこれら結果を示しているが、標準化や推奨するには十分な情報とは言えない。子宮体癌の経過観察期間を検討するために、1991～2000年の当センターでの治療症例296例を検討した。この中で子宮体癌再発を確認した63例を対象とし、再発までの期間と再発部位・予後を検討したので報告する。検討した63例の初回治療開始から再発までの期間の平均は26.4月（95% CI 18.3–30.9）、中央値は14.9月（95% CI 11.1–18.8）であった。再発時期を検討すると、初回治療開始から1年以内の再発が26例（41.3%）、1～2年の間が17例（27.0%）、2～3年の間が8例（12.7%）、3～5年が4例（6.3%）で、5年以降の再発が8例（12.7%）であった。中でも高分化型類内膜腺癌で5年以降の再発が36.4%（4/11）と比較的高率であった。再発後の生存率や生存期間は再発までの期間が長い程延長する傾向にあった。子宮体癌は治療開始後5年以降でも再発する症例が10%以上あり、長期間に渡る経過観察が必要であると考えられた。

[緒　言]

悪性腫瘍の取り扱いは、診断・治療とその後の経過観察の3要素から成り立っている。治療や診断に関する研究や報告は多数あるものの、経過観察に関する報告は非常に少ない。2006年に発行された婦人科腫瘍学会編集の子宮体癌治療ガイドラインでは1～3年目は1～3ヶ月毎、4～5年目では6ヶ月毎、6年目以降では1年毎の経過観察を推奨しており、2001年に発行されたAmerican Cancer Society's Clinical Oncologyでは1～3年目は3～6ヶ月毎、4年目以降は6ヶ月毎の経過観察を推奨している。これらの根拠は子宮体癌の経過観察に関する後方視的な報告[1)–13)]（表1）で、主に再発例の初回治療後から再発までの期間と再発時の状況、その治療成績、経過観察時の検査などからこれら結果を示しているが、標準化や推奨するには十分な情報とは言えない。

今回は子宮体癌の再発時期を検討し、その経過観察方針を検討したので報告する。

[方　法]

子宮体癌の経過観察期間を検討するために、1991～2000年の当センターでの治療症例296例の中で子宮体癌再発を確認した63例を対象とし、再発までの期間と再発部位・予後を検討し

表１：子宮体癌の経過観察に関する文献

著　者	年	症例数	再発例	期　間	＜１年	＜２年	＜３年	＜４年	＜５年	＞６年
Morice *et al.*	2001	351	27	42	3	4	6	12	12	12
Owen *et al.*	1996	97	17		3～4	6	12	12	12	12
Gadducci *et al.*	2000	133	24	53	3～4	3～4	6	6	6	12
Agboola *et al.*	1997	432	50	55	3	4	6	6	6	12
Gordon *et al.*	1997	111	17		3	6	12	12	12	なし
Ng *et al.*	1997	86	14	26	1～2	1～2	3	6	6	
Salvesen *et al.*	1997	249	47	108	3	6	12	12	12	12
Reddoch *et al.*	1995	354	44		3	4	4	6	6	なし
Berchuck *et al.*	1995	398	39		3	3	4	6	6	なし
Shumsky *et al.*	1994	317	53		3	4	4	6	6	6
Podczaski *et al.*	1992	300	47		3	3	3	6	6	12
MacDonald *et al.*	1990	101	19		3	3	3	6	6	なし

た。再発は臨床的・病理学的に診断し、生存率はKaplan-Meier法で推定、統計解析にはSPSS (ver.12) を使用した。

[成　績]

検討した63例の初回治療開始から再発までの期間の平均は26.4月 (95% CI 18.3−30.9)、中央値は14.9月 (95% CI 11.1−18.8) であった。再発時期を検討すると、初回治療開始から１年以内の再発が26例 (41.3%)、１～２年の間が17例 (27.0%)、２～３年の間が８例 (12.7%)、３～５年が４例 (6.3%) で、５年以降の再発が８例 (12.7%) であった (表２)。

進行期別に再発時期を検討すると、５年以降の再発がⅠ−Ⅱ期で11.1% (3/27)、Ⅲ期で25.0% (5/20) であったのに対し、Ⅳ期では認めなかった (表２)。組織型別の検討では、５年以降の再発が高分化型類内膜腺癌で36.4% (4/11) と比較的高率であったが、中分化型内膜腺癌で9.5% (2/21)、低分化型類内膜腺癌で5.9% (1/17)、その他腺癌で16.7% (1/6)、肉腫で０% (0/8) であった (表２)。

表２：子宮体癌の進行期・組織型別再発時期

			計	＜１年		１～２年		２～３年		３～５年		＞５年	
			n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
合　計			63	26	41.3	17	27.0	8	12.7	4	6.3	8	12.7
進行期	Ⅰ−Ⅱ期		27	8	29.6	9	33.3	4	14.8	3	11.1	3	11.1
	Ⅲ期		20	7	35.0	4	20.0	4	20.0	0	0.0	5	25.0
	Ⅳ期		16	11	68.8	4	25.0	0	0.0	1	6.3	0	0.0
組織型	類内膜	高分化	11	2	18.2	1	9.1	2	18.2	2	18.2	4	36.4
		中分化	21	8	38.1	6	28.6	3	14.3	2	9.5	2	9.5
		低分化	17	9	52.9	6	35.3	1	5.9	0	0.0	1	5.9
	他腺癌		6	3	50.0	1	16.7	1	16.7	0	0.0	1	16.7
	肉　腫		8	4	50.0	3	37.5	1	12.5	0	0.0	0	0.0

(1991～2000年　愛知県がんセンター中央病院婦人科部)

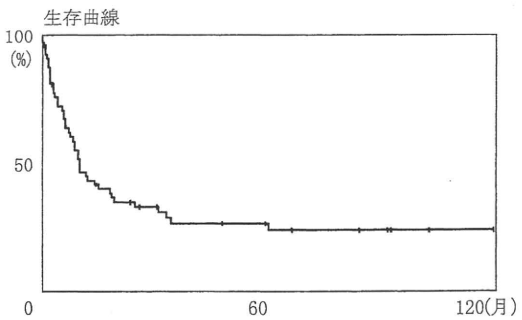
表３：子宮体癌の部位別再発時期

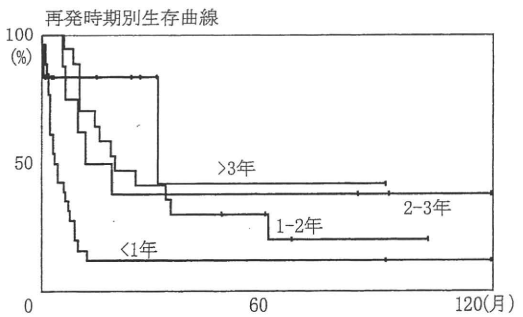
	計	＜１年		１～２年		２～３年		３～５年		＞５年	
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
合　　計	63	26	41.3	17	27.0	8	12.7	4	6.3	8	12.7
脳	2	2	100.0	0	0.0	0	0.0	0	0.0	0	0.0
肺	18	9	50.0	4	22.2	1	5.6	1	5.6	3	16.7
肝	5	3	60.0	2	40.0	0	0.0	0	0.0	0	0.0
皮　　膚	3	0	0.0	3	100.0	0	0.0	0	0.0	0	0.0
骨	6	4	66.7	1	16.7	0	0.0	0	0.0	1	16.7
腹　腔　内	14	7	50.0	3	21.4	2	14.3	1	7.1	1	7.1
骨　盤　内	17	6	35.3	5	29.4	2	11.8	1	5.9	3	17.6
膣・膣　断　端	7	2	28.6	3	42.9	1	14.3	1	14.3	0	0.0
頚・縦隔リンパ節	5	2	40.0	0	0.0	2	40.0	0	0.0	1	20.0
傍大動脈リンパ節	11	5	45.5	1	9.1	2	18.2	0	0.0	3	27.3

（1991～2000年　愛知県がんセンター中央病院婦人科部）

部位別に再発時期を検討したが、５年以降の再発部位として頻度が高いのは傍大動脈リンパ節27.3%（3/11）、頚・縦隔リンパ節20.0%（1/5）、骨盤内17.6%（3/17）、肺16.7%（3/18）、骨16.7%（1/6）であった（表３）。

再発症例全体の３年生存率は25.9%で、再発時期別に検討すると、初回治療開始から１年以内の再発で11.5%、１～２年の間で29.4%、２～３年の間で37.5%、５年以降で41.7%であった（図１）。また全体の再発後生存期間の中央値は10.6月（95%信頼区間7.1−14.1月）で、再発時期別に検討すると、初回治療開始から１年以内の再発で中央値が4.0月（95%信頼区間2.4−5.7月）、１～２年の間で19.8月（95%信頼区間7.0−32.7月）、２～３年の間で12.1月（95%信頼区間0.0−24.5月）、５年以降で31.5月（95%信頼区間0.0−74.6月）と、再発までの期間が長い程生存率や生存期間が長い傾向にあった。





		生存率				生存期間		
再発時期	症例数	1年	2年	3年	5年	中央値	95%信頼区間	p
全体	63	46.6%	34.2%	25.9%	25.9%	10.6月	7.1-14.1月	
<1年	26	15.4%	11.5%	11.5%	11.5%	4.0月	2.4-5.7月	<0.001
1-2年	17	70.6%	47.1%	29.4%	29.4%	19.8月	7.0-32.7月	
2-3年	8	62.5%	37.5%	37.5%	37.5%	12.1月	0.0-24.5月	
>3年	12	83.3%	83.3%	41.7%	41.7%	31.5月	0.0-74.6月	

（1991−2000年　愛知県がんセンター病院婦人科統計）

図１：子宮体癌の再発後治療成績