子宮体癌治療のCONTROVERSY

9．化学療法の適応と限界
―進行・再発体癌に対する治療戦略

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Key Words/子宮体癌，化学療法

要旨

子宮体癌化学療法は，単剤phase Ⅱ studyの結果からadriamycinを中心としたregimenの有効性について検討が行われてきたが，近年，taxanesの出現によってより効果的な新規regimenへの移行が期待されている．また，体癌に対する化学療法の有効性についても放射線療法との比較からのphase Ⅲ studyによる検証も進行しており，子宮体癌化学療法には新たな展開と進歩が認められつつある．そこで，これまでの臨床試験の検討から体癌化学療法の現況と問題点ならびに将来的展望について解説する．

はじめに

子宮体癌は，子宮頸癌あるいは卵巣癌などの他の婦人科癌と比較し，一般に予後良好とされるが，近年，全子宮癌に占める体癌比の著明な増加傾向が報告されており，今後，体癌の長期予後改善のための標準的治療法の確立が重要な課題となるものと考えられる．本邦における体癌への治療対応は手術術式や後療法を含めて施設によって異なった対応がなされているのが現状であり，体癌に対する化学療法の適応基準や治療regimenの選択についても，統一された治療指針は確立されていない．とくに体癌化学療法のregimenについては，過去にいくつかのrandomized phase Ⅲ trialが行われてきたものの，多くの報告はcase reportあるいはphase Ⅱ studyによる検証に留まっており，現在のところ体癌においては卵巣癌で行われてきた大規模phase Ⅲ trialの集積に基づいた，より効果的な化学療法regimenへの変遷には至っていない．したがって，体癌化学療法は，将来的新規薬剤を用いた新たなregimenへの発展の可能性を含む興味深い分野と言える．今後，共に体癌化学療法に関する臨床的検証が進行するものと考えられるが，これまでのclinical trialの結果から考えられる現時点での臨床的問題点は，以下の2点に集約される．すなわち，放射線治療

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との有効性の比較に基づいた化学療法の有効性の検証，ならびに従来体癌治療の key drug として用いられてきた adriamycin 併用の regimen から，卵巣癌を中心に有効性の証明されている taxanes を用いた新規 regimen 移行への可能性の検証である．そこで，本稿においては体癌化学療法の現況と問題点および今後の方向性について，近年の国内外における clinical trial の動向をもとに解説を試みたい．

体癌に対する化学療法の有効性の検証

これまでの進行体癌に対する化学療法の有効性の検証は，phase Ⅱ study による検討が中心に行われてきたため，とくに化学療法と共に体癌に効果的とされる放射線治療を対照とした有効性の比較は行われておらず，体癌治療における化学療法の優位性については不明であった．しかし，米国 Gynecologic Oncology Group (GOG) においては，1992年から stage Ⅲ，Ⅳ進行体癌を対象とした放射線療法 (whole abdominal irradiation;WAI) と化学療法 (doxorubicin + cisplatin;AP) の randomized comparative phase Ⅲ study (GOG 122，図1) が activate され，進行体癌に対する治療法の選択と有効性の検証が行われてきた．本試験は2000年に症例登録が終了し，現在解析が進んでおり，最終結果の論文報告は未だなされてはいないが，2003年の American Society of Clinical Oncology (ASCO) annual meeting において quality of life の評価を中心とした中間解析結果が報告された．中間解析報告によると，stage Ⅲ，Ⅳの進行体癌治療では現時点において AP arm が progression free survival，overall survival のいずれにおいても WAI arm にまさるとする興味深い結果が示され，体癌に対する化学療法の優位性が放射線治療との比較からはじめて証明され，注目を浴びている．現在 GOG では，毒性軽減による認容性向上を目指した新規 regimen 設定の検討を行っている模様であるが，今回の protocol 122 は進行体癌治療における化学療法の有用性を randomized phase Ⅲ study によって証明された有意義な臨床試験であり，体癌に対する将来的な化学療法の展開のための根拠を示す有意義な解析結果として最終報告が待たれている．

体癌に対する化学療法適応の問題点

化学療法は進行体癌の予後改善への寄与が期待される有用な治療法ではあるが，骨盤・傍大

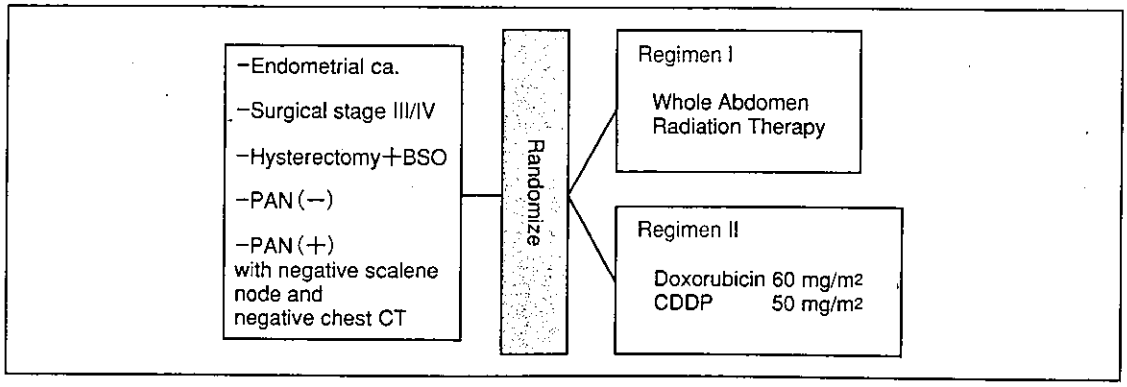

図1 GOG122

動脈リンパ節転移や深部筋層浸潤，あるいは腹膜細胞診陽性など，術後再発に関するhigh-risk例の選択条件と術後補助療法の要否については未だ議論の余地が残されている．通常，high-risk体癌とは，FIGO surgical stagingに反映される進行因子と組織学的分化度や脈管侵襲陽性などの予後不良因子を有する例を意味し，これらの条件を満たす例は一般的に再発予防を目的とした術後補助療法が施行されている．High-risk規定因子のなかで腹膜細胞診は，FIGO staging criteriaにおいてもextra uterine spreadの判定条件とされ，現在も腹膜細胞診陽性例は他の進行因子の有無にかかわらず単独でstage Ⅲと診断されている．しかし，病変が体部に限局した早期体癌においても腹膜細胞診をextra uterine spreadと判定し，high-risk体癌として術後補助療法を施行すべきか否かについては不明である．文献上も早期体癌における腹膜細胞診を再発危険因子であるとの報告[2]，あるいは再発危険因子としての有用性を認めない[3]とする異なった理解がなされており，早期体癌における腹膜細胞診の意義については未だ意見の一致をみていない．近年は病変が体部に限局する早期体癌に対しては放射線および抗癌剤を用いた術後補助療法の有効性を認めないとする報告[4]が主流を占めてきており，最終的にはcomparative randomize studyによる検証が必要ではあるが，今後，腹膜細胞診所見以外の再発危険因子を認めないstage Ⅰ体癌については，腹膜細胞診の結果によらず化学療法などの術後補助療法は省略されていく方向にあるものと考えられる．化学療法は進行癌の予後改善に寄与する有効な治療法ではあるが，有害事象を有する治療法であることから常に治療の適応にあたっては患者benefitが考慮されねばならず，婦人科癌において化学療法が標準的治療とされている卵巣癌についても，National Comprehensive Cancer Network（NCCN）guidelineでは明細胞腺癌を除くstage Ⅰの高分化型上皮性卵巣癌に対する術後化学療法は省略可能であることがすでに示されている．したがって，今後，進行・再発体癌に対しても，より効果的なregimenの検討と共に，これまでのevidenceの再検討から患者に対するbenefitが考慮された化学療法適応のための治療guidelineの作製が必要になるであろう．

体癌化学療法regimenの変遷と方向性

体癌化学療法におけるclinical trialは，前述のようにphase Ⅱ studyが多い．これまでの体癌化学療法は，過去のphase Ⅱ studyの結果からadriamycin（doxorubicine）が単剤で26%の奏効率が認められたため，adriamycinがkey drugとして用いられてきた．併用化学療法のphase Ⅱ studyにおいても，adriamycin（ADM）を用いたCAP（CPA＋ADM＋CDDP），CA（CPA＋ADM）あるいはAP（ADM＋CDDP）などのregimenの有効性の検討が中心として行われてきており，CAP療法で31～56%，CA療法で31～46%，AP療法で33～81%の奏効率が報告されている．しかし，ADM単剤とADM併用化学療法の有効性の比較が行われたADM vs CA[5]およびADM vs AP[6]のrandomized comparative phase Ⅲ trialの結果では，併用化学療法の明確な優位性は証明されず，新規薬剤を用いたより効果的なregimenの設定が求められている．近年にわたって体癌化学療法の新たなkey drug設定のためのphase Ⅱ trialは経口薬を含めた種々の薬剤について検証されているが，その奏効率はvincristine 18%，iphosphamide 15%，leuprolide 0%（stable disease；SD:32%），oral etoposide 14%，tamoxifen 10%，danazol 0%（SD:27%），liposomal doxorubicin

9.5%と報告され，単剤でADMを明らかに上回る有効性が得られていないことから，従来のADM baseの併用化学療法からの効果的な新規regimenへの変遷はなされていないのが現状である．しかし，近年，婦人科癌においてとくに卵巣癌にその有効性が確認されているtaxanesが出現し，体癌化学療法に対しても有効性の期待できる新規治療薬剤として治療応用の期待が高まっている．これまでに報告されているpaclitaxelの単剤phase Ⅱ studyの奏効率は35.7%[7]，37%[8]であり，一方，docetaxelについては現時点ではcase report[9]に留まるものの，両薬剤ともにいずれも体癌に対してADMを上回る有効性が期待されている．近年報告されたAPとAT（adriamycin＋paclitaxel）のrandomized phase Ⅲ study（GOG 163）[10]では，ATの優位性が証明されなかったものの，GOG 163はpaclitaxelがCDDPに比較して遜色のない奏効性を示した結果とも考えられ，必然的に現在は卵巣癌化学療法に標準的治療として用いられているtaxanes/platinum併用化学療法の有効性が期待されることとなった．GOGではprotocol 163の解析結果を受けて，進行・再発体癌に対するadriamycin/paclitaxel/CDDP（TAP）の有効性の検証（AP versus TAP，GOG 177，図2）が開始され，さらに，The European Organization of Research and Treatment of Cancer（EORTC）においても，同様に進行・再発体癌に対するTAPの有効性の検証（EORTC 55984）が始まっている．現時点におけるGOG 177の中間解析結果では，TAPがAPに比較して奏効率・1年生存率のいずれにおいてもまさるとする報告がなされているが[11]，同時にTAPは毒性においてもAPを上回る結果が示されたことから実地臨床応用を疑問視する意見もある．したがって，現在は治療認容性の考慮から，よりsimplifyされたtaxanes/platinumの体癌に対する有効性の検証が望まれている．

本邦においても体癌治療へのtaxanesの適応を望む声が多く，すでに保険適用獲得を目的としたpaclitaxelおよびdocetaxelの単剤phase Ⅱ studyが開始されており，すでに症例登録が終了し，現在有効性の解析が行われているが，早晩両薬剤ともに体癌に対する適応承認が得られる見込みである．さらに，体癌に対するtaxanes/platinum併用化学療法の有効性については，婦人科悪性腫瘍化学療法研究機構（Japan Gynecologic Oncology Group;JGOG）においてtaxanes（paclitaxel，docetaxel）/platinum（CBDCA，CDDP）を用いた全国レベルの新規trialによる検証が計画されており，体癌化学療法におけるtaxenes/platinumの有効性が本邦から発信される可能性が期待されている．すなわち，今後の体癌化学療法はpaclitaxel/platinum，

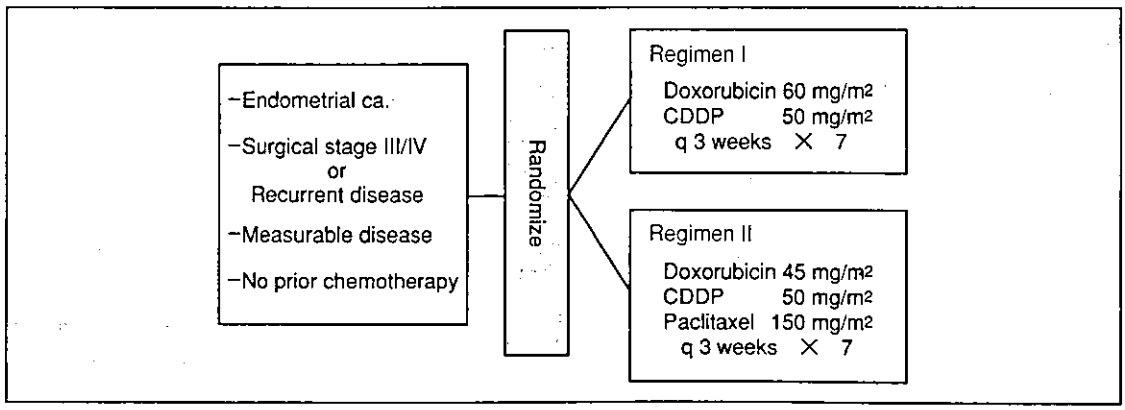

図2 GOG177

docetaxel/platinum あるいは paclitaxel/platinum/ADM といった taxanes を key drug とした新規 regimen の検討が中心に進行していくものと推察される．

体癌化学療法の将来的展望

体癌に対する化学療法の有効性の期待は，体癌の大部分の histologic subtype が卵巣癌において化学療法感受性が高いとされている類内膜腺癌であることも一因と言える．したがって，体癌は化学療法感受性腫瘍として卵巣癌と同様に randomized phase Ⅲ trial を用いた検証に基づく，より効果的な regimen への変遷がなされるべきである．しかし，本邦におけるこれまでの体癌に対する regimen の選択は，単に卵巣癌における regimen の変遷に追従してきた感が否めず，体癌における regimen の変遷が果たして有効であったか否かについては不明である．ちなみに，卵巣癌治療に用いられてきた各種 regimen の体癌に対する奏効性についてみると，CAP（cyclophosphamide ＋ adriamycin ＋ CDDP）[12] では，overall response rate（OR）47.1%，complete response rate（CR）17.6%であり，TP（paclitaxel ＋ CDDP）[13] では OR 67%，CR 29%，さらに TJ（paclitaxel ＋ CBDCA）[14] では OR 56%と報告されており，phase Ⅱ study の結果であるため，詳細な比較は困難ではあるが，化学療法感受性とされる類内膜腺癌であっても体癌に対する化学療法の奏効性は卵巣癌に比較するとやや不良である印象を受ける．今後の体癌に対する taxanes ＋ platinum の phase Ⅱ study および taxanes ＋ platinum と adriamycin-base chemotherapy との comparative study の結果が待たれるが，少なくとも体癌に対しては卵巣癌の治療 regimen によって同等の成績が得られるとは言いがたい側面もあり，体癌に対しては卵巣癌とは異なる独自の regimen の設定も将来的視野に入れねばならないものと考えられる．また，これまで放射線療法と化学療法はいずれもが進行・再発体癌の治療に選択されてきたにもかかわらず，近年，頸癌において有効性が報告されている platinum concurrent chemoradiation（CRT）の有効性に関する検証も未だ行われてはおらず，今後 neoadjuvant setting を含めて体癌に対する CRT の有効性の検証についてもより有効な併用薬剤の検討とともに行われていく必要があろう．

おわりに

近年の婦人科癌化学療法はめざましい進歩を遂げており，clinical trial の結果から数多くの精度の高い新たな evidence が報告されてきている．しかし，本邦においてはこれまで欧米で行われた clinical trial の結果に追従して化学療法の変遷がなされてきた事実は否めず，結果的に有効性が証明されても認容性から本邦女性への適応が困難な regimen も多い．体癌はより有効な化学療法 regimen への変遷が期待される癌腫であるため，今後，各施設の協力のもと体癌に対する phase study の症例蓄積と有効性の期待される新規 protocol の検証を継続し，本邦から体癌化学療法の新たな evidence が発信されることを願う．

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The Effect of Granisetron on In Vitro Metabolism of Paclitaxel and Docetaxel

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PURPOSE

Paclitaxel and docetaxel are effective anticancer agents; however, these agents can be associated with the debilitating side effects of nausea and vomiting, thereby necessitating the administration of concomitant antiemetic agents. This increases the potential for drug–drug interactions through inhibition or induction of the cytochrome P450 (CYP) enzymes. The 5-HT_3-receptor antagonists are currently regarded as the antiemetic 'gold standard' and this study was undertaken to investigate the effects of granisetron on the metabolism of paclitaxel and docetaxel in human liver microsomal preparations in vitro.

METHODS

Paclitaxel, 5 nM, and docetaxel, 1.25 nM, were incubated in the presence of granisetron, 0, 10, 100, and 1000 pM, in human liver microsomal preparations (500 μg). The levels of unchanged paclitaxel and docetaxel in the incubation mixture were determined by high-performance liquid chromatography. Ketoconazole, 10 nM, a potent inhibitor of CYP3A metabolism, served as a positive control.

RESULTS

In the absence of granisetron, unchanged paclitaxel and docetaxel levels measured were 27.2 ± 2.8% and 44.3 ± 4.0% of control, respectively. Ketoconazole prevented the breakdown of both paclitaxel and docetaxel, to the degree that no unchanged paclitaxel or docetaxel was detected in the incubation mixture. Granisetron had no effect on the rate of reduction of either paclitaxel or docetaxel; unchanged paclitaxel and docetaxel decreased to 25.0 ± 1.5%, 26.4 ± 1.0%, and 27.6 ± 6.4%, and 44.2 ± 1.5%, 41.2 ± 4.1%, and 43.1 ± 0.5%, respectively.

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DISCUSSION

The results from this study suggest that granisetron neither inhibits nor induces the enzymes involved in the metabolism of paclitaxel or docetaxel. Thus, granisetron can be used safely as a supportive care agent to treat paclitaxel or docetaxel chemotherapy-induced nausea and vomiting with minimal risk of drug–drug interactions. *(Cancer J 2003;9:67–70)*

KEY WORDS

Granisetron, paclitaxel, docetaxel, ketoconazole, CYP3A, metabolism, human liver microsomes

Paclitaxel and docetaxel are effective anticancer agents when administered in combination with platinum compounds for the treatment of ovarian,[1-3] lung,[4] and breast[5] cancer. Unfortunately, these chemotherapy regimens are still associated with debilitating nausea and vomiting side effects of therapy. Since the introduction of the 5-HT_3-receptor antagonist antiemetic agents, however, more patients are able to achieve good control of emesis related to chemotherapy regimens.

Granisetron has been used successfully in clinical trials to control nausea and vomiting in patients undergoing moderately or severely emetogenic chemotherapy,[6,7] and is a potent and selective antagonist at the 5-HT_3-receptor.[8] However, concomitant administration of chemotherapy agents with supportive care agents increases the likelihood for in vivo drug–drug interactions via the cytochrome P450 (CYP) enzyme system.[9] Paclitaxel is metabolized primarily by hydroxylation via CYP2C8 to 6α-hydroxypaclitaxel and CYP3A4 to 3′-(p-hydroxyphenyl) paclitaxel,[10] and docetaxel is hydroxylated by CYP3A4 to hydroxydocetaxel.[11] Granisetron metabolism is also mediated via the CYP3A subfamily, where 7-hydroxygranisetron is the major metabolite produced with a small degree of metabolism to 9′-desmethylgranisetron.[12] Metabolism of granisetron via the CYP3A isoenzymes thereby increases the potential for an interaction between itself and either paclitaxel or docetaxel.

A previous study demonstrated that granisetron does not inhibit the activities of CYP1A2, CYP2A6, CYP2B6, CYP2C9/8, CYP2C19, CYP2D6, CYP2E1, or CYP3A at

concentrations up to 250 nM/mL[12]; however, the current study was undertaken to investigate the effects of granisetron specifically on the in vitro metabolism of paclitaxel and docetaxel in human liver microsomes.

METHODS

Chemicals

Granisetron was obtained from Nippon Roche K.K. (Tokyo, Japan). Paclitaxel was obtained from Sigma Chemical Co. (St. Louis, MO, USA), docetaxel was from Aventis Pharma Ltd. (Tokyo, Japan), and ketoconazole was from Biomol Research Laboratories, Inc. (Plymouth Meeting, PA, USA). All other reagents were purchased from commercial sources and were of the highest grade.

Human Liver Microsomes

Three batches of pooled human liver microsomes (International Institute for the Advancement of Medicine: IIAM, Scranton, PA, USA), collected from five men and five women donors, were used. They were preserved at –80°C until the time of use.

Analytical Procedures

Human liver microsomes, 500 μg, were incubated at 37°C in the presence of 0.1 M potassium phosphate buffer (pH 7.4) and 0.1 mM NADPH in a final volume of 0.5 mL. Preliminary experiments determined the incubation time and the concentration of paclitaxel and docitaxel. Based on the findings of these studies, granisetron (final concentration 10, 100, and 1000 pM) was incubated with the human liver microsome preparation for 60 minutes in combination with either paclitaxel, 5 nM (10 nM/mL), or docetaxel, 1.25 nM (2.5 nM/mL). The levels of unchanged paclitaxel and docetaxel in the incubation mixtures were determined by high-performance liquid chromatography (HPLC). Ketoconazole, 10 nM, a potent inhibitor of CYP3A4, served as a positive control.

HPLC Conditions

HPLC was performed according to the method of Sparreboom et al.[13] The LC-10A System (Shimadzu Co., Tokyo, Japan) was used as the determination device with an Inertsil® separation column (150 × 4.6 mm ID, 5 μM, GL Sciences Inc., Tokyo, Japan) with a guard column (Guard Pal Inserts Nova Pak C18, Waters Co., Milford, CT, USA). The flow rate of the mobile phase was set at 1.0 mL/min, column temperature was 60°C and the wavelength for UV detection was 230 nM. Retention times for unchanged paclitaxel and docetaxel in the human liver microsome preparations were 7.5 and 8.8 minutes, respectively (Fig. 1), and the concentration of each taxane was calculated using the area under the peak. The limit of detection for paclitaxel and docetaxel was 0.3 nM/mL.

Statistical Analysis

The data were analyzed with one-way analysis of variance (ANOVA), followed by Bonferroni's multiple *t*-test. A value of $P < 0.05$ was deemed significant.

RESULTS

Preliminary experiments established optimum conditions of 60-minute incubation time with paclitaxel and docetaxel concentrations of 5 nM and 1.25 nM, respectively (Fig. 2). In the presence of NADPH, ketoconazole (10 nM), inhibited CYP3A4 metabolism and prevented the breakdown of both paclitaxel and docetaxel in the human microsomal preparations (Fig. 3). In the absence of granisetron, the amount of unchanged paclitaxel (5 nM) and docetaxel (1.25 nM) in the incubation mixture decreased by 27.2 ± 2.8% and 44.3 ± 4.0%, respectively (Fig. 3). Granisetron, 10, 100, and 1000 pM, had no effect on the rate of reduction of either paclitaxel or docitaxel ($P > 0.05$; Fig. 3).

DISCUSSION

Metabolism of granisetron is primarily via the CYP3A isoenzymes and this study confirms that granisetron

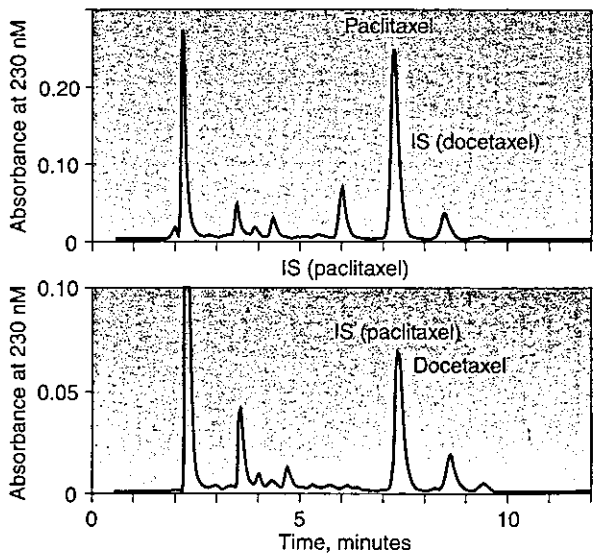

FIGURE 1 Typical HPLC chromatograms of paclitaxel (upper panel) and docetaxel (lower panel) separated from human liver microsomal preparations. Paclitaxel and docetaxel were used as internal standards (IS) for the determination of docetaxel and paclitaxel, respectively.

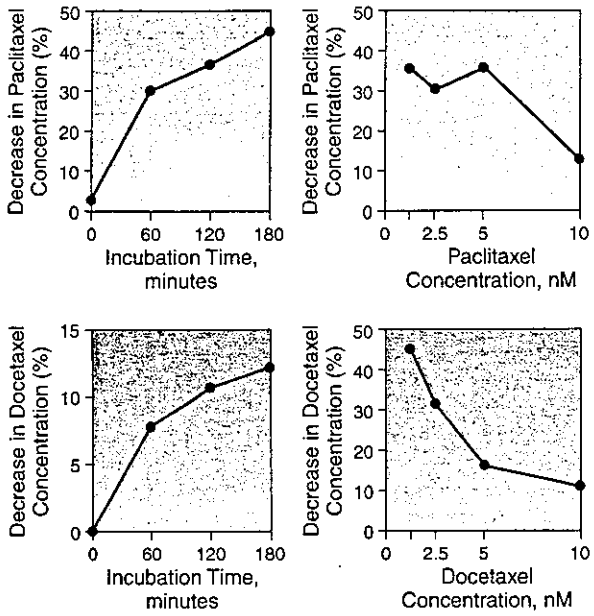

FIGURE 2 Effect of incubation time (60, 120, and 180 minutes) on paclitaxel and docetaxel (5 nM) metabolism (left panel) and concentration of paclitaxel and docetaxel (final concentration: 1.25, 2.5, 5, 10 nM) (right panel) in human liver microsomes.

neither inhibits nor induces the enzymes involved in the metabolism of paclitaxel or docetaxel in an in vitro human liver microsomal preparation. These results are in agreement with Bloomer et al, who demonstrated that granisetron does not inhibit the activity of a number of CYP isoenzymes at concentrations between 2 and 5 μM.[12] In this study, granisetron did not interact with the breakdown of these taxanes, even at concentrations up to 30-fold higher than the reported maximum plasma concentration (C_{max}) in vivo.[14] The concentration of paclitaxel and docetaxel investigated in this study were similar to the C_{max} reported for intravenous administration of paclitaxel, 210 mg/m², and docetaxel, 60 mg/m² (10 nM/mL vs. 7.9 nM/mL, and 2.5 nM/mL vs. 1.9 nM/mL for paclitaxel and docetaxel, respectively).[15,16]

Ketoconazole is a selective and potent inhibitor of CYP3A isoenzymes, with a K_i less than 1 μM,[17] and in the present study, ketoconazole, 10 nM, potently inhibited the metabolism of both paclitaxel and docetaxel. Both docetaxel and paclitaxel are metabolized by CYP3A4; however, paclitaxel is partly metabolized by CYP2C8. Nevertheless, hydroxylation of paclitaxel was completely inhibited by ketoconazole. However, at the concentration used in this study, ketoconazole can also inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP4 isoenzymes.[17]

It has been estimated that cancer patients receive up to 10 different medications during an average hospital stay.[9] It is, therefore, imperative that drug–drug interactions are minimized, and that potential interactions are identified and prevented. The 5-HT_3-receptor antagonists, regarded as the antiemetic "gold standard," are prescribed routinely for patients undergoing moderately or highly emetogenic chemotherapy,[7] and currently available agents include granisetron, dolasetron, ondansetron, and tropisetron. Granisetron is metabolized exclusively by the CYP3A isoenzymes, limiting its potential for drug interactions. This is in contrast to ondansetron, which—in addition to the CYP3A isoenzyme—is metabolized by CYP2D6, CYP1A2, and to a small extent by CYP1A1.[9] Therefore, the possibility exists for multiple drug–drug interactions between ondansetron and medications that are also metabolized by these isoenzymes. Dolasetron and tropisetron, while being metabolized by members of the CYP3A group, are also broken down by CYP2D6.[9]

Because the taxanes paclitaxel and docetaxel are predominantly metabolized by CYP3A4, and these agents can cause debilitating side effects of nausea and vomiting, consideration must be given to the choice of antiemetic agent offered to patients. The results from this

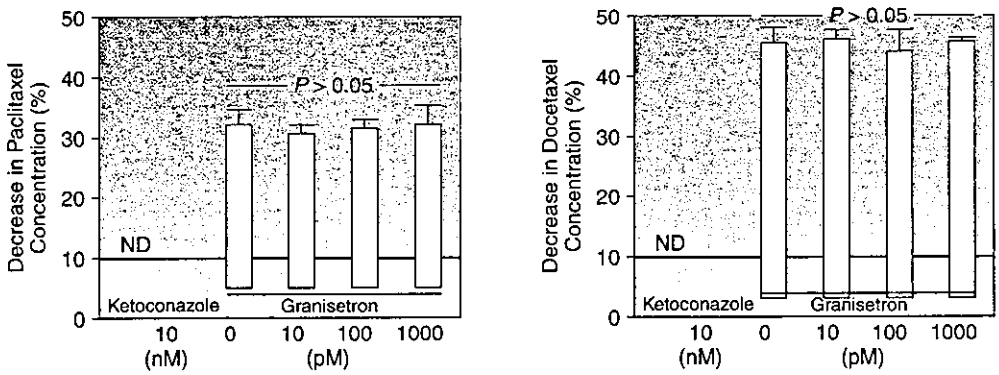

FIGURE 3 Effect of granisetron on the metabolism of paclitaxel, 5 nM (left panel) and docetaxel, 1.25 nM (right panel) in human liver microsomes. Data are the mean ± SD of three determinations. ND, not detected; $P > 0.05$ versus no granisetron.

study suggest that granisetron can be used safely as a supportive care agent to treat paclitaxel or docetaxel chemotherapy-induced nausea and vomiting without the risk of drug–drug interactions.

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子宮癌

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abstract

子宮頸癌，子宮体癌においてはsentinel lymph node navigation surgeryが適応となるのかその妥当性についてようやく検討されはじめている段階である．当科での検討やこれまでの報告からは子宮頸癌においては今後検討すべき問題は残ってはいるものの，臨床応用に向けて妥当な結果が得られつつある．一方，子宮体癌においてはトレーサの投与法すら統一した見解は得られていない．当科においては子宮鏡下に^{99m}Tc-phytateを投与する方法を施行し，術前のシンチグラフィと術中のγプローブも併用することにより良好なセンチネルリンパ節の検出がなされている．今後，これらの結果を踏まえ子宮癌でのセンチネルリンパ節の概念の妥当性がさらに検証されることにより，必要最小限の個別化されたリンパ節の生検が可能になり，新たな低侵襲手術が実現されることが期待される．

I はじめに

婦人科領域におけるsentinel lymph node navigation surgeryは，現在外陰癌においては臨床試験が行われてはいる．しかし子宮癌に関しては，限られた施設においてその妥当性が検証されつつあるというのが現状である．そこで本稿では子宮頸癌，子宮体癌における検証の状況を文献レビューするとともに，われわれのデータも交えて解説する．

II 子宮頸癌

1）適応症例

sentinel lymph node navigation surgeryを応用するのは系統的リンパ節郭清を施行する症例になるので，子宮頸癌の場合にはⅠa2期以上であることが前提条件となる．ただし，子宮頸癌の場合には，トレーサを経腟的に子宮頸部病変に注入し，注入した局所からのリンパの流れを追うことになるため，病変が旁子宮結合織にまで及ぶようなⅡb期以上の症例に対してはあまり意味をなさないと考えられる．原発巣の腫瘍径の大きさからはこれまでの限られた報告では同定率に差はないとするもの[1), 2)]と4cmを超える症例では同定率が低下するとするもの[3)]がある．当科での検討では腫瘍径が4cmを超えるⅠb2期，Ⅱa期の3例でセンチネルリンパ節が同定できなかったがこれらの症例は臨床的に腫大したリンパ節を認め，また実際に転移を認めた症例でもあり，転移によるリンパ流の変化やトレーサの取り込みの減少もかかわっている可能性があり今後の検討が必要である．

2）方法

同定法としては他の癌腫と同様に色素法[1), 3)]やラジオアイソトープ（RI）法との併用法[2), 4)]の報

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	症例数	SN同定率(%)	感度(%)	特異度(%)	SN平均個数
Malur, et al	20	90	100	100	1.3
Levenback, et al	39	100	87.5	97	3.4
東北大学	15	87	100	100	2.3

表1
子宮頸癌における
センチネルリンパ節の同定

告がある．色素法で用いられるものはisosulphan blueとpatent blue violetであり，われわれはpatent blue violetを用いている．一方，RI法では^{99m}Tc-colloidal albuminやfiltered ^{99m}Tc-sulfur colloidなどが用いられているが，RI法の場合の最適粒子径についてはまだ確立されていない．例えばわれわれが^{99m}Tc-phytateを使用して同定したセンチネルリンパ節はすべて骨盤内であったが，他の施設では別の粒子径のものを用いることにより傍大動脈領域に約10%の割合でセンチネルリンパ節を同定したと報告[2]している．子宮頸癌の部位別のリンパ節転移頻度からは傍大動脈リンパ節は1次リンパ節とは考えにくいが，用いた粒子径が十分に大きくない場合には2次リンパ節である傍大動脈節に比較的早期に流入してしまい，センチネルリンパ節として同定される可能性があると思われる．

注入方法に関しては各報告とも比較的一致している．RI法の場合には手術前日に経腟的に子宮頸部の12時，3時，6時，9時方向の4カ所に1～2mLを投与する．色素法の場合には術中に同部位に2～4mLを投与する．

われわれは実際には両法を併用している．というのは，子宮頸癌の手術の場合，後腹膜の展開をしないとリンパ節の検索ができず，またその展開によってもリンパ流が影響される可能性があるために，流れの速い色素法のみでの正確なセンチネルリンパ節の同定は難しいと考えるからである．すなわち色素法は可視できることからRI法のγプローブによるnavigationの補助として有用と考えている．

一方，RI法では，RI注入後数十分でセンチネルリンパ節に移行し，翌日のリンパシンチグラフィでもそのまま同部位にとどまっていること，少数例ではあるが24時間後になってはじめてリンパシンチグラフィ上での集積が確認されることがあること，などを経験している．このようなことからわれわれは投与時のシンチグラフィと手術直前のシンチグラフィをルーチンに行っている．さらに術中にはγプローブによるセンチネルリンパ節の検索を行う．実際の手技上，シンチグラフィによるマッピングを術前に行っておくことはセンチネルリンパ節が表在性のリンパ節のみに限局していない子宮頸癌において非常に有用である．

3）成績

色素法単独では同定率が低く，また前述の理由もあるので，RI法と色素法を併用した成績について言及する．われわれの成績とこれまでの併用法の報告[2),4)]をまとめて表1に示したが，センチネルリンパ節の検出率もおおむね90%前後であり，転移の診断法としての感度，特異度ともに十分に高い成績といえる．われわれの場合，同定されるセンチネルリンパ節の個数も平均2.3（range：1～5）であるので，今後，術中に生検して迅速病理診断を行うことも可能な結果と考えている．

Ⅲ 子宮体癌

子宮体癌に対してリンパ節郭清を行う場合，骨盤内リンパ節の郭清にとどまらず傍大動脈リンパ節（326b1，326b2）までの系統的郭清も含むことが多い．これは子宮体部からのリンパ流に関する研究から子宮体癌にとっては傍大動脈節も一次リンパ節であること，また臨床的検討でもリンパ節転移陽性例のうちの約20%は傍大動脈リンパ節のみに転移があるためである[5)]．しかしこの傍大動脈リンパ節の取り扱いについては以前より国内外で多くの議論がなされており統一された見解はない．これは，傍大動脈リンパ節領域の郭清の診断的意義は認めるものの治療的意義が明らかでない点と，一方で郭清による医療側と患者側の双方のさまざまな負担が増すという点のジレンマによる．このような状況から郭清ではなく生検にとどめるという意見もあるが，広い後腹膜の郭清範囲の一体どこを生検すればよいのか実際の臨床上的確に知ることは難しい．腫大したリン

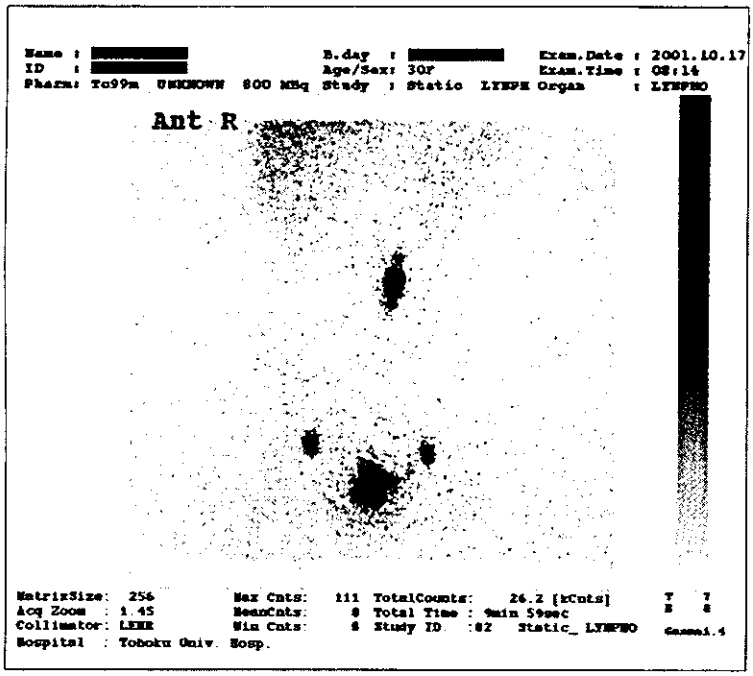

図1
骨盤内リンパ節，傍大動脈リンパ節同定症例のシンチグラフィ

パ節を生検するとはいっても実際には腫大のないリンパ節に転移が陽性であることはしばしば経験することである．このようなジレンマを抱える子宮体癌の手術にあたってセンチネルリンパ節の検討は方法論としては非常に有用と考えられるが，実際には子宮体癌のセンチネルリンパ節の同定に関する満足すべき報告はほとんどないのが現状である．

1）適応症例

われわれは術前の診断で基本的に癌病巣が子宮体部に限局しているとした症例を対象としている．すなわち子宮頸部に病変が及んでいるⅡ期の症例はその子宮頸部からのリンパの流れも考慮しなければいけないために除外している．また，病巣への注入に子宮鏡を用いているため，子宮鏡の挿入が不可能なほど，腫瘍が子宮腔内に充満している症例も除外している．

2）方法

術中にisosulphan blueやpatent blue violetを直接子宮筋層に注入してセンチネルリンパ節の同定を試みた報告[6),7)]があるが，残念ながら検出率は70%前後と低い．これは他の癌でも指摘される手技上のlearning curveの問題もあると考えられるが，色素がセンチネルリンパ節にとどまっている時間が短いために，骨盤内のみならず傍大動脈領域の広い範囲の後腹膜を短時間に観察し生検するのは熟練を要するためではないかとも考えられる．そこでわれわれは手術前日に^{99m}Tc-phytateを子宮鏡下に腫瘍を観察しながら，子宮内膜下に直接注入する方法を用いている．具体的には腫瘍が限局性の場合には腫瘍を取り囲むようにその周囲4カ所に注入する．子宮内腔にびまん性かつ広範囲に腫瘍が存在する場合には子宮底部，前後，左右壁に注入している．子宮頸癌と同様に投与時のシンチグラフィと手術直前のシンチグラフィをルーチンに行い，手術中にはγプローブによりセンチネルリンパ節を検索する．**図1**に注入当日のシンチグラフィの一例を提示したが，この症例では骨盤内と傍大動脈リンパ節が同定された．

3）成績

当科にて検討した28例の成績をまとめて**表2**に示した．センチネルリンパ節の検出率は82%で，センチネルリンパ節の平均の個数は3.1（range：1～9）であった．センチネルリンパ節として同定された領域を解析すると傍大動脈領域のみの症例が3例，骨盤内領域のみが5例，残りの15例が両領域にまたがってセンチネルリンパ節が存在していた．傍大動脈リンパ節が同定された場合の平均個数は1.7（range：1～4）で実際の臨床に応用されれば郭清の負担をかなり減らすことができると考えられる．興味深いこ

	症例数	SN同定率(%)	感度(%)	特異度(%)	SN平均個数
東北大学	28	82	100	100	3.1

表2
子宮体癌における
センチネルリンパ節の同定
(2001.7～2003.1)

とに，子宮筋層への浸潤が1/2に満たない症例では22例中21例でセンチネルリンパ節が検出されたのに対し，1/2を超える症例では6例中2例の検出にとどまった．これは他の癌でもいわれているように，癌が進行してきた場合，病巣周囲のリンパ管が閉塞してしまいセンチネルリンパ節の同定率が下がってしまうのではないかと考えられ，今後適応を考えるうえでもさらなる検討が必要である．

Ⅳ おわりに

子宮癌に対するsentinel lymph node navigation surgeryはまだ検討が始まったばかりであり，骨盤内のリンパ節の場合にはどのコロイドが最適なのか，また至適投与法はどうかなど，今後の検討課題も多い．さらに臨床応用の際には，術中の迅速診断での微小転移の診断方法も重要な課題となるであろう．現在のところ子宮癌の手術療法では，結果的に不必要なリンパ節郭清が施行され骨盤内のリンパ嚢胞や下肢のリンパ浮腫などの副障害が生じているといわざるをえない．センチネルリンパ節の概念の妥当性について，検討がさらに進んでいくことを期待している．

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Sentinel lymph node detection in patients with endometrial cancer

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Abstract

Objective. The purpose of this study was to examine the feasibility of sentinel lymph node (SLN) detection in patients with endometrial cancer using preoperative lymphoscintigraphy and an intraoperative gamma probe.

Patients and methods. Between June 2001 and January 2003, 28 consecutive patients with endometrial cancer who were scheduled for total abdominal hysterectomy, bilateral salpingo-oophorectomy, total pelvic lymphadenectomy, and paraaortic lymphadenectomy at Tohoku University School of Medicine underwent sentinel lymph node detection. On the day before surgery, preoperative lymphoscintigraphy was performed by injection of 99m-Technetium (^{99m}Tc)-labeled phytate into the endometrium during hysteroscopy. At the time of surgery, a gamma-detecting probe was used to locate radioactive lymph nodes.

Results. At least one sentinel node was detected in each of 23 of the 28 patients (82%). The mean number of sentinel nodes detected was 3.1 (range, 1–9). Sentinel nodes could be identified in 21 of 22 patients (95%) whose tumor did not invade more than halfway into the myometrium. Eighteen patients had radioactive nodes in the paraaortic area. Most patients had a sentinel node in one of the following three sites: paraaortic, external iliac, and obturator. The sensitivity and specificity for detecting lymph node metastases were both 100%.

Conclusion. The combination of preoperative lymphoscintigraphy with intraoperative gamma probe detection may be useful in identifying sentinel nodes in early-stage endometrial cancer.

Keywords: Sentinel lymph node; Endometrial carcinoma; ^{99m}Tc-phytate

Introduction

Endometrial cancer is the most common type of gynecological malignancy in Western countries [1]. The primary surgical procedures for patients with endometrial cancer include total abdominal hysterectomy and bilateral salpingo-oophorectomy with clinical or pathologic assessment of the regional lymph nodes. The question of whether or not to perform systematic pelvic lymphadenectomy and paraaortic lymphadenectomy remains controversial in many countries because of the inability to predict those patients who would benefit from node resection. The incidence of lymph node metastasis in patients with clinical stage I and occult stage II endometrial carcinoma is approximately 10% [2]. Among patients with lymph node metastasis, approximately 50% had lymph node metastasis in the pelvic area, 30% in both the pelvic and paraaortic areas, and 20% in the paraaortic area alone. Complete pelvic and paraaortic lymphadenectomy may produce severe surgical sequelae such as lymph cyst, lymphedema, massive bleeding, ileus, and urologic or vascular injury. To minimize these sequelae, some institutions perform retroperitoneal lymphadenectomy on only high-risk patients who have risk factors such as deep myometrial invasion, isthmus-cervix extension, extrauterine spread, special histological types, high grade, enlarged lymph nodes, etc. However, patient selection according to these factors is far from ideal, because over half of these high-risk patients are negative for lymph node metastasis.

In an effort to avoid complete systematic lymphadenectomy whenever possible, the sentinel lymph node (SLN) concept has been applied to the treatment of malignancies of various organs [3]. In the case of gynecological malignancies, the feasibility of this concept has been examined

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in patients with vulvar cancer [4,5] and to a lesser extent with uterine cervical cancer [6]. Phase III studies of sentinel node detection in vulvar cancer are currently in progress in the USA and in Europe. However, only three reports [7–9] of sentinel node detection utilizing blue dye in endometrial carcinoma have been published, and these studies did not establish the feasibility of the method for these cases.

The aim of the present study is to examine the feasibility of sentinel lymph node detection using preoperative lymphoscintigraphy and an intraoperative gamma probe for patients with endometrial cancer with the goal of avoiding unnecessary lymph node resection.

Materials and methods

Patients

Between June 2001 and January 2003, consecutive patients undergoing laparotomy for endometrial cancer at Tohoku University Hospital were enrolled in this study. The study design was explained to the patients, and only patients who provided written informed consent participated in the study. However, excluded were patients with obvious cervical invasion and obvious extrauterine spread at their preoperative evaluation with MRI, CT, and transvaginal ultrasonography. The lymph node spread pattern from the uterine cervix was taken into consideration in this evaluation. The patients were scheduled for total abdominal hysterectomy, bilateral salpingo-oophorectomy, total pelvic lymphadenectomy, and paraaortic lymphadenectomy to the level of renal veins.

Lymphoscintigraphy with 99m-Technetium

On the day before surgery, the patient was carried to the clinic of Nuclear Medicine and Radiology Department, and preoperative lymphoscintigraphy was performed by injection into the endometrium of 2.0 ml of fluid containing 38–70 MBq 99m-Technetium (^{99m}Tc)-labeled phytate (DRL, Tokyo, Japan) dissolved with patent blue as the followings. In this study, we used blue dye not to detect sentinel nodes, but to ensure the injection under the endometrium without leakage. After the uterine cervix was dilated with laminaria for 15 h, a hysteroscope, 5.5 mm in diameter, was inserted into the uterine cavity with physiological saline. Tumors in every patient were observed through the hysteroscopy. We only judged cases with apparently focal tumorous lesion as focal. These cases could be reconfirmed by postoperative histopathological examination. Visually directed injection of [^{99m}Tc] phytate with blue dye under the hysteroscopic observation was performed with a 21-gauge needle at four sites under the endometrium around the tumor. During the procedure, no anesthesia was requested. For patients with multiple or diffuse tumors in the uterine cavity, ^{99m}Tc-radiocolloid was injected into the following five sites: the fundus, the right mid-lateral wall, the left mid-lateral wall, and the mid-anterior or mid-posterior wall. Dynamic lymphoscintigraphy was performed, and hot spots, indicating sentinel lymph nodes, were identified within 10 min in most cases. The first lymphoscintigram was taken at this time, and the second lymphoscintigram was taken the next morning just before the patient entered the operating room. Phytate is 200–1000 nm in diameter and half-life of ^{99m}Tc is short at 6 h. Total radioactivity used for one person was 2 mCi, which is much less than used for the standard bone scintigram at 20–50 mCi. Even if one operator performed the present procedure of sentinel node detection 500 times, the operator's total exposure would be much less than 50 mSv per year, which is the maximum allowable exposure per year as proposed by International Commission on Radiological Protection (ICRP) 1977. The irrigation fluid used through the hysteroscopic procedure was collected in the clinic and disposed of according to the laws for the disposal of radioactive waste in Japan.

Intraoperative lymphatic mapping and sentinel lymph node identification

Before starting lymphadenectomy, the radioactive lymph node was located by using a gamma-detecting probe (Navigator GPS, RMD: Watertown, MA). After lymphadenectomy, the area of lymphadenectomy was surveyed with the probe to confirm that no radioactive tissue remained. When the gamma-detecting probe registered counts over 10-fold above background radiation levels, the node was considered radioactive. All radioactive nodes were considered sentinel lymph nodes. All surgically removed lymph nodes were reexamined with the gamma-detecting probe ex vivo.

Pathology

All surgically removed lymph nodes, including the sentinel lymph nodes, were examined histopathologically using routine hematoxylin and eosin (H&E) staining. At least one section from each lymph node divided at the maximal diameter was reviewed by two independent pathologists. Lymph nodes that were diagnosed as negative for metastasis by routine H&E staining were immunostained with an anti-cytokeratin antibody (MNF116, DAKO, Japan) to detect cytokeratin, which is characteristic of micrometastatic cancer cells.

Results

Patient characteristics

The characteristics of 28 patients enrolled on the study are summarized in Table 1. Patient ages ranged from 29

Table 1
Patient characteristics

Case	Age	Stage	Histology	Myometrial invasion	Tumor distribution	Washing cytology
1	57	IIIC	G1	>1/2	not focal	–
2	57	IA	s/p	<1/2	focal	–
3	60	IB	G2	<1/2	focal	–
4	49	IIIA	G1	<1/2	not focal	+
5	65	IC	G1	>1/2	not focal	–
6	71	IA	G1	<1/2	focal	–
7	30	IA	G1	<1/2	focal	–
8	37	IIB	G1	<1/2	focal	–
9	53	IA	G1	<1/2	focal	–
10	58	IB	G2	<1/2	not focal	–
11	63	IIIC	G3	>1/2	not focal	+
12	59	IC	G1	>1/2	not focal	–
13	48	IC	G1	>1/2	not focal	–
14	52	IB	G2	<1/2	focal	–
15	29	IB	G1	<1/2	focal	–
16	48	IB	G1	<1/2	not focal	–
17	67	IIA	G2	<1/2	focal	–
18	53	IB	G1	<1/2	focal	–
19	50	IIA	G1	<1/2	not focal	–
20	49	IB	G1	<1/2	focal	–
21	47	IA	G1	<1/2	not focal	–
22	70	IA	s/p	<1/2	focal	–
23	59	IB	G1	<1/2	focal	–
24	49	IA	G1	<1/2	focal	–
25	56	IB	G1	<1/2	focal	–
26	63	IC	G1	>1/2	not focal	–
27	60	IB	G1	<1/2	focal	–
28	56	IB	G2	<1/2	not focal	–

s/p: serouspapillary.

to 71 years (median 56 years). The mean number of lymph nodes removed was 42.9 (range: 22–75) for pelvic lymph nodes and 27.9 (range: 6–46) for paraaortic lymph nodes.

Detection rates and sites of sentinel lymph nodes

Preoperative lymphoscintigraphy detected at least one hot spot indicating a sentinel lymph node in 19 of 28 patients (68%) (Fig. 1). For four of the remaining nine patients, an intraoperative or ex vivo survey with the gamma probe for hot spots identified sentinel lymph nodes. Altogether, the detection rate for sentinel lymph nodes was 82% (23 of 28). Among 22 patients with a superficial myometrial invasion, sentinel node identification was missed in only one case. On the other hand, among six patients with deep myometrial invasion, four patients were missed. The detection rate for the former group was significantly higher than that for the latter group: 95% (21/22) versus 33% (2/6) ($P = 0.003$, Fisher's Exact Test). The mean number of sentinel nodes detected was 3.1 (range: 1–9).

The location and number of sentinel nodes detected are summarized in Table 2. The paraaortic region was a critical site for sentinel nodes: paraaortic nodes (18 patients), external iliac nodes (11 patients), and obturator basin (10 patients). Three patients had sentinel nodes only in the paraaortic area, five patients had them only in the pelvic area, and fifteen patients had nodes in both areas. Four patients had sentinel nodes in the right side of the paraaortic area above the inferior mesenteric artery and eight patients had sentinel nodes in the area below the inferior mesenteric artery. Eight patients had sentinel nodes in the left side of the paraaortic area above the inferior mesenteric artery where it was near left renal vessels and five patients had sentinel nodes in the area below the inferior mesenteric artery.

Sensitivity and specificity of SLN for detecting lymph node metastasis

Two patients were diagnosed as having lymph node metastasis after the routine H&E staining. Lymph nodes judged to be metastasis-negative according to the routine H&E staining were stained immunohistochemically with an anti-cytokeratin antibody to detect micrometastases, but no positive antibody signals were detected in any of these lymph nodes.

Among 23 patients with at least one SLN, only 1 patient (case 11) had metastatic lymph nodes. This patient had seven metastatic lymph nodes, one of which was at the external iliac basin and was successfully detected as an SLN. Among the other 22 patients with at least one SLN, all of the SLNs were metastasis-negative and all of the other lymph nodes were metastasis-negative. These results thus indicated that SLN detection gave 100% sensitivity (1/1)

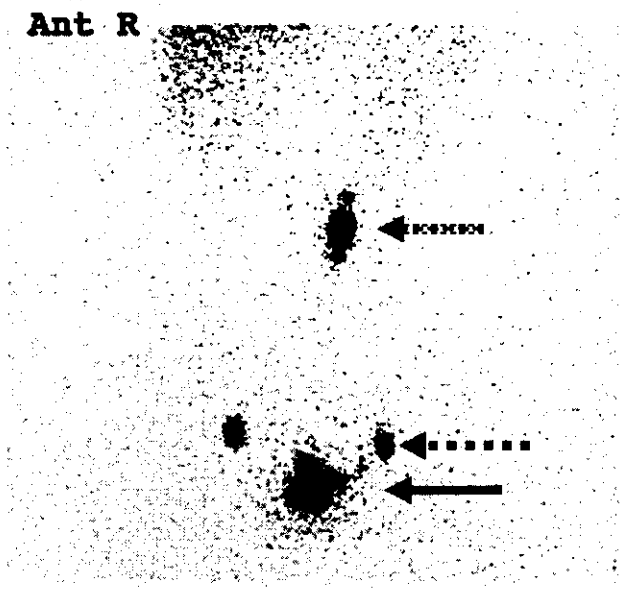

Fig 1. Preoperative lymphoscintigram for case 7. Hot nodes are visible in the pelvic and paraaortic areas. ◀┅┅: paraaortic lymph node ◀┈┈: pelvic lymph node ◀—: injection site in the uterus.

Table 2
Location and number of sentinel nodes

Case	Paraaortic				Common iliac		Sacral		External iliac		Internal iliac		Obturator		Supra-inguinal		Total
	Upper		Lower														
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	1[a]	0	0	0	0	0	0	0	0	0	0	0	0	0	1
3	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	3
4	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	3
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	1	0	0	0	0	1	0	0	0	0	1	0	0	3
7	0	3	0	1	0	0	0	0	1	1	0	0	0	0	0	0	6
8	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
9	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
10	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
11	0	0	0	0	0	0	0	0	0	1[a,b]	0	0	0	0	0	0	1
12	0	1[a]	0	0	0	0	0	0	0	1[a]	0	0	0	0	0	0	2
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	4
15	0	1	1	0	1	0	0	0	0	0	0	1	0	0	0	0	4
16	1	0	1	0	0	0	0	0	0	0	1	0	1	2	0	0	6
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	3
19	0	0	2	0	0	0	0	0	0	1	1	0	0	0	0	0	4
20	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	3
21	0	0	1	0	0	0	0	0	0	2	0	0	0	0	0	0	3
22	0	0	0	0	0	0	0	0	0	1[a]	0	0	0	0	0	0	1
23	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	3
24	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	3
25	1	0	0	3	1	0	0	0	1	2	0	0	1	0	0	0	9
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
28	0	0	1	0	1	0	0	0	0	1[a]	0	0	1	0	0	0	4
Total	4	10	9	7	4	0	1	0	6	12	2	1	7	7	0	1	71

The landmark separating upper and lower is inferior mesenteric artery.
Case 1: this patient had three swelling and palpable lymph nodes with high suspicion of metastasis upon inspection.
[a] Lymph node detected only by gamma probe.
[b] Metastasis-positive lymph node.

and 100% specificity (22/22) in detecting lymph node metastases.

Among the remaining five patients in whom an SLN was not detected, one patient (case 1) had three metastatic lymph nodes, which were swollen and palpable during lymphadenectomy. These were strongly suspected to be metastatic even on inspection during the surgery.

Discussion

We identified SLN for endometrial cancer with a success rate of 82%, which is comparable to the SLN detection rates for vulvar cancer [5] (86%) and cervical cancer [6] (85%). In the 22 patients whose SLNs were metastasis-negative, all the other lymph nodes were also metastasis-negative, indicating a sensitivity of 100%. In previous reports of SLN in endometrial cancer, the detection rates of SLN were not satisfactory. Echt et al. [8] reported that no sentinel nodes were identified using the isosulfan blue dye method for eight patients with endometrial cancer. They injected the dye directly into the subserosal myometrium after the abdominal cavity was opened. Holub et al. [9] reported that sentinel nodes could be identified with patent blue dye, resulting in a 72% detection rate (18/25). They also injected the dye into the subserosal myometrium and the cervix subserosal myometrium intraoperatively. However, since they did not seem to be concerned with the paraaortic lymph nodes, no information about paraaortic nodes was available from their report. Burke et al. [7] used the isosulfan blue dye method, injecting it into the subserosal myometrium intraoperatively. They detected SLN with a 67% success rate (10/25). Their detection rate was lower than that seen in the present study, but they also detected SLNs at paraaortic sites.

Our higher detection rate for SLNs were possibly due to the following factors. Firstly, we used a radioisotope, which could remain at the SLN much longer than dyes. In our preliminary studies with injection of blue dye through a hysteroscope, it was difficult to survey all sentinel nodes with the blue dye alone in the broad retroperitoneal lymph node area from the level of renal vessels to the level of bilateral inguinal ligaments, and to the bottom of the pelvic

cavity through the bilateral internal iliac vessels. We noticed that the blue dye sometimes passed through the SLN within 15 min and became invisible during our search of the broad retroperitoneal space. Since the method using blue dye alone was limited to use as the intraoperative procedure, we chose a combination of preoperative lymphatic mapping with intraoperative probe detection. However, for future laparoscopic lymphadenectomies, the combination of ^{99m}Tc and blue dye would make it easier to detect sentinel nodes because it was visible intraoperatively.

Secondly, we injected radioisotope dissolved with the blue dye for hysteroscopic guidance, which allowed us to confirm the precise points of injection into the endometrium. The drainage of radioisotope injected into the endometrium mimics the natural lymphatic drainage of cancer cells arising in the endometrium. With this technique, we identified sentinel nodes both in the pelvic and paraaortic areas, as observed by Burke et al. [7]. Eighteen of the 23 patients with SLN had hot spots in the paraaortic region. Also, only the paraaortic lymph nodes were detected as SLN in three patients. It thus appears that the paraaortic basin is a very important primary site for lymphatic drainage and that both paraaortic lymphadenectomy and pelvic lymphadenectomy are important in management of women with endometrial cancer.

Thirdly, we think the intraoperative survey with a gamma probe is more sensitive for the detection of SLNs than preoperative lymphoscintigraphy. Four patients who were found intraoperatively to have a sentinel node were not detected on preoperative lymphoscintigraphy.

Moreover, it would clearly be very useful to locate the SLNs preoperatively by scintigraphy. If considering omission of systematic lymph node resection for endometrial carcinoma, the information obtained preoperatively for the area surrounding the lymph node biopsy would be very useful for preparing the approach to the lymph nodes. For example, this information would be of great use in preparing for procedures such as skin incision, choosing laparotomy or laparoscopy, making decisions on operation time and surgical position, preparing instruments, etc.

The location and incidence of SLNs identified in this report appear very similar to those found for lymph node metastasis of endometrial cancer in another report. Among patients with lymph node metastases, approximately 50% had lymph node metastasis in the pelvic area, 30% in both the pelvic and paraaortic areas, and 20% in the paraaortic area alone [2]. In the pelvic nodes, the obturator basin and the external iliac basin were common sites of SLN. This was consistent with a previous study of the incidence and location of lymph node metastases in endometrial cancer, as determined by performing systematic lymphadenectomy [10].

We suspect that the location of carcinoma in the uterine cavity is also related to that of sentinel nodes. By injecting five sites in the uterine cavity, we may detect more sentinel nodes than true sentinel nodes. However, we believe that the sentinel nodes we do detect include all true sentinel nodes. Lymphatic mapping will make it possible to biopsy more precisely and more easily in the broad regional lymph node area even in such cases.

SLNs were not identified in five patients, and this detection failure seemed to be related to the depth of myometrial invasion. In six patients with deep myometrial invasion (>1/2), two had a radioactive node, and one patient had multiple lymph node metastases, and nodes were swollen and palpable intraoperatively. In the cases of deep invasion, the lymphatic flow may be disturbed, or the involved lymph nodes may no longer filter lymph, as described previously [11]. Alternatively, for patients who fail SLN detection, lymphatic mapping may not be necessary.

Using our method, most of the SLNs were identified by the first lymphoscintigram immediately after injection. However, for four patients, sentinel lymph nodes were detected for the first time 19 h after ^{99m}Tc injection, at the time of the second scintigram. Since lymphatic drainage from the endometrium seems complex and variable among the patients; not only one scintigram but also a second scintigram should be taken and evaluated to identify SLNs according to our method.

Our data suggest that the combination of preoperative lymphoscintigraphy with intraoperative probe detection may be useful in identifying sentinel nodes in early endometrial cancer. We hope that the value of the sentinel node concept will be proven in endometrial cancer by additional larger studies applying this technique. Moreover, this technique may also be applicable to laparoscopic surgery. We currently require a long skin incision for this surgery, but if we survey sentinel nodes with a laparoscopic gamma probe, we may be able to reduce the length of the skin incision, even if sentinel nodes are detected in both the paraaortic and pelvic areas. In order to take adequate and quick samplings of SLNs from such a broad area under the laparoscopic procedure, it is critically important to predict where SLNs are before surgery is begun. We believe that our ^{99m}Tc method makes this possible.

It is further hoped that this method of SLN detection will improve the management of the large majority of women with 'early' endometrial cancers by sparing them unnecessary and potentially harmful total lymphadenectomies.

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