suggest that the perioperative IPC device in multiple prophylaxes condition might reduce the incidence of PE after gynecologic surgery.

Currently, low–molecular weight heparin (LMWH) or fondaparinux are recommended for thromboprophylaxis in open gynecologic surgery patients.[22] Mechanical thromboprophylaxis is recommended in cases with moderate VTE risk and high bleeding risk.[22] In high-risk abdominal surgery such as cancer surgery, dalteparin (2500 units) is given 2 hours before the induction of anesthesia and 12 hours later. Thereafter, dalteparin is given at a daily dose of 5000 units.[24] For patients undergoing major gynecologic procedures, thromboprophylaxis with LMWH throughout the hospitalization period is recommended.[22] For selected high-risk patients, including those undergoing cancer surgery, extended prophylaxis with LMWH for 4 weeks is recommended.[22,25]

We are now practicing thromboprophylaxis according to the recommended guidelines. However, LMWH use was restricted during the study period even for cancer surgery because of the Japanese medical insurance system and because the incidences of DVT and PE were assumed to be very low in Japan. In 2002, the rate of perioperative PE was estimated to be 0.044% (369/837,540) in registered cases.[26] We felt the incidence rate of PE was larger than the aforementioned reported number and performed thromboprophylaxis with LMWH. However, because of the restriction of the Japanese medical insurance system, we used a small dose and a shorter dosing period of dalteparin during the current study period.

LMWH and fondaparinux have finally been approved for postoperative use in gynecologic patients in Japan in 2009. However, the first injections of LMWH and fondaparinux are permitted for 24 hours after surgical closure in Japan, and additional use of the IPC device is necessary.

A recent study reported that 6.4% of postoperative VTE in ovarian cancer patients were recognized during first-line chemotherapy and 4.8% of the VTE cases were detected during the follow-up period.[27] We now continue thromboprophylaxis with LMWH for a longer period in ovarian cancer patients.

A VFP showed an adverse effect on PE occurrence based on a univariate analysis, although this was not confirmed by the multivariate analysis. In gynecologic surgery cases, mechanical thromboprophylaxis using the IPC device is effective when it is used before the initiation of surgery and continued until the patient is fully ambulatory.[11,20] The IPC device is generally not used for patients with an active thrombus because of the potential for embolism.[28] In our study, VFPs were either used postoperatively after intraoperative IPC device use with a short interruption, or they were used only postoperatively. Venous thrombi might develop intraoperatively or in the immediate postoperative period; therefore, prophylaxis must be provided in the perioperative period to reduce thromboembolic complications,[21] although the VFP and the IPC device are not of the same modality. The VFP should also be used continuously throughout the operation and the postsurgical state in gynecologic surgery.

The lithotomy position was not associated with a high incidence of DVT.[29,30] In our series, the incidence of PE among the patients who underwent surgery in the lithotomy position was significantly low. The venous return might thus be easier in the lithotomy position population because the lower limbs are elevated.

In conclusion, there are a substantial number of asymptomatic cases among the patients who experience postoperative PE in gynecologic oncology surgery. Increasing age, a longer operation time, and obesity were all found to be risk factors for PE in such conditions, including asymptomatic cases. Under multimodal prophylactic conditions, the perioperative type of IPC device significantly reduced the incidence of PE. Identifying the presence of hypoxia without symptoms or with minimal symptoms is the best way to avoid a diagnostic delay of postoperative PE.

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特集 胸水・腹水の病理

腹腔内洗浄細胞診の診断と臨床的意義　Ⅱ．婦人科悪性腫瘍

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野河孝充*

はじめに

婦人科領域における腹腔内洗浄細胞診は子宮頸癌，子宮体癌，卵巣癌で行われている．細胞診の目的は，進行期の決定，組織型の診断であり，細胞診検体は，①腹水，②腹腔内洗浄液―部位別（Douglas窩・回盲部・S状結腸部・右横隔膜下），あるいは腹腔内全体―，③腫瘍表面および腹腔内擦過，④腫瘍割面捺印細胞診が挙げられる．

特に子宮体癌，卵巣癌の腹腔内洗浄細胞診は進行期の決定に必須であり，悪性細胞の有無を確認することは適切な術後治療法を選択する上で極めて重要である．明らかな癌性腹水を有する進行癌は集学的治療が施行され，早期癌でも腹腔内洗浄細胞診が陽性であれば，予後に重大な影響を及ぼすため，その判定は慎重を要する．そのためには，適正な腹腔洗浄液の採取と細胞標本の作製が必要である．

本稿では子宮体癌，卵巣癌の臨床と腹腔内洗浄細胞診の臨床的意義を中心に記載したい．

Ⅰ．腹腔内洗浄細胞標本の作製

婦人科悪性腫瘍症例の術中細胞診は臨床的に必須であり，開腹直後に腹水量，腹水の性状，色調を記録する．腹水のある症例ではDouglas窩の貯留腹水を十分に撹拌して採取，腹水のないまたは少量の腹水例には生理的食塩水（生食）50 mLで部位別に，あるいは腹腔内を生食で充満し，採取している．子宮頸癌ではDouglas窩，子宮体癌ではDouglas窩・回盲部・S状結腸部・右横隔膜下，卵巣癌では腹腔内全体の洗浄液から採取することを原則としている．

洗浄液検体が腹水などの体腔液の処理と異なる点は，生食で腹腔内を十分に洗浄し，腹膜面に付着あるいは浮遊する腫瘍細胞を十分に採取する操作が肝要である．蛋白質に富む体腔液は粘稠性であるが，生食の洗浄により，スライドガラスへの細胞付着力がより低下する．染色操作中の細胞剥離を防ぐため，2%ポリエチレングリコール加・95%エタノールで湿固定後，ドライヤーで急速冷風乾燥し，その後の染色過程は通常の液状検体と同様に扱っている[1,2]．

Ⅱ．子宮頸癌

子宮頸癌の腹腔内洗浄細胞診は臨床進行期の決定には採用されておらず，病変が子宮頸部に限局する症例（Ⅰa，Ⅰb1期）では，腫瘍細胞が出現する可能性はほとんどない．一方，Ⅰb2期や腺癌の内膜浸潤例では経卵管的腹腔内播種が必ずしも否定できない．腺癌では扁平上皮癌に比し，付属器転移をきたしやすく，開腹時の腹腔内洗浄細胞診は入念にする必要がある．

Ⅲ．子宮体癌

子宮体癌は近年増加傾向にあり，子宮癌全体の割合も50%に達し，女性の平均寿命の高齢化や子宮体癌検診の普及と啓発に伴い，今後さらに増加すると予想される．腹腔内洗浄細胞診は進行期の決定に必須であり，surgical staging（1988）[3]による適切な治療が望まれる．細胞診陽性例はⅢa期に分類され，前臨床的腹膜播種としての予後因子の一つとされている[4]．再発形式には，肺，肝などの遠隔転移や腹腔内播種が多いことからも[5]，腹腔内洗浄細胞診は臨床的にも重要である．

1987～2001年の間に四国がんセンターで基本術式と腹腔内洗浄細胞診を施行した子宮体癌284例（FIGOⅠ～Ⅳ期，組織型：類内膜腺癌237例，腺扁平上皮癌16例，漿液性腺癌8例，明細胞腺癌3例）を対象に長

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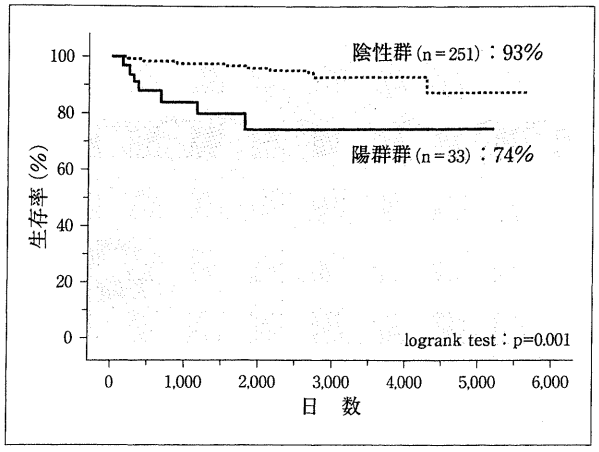

図1 子宮体癌における腹腔内洗浄細胞診陰性群(n=251)，陽性群(n=33)の15年生存率(Kaplan-Meier法)

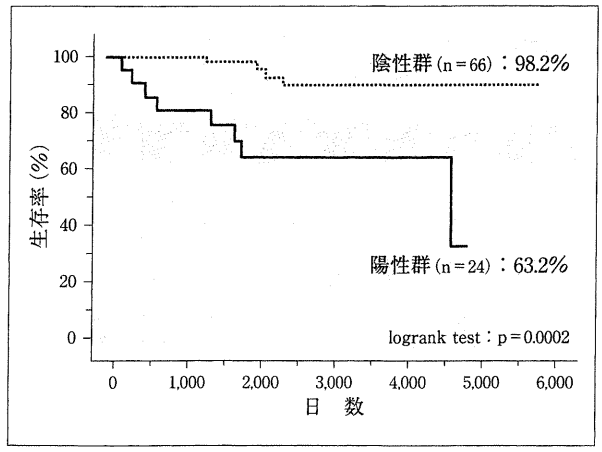

図2 卵巣癌pT1，pT2における腹腔内洗浄細胞診陰性群(n=66)，陽性群(n=24)の5年生存率(Kaplan-Meier法)

期予後を検討した．腹腔内洗浄細胞診陰性群(n=251)，陽性群(n=33)の15年生存率は93%，74%と陽性群に予後不良である(p=0.001，**図1**)．陽性群33例のpTでは，pT1：20/228(8.8%)，pT2：2/33(6.1%)，pT3：11/23(47.8%)と子宮外進展例に多く，組織型別では，類内膜腺癌G1：7/129(5.5%)，G2：18/101(16.8%)，G3：2/27(7.4%)，腺扁平上皮癌4/16(25.0%)，漿液性腺癌2/6(33.3%)と腺扁平上皮癌，漿液性腺癌に陽性率が高かった．病変の子宮内限局例における腹腔内洗浄細胞診陽性の機序は卵管腔内に腫瘍細胞が観察されることからも経卵管的腹腔内播種が考えられている[6]．早期例のリンパ節転移あるいは腹腔内播種を認めない腹腔内洗浄細胞診陰性例は極めて予後良好であるが[7]，陽性例は予後不良であることから化学療法の適応である[8]．

Ⅳ．卵 巣 癌

卵巣癌の腹腔内洗浄細胞診は手術時肉眼的に明らかでない癌細胞の卵巣外進展を確認するために必須である．卵巣腫瘍取扱い規約[9]によると，卵巣に限局するⅠ期，骨盤内臓器に進展するⅡ期で，腹腔内細胞診が陽性の場合それぞれⅠc期，Ⅱc期に分類され，さらに腹腔内洗浄細胞診陽性でⅠc(1)orⅡc(1)，腹水細胞診陽性でⅠc(2)orⅡc(2)に細分類されている．肉眼的に播種所見のないpT1，pT2において腹腔内洗浄細胞診の威力が十分に発揮される．腹腔内洗浄細胞診は組織像を反映することから[10]，組織型の推定が可能であり，また，腹腔内洗浄細胞診陽性は所属リンパ節転移や再発，予後に関与するとされ[11,12]，適切な腹腔細胞診の採取と診断は臨床的意義があると考えられる．

1987～2003年の間に四国がんセンターで初回治療を行った上皮性卵巣癌のうち，腹腔内洗浄細胞診の臨床的意義が関与するpT1 68例，pT2 27例を対象に予後を検討した(**表1**)．pT1c，pT2cの5年生存率は83.9%，74.5%で，腹腔内洗浄細胞診でpT1c，pT2cに分類された21例は，被膜破綻，被膜浸潤により分類された43例に比し，予後不良である．腹腔内洗浄細胞診が施行された92例で，陽性24例(26.1%)，疑陽性2例(2.2%)，陰性66例(71.7%)であった．リンパ節転移は10/92(10.5%)にみられ，腹腔内洗浄細胞診陰性例では2/66(3.0%)にリンパ節転移が認められた．疑陽性例で1/2(50.0%)，陽性例で7/24(29.1%)にリンパ節転移がみられ，疑陽性以上で有意にリンパ節転移が高率であった(p=0.0005)．腹腔内洗浄細胞診陽性群(n=24)，陰性群(n=66)の5年生存率は63.2%，98.2%であった(n=0.0002，**図2**)．腹腔内洗浄細胞診は剝離細胞診であるため，細胞自体の変性が懸念されるが，腹腔内洗浄細胞診陽性24例のうち再鏡検できた18/22(81.8%)に組織像を正確に反映した細胞所見が得られた．

Ⅴ．腹腔内洗浄細胞診所見

検体の種類，採取法，処理法により，細胞所見が異なることは周知の事実であり，特に洗浄細胞診は単なる腹水や擦過検体とは異なる所見を呈する．各組織型

表1　対象症例

	pT1			pT2			p-value
		n	%		n	%	
進行期TNM	pT1a	25	36.8%	pT2a	2	7.4%	
	pT1b	2	2.9%	pT2b	2	7.4%	
	pT1c	41	60.3%	pT2c	23	85.2%	
組織型	漿液性腺癌	9	13.2%		7	25.9%	
	類内膜腺癌	16	23.5%		13	48.1%	
	明細胞腺癌	28	41.1%		5	18.5%	
	粘液性腺癌	15	22.1%		2	7.4%	
腹腔洗浄細胞診	陽性[a]	14	21.2%		10	38.5%	0.1151
	疑陽性	1	1.5%		1	3.8%	
	陰性	51	77.3%		15	57.7%	
リンパ節転移	あり[b]	3	4.4%		7	25.9%	0.0049
	なし	65	95.6%		20	74.1%	

[a,b]：p-value by Fisher's exact test.

表2　各組織型における腹腔内洗浄細胞所見と治療

組織型	出現様式	核	細胞質	石灰化物質	治療
漿液性腺癌	乳頭状，大小の集塊，軽度重積性	円形～類円形，核縁の軽度肥厚，クロマチンは微細顆粒状，1～複数個の核小体	好塩基性，空胞	＋	薬剤感受性良好
粘液性腺癌	乳頭状，重積性，背景に粘液物質	円形～楕円形で不整，核縁肥厚，クロマチンは細顆粒状，核小体	好塩基性，豊富な粘液空胞	－～±	薬剤感受性不良
類内膜腺癌	乳頭状，樹枝状，軽度重積性	円形，核縁の軽度肥厚，クロマチンは細顆粒状，1～複数個の核小体	好塩基性，空胞，ライトグリーン好性	－～±	薬剤感受性良好
明細胞腺癌	乳頭状，大型球状，シート状，ミラーボール状	円形～楕円形，大型核，核縁肥厚，クロマチンは細顆粒状，著明な核小体	空胞状，淡明，好塩基性	－～±	薬剤感受性不良
顆粒膜細胞腫	重積性集塊，裸核状，シート状	円形～楕円形，軽度肥厚，クロマチンは細顆粒状，核小体	好塩基性，弱好酸性	－	薬剤感受性不良，一部良好
未分化胚細胞腫	大型の腫瘍細胞，シート状，背景にリンパ球	円形，クロマチンは顆粒状，著明な核小体	好塩基性，小胞状	－	放射線感受性良好，薬剤感受性良好
未熟奇形腫(G3)(未熟神経上皮)	重積性集塊，シート状，管腔様構造	円形～楕円形，クロマチンは細顆粒状	好塩基性	－	薬剤感受性良好

における腹腔内洗浄細胞所見を提示する(**表2**).

漿液性腺癌は，比較的小型均一で極めてN/C比の高い細胞が腺房状，乳頭状集塊を示し，小型集塊で，重積性が著明で辺縁平滑である．核は円形～類円形，核クロマチンは細顆粒状，好酸性の核小体が1～複数個認められる．胞体は好塩基性で辺縁明瞭で乏しく，時にpsammoma bodyが観察されるが，特異的ではない(**図3**).

類内膜腺癌は，漿液性腺癌と子宮内膜癌類似の細胞所見，乳頭状，樹枝状の重積性集塊が特徴的で，30～50個位の腫瘍細胞が集団となり，漿液性腺癌に比べ，集塊も大型である．低分化型では小型集塊が出現し，漿液性腺癌と比較して集塊辺縁は平滑さを欠き，核の大小，異型性も強い(**図4**).

明細胞腺癌は特徴的なミラーボール状集塊，シート状，乳頭状集塊が出現し，核径は大きく，核縁も明瞭である．好酸性の腫大した核小体が1～複数個観察され，豊富で淡明な胞体が特徴的である．乳頭状集塊の中には特徴的なhobnail状細胞が観察される(**図5**).

粘液性腺癌は，空胞状～オレンジ色調に染色される粘液産生，背景も粘液性，他の組織型に比べて異型性が乏しい．重積性乳頭状集塊では，核の大小不同，クロマチンの増量，核小体の出現など異型性は十分に観察される(**図6**).

Ⅵ．腹腔内洗浄細胞診の臨床的意義

卵巣癌治療ガイドライン[13]によれば，腹水を認めない場合でも十分量の生食で腹腔内全体を洗浄して採取し，さらに骨盤腹膜，左右腸骨窩腹膜，横隔膜下面からの擦過細胞診を採取することが望ましいとされている．子宮体癌，卵巣癌の腹腔内洗浄細胞診陽性例は臨床的に予後不良であり，陽性例に対する術後補助療法はハイリスク群として個別化が極めて重要である．適

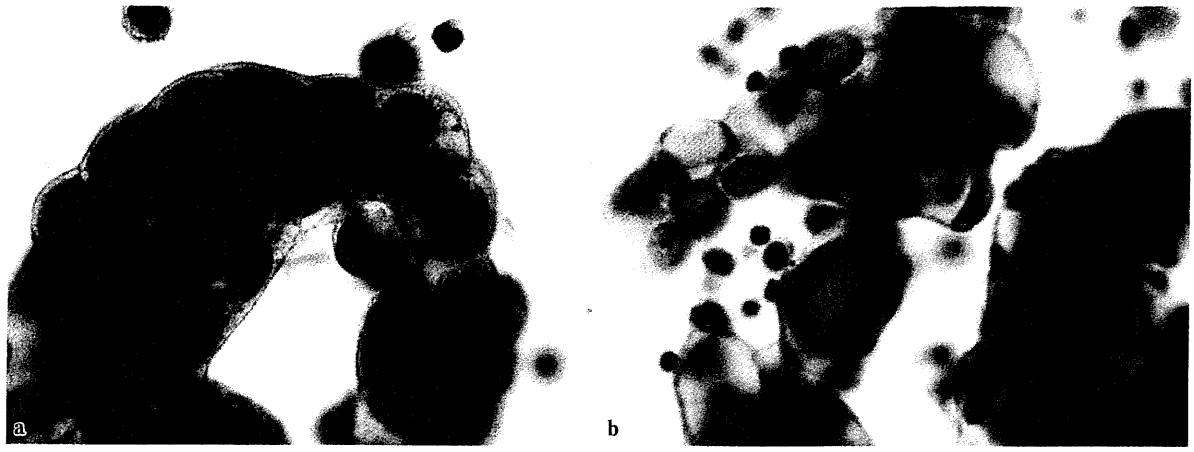

図3　漿液性腺癌（Papanicolaou 染色）　a：辺縁は丸みを帯び，比較的小型均一，円形～類円形の核，核クロマチンは細顆粒状，1～複数個の核小体を有し，好塩基性の胞体は乏しく，N/C 比は極めて高い．b：乳頭状集塊の中央に psammoma body が観察される．

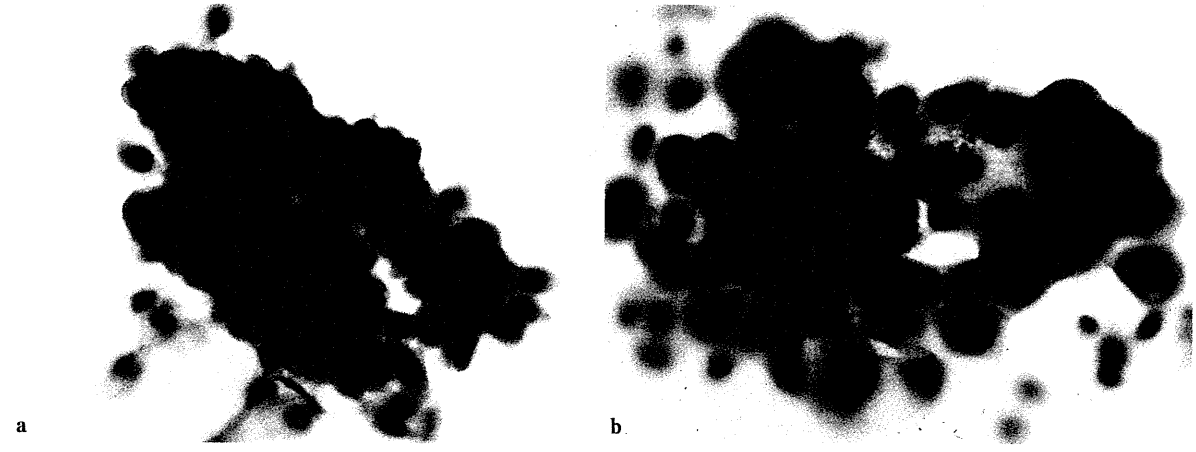

図4　類内膜腺癌（Papanicolaou 染色）　a：大小不同の異型細胞が重積性集塊を形成し，腺腔がみられる．b：核は円形～類円形，核クロマチンは顆粒状，核小体が観察され，N/C 比は高い．

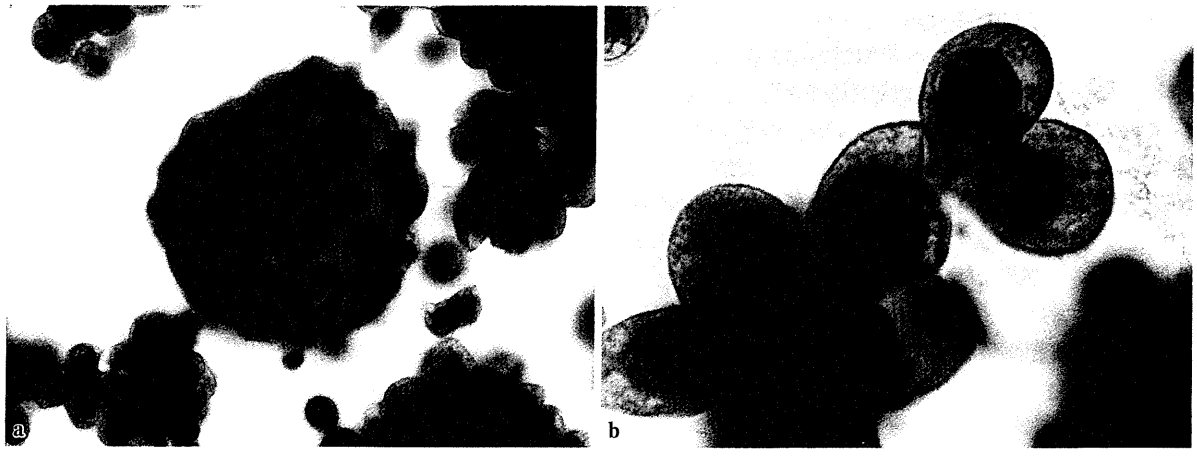

図5　明細胞腺癌（Papanicolaou 染色）　a：ミラーボール状の集塊，乳頭状集塊がみられる．b：特徴的な hobnail 状細胞が観察される．

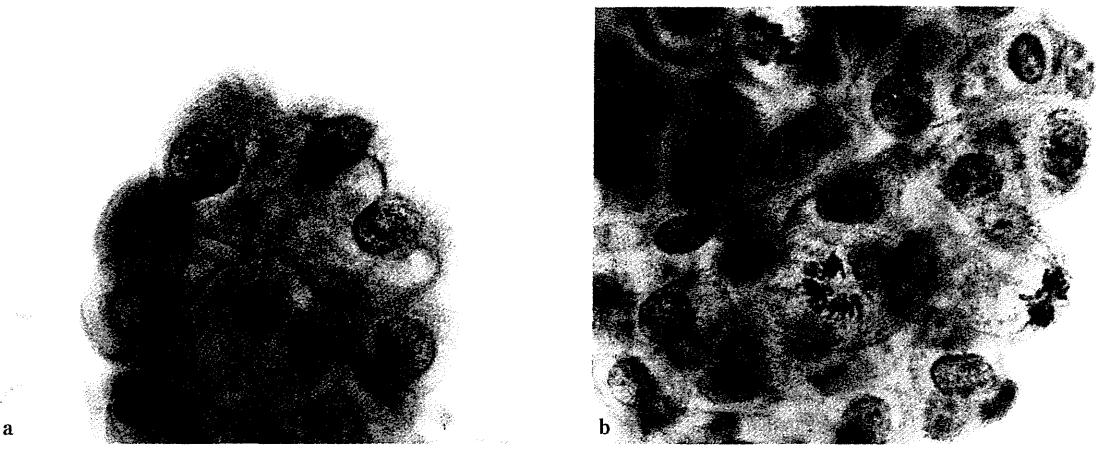

図6　粘液性腺癌（Papanicolaou染色）　a：粘液産生を有する異型細胞が小集塊を形成している．b：核は円形～類円形，核クロマチンは細顆粒状，核縁肥厚，核小体が観察される．細胞境界は不明瞭，胞体は豊富でライトグリーン好性で，核分裂像が散見される．

切な腹腔内洗浄液の採取と標本を作製し，臨床側と検査側の密接な連携のもとに悪性細胞の有無を慎重に判定する．

ま と め

婦人科悪性腫瘍における腹腔内洗浄細胞診の採取法，臨床的意義および細胞所見について治療，予後の面から有用性を検討した．

病変が頸部に限局する子宮頸癌では，腹腔内洗浄細胞診陽性例はみられないが，腺癌では注意深い検索が必要である．病変が子宮内に限局する子宮体癌では，経卵管的に腹腔内洗浄細胞診が陽性となり，付属器転移や漿膜浸潤例ではさらに陽性率が高い．病変が卵巣に限局する卵巣癌の腹腔内洗浄細胞診陽性例は予後不良である．したがって，予後不良例には効果的な薬剤の選択，追加治療の可否を決定することが，治療成績の改善や患者のQOLの面から必要である．

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AJR FOCUS ON: AJR WOMEN'S IMAGING

MRI of Endometriotic Cysts in Association With Ovarian Carcinoma

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OBJECTIVE. Although mural nodules are considered to be the most important hallmark in the recognition of ovarian cancers accompanied with endometriotic cysts, benign neoplasms and even inflammatory diseases can show similar MRI findings. We sought to clarify the MRI characteristics of malignancy accompanied with endometriotic cysts of the ovary.

MATERIALS AND METHODS. Contrast-enhanced MRI was performed and endometriosis was pathologically confirmed in 49 patients with endometriotic cysts displaying mural nodules. Malignancy was pathologically diagnosed in 33 patients and benignity, in 16. Clinical data including patient age and MRI findings in terms of the size of the endometriotic cysts, number of loculi, presence of shading of the cysts, size of the mural nodules, signal intensity of the mural nodules on T1- and T2-weighted images, and contrast enhancement of the mural nodules were retrospectively reviewed. Statistical analysis of each parameter used the Mann-Whitney *U* test.

RESULTS. The mean age of the patients and mean size of the endometriotic cysts were significantly higher in patients with a malignant condition than in those with a benign condition. Contrast enhancement of the mural nodules was observed in 97% of malignant and 44% of benign tumors. The size of the mural nodules was significantly larger in patients with a malignant condition than in those with a benign condition. Differences in size between the bilateral diseases, multilocularity, existence of shading, and the signal intensities of mural nodules were not significantly different between the malignant and benign conditions.

CONCLUSION. Endometriotic cysts with enhanced mural nodules are not always complicated with malignancy. In elderly patients, the presence of large enhanced nodules on large endometriotic cysts is more likely to indicate malignancy.

The number of patients with endometriosis is increasing in the developed countries. In addition, the number of patients desiring conservative observation is also increasing because a higher number of nulliparous women are in their 30s than before. On the other hand, endometriotic cysts have drawn attention as a potential source of ovarian carcinomas [1–3]. Several clinical and imaging risk factors have been reported, such as age of more than 40 years, large cyst size, lack of shading on MRI, and so on [4–6]. Investigators have also reported that patients with endometriotic cysts have decreased dysmenorrhea after malignant transformation occurs [5]. Of these findings, enhancement of mural nodules seems to be the most valuable imaging finding [6, 7]; however, benign conditions with this finding have been also reported [8–14].

The purpose of this study was to clarify the MR findings of ovarian cancer in association with endometriotic cysts by comparing the findings in benign and malignant lesions in detail.

Materials and Methods

From a review of our PACS for the period of April 1997 to November 2006, we found 71 cases with findings that could be suspicious for ovarian cancer in association with endometriosis. Patients were initially selected for entry in this study by gynecologists in an outpatient clinic. We picked primary candidates who had cystic adnexal masses with some solid parts on transvaginal or transabdominal ultrasound by reviewing the order form for the pelvic MR examination. Patients with adnexal masses that showed MR characteristics of endometriotic cysts and mural nodules or eccentric cyst-wall thickening were included as secondary candidates and a contrast study was added. Our MR criteria for the endometriotic cysts were hyperintense masses with a thick wall or septa on fat-saturated T1-weighted images and at least one of the following findings:

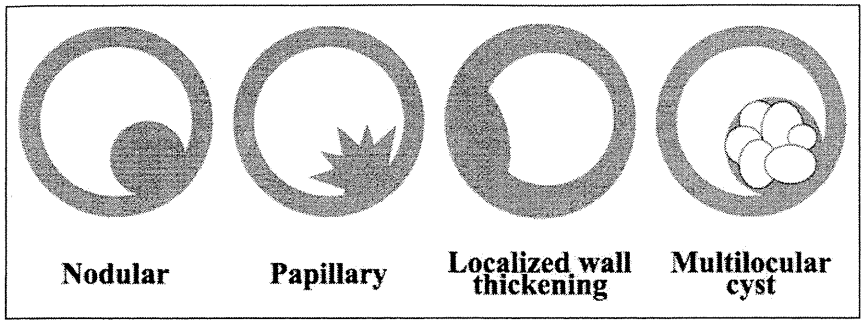


Fig. 1—Illustration shows morphologic classification of protruded cyst wall. We classified morphologic pattern of protruded cyst wall into four types: nodular, papillary, localized wall thickening, and multilocular cyst.

shading on T2-weighted images, multilocular cyst, or adhesion to the surrounding organ. Shading is a characteristic finding of endometriotic cysts, as reported by Nishimura et al. [15], and is defined as a centrally or peripherally located low-intensity area in the hyperintense cyst. The mural nodules were defined as focal bulging of the cyst wall toward the center of the cyst at an acute angle. For inclusion in the study, the secondary candidates were required to have MR characteristics of both the endometriotic cysts and mural nodules or eccentric cyst-wall thickening. Surgical removal was performed in 55 of 66 secondary candidates; however, ectopic endometrial tissue was not observed in the surgical specimen in six cases. Therefore, 49 cases with histopathologically confirmed ovarian endometriotic cysts were included in this study.

MR examinations were performed using 1.5-T superconducting units (Gyroscan, Philips Healthcare). Images were obtained with a phased-array body coil in all patients. Butyl scopolamine (Buscopan, Boehringer Ingelheim) was given intramuscularly just before the examination to reduce bowel peristalsis. Axial T1-weighted images, T2-weighted images, and fat-saturated T1-weighted images were obtained. Contrast enhancement was also performed with IV administration of 5 mmol of gadopentetate dimeglumine (Magnevist, Bayer HealthCare). The field of view (FOV) was 28 cm in all sequences except a 3D dynamic contrast study.

T1-weighted images were obtained with a spin-echo sequence (TR range/TE range, 340–545/11–20; slice thickness, 4–10 mm; intersection gap, 0.4–2 mm; 2–4 excitations), and T2-weighted images were obtained with a fast spin-echo sequence (TR/TE, 1,800/100; echo-train length, 16; slice thickness, 4–10 mm; intersection gap, 0.4–2 mm; 2 excitations). Fat-saturated T1-weighted images were obtained using a spectral presaturation with inversion-recovery sequence (425–680/10–12); the slice thickness and intersection gap were the same as those used for T1-weighted imaging before contrast administration with 2–3 excitations.

After administration of contrast material, fat-saturated T1-weighted images were obtained using the same parameters as those used before contrast enhancement in six patients, a 2D dynamic contrast study with subtraction with turbo field-echo imaging (12/4.6; slice thickness, 8–10 mm; 4 or 6 planes; 6 excitations; temporal resolution, 31 milliseconds) was used in 34 patients, and a 3D dynamic contrast study with subtraction with T1 high-resolution isotropic imaging (4.3/2.0; FOV, 40 cm; slice thickness, 4 mm with 2-mm overlap; 40–80 planes; 1–2 excitations; temporal resolution, 20–40 seconds) was performed in nine patients.

MR findings were retrospectively reviewed without the knowledge of surgical or pathologic findings by two radiologists in consensus who were familiar with gynecologic MRI. They evaluated the size and nature of the endometriotic cysts: whether disease was unilateral or bilateral, the ratio of the maximum diameter of the affected cyst to the contralateral cyst, whether cysts were unilocular or multilocular, and the presence of shading. A patient was considered to have bilateral disease only when the contralateral ovary had another lesion that met our criteria for endometriotic cysts. The ratio of the maximum diameter of the affected cyst to the contralateral cyst was calculated only when the patient had bilateral disease. In other words, we excluded the cases with unilateral disease from that statistical analysis.

We also evaluated the size and nature of the mural nodules: shape, the maximum diameter, signal intensity compared with the outer myometrium on T1- and T2-weighted images, and contrast enhancement. We classified the morphologic pattern of the protruded cyst wall into four types (Fig. 1). The first type was the nodular type in which one or more mural nodules had a smooth margin over the entire surface of the mural nodules. The second type was the papillary type in which one or more mural nodules had a papillary surface. The third type was multilocular cysts in which the mural nodules were composed of cysts with thin septa. The fourth type was localized wall thickening in which the eccentric cyst-wall thickening was at an obtuse angle. The localized wall thickening type was slightly different from the other three types, although we included cysts of this type in our study because cyst-wall thickening has been reported as a sign for malignant cystic adnexal masses [16].

Statistical analysis between benign and malignant diseases was also performed using the Mann-Whitney *U* test (Prism 4, GraphPad Software) for Macintosh (Apple Computer) to evaluate for differences in patients' age, maximum cyst diameter, and type of protruded cyst wall.

Results

The final pathologic diagnoses are summarized in Table 1. Thirty-three patients had a malignant condition (Fig. 2) and 16, a benign condition (Fig. 3). Only one diagnosis in the benign category was a mucinous cystadenoma, and the others were not associated with neoplasms. In the malignant group, four cases were borderline epithelial neoplasms, 28 were carcinomas, and the remaining one was adenosarcoma. The histologic subtype was se-

TABLE 1: Histopathologic Diagnosis of the Cases

Histopathology	No. of Cases
Malignant condition	
Borderline malignancy	
Serous	2
Mucinous	1
Endometrioid	1
Adenocarcinoma	
Serous	5
Clear cell	8
Endometrioid	11
Mixed	3
Undifferentiated carcinoma	1
Adenosarcoma	1
Benign condition	
Benign neoplasm	
Mucinous cystadenoma	1
Endometriosis with inflammation	1
Pure endometriosis	14

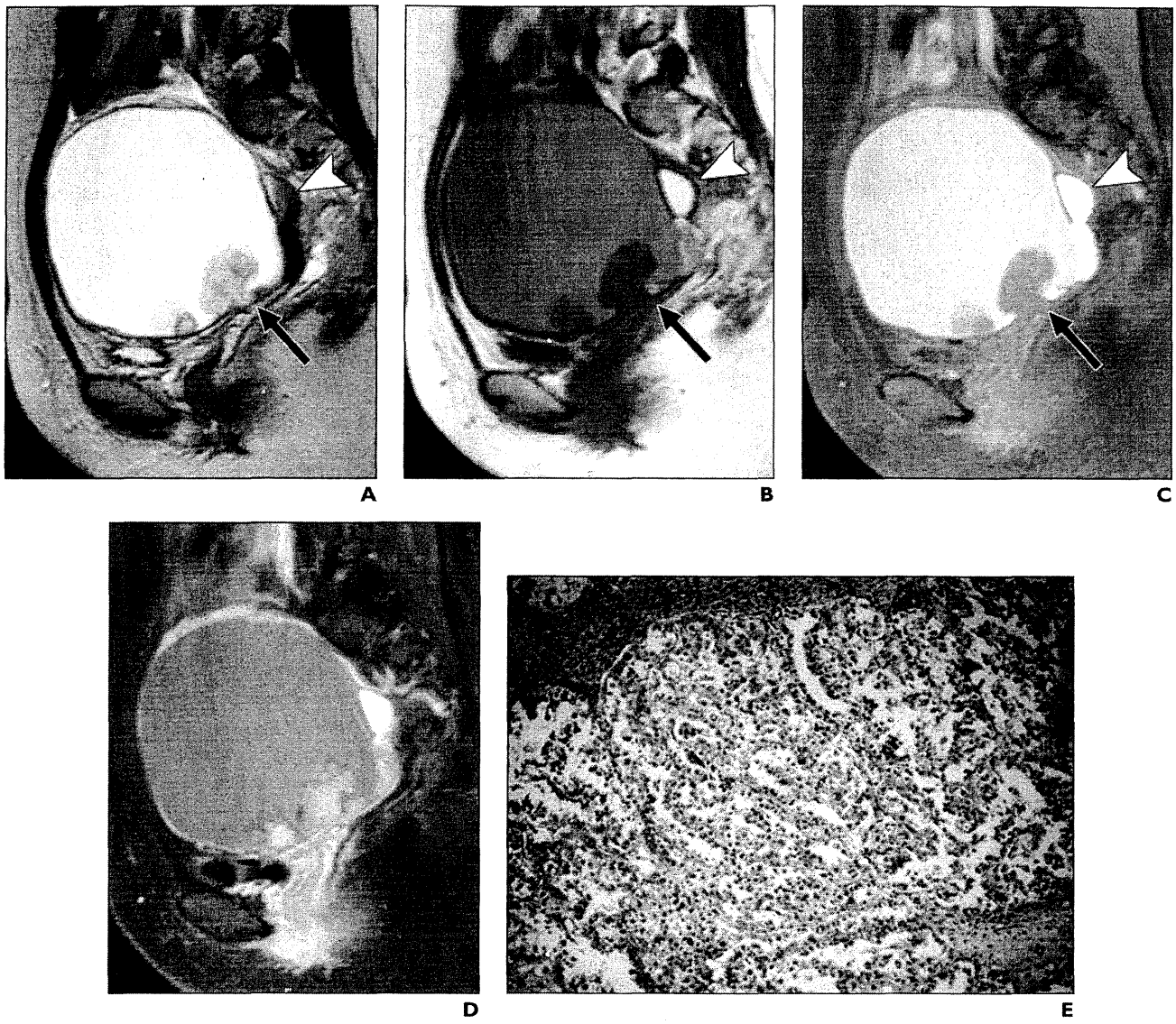
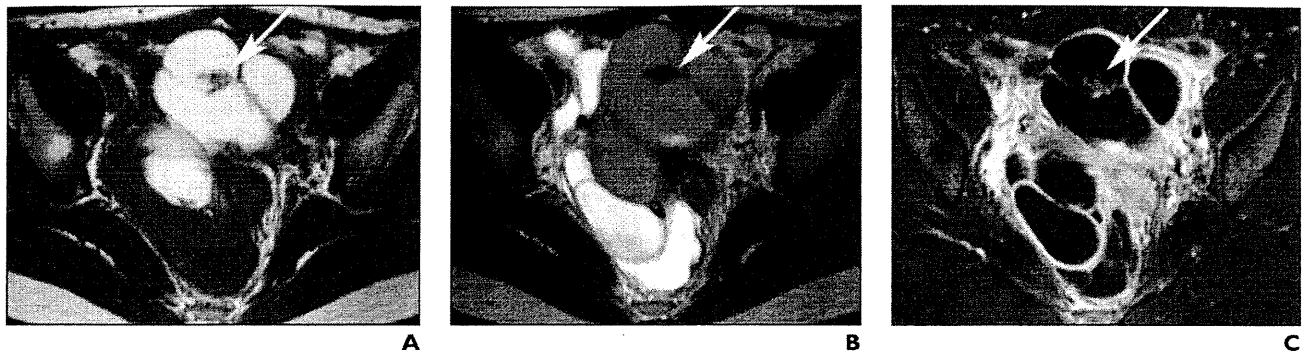


Fig. 2—Clear cell adenocarcinoma arisen from endometriotic cyst of left ovary (International Federation of Gynecology and Obstetrics stage Ic) in 35-year-old woman.
A–C, There are two cysts in pelvis: Larger cyst shows high signal on T2-weighted image (**A**) (TR/TE_{eff}, 1,800/100) and slightly high signal on T1-weighted image (**B**) (TR/TE, 594/10). Signal was not suppressed by fat-suppressed T1-weighted image (**C**) (680/10). There are two papillary projections (*arrows*) on floor of cyst that show high signal on T2-weighted image and low signal on T1-weighted image. We can also see another cyst (*arrowheads*) that is diagnosed as typical endometriotic cyst in contralateral ovary. It shows high signal intensity on T1-weighted images and diffusely low signal intensity on T2-weighted image. Note lack of shading on T2-weighted image in endometriotic cyst with malignancy.
D, After administration of gadolinium-based contrast medium, enhanced fat-saturated T1-weighted image (680/10) shows that center parts of nodules were strongly enhanced.
E, Photomicrograph of histologic specimen shows that tumor is composed of tumor cells deranged in papillary fashion, accompanied by ectopic endometrial glands with stroma. (H and E, low-power field)

rous in two cases, mucinous in one case, and endometrioid in one case for the borderline malignancies, whereas the histologic subtype was serous in five, clear cell in eight, endometrioid in 11, and mixed in three for adenocarcinomas. Postoperative clinical stage, established using the International Federation of Gynecology and Obstetrics classification system of 29 malignant ovarian tumors, was Ia in eight, Ib in two, Ic in six, IIc in three, IIIa in one, and IIIc in nine.

The imaging characteristics of the study group are summarized in Table 2.

The mean age of the patients with a benign condition was 36 years (range, 25–57 years), whereas that of patients with a malignant condition was 44 years (range, 26–65 years) (Fig. 4). The mean age was significantly higher in the malignant group than in the benign group ($p < 0.05$, Mann-Whitney U test). The mean maximum cyst diameter was 7.8 cm (range, 3.2–14.2 cm) in the benign group and 11.2 cm (range, 4.0–19.2 cm) in the malignant group (Fig. 5). It was also significantly larger in the malignant group ($p < 0.05$, Mann-Whitney U test). Disease was unilateral in seven of the 16 benign cases and 12 of the 33 malignant



A B C

D

Fig. 3—Endometriotic cysts of bilateral ovaries in 35-year-old woman. There are two multilocular cystic masses in pelvic cavity. One is located at right posterolateral side of uterus and other, at left anterolateral side.
A–C, Both cysts show high signal intensity with hypointense capsule and septa on T1-weighted image (**A**) (TR/TE, 594/10). Left anterior mass (*arrows*) has papillary projection on wall of cyst with low signal intensity on both T1-weighted image and T2-weighted image (**B**) (TR/TE_{eff}, 1,800/100) and shows contrast enhancement on enhanced fat-saturated T1-weighted image (**C**) (680/10). Content of cyst with papillary projection shows low signal intensity on T2-weighted image in contrast to Figure 2B due to shading.
D, Photomicrograph shows that papillary projection is composed of fibrotic tissue with hemorrhage within endometriosis. On the other hand, right posterior mass that partly included hyperintense fluid on T1-weighted images that showed shading on T2-weighted images can be also diagnosed as endometriotic cyst. It does not show any protrusion of cyst wall. (H and E, low-power field)

cases. The ratio of the maximum diameter of the affected cysts to the maximum diameter of the contralateral cysts was larger in the malignant group (range, 0.6–296.3; mean, 29.6) than in the benign group (range, 0.5–5.7; mean, 2.2); however, the difference was not statistically significant.

Thirteen of the 16 benign cysts showed shading on T2-weighted images, whereas shading was seen in only 11 of the 33 malignant cysts. The shape of the cyst wall protrusion was nodular in 11, papillary in three, multilocular cystic in 0, and localized wall thickening in two in the benign group and was 17, 14, two, and 0 in the malignant group, respectively. Nodular- and papillary-shaped mural nodules were seen in both groups; however, localized wall thickening was seen in only the benign group. The mean maximum diameter of the mural nodules was 1.2 cm (range, 0.4–2.3 cm) in benign and 4.3 cm (range, 1.0–8.7 cm) in malignant lesions. It was also statistically larger in the malignant group ($p < 0.0001$, Mann-Whitney U test) (Fig. 6).

The signal intensity of the mural nodules varied in both groups on T1- and T2-weighted images. On T1-weighted images, the malignant mural nodules showed high signal in two patients, intermediate signal in seven, and low signal in 24, whereas the benign mural nodules showed signal in three, four, and 9, respectively. On the other hand, on T2-weighted images, the malignant mural nodules showed high signal in 18 patients, intermediate signal in nine, and low signal in six, whereas the benign mural nodules showed signal in nine, two, and five, respectively. All but one malignant lesion had enhancing mural nodules, but there were seven benign masses with enhancing mural nodules (Figs. 2 and 3).

Discussion

Endometriosis is defined as the presence of endometrial tissue outside the endometrium and myometrium. This condition is predominantly found in women of reproductive age and typically causes pelvic pain and infertility. Ovaries are one of the most common sites that endometriosis affects. One of the major treatment options is surgical removal of the ovaries; however, preservation of the reproductive function is desirable in most women with endometriosis [17]. Development of hormonal therapy, such as gonadotropin-releasing hormone agonist and the tendency to put off marriage in developed countries have caused the rate of hysterectomy from endometriosis to decrease [18]. This phenomenon results in an increased number of patients with endometriosis seeking care in outpatient clinics. On the other hand, malignant tumors that develop from endometriotic cysts have come to the attention of gynecologists [1, 2, 19]. Although the exact prevalence of malignant tumors arising from endometriotic cysts of the ovary is unknown, studies in Japan have indicated a prevalence of approximately 0.7% [20, 21]. Investigators have also reported that clear cell and endometrioid adenocarcinomas are the malignancies most commonly seen in ovarian endometriosis [22, 23].

In our series, 11 of the 33 malignant tumors were endometrioid adenocarcinoma, which was the leading pathology, and eight were clear cell adenocarcinoma. These findings with regard to prevalence are similar to those in previous reports. The results of a clinicopathologic study also indicated that ovarian cancer

TABLE 2: Patient Age and Imaging Characteristics of the Cases

Characteristic	Pathologic Diagnosis		*p*
	Benign	Malignant	
Patient age (y)			< 0.05
Mean	36	44	
Maximum cyst diameter (cm)			< 0.05
Mean	7.8	11.2	
Unilateral vs bilateral, no. of cases			—
Unilateral	7	12	
Bilateral	9	21	
Ratio of maximum diameter of affected cyst to maximum diameter of contralateral cyst			NS
Mean	2.2	29.6	
Shading present, no. (%) of patients	13/16 (81.3)	11/33 (33.3)	—
Shape of mural nodules, no. of cases			—
Nodular	11	17	
Papillary	3	14	
Multilocular cystic	0	2	
Localized wall thickening	2	0	
Maximum diameter of mural nodules (cm)			< 0.0001
Mean	1.2	4.3	
Signal intensity of mural nodules			
T1-weighted imaging			—
High	3	2	
Intermediate	4	7	
Low	9	24	
T2-weighted imaging			—
High	9	18	
Intermediate	2	9	
Low	5	6	
Enhancement of mural nodules present, no. (%) of cases	7/16 (43.8)	32/33 (97.0)	—

Note—Dash (—) indicates not applicable. NS = not statistically significant.

with endometriotic cysts tended to show at an earlier stage and to be associated with a better prognosis than conventional ovarian cancer without endometriosis [3, 24]. Tanaka et al. [6, 12] reported enhancing mural nodules were the most important risk factor for ovarian cancer arising from endometriosis; however, other pathologic conditions with such imaging findings have also been reported [8, 9, 11–14] including polypoid endometriosis [14], decidualized endometriotic cysts during pregnancy [11, 12], Müllerian mucinous borderline tumors [13], and so on. Therefore, other imaging criteria are needed to detect coexisting malignancy.

Kobayashi et al. [4, 21] reported that postmenopausal women had a high risk of ovarian cancer arising from endometriosis during a follow-up period of up to 17 years in a cohort of patients with ovarian endometriomas. Our study also indicated that patients with malignancy were significantly older than those without malignancy. In the era of MRI, radiologists can easily diagnose ovarian endometriotic cysts with multilocular cystic masses [25], adhesions [26], hyperintense fluid on T1-weighted images, and shading on T2-weighted images [15, 25]. Therefore, we should pay attention to the possibility of coexisting malignancy when diagnosing endometriotic cysts of the ovaries especially in patients older than 45 years.

Kobayashi et al. [21] reported that there is an increased risk of malignancy in endometriotic cysts larger than 10 cm. Our study showed the mean diameter of the cysts with malignancy was 11.2 cm, which was significantly larger than that of cysts without malignancy. On the other hand, Tanaka et al. [6] reported that endometriotic cysts with malignancy tended to show unilateral disease or were larger compared with contralateral disease. In this study, 44% of patients with benign findings showed unilateral disease, whereas only 36% of patients with malignant conditions had unilateral disease. Therefore, larger cyst size seems to be a risk factor for malignancy, although asymmetric cyst size did not show a statistically significant correlation with coexisting malignancy.

Lack of shading on T2-weighted images has been reported as another risk factor for malignancy [6]. In this study, 81% of benign cysts showed shading on T2-weighted images, whereas shading was seen in only 33% of the malignant cysts. Because epithelial ovarian carcinomas typically appear as predominantly cystic mixed masses [16], the tumor cells are expected to produce some fluid. On the other hand, hemorrhagic fluid is within the endometriotic cysts before carcinoma develops, which causes shading that appears as prominent low intensity within a loculus on T2-weighted images [15]. Therefore, dilution of the hemorrhagic contents by nonhemorrhagic fluid produced by the malignant tumors may be a cause of lack of shading.

Mural nodules with contrast enhancement seem to be the most valuable imaging finding suggestive of coexisting carcinoma [6, 7]; however, other conditions with this finding have also been reported [8–13]. Polypoid endometriosis is an uncommon and distinctive form of endometriosis with histologic features simulating an endometrial polyp. It has been defined as "exophytic or polypoid, tumor-like masses that project from a serosal or mucosal surface or from the lining of an endometriotic cyst" [27]. This entity, associated with tamoxifen therapy against breast cancer, has also been reported in the pathology literature [27, 28]. Kraft and Hughes [9] and Takeuchi et al. [14] independently reported one patient with polypoid endometriosis that showed mural nodules on the endometriotic cysts of the ovary. This entity and nodular endometriosis reported by Onbas et al. [10] showed intense enhancement with gadolinium-based contrast materials. In fact, seven of 16 cases without malignancy in our study also showed mural nodules with contrast enhancement. In these cases, one had granulomatous tissue within the ectopic endometriotic tis-

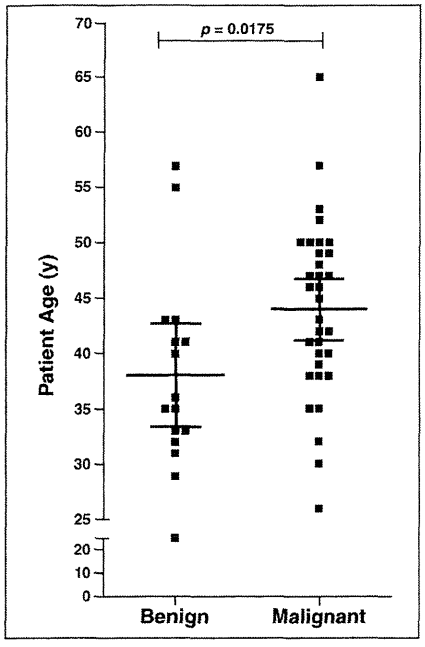


Fig. 4—Statistical analysis using Mann-Whitney *U* test reveals that age of patients in malignant group is significantly higher than benign group ($p < 0.05$). Long horizontal bar indicates mean and short bars, ± 1 SD.

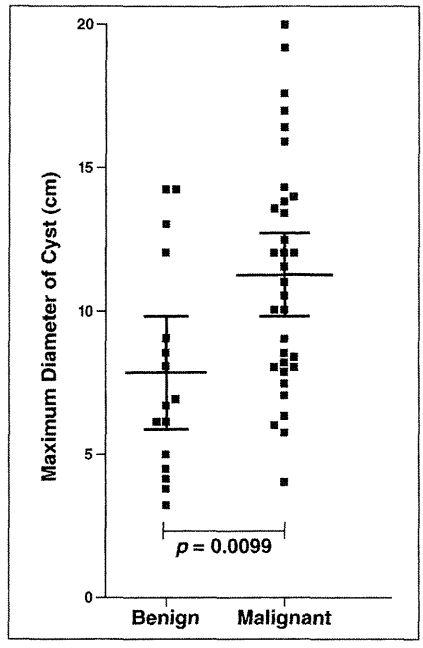


Fig. 5—Statistical analysis using Mann-Whitney *U* test reveals maximum diameters of cysts in malignant group are significantly higher than those in benign group ($p < 0.0099$). Long horizontal bar indicates mean and short bars, ± 1 SD.

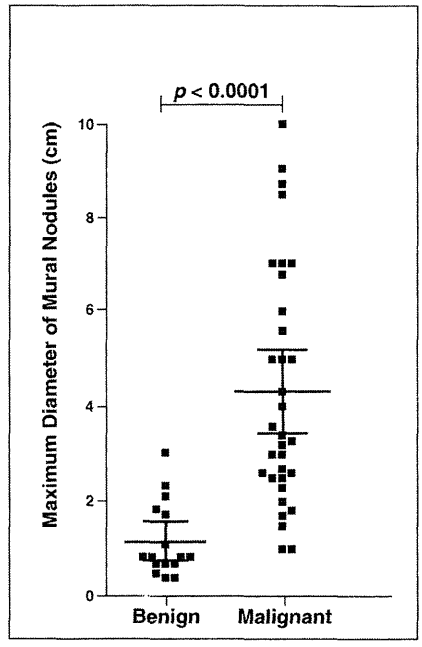


Fig. 6—Statistical analysis using Mann-Whitney *U* test reveals maximum diameters of mural nodules in malignant group are significantly higher than those in benign group ($p < 0.0001$). Long horizontal bar indicates mean and short bars, ± 1 SD.

sue; however, most of the cases were composed of only endometriosis. Thus, even benign endometriotic tissue can produce a mural nodule with contrast enhancement.

Deciduosis of the ectopic endometrial tissue is another cause of mural nodules on the endometriotic cysts [11, 12]. Decidualized endometriotic cysts usually show extremely high intensity on T2-weighted images and are isointense to the placenta on all MR sequences [12]. Therefore, we believe that they may be distinguished from malignancy by clinical findings and the signal intensity of the mural nodules. Kataoka et al. [13] reported cases of Müllerian mucinous borderline tumor arising from endometriotic cysts. In their study, the tumors appeared as mural nodules on the endometriotic cysts, which showed prominent high signal intensity on T2-weighted images [13]. One of the patients in our study also had a Müllerian mucinous borderline tumor in which the mural nodules showed very high signal intensity on T2-weighted images. On the other hand, 17 other malignant and nine benign cases in our study showed hyperintense mural nodules on T2-weighted images. Outwater et al. [29] reported that large papillary projections corresponding to neoplasms had distinct internal architecture including a fibrous stalk supporting clumps of edematous papillae. They also mentioned that even a functional ovarian cyst could make nondescript papillary projections that show intermediate signal on T2-weighted images. Because we studied only the signal intensity of the mural nodules but not the internal architecture, we cannot comment about this issue. The results of our study did indicate that the signal intensity on T2-weighted images varied in both benign and malignant groups. In addition, even papillary projections as small as 1 cm in diameter were within malignant tumors. Therefore, we speculate that we cannot accurately diagnose the pathology of mural nodules by their signal intensity.

The size of mural nodules has not been evaluated in any other study, to our knowledge, concerning neoplasms accompanied by endometriotic cysts. Our study revealed that the maximum diameter of the mural nodules was significantly larger than that of benign conditions. We speculate that this characteristic may be the third point to distinguish malignancy arising from endometriosis from benignancy. However, there was some overlap between the malignant and benign groups. The smallest mural nodule of the malignant group was 1.0 cm, whereas the largest mural nodule of the benign group was 3.0 cm. Therefore, the findings are indeterminate for mural nodules with a diameter of between 1.0 and 3.0 cm.

The differential diagnosis of endometriosis is important because we had to remove six cysts that met our MR criteria but did not have endometriosis by pathologic examination. We believe that the adhesive findings may be a hallmark of endometriosis; however, our criteria did not include imaging findings suggesting adhesion such as posterior cul-de-sac obliteration, retroversion of the uterus, or elevation of the posterior vaginal fornix [30]. Therefore, six cases without endometriosis met our MR criteria for endometriotic cysts. In these cases, three of the six were primary epithelial ovarian carcinoma, two were epithelial ovarian tumor of borderline malignancy, and the remaining one was a metastatic tumor of the endometrial carcinoma. Radiologists should know that malignant ovarian tumors—even borderline malignancies—may have bleeding and may mimic endometriotic cysts.

There are some limitations in this study. First, there was selection bias in the study population. We selected cases with endometriosis using findings of unenhanced MRI. As others have previously reported, endometriosis in mild disease cannot be diagnosed even with fat-saturated T1-weighted images [26, 31]. Therefore, endometriosis with mild disease or atypical MR findings might have been excluded from this study. On the other hand, nine of

33 cases with malignancy had stage IIIc disease. Some of these were apparently malignant by ancillary criteria including intraperitoneal dissemination or lymph node metastases [16]. Thus, an advanced stage of disease might cause significant differences between malignancy and benignancy. If the study population is limited to those with stage I disease, then further evaluation will be needed.

In this study, our cases did not always match the criteria for ovarian carcinoma arising from endometriosis advocated by Sampson [1]. According to those criteria, the ovarian carcinomas should include the transitional pathology between the benign endometrial tissue with their stroma and the malignant tumors. However, we did not see such transitional lesions histopathologically in our cases. Therefore, our cases may include cases with endometriotic cysts incidentally seen with other pathology, as reflected in the title of our article.

The third limitation is that the MR protocols used were not uniform, with different parameters such as slice thickness or number of excitations, because of the retrospective nature of this study. In this study, we emphasized the size of the mural nodules, some of which were less than 1 cm. Because strict calculation is needed in this kind of study, a 10-mm slice thickness seemed inadequate.

The results of our study revealed that malignant tumors associated with endometriotic cysts tended to appear in older patients, in patients with larger endometriotic cysts, and in patients with endometriotic cysts without shading on MRI, as previously reported. Enhanced mural nodules are still an important finding, but there are some exceptions. We emphasize the importance of the size of the mural nodules in diagnosing malignancy associated with endometriotic cysts. Despite some overlap, the presence of mural nodules larger than 3 cm in maximum diameter was a strong indicator of coexisting malignancy in our study.

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EXPERT REVIEWS

Neoadjuvant chemotherapy for advanced ovarian cancer: overview of outcomes and unanswered questions

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Neoadjuvant chemotherapy for advanced ovarian cancer was initially administered as an alternative treatment for patients not suitable for primary debulking surgery (PDS) because of unresectable tumor or poor performance status. Accumulation of favorable outcomes of this treatment compared with standard treatment starting with PDS made this strategy a candidate for prospective, randomized Phase III studies without limiting the subjects to patients who were unsuitable for PDS. Among the four Phase III studies to date, the earliest study from the European Organization for Research and Treatment of Cancer (EORTC) has revealed noninferior survival with less-serious morbidity in the neoadjuvant chemotherapy arm. These data suggest that neoadjuvant chemotherapy followed by surgical cytoreduction is an acceptable management strategy for patients with advanced ovarian cancer. In this article, we review the treatment outcomes and discuss some unanswered questions, as well as possible future research in this area.

Keywords: interval debulking surgery • neoadjuvant chemotherapy • optimal surgery • ovarian cancer • primary debulking surgery • prognosis • standard treatment

Primary debulking surgery (PDS) followed by chemotherapy (PDS-CT) has been considered a standard treatment procedure for patients with advanced ovarian cancer. Griffiths first demonstrated that survival time was inversely proportional to residual mass size after PDS, and the observation was reproduced and confirmed by many succeeding studies [1]. The goal of debulking surgery is to remove as much of the bulky tumor as possible. According to a recent definition, an optimal surgery achieves a maximum residual tumor size of <1 cm in diameter, which leads to much better survival compared with suboptimal debulking (i.e., nonoptimal debulking). Disappointingly, optimal debulking can be achieved in only 30–60% of stage III/IV ovarian cancers at average institutions [2,3], and physicians often hesitate to perform aggressive debulking surgery in patients with impaired performance status (PS) owing to highly advanced disease.

Another treatment strategy, consisting of neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) followed by postsurgical chemotherapy (NAC-setting treatment or NACT), emerged as an alternative approach to PDS-CT in patients with apparently unresectable, bulky tumors or poor PS. The strategy arose from an adoption of IDS as secondary debulking after suboptimal PDS and later an omission of PDS in patients who supposedly would have little benefit from PDS.

Many retrospective studies revealed that survival of patients treated by NACT was comparable with that of patients treated by PDS-CT, although the NACT group had more advanced disease and/or poorer PS. Based on these favorable results for NACT, several prospective studies to assess the efficacy of NACT were conducted. Furthermore, prospective Phase III randomized studies have been conducted without limiting the subjects to patients with apparently unresectable tumors and/or poor PS, and extended target diseases to not only ovarian cancer but also tubal and peritoneal cancers.

The results of the first Phase III NAC trial by the European Organization for Research and Treatment of Cancer (EORTC) have been

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recently published [4]. Results from other Phase III studies conducted in the UK, India and Japan are expected in the next few years. In this article, we review the outcomes of NACT, focusing on a comparison with that of PDS setting treatment, and discuss some of the questions concerning NACT.

Outcome of NACT

Comparable outcomes & reduced morbidity of NACT compared with PDS-CT in retrospective & prospective, nonrandomized comparative studies

To date, numerous retrospective studies reporting treatment results and complications of NACT have been published. Among these, studies comparing treatment outcomes (Table 1) [5–16] and complications related to debulking surgery (Table 2) [5,7,8,10,12,14–17] between PDS-CT and NACT are summarized. In most of the studies, NACT was administered to patients who had older age, more advanced disease or a lower PS, whereas characteristics of subjects for NACT and PDS-CT were not statistically different in studies by Jacob *et al.* [5], Vrščaj *et al.* [9] and Morice *et al.* [10]. In these highly biased settings unfavorable to NACT, all of the studies showed a similar or higher proportion of optimal debulking surgery in NACT, and all but one study by Steed *et al.* yielded noninferior outcomes of NACT compared with those of PDS-CT (Table 1) [14]. After controlling for age, the International Federation of Gynecology and Obstetrics stage, histologic grade and pleural effusions, even the study by Steed *et al.*, demonstrated no statistical difference in overall survival (OS; p = 0.95) between NACT and PDS-CT. As for the invasiveness of debulking surgery,

Table 1. Comparison of outcomes between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in retrospective studies.

Study (year)	Treatment	Patients (n)	Survival		Optimal debulking surgery			Ref.
			MST	Significance	Definition (cm)	Proportion	Significance	
Jacob *et al.* (1991)	PDS-CT	18	18 months		<2	39 (7/18)		[5]
	NACT	22	16 months	NS	<2	77 (17/22)	p = 0.02	
Onnis *et al.* (1996)	PDS-CT	284	21%†		<2	29 (83/284)		[6]
	NACT	88	19%†	NS	<2 cm	42 (37/88)	p = 0.027§	
Schwartz *et al.* (1999)	PDS-CT	206	2.18 years		NA	NA		[7]
	NACT	59	1.07 years	NS	NA	NA		
Kayikçioğlu *et al.* (2001)	PDS-CT	158	38 months		0	14 (22/158)		[8]
	NACT	45	34 months	NS	0	49 (22/45)	p < 0.001	
Vrščaj *et al.* (2002)	PDS-CT	55	26 months		<1	22 (12/55)		[9]
	NACT	20	25 months	NS	<1	60 (12/20)	p = 0.001	
Morice *et al.* (2003)	PDS-CT	34	22 months		<2	94 (32/34)		[10]
	NACT	34	26 months	NS	<2	94 (32/34)	NS	
Loizzi *et al.* (2005)	PDS-CT	30	40 months		<1	60 (18/30)		[11]
	NACT	30	32 months	NS	<1	63 (19/30)‡	NS§	
Everett *et al.* (2006)	PDS-CT	102	42 months		<1	54 (55/102)		[12]
	NACT	98	33 months	NS	<1	86 (84/98)	p < 0.001	
Inciura *et al.* (2006)	PDS-CT	361	25 months		<2	67 (242/361)		[13]
	NACT	213	24 months	NS	<2	63 (134/213)	NS	
Steed *et al.* (2006)	PDS-CT	66	3.7 years		<2	50 (33/66)		[14]
	NACT	50	2.4 years	p = 0.03	<2	52 (26/50)‡	NS§	
Hou *et al.* (2007)	PDS-CT	109	47 months		<1	71 (77/109)		[15]
	NACT	63	46 months	NS	<1	95 (60/63)	<0.001	
Colombo *et al.* (2009)	PDS-CT	142	38 months		<1	63 (89/142)		[16]
	NACT	61	26 months	NA	<1	84 (51/61)	p = 0.003§	

†Shows 5-year survival rates.
‡Recalculated as to include all patients into denominators.
§Calculated using Fisher's exact test because the values are not available.
MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

Table 2. Comparison of surgical invasiveness between primary debulking surgery and interval debulking surgery in retrospective studies.

Study (year)	Treatment	Patients (n)	Blood loss	Blood transfusion	Bowel resection	Stoma	Surgical complications	Stay in ICU	Duration of hospitalization	Ref.
Jacob *et al.* (1991)	PDS-CT	18	44% (>2000 ml)							[5]
	NACT	22	31% (>2000 ml)							
			NA							
Schwartz *et al.* (1999)	PDS-CT	206	1000 ml					1.26 days	11 days	[7]
	NACT	59	600 ml					1.03 days	7 days	
			p = 0.001					p = 0.01	p < 0.001	
Kayikçioglu *et al.* (2001)	PDS-CT	158			16% (colon)	11%				[8]
	NACT	45			2% (colon)	0%				
					p = 0.01	p = 0.02				
Morice *et al.* (2003)	PDS-CT	28		39%	61%	7%	36% (severe)			[17]
	NACT	57		21%	19%	5%	7% (severe)			
				NS	p = 0.01	NS	p = 0.01			
Morice *et al.* (2003)	PDS-CT	34		56%	73%		53%	36%	20 days	[10]
	NACT	34		18%	18%		12%	12%	12 days	
				p < 0.001	p < 0.001		p < 0.001	p = 0.02	p < 0.001	
Everett *et al.* (2006)	PDS-CT	102		2.47 U	11%		15%	1.8 days	6 days	[12]
	NACT	98		3.02 U	16%		17%	1.5 days	6 days	
				NS	NS		NS	NS	NS	
Steed *et al.* (2006)	PDS-CT	66			5% (colon)					[14]
	NACT	50			2%† (colon)					
					NS					
Hou *et al.* (2007)	PDS-CT	109	1033 ml	2.4 U	22% (colon)	3%	34%	1.6 days	8.5 days	[15]
	NACT	63	546 ml	1.2 U	5%† (colon)	0%	28%†	2 days	5.7 days	
			p < 0.0001	p = 0.03	p = 0.004‡	NA	NS	NS	p < 0.0001	
Colombo *et al.* (2009)	PDS-CT	142			51%	4%	12% (major)		14 days	[16]
	NACT	61			51%	8%	13% (major)		14 days	
					NA	NS‡	NS		NS	

†Patients who did not underwent interval debulking surgery are not included in denominators.
‡Calculated using Fisher's exact test.
NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

several studies revealed significantly less invasiveness in the NACT group. For example, compared with the PDS group, the NACT group had a smaller amount of blood loss, lower rate or amount of blood transfusion, lower rate of bowel resection, lower rate of splenectomy, lower rate of surgical morbidities, shorter and less frequent stay in an intensive care unit (ICU) and shorter duration of hospitalization (Table 2). In addition to the benefits for the NACT group compared with the PDS-CT group described in Table 2, a significantly lower frequency of tumor invasion to the appendix (22 vs 80%; $p < 0.001$) [8], a lower rate of permanent colostomy (6 vs 24%; $p = 0.04$) [10], a lower rate of complications requiring surgery (3 vs 21%; $p = 0.03$) [10], and a shorter duration of surgery (211 vs 276 min; $p < 0.0001$) [15] were also reported.

Kuhn *et al.* [18], Hegazy *et al.* [19] and Lee *et al.* [20] conducted similar comparisons by nonrandomized, prospective studies (Table 3). Kuhn *et al.* offered a NACT protocol to patients with stage IIIC ovarian cancer with an estimated >500 ml of ascites [18]. Patients who agreed with the proposal received NACT, and the other patients who refused the proposal received conventional PDS-CT treatment. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgeries in the NACT group and an improved median survival time (MST) in the NACT group.

Hegazy *et al.* chose NACT or PDS-CT for the patients with stage III/IV ovarian cancer according to tumor resectability estimated by diagnostic laparotomy or laparoscopy. Patients who received NACT because of tumor unresectability were older than the patients who received PDS-CT (average age: 58.7 vs 53.6 years, respectively; $p = 0.04$) [19]. They reported no difference in proportion of optimal surgery and OS.

Lee *et al.* selected patients who received NACT for stage IIIC/IV ovarian cancer according to diagnoses based on imaging studies, such as computed tomography (CT) or MRI [20]. Patients who refused NACT received PDS-CT. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgery in the NACT group, but the improvement did not impact survival.

As for surgical invasiveness of NACT compared with PDS-CT, two studies [19,20] showed statistically significant reductions of blood loss, and one study showed a reduction in the duration of ICU stay and hospitalization [19].

Giannopoulos *et al.* compared the parameters of surgical invasiveness between PDS-CT ($n = 29$) and NACT ($n = 35$) in the treatment of stage IIIC/IV ovarian cancer [21]. Patients treated with NACT were nonrandomly selected according to the unresectability of tumors evaluated by laparoscopy or CT imaging. They demonstrated that median, intraoperative blood loss (500 vs 1000 ml; $p = 0.043$), median hospital stay (7 vs 8 days; $p = 0.005$), and possibility of admission to the ICU (5.7 vs 48.3%; $p < 0.001$) were significantly less in the NACT group than in the PDS-CT group.

From these retrospective or nonrandomized, prospective, comparative studies, NACT did not seem to compromise the survival of patients with advanced-stage ovarian, tubal or peritoneal cancer and seemed to greatly reduce surgical invasiveness.

Increased possibility of optimal surgery by NACT but rather poor survival in meta-analyses

Bristow *et al.* selected 22 cohorts from 21 studies and performed a meta-analysis in order to determine the OS and relative effect of multiple, prognostic variables in cohorts of patients with advanced-stage ovarian cancer treated with NACT (Table 4) [22]. The main selection criteria for the study were:

- Subjects were predominantly (>90%) patients with stage III/IV epithelial ovarian cancer;
- Subjects underwent NAC that included cisplatin (CDDP) or carboplatin (CBDCA);
- Subjects underwent NAC prior to cytoreductive surgery.

The target period for the Medline search was from 1 January 1989 to 30 September 2005. Using linear regression models, the effects of six variables (i.e., the proportion of maximal interval cytoreduction, stage IV disease, taxane use, median number of NAC cycles, median age and year of publication) on MST were assessed. The weighted mean MST was 24.5 months, and the weighted mean proportion of maximum cytoreduction was 65.0%. All variables other than median age were significantly correlated to MST. Each 10% increase in maximum cytoreduction was associated with a 1.9-month increase in MST, and each incremental increase in NAC cycles was associated with a 4.1-month decrease in MST. The authors reported that the survival outcome of NAC was equivalent to that of suboptimal PDS (>1 cm) followed by six cycles of CDDP and cyclophosphamide in the Gynecologic Oncology Group (GOG) 111 trial (24.5 vs 24 months). They concluded that NACT is associated with inferior OS compared with PDS-CT. However, this conclusion was not surprising because NACT was initially predominantly administered to older patients, with more advanced-stage disease, or patients with low PS, as mentioned earlier.

Recently, Kang *et al.* published the results of a similar meta-analysis (Table 4) [23]. The main selection criteria for this study were identical with the preceding study. The target period for the Medline search was extended until 30 June 2008. Although the number of selected studies were the same, seven studies were excluded and seven newer studies were included. To produce more reliable results, they chose a random-effects model instead of a simple linear regression model. The weighted mean MST was 27.5 months, and the weighted mean proportion of maximum cytoreduction was 70.0%. Again, the proportion of maximal interval cytoreduction, taxane use and year of publication were significantly associated with MST. However, the proportion of stage IV disease and median number of NAC cycles did not have a statistically significant association with MST. Furthermore, they examined ten comparative studies between NACT and PDS-CT, and analyzed the proportion of optimal cytoreduction. They found that the risk of suboptimal cytoreduction in the NACT group was reduced to 0.5 (95% CI: 0.29–0.86; $p = 0.012$) compared with the PDS-CT group, and concluded that NACT helped gynecologic oncologists to achieve an increased rate of optimal cytoreduction.

Table 3. Comparison between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in nonrandomized prospective studies.

Variable/group	Kuhn et al.			Vergote et al.			Lecuru et al.		
	PDS-CT (n = 32)	NACT (n = 31)	p-value	PDS-CT (n = 32)	NACT (n = 27)	p-value	PDS-CT (n = 22)	NACT (n = 18)	p-value
Characteristics									
Age (years)	66 (median)	61 (median)	NS	53.6	58.7	p = 0.04	46.8	45.0	NS
Performance status 2 (%)							32	28	NS
Stage IV (%)				56	59	NS	9	11	NS
Perioperative data									
Performance of IDS		97% (30/31)			67% (18/27)			100% (18/18)	
Definition of optimal surgery	<2 cm	<2 cm		<1 cm	<1 cm		<2 cm	<2 cm	
Proportion of optimal surgery	63% (20/32)	84% (26/31)	p = 0.04	62% (20/32)	48% (13/27)	NS	46% (10/22)	78% (14/18)	p = 0.04
Blood loss				735 ml	420 ml	p = 0.02	1061 ml	620 ml	p = 0.04
Blood transfusion (median)	2 U	2 U	NS						
Duration of surgery	270 min	260 min	NS	190 min	150 min	NS			
Duration of ICU stay				4.4 days	1.7 days	p = 0.03			
Duration of hospitalization				15.9 days	10.5 days	p < 0.05	10.4 days	9.7 days	NS
Organ resection									
Intestinal resection	11	9	NS				3	1	NA
Other organ resection				11 in total	4 in total	NS	2	0	NA
Complications									
Ileus	3	0	NS						
Wound infection				2	2	NS			
Wound dehiscence	1	3	NS						
Fever >3 days	7	2	NS	7	1	NS			
Cystitis	2	1	NS						
Atelectasis	1	1	NS	1	1	NS			
Pleural effusion				2	0	NS			
Thromboembolism	1	1	NS	3	1	NS			
Survival									
MST	23 months	42 months	p = 0.007	28 months	25 months	NS	55 months	53 months	NS
PFS				19 months	21 months	NS	17 months	15 months	NS

IDS: Interval debulking surgery; MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy; PFI: Progression-free interval; PFS: Progression-free survival.

Final comparisons by prospective, randomized Phase III trials

Although NACT seems to be a promising approach for the treatment of patients with advanced-stage ovarian cancer, to become a standard treatment, it is necessary to demonstrate the superiority of NACT in treatment outcome or to show the noninferiority of NACT in treatment outcome and lower toxicity compared with PDS-CT. The most reliable and quickest way to demonstrate superiority or noninferiority of NACT is to conduct a randomized Phase III study comparing NACT and PDS-CT. Until now, at least four Phase III studies have begun in Europe [4,24], India (ClinicalTrials.gov identifier: NCT00715286 [101]) and Japan (TABLE 5) [25]. Subjects were patients with stage III/IV or IIIC/IV disease. In all studies, patients who were not suitable for PDS because of medical contraindication or poor PS were excluded. Target diseases included not only ovarian cancer but also tubal and peritoneal cancers in three European or Japanese studies.

The results of the earliest study by Vergote *et al.* in the EORTC trial (EORTC55971) have recently been published [4]. They compared NACT, which consisted of three cycles of NAC followed by IDS, and three cycles of postsurgical chemotherapy with PDS-CT, consisting of PDS followed by six cycles of postsurgical chemotherapy. The chemotherapy regimen was a combination of platinum and taxane chosen by each institution. Patients with biopsy- or cytology-proven stage IIIC/IV ovarian, tubal or peritoneal cancer were enrolled in the study. The study was open from September 1999 to December 2006 and 718 patients were enrolled. The outcome of 670 patients randomized into two treatment arms was analyzed. The largest residual tumor was ≤1 cm in diameter in 41.6% of patients after PDS and in 80.6% of patients after IDS. Although statistical analyses were not performed, postoperative infections, venous complications, fistula, hemorrhage and postoperative mortality tended to be lower after IDS in the NACT group than after PDS. The MST was 29 months in the PDS-CT group and 30 months in the NACT group, and the median progression-free survival (PFS) in both groups was 12 months in the intent-to-treat analysis. The hazard ratio for death in the NACT group compared with that in the PDS-CT group was 0.98 (90% CI: 0.84–1.13; p = 0.01 for noninferiority). They concluded that NACT was not inferior to PDS-CT as a treatment option for patients with bulky stage IIIC/IV ovarian carcinoma.

In March 2004, Kehoe *et al.* at the Medical Research Council Clinical Trials Unit (MRC-CTU) had started a Phase III part of a Phase II/III study named Chemotherapy or Upfront Surgery (CHORUS) [24]. The planned accrual number was 150 individuals in the Phase II part and 400 in Phase III part. The Phase III part of the study closed in August 2010. One of the distinct characteristics of the study was that patients were enrolled into the study based only on imaging diagnosis without cytological or histological confirmation. Other characteristics included that the chemotherapy regimen was a single-agent CBDCA or a combination with other agents chosen for each patient, and that the study was designed to demonstrate the noninferiority of NACT in OS by combining the data with that from the EORTC 55971 trial. The follow-up data are still accumulating, thus the results of the study have not yet been published.

The Japan Clinical Oncology Group (JCOG) conducted a similar Phase III study (JCOG0602) [25] after successfully completing a feasibility study (JCOG0206) [26,27]. Patients were enrolled into the study with a clinical diagnosis of stage III/IV ovarian, tubal or peritoneal cancer based on imaging studies, cytological diagnoses, serum CA125 (>200 U/ml) and carcinoembryonic antigen (CEA) titer (<20 ng/ml). Histological diagnosis, instead of cytology, was allowed in patients with available lesions without laparoscopy or laparotomy. Diagnostic laparoscopy or laparotomy after enrollment was not performed because their preceding feasibility study showed that target disease (i.e., stage III/IV ovarian, tubal and peritoneal cancer) can be diagnosed reliably using the same criteria adopted in this study. This means eliminating an extra surgical procedure for the purpose of the clinical trial in both treatment arms, and it has the advantage of allowing NACT to start earlier. Other special characteristics of the study were that the regimen of chemotherapy was restricted to a combination of paclitaxel (PTX) and CBDCA, the number of cycles of NAC was four, and the number of cycles of chemotherapy was eight in total, considering the advanced stage of the subjects.

Kumar *et al.* from the All India Institute of Medical Sciences are conducting a Phase III study. They set the target disease as stage IIIC/IV ovarian cancer [28,29]. Stage IV disease was restricted to disease upstaged owing to pleural effusion. Cytological or histological diagnosis was necessary before enrollment. The study started in November 2001 and is open according to information last updated on 14 July 2008 (ClinicalTrials.gov identifier: NCT00715286 [101]).

From the favorable results of the EORTC study, NACT may be one of treatment options available for patients with bulky stage IIIC or IV ovarian, tubal and peritoneal cancer. Furthermore, NACT would be expected to become a standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed and several problems are resolved by the following studies.

Problems & questions about NACT

As NACT becomes more widely used, several problems that should be solved or questions that should be answered will arise. We will discuss some of these important issues next.

How should target diseases be diagnosed before NACT?

In the PDS-CT treatment setting, the aims of surgery are to confirm the diagnosis of ovarian, tubal or peritoneal cancer; determine an accurate stage of the disease; and reduce bulky tumors.

We understand that it is necessary in principle to perform diagnostic laparoscopy or laparotomy in order to confirm diagnosis and stage of the disease before chemotherapy also in the setting of NACT. However, the procedure may spoil the merits of NACT, such as less-invasiveness and immediate initiation of treatment. How to quickly and accurately confirm the diagnosis of the disease before NACT is a major problem.

The MRC-CTU study allowed patients to enroll on the basis of diagnoses using imaging studies without cytological or histological confirmation [24]. To exclude gastrointestinal cancer,