Both PNQ sensory and motor scores were strongly correlated with the Ntx subscale scores and showed moderate correlation with the FACT-G total score, implying that the PNQ appears to have acceptable concurrent validity. The significant correlation observed between the PNQ sensory scores and the NCI-CTC sensory score was comparable to that reported in a previous study, which also showed associations between the Ntx subscale and the NCI-CTC [13].

The PNQ exhibited a good capability to measure changes in patients' perceived symptoms over time. This finding suggests that the PNQ would be useful for addressing potential issues in clinical decision-making, such as the need for earlier dose modification, treatment cessation, or when considering a prophylactic intervention to prevent the CIPN from escalating to a serious AE level. Furthermore, this suggests that the PNQ might be considered as the primary source of information on CIPN in clinical trials.

The CIPN-related symptoms reported by some patients at baseline, i.e., before the commencement of taxane therapy, were more likely to be related to effects from their prior breast surgery. Indeed, sensory disturbances in the hands, likely to be related to the residual effects of surgery, were reported significantly more frequently than those reported in the feet, as assessed by the Ntx subscale (data not shown).

One of the potential limitations of this study is that we did not show the data on reliability of the PNQ. We are now examining the test–retest reliability for patients with breast, ovarian, or lung cancer. These data will be presented in another paper. Another potential limitation of this study is that the data were only collected from women receiving taxane chemotherapy for breast cancer, so no comparison could be made with CIPN symptom levels reported with other chemotherapy regimens. In addition, the impact of prior breast surgery might have confounded the level of responsiveness of the PNQ with taxane chemotherapy in this study. Research investigating whether the results of the study are generalizable to other patient populations and/or treatment regimens is planned for future studies of the PNQ.

In conclusion, our findings show that physicians are more likely to underrate CIPN symptoms in comparison with patients, thereby emphasizing the importance of assessing patient-reported outcomes using the PNQ. The data show that the PNQ appears to have an applicable and practical level of feasibility and validity for diagnosing and grading CIPN. The PNQ would be useful in the clinical setting, not only for the identification of CIPN-related symptoms, but also to aid treatment-related decisions. In a future report, we are planning to evaluate the difference in neurotoxic symptoms between anthracycline–cyclophosphamide combination therapy followed by taxane chemotherapy compared with taxane monotherapy in the N-SAS BC 02 trial.

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Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial

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Summary

Background Paclitaxel and carboplatin given every 3 weeks is standard treatment for advanced ovarian carcinoma. Attempts to improve patient survival by including other drugs have yielded disappointing results. We compared a conventional regimen of paclitaxel and carboplatin with a dose-dense weekly regimen in women with advanced ovarian cancer.

Methods Patients with stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were eligible for enrolment in this phase 3, open-label, randomised controlled trial at 85 centres in Japan. Patients were randomly assigned by computer-generated randomisation sequence to receive six cycles of either paclitaxel (180 mg/m^2; 3-h intravenous infusion) plus carboplatin (area under the curve [AUC] 6 mg/mL per min), given on day 1 of a 21-day cycle (conventional regimen; n=320), or dose-dense paclitaxel (80 mg/m^2; 1-h intravenous infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle (dose-dense regimen; n=317). The primary endpoint was progression-free survival. Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00226915.

Findings 631 of the 637 enrolled patients were eligible for treatment and were included in the ITT population (dose-dense regimen, n=312; conventional regimen, n=319). Median progression-free survival was longer in the dose-dense treatment group (28·0 months, 95% CI 22·3–35·4) than in the conventional treatment group (17·2 months, 15·7–21·1; hazard ratio [HR] 0·71; 95% CI 0·58–0·88; p=0·0015). Overall survival at 3 years was higher in the dose-dense regimen group (72·1%) than in the conventional treatment group (65·1%; HR 0·75, 0·57–0·98; p=0·03). 165 patients assigned to the dose-dense regimen and 117 assigned to the conventional regimen discontinued treatment early. Reasons for participant dropout were balanced between the groups, apart from withdrawal because of toxicity, which was higher in the dose-dense regimen group than in the conventional regimen group (n=113 *vs* n=69). The most common adverse event was neutropenia (dose-dense regimen, 286 [92%] of 312; conventional regimen, 276 [88%] of 314). The frequency of grade 3 and 4 anaemia was higher in the dose-dense treatment group (214 [69%]) than in the conventional treatment group (137 [44%]; p<0·0001). The frequencies of other toxic effects were similar between groups.

Interpretation Dose-dense weekly paclitaxel plus carboplatin improved survival compared with the conventional regimen and represents a new treatment option in women with advanced epithelial ovarian cancer.

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Introduction

Paclitaxel and carboplatin given every 3 weeks is currently considered standard first-line chemotherapy for advanced epithelial ovarian cancer. The consensus statements on the management of ovarian cancer at the 3rd International Gynecologic Cancer Consensus Conference in 2004 recommended intravenous paclitaxel (175 mg/m^2 over 3 h) plus intravenous carboplatin (area under the curve [AUC] 5·0–7·5 mg/mL per min) given every 3 weeks for six cycles for first-line chemotherapy.[1] Paclitaxel and carboplatin have been combined with other drugs, given either concurrently or sequentially, in the hope of prolonging survival in women with advanced ovarian cancer, but the results of several randomised trials have been disappointing.[2–4] In particular, the recently reported randomised trial of the Gynecologic Oncology Group, an international collaborative study enrolling more than 4500 patients, showed that the addition of new cytotoxic drugs to paclitaxel plus carboplatin did not improve progression-free or overall survival.[2]

Dose-dense weekly administration of paclitaxel is another strategy to enhance antitumour activity and prolong survival. Preclinical studies have suggested that duration of exposure is an important determinant of the cytotoxic activity of paclitaxel.[5] Adequate cytotoxicity can be achieved at fairly low concentrations of the drug provided that exposure is extended.[5,6] Several phase 2 clinical trials of dose-dense weekly paclitaxel and carboplatin have shown promising efficacy and favourable tolerability in women with ovarian cancer.[7–9]

We undertook a phase 3, randomised controlled trial to compare conventional paclitaxel and carboplatin given every 3 weeks with dose-dense paclitaxel given every week plus carboplatin (every 3 weeks) as first-line treatment in women with advanced ovarian cancer.

Methods

Patients

Patients from 85 centres in Japan were eligible for enrolment in this phase 3, open-label, randomised trial if they had a histologically or cytologically proven diagnosis of stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. If only the results of cytological examinations were available, patients needed to have the following criteria: (1) a cytological diagnosis of adenocarcinoma; (2) an abdominal mass more than 2 cm in diameter on abdominal images; and (3) a CA125/carcinoembryonic antigen (CEA) ratio[10] of more than 25, or no evidence of gastrointestinal cancer if CA125/CEA ratio was less than or equal to 25. Previous chemotherapy was not allowed. Patients needed to be aged 20 years or older, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3,[11] and to have adequate organ functions, defined as absolute neutrophil count 1·5 cells×10^9 per L or more, platelet count 100×10^9 per L or more, serum bilirubin 25·7 μmol/L or less, serum aspartate aminotransferase 100 IU/L or less, and serum creatinine 132·6 μmol/L or less. Patients were excluded if they had an ovarian tumour with a low malignant potential, or synchronous or metachronous (within 5 years) malignant disease other than carcinoma in situ.

All patients gave written informed consent before enrolment in this study. The study protocol was approved by the institutional review boards at all participating centres. The protocol was coordinated by the Japanese Gynecologic Oncology Group (protocol number 3016).

Randomisation and masking

Patients were randomly assigned to receive paclitaxel and carboplatin in either a conventional regimen (control) or a dose-dense regimen (intervention). Randomisation was by telephone or fax from a central registration centre located at University of Toyama (Toyama, Japan), and the random allocation table was computer-generated by use of the SAS PROC PLAN. Randomisation was stratified by residual disease (≤1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics (FIGO) stage (II *vs* III *vs* IV),[12] and histological type (clear-cell or mucinous tumours *vs* serous or other tumours), with adequate balancing within each institution. Patients and clinicians were not masked to treatment assignment.

Procedures

Both study groups received carboplatin at a dose calculated to produce an AUC of 6 mg/mL per min on day 1 of a 21-day cycle. Carboplatin was given as an intravenous infusion over 1 h. The control group also received paclitaxel given as a 3-h intravenous infusion at a dose of 180 mg/m^2 on day 1. In the dose-dense group, paclitaxel was given as a 1-h intravenous infusion at a dose of 80 mg/m^2 on days 1, 8, and 15. The dose of carboplatin was calculated with the formula of Calvert and colleagues,[13] by use of creatinine clearance instead of glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[14] Standard premedication was given to prevent hypersensitivity reactions to paclitaxel. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy.

Patients needed to have an absolute neutrophil count of 1·0×10^9 cells per L (amended from 1·5×10^9 cells per L on April 11, 2005, because of frequent occurrence of delaying) or more and a platelet count of 75×10^9 per L or more to receive subsequent cycles of therapy in both groups. Patients in the dose-dense regimen group also had to have an absolute neutrophil count of 0·5×10^9 cells per L or more and a platelet count of 50×10^9 per L (amended from 75×10^9 per L on April 11, 2005) or more before they received paclitaxel on days 8 and 15. Treatment was delayed for a maximum of 3 weeks (amended from 2 weeks on April 11, 2005).

The dose of carboplatin was reduced for haematological toxicity, and paclitaxel was reduced for non-haematological toxicity with dose reduction levels as follows: carboplatin AUC 5 mg/mL per min (level 1) or AUC 4 mg/mL per min (level 2) in both groups; paclitaxel 135 mg/m^2 (level 1) or 110 mg/m^2 (level 2) in the conventional treatment group, and paclitaxel 70 mg/m^2 (level 1) or 60 mg/m^2 (level 2) in the dose-dense treatment group. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count less than 0·5×10^9 cells per L persisted for 7 days or more, the platelet count was less than 10×10^9 per L, the platelet count was between 10×10^9 per L and 50×10^9 per L with bleeding tendencies, or the treatment was delayed for haematological toxicity for more than 1 week. In general, patients did not receive prophylactic granulocyte-colony stimulating factor (G-CSF) unless they had treatment delays or neutropenic complications after treatment. The dose of paclitaxel was reduced in patients who had grade 2 or higher peripheral neuropathy.

Interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both, were allowed. These procedures were done within 6 weeks after chemotherapy, and subsequent chemotherapy was restarted within 6 weeks after surgery.

The primary endpoint of this trial was progression-free survival, defined as the time from the date of randomisation to the date of the first occurrence of any of the following events: death from any cause; appearance of any new lesions that could be measured or assessed clinically;

or CA125 criteria of disease progression.[15] The CA125 criteria of disease progression were defined as (1) patients with raised CA125 concentration before treatment with a return to normal after treatment needed to show re-elevation of CA125 greater than or equal to two times the upper normal limit; (2) patients with raised CA125 before treatment that did not return to normal needed to show evidence of CA125 greater than or equal to two times the nadir value; or (3) patients with CA125 in the normal range before treatment needed to show evidence of CA125 greater than or equal to two times the upper normal limit, with raised CA125 recorded on two occasions at least 1 week apart. In patients with measurable disease, clinical or radiographical tumour measurements had priority over CA125 concentration, and progression during treatment could not be declared on the basis of CA125 alone.

Secondary endpoints were overall survival, response rate, and adverse events. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat (ITT) principle. Clinical response was assessed in eligible patients with lesions that could be measured in two dimensions. The assessment of response had to be confirmed on two occasions at least 4 weeks apart. A complete response was defined as the complete disappearance of all measurable and assessable lesions, determined by two observations not less than 4 weeks apart. A partial reponse was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of measurable lesions, determined by two observations not less than 4 weeks apart. Stable disease was defined as a steady state of response less than a partial response or as an increase of less than 25% in the sum of the products of the perpendicular diameters of measurable lesions, lasting at least 4 weeks. Progressive disease was defined as an unequivocal increase of at least 25% in the sum of the products of the perpendicular diameters of measurable lesions. The appearance of new lesions also constituted progressive disease. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[16]

Radiological studies to record the status of all measurable lesions noted at baseline were repeated after two, four, and six cycles of chemotherapy. Once patients discontinued the protocol therapy, disease status was assessed every 3 months for the first 2 years and every 6 months thereafter. Follow-up monitoring included clinical examinations and CA125 concentration estimation; routine CT scans were not required, but were requested if CA125 concentration rose, symptoms of relapse developed, or both.

Statistical analysis

Our hypothesis was that the dose-dense regimen would prolong progression-free survival compared with the conventional regimen. At the beginning of the study in April, 2003, a sample size of 380 patients with no interim analysis was initially planned to detect a 37·5% improvement in median progression-free survival in the conventional regimen group (from 16 months to 22 months) with 80% power, two-sided log-rank test, and alpha level of 0·05. In January, 2005, the sample size was increased to 600 patients during the trial to account for the higher accrual of patients and to detect a shorter prolongation of progression-free survival. This amendment of the protocol was made without interim analysis and was approved by the data and safety monitoring committee. The increased sample size would enable the detection of a 31·3% improvement (from 16 months to 21 months) in median progression-free survival with 80% power, two-sided log-rank test, at an alpha level of 0·05, an accrual of 3 years, and a follow-up of 1·5 years. Following the data safety monitoring committee's instructions, interim analysis was planned after 380 patients had been randomly assigned to treatment, and multiplicity by multiple look was adjusted with the

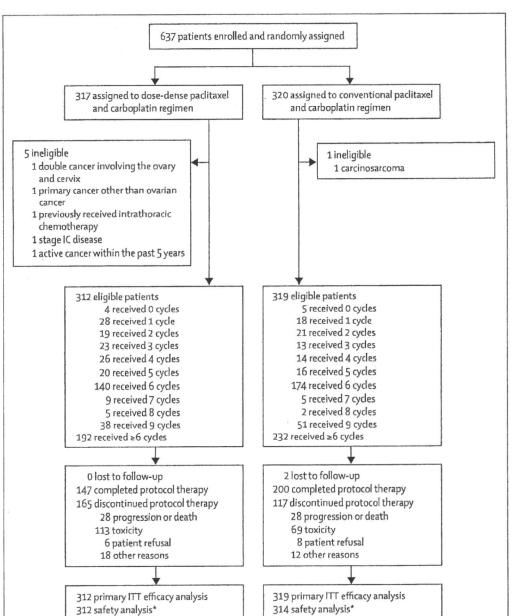

Figure 1: **Trial profile**
ITT=intention-to-treat. *Analysis of safety includes all randomised women who had received at least one cycle of treatment (one ineligible patient in each group did not receive treatment).

	Dose-dense regimen group (n=312)	Conventional regimen group (n=319)
Age (years)	57 (25–87)	57 (25–84)
FIGO stage		
II	62 (20%)	54 (17%)
III	202 (65%)	215 (67%)
IV	48 (15%)	50 (16%)
ECOG performance status		
0 or 1	283 (91%)	287 (90%)
2	23 (7%)	20 (6%)
3	6 (2%)	12 (4%)
Disease		
Ovarian	260 (83%)	276 (87%)
Fallopian tube	14 (4%)	18 (6%)
Primary peritoneal	38 (12%)	25 (8%)
Surgery		
Cytology only	35 (11%)	35 (11%)
Primary debulking	277 (89%)	284 (89%)
Interval debulking	34 (11%)	29 (9%)
Secondary/second-look	38 (12%)	56 (18%)
Residual disease		
≤1 cm	144 (46%)	145 (45%)
>1 cm	168 (54%)	174 (55%)
Histological type		
Serous adenocarcinoma	173 (55%)	182 (57%)
Endometrioid adenocarcinoma	38 (12%)	39 (12%)
Clear-cell carcinoma	31 (10%)	37 (12%)
Mucinous adenocarcinoma	23 (7%)	11 (3%)
Other types	47 (15%)	50 (16%)
Histological grade		
Well differentiated	42 (13%)	40 (13%)
Moderately differentiated	60 (19%)	71 (22%)
Poorly differentiated	79 (25%)	72 (23%)
Unknown/not applicable	131 (42%)	136 (43%)

Data are n (%) or median (range). FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics of study patients**

O'Brien-Fleming alpha-spending function. At the first interim analysis in December, 2005, the data safety monitoring committee reviewed the results and approved continuation of the planned follow-up.

The cumulative survival curve and median progression-free survival time were estimated by use of the Kaplan-Meier method. Adverse events were analysed in all randomised women who had received at least one cycle of treatment. Proportions of adverse events were compared between the groups by the use of two-sided χ^2 tests or two-sided Fisher's exact tests. Responses were compared by the use of Fisher's exact test. All analyses were performed with SAS software, version 8.2. This trial is registered with ClinicalTrials.gov, number NCT00226915.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April, 2003, and December, 2005, 637 patients were enrolled at 85 centres. Figure 1 shows the trial profile. Table 1 shows the baseline characteristics of the 631 eligible patients whose data were included in the ITT analysis.

The median number of treatment cycles was six in both groups (figure 1). The proportion of patients who received six or more cycles of treatment was higher in the conventional regimen group (232 [73%] of 319) than in the dose-dense regimen group (192 [62%] of 312). The main reason for discontinuing treatment was toxicity. Haematological toxicity was the most common form of toxicity leading to the discontinuation of treatment (68 [60%] of 113 patients assigned to the dose-dense regimen *vs* 30 [43%] of 69 assigned to the conventional regimen; p=0·03). The proportions of patients who discontinued treatment because of neurotoxicity were low in both groups (three [3%] *vs* five [7%]). Other reasons for discontinuation of treatment because of toxic effects were patient refusal (13 [12%] *vs* 12 [17%]), allergic reaction (four [4%] *vs* seven [10%]), and other toxic effects (25 [22%] *vs* 15 [22%]).

At least one treatment cycle was delayed in a higher proportion of patients in the dose-dense treatment group (236 [76%] of 312) than in the conventional treatment group (213 [67%] of 319; p=0·02). The dose of the study drugs was reduced in a higher proportion of patients assigned to the dose-dense regimen (150 [48%] of 312) than in those assigned to the conventional regimen (112 [35%] of 319; p=0·001). The mean delivered dose intensity of carboplatin was lower in the dose-dense regimen group (AUC per week 1·54 mg/mL per min [SD 0·37]) than in the conventional regimen group (AUC per week 1·71 mg/mL per min [SD 0·36]), and the mean delivered dose-intensity of paclitaxel was higher (63·0 mg/m² per week [SD 13·0] *vs* 51·7 mg/m² per week [SD 10·6]). The mean relative dose intensities of carboplatin and paclitaxel were both lower in the dose-dense regimen group (77% [SD 18] and 79% [SD 15], respectively) than in the conventional regimen group (85% [SD 18], and 86% [SD 18], respectively).

At the time of last follow-up (December, 2007), with a median duration of follow-up of 29 months, there had been 160 disease progression events in the dose-dense treatment group and 200 in the conventional treatment group. Median progression-free survival was 28·0 months (95% CI 22·3–35·4) in the dose-dense treatment group and 17·2 months (15·7–21·1) in the

conventional treatment group (figure 2; unadjusted hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0015, log-rank test). When the analysis was done with data from all 637 patients who were randomly assigned to treatment, the result was similar (p=0·0019). After adjustment for FIGO stage, residual disease, and histological type according to the preplanned analysis, the HR was 0·65 (0·53–0·80; p=0·0001). We subsequently undertook unplanned sensitivity analyses. The differences between groups were still significant when only clinical progression was defined as progression (p=0·0018), when data on patients who received second-line therapy before progression were censored (dose-dense regimen, n=3; conventional regimen, n=5; p=0·0018), or when data on patients who underwent interval or secondary surgery, or both, were censored (dose-dense regimen, n=71; conventional regimen, n=85; p=0·0092).

Analysis of overall survival was done in December, 2007, at the same time as the analysis of progression-free survival. The overall survival at 2 years was 83·6% in the dose-dense treatment group and 77·7% in the conventional treatment group (p=0·049). We updated the overall survival analysis in December, 2008, with median follow-up period of 42 months. Although median overall survival had not been reached in either group, overall survival at 3 years was higher in the dose-dense treatment group (72·1%) than in the conventional treatment group (65·1%; unadjusted HR 0·75, 0·57–0·98; p=0·03 log-rank test; figure 2).

A Cox proportional-hazards model was used to examine the effect of baseline clinical characteristics and conventional prognostic factors on the treatment effect (figure 3). Progression-free survival was longer in the dose-dense treatment group than in the conventional treatment group across all subgroups of patients apart from in those with clear-cell or mucinous tumours. In this subgroup of patients, the HR in the dose-dense treatment group was similar to that in the conventional treatment group.

Clinical response was assessed in 282 patients who had measurable disease at study entry. The overall response rate was similar between groups (conventional regimen, 72 [53%] of 135 patients; dose-dense regimen, 82 [56%] of 147 patients; p=0·72; table 2). Because patients who underwent suboptimally debulked surgery (>1 cm of residual disease) were allowed to undergo interval debulking surgery in this study, response sometimes could not be confirmed on repeated imaging. If these unconfirmed responses are taken into account (44 patients), the overall response rate was 70% (94 of 135 patients) in the conventional treatment group compared with 71% (104 of 147 patients) in the dose-dense treatment group (p=0·90).

Treatment-related adverse events were analysed in patients who received at least one cycle of the study treatment (table 3). The frequency of grade 3 or 4 anaemia was higher in the dose-dense treatment group than in the conventional treatment group (p<0·0001). Recombinant erythropoietin was not used to treat anaemia because it was not approved in Japan. G-CSF was used in 187 (60%) patients assigned to the dose-dense regimen and in 214 (67%) assigned to the conventional regimen. The frequency of neuropathy did not differ between study groups.

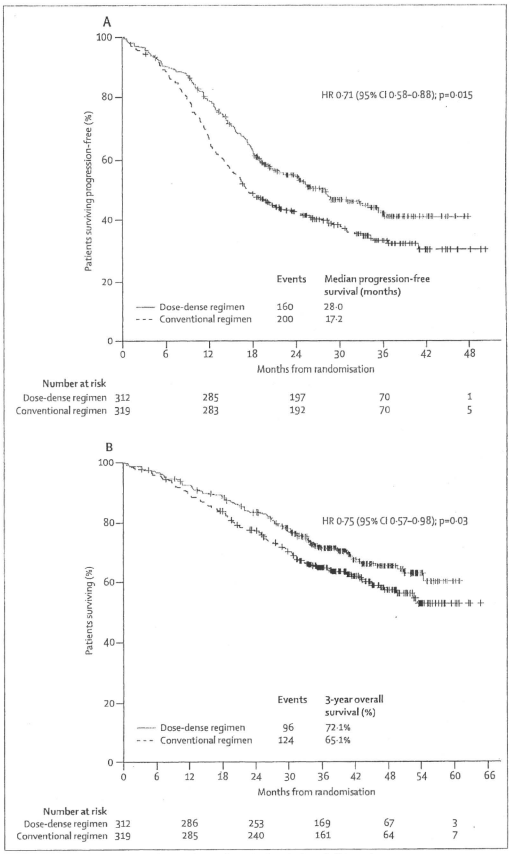

Figure 2: **Progression-free survival (A) and overall survival (B) in 631 eligible patients**
HR=hazard ratio.

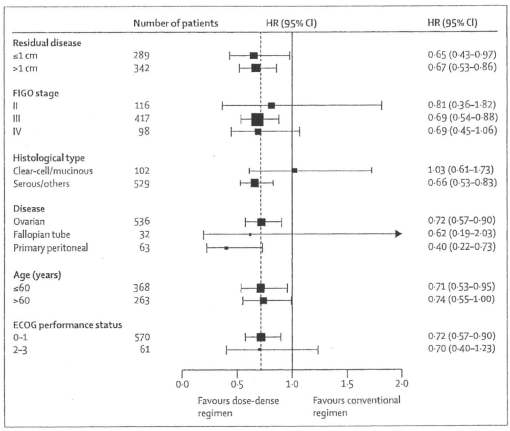

Figure 3: **Progression-free survival according to baseline characteristics**
FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. The hazard ratios (HRs; 95% CIs) are for patients assigned to conventional paclitaxel and carboplatin, compared with those assigned to dose-dense paclitaxel and carboplatin, and were obtained from the unadjusted Cox model. The dashed vertical line indicates a hazard ratio of 0·71, which is the value for all patients, and the solid vertical line indicates a hazard ratio of 1·00, which is the null-hypothesis value.

	Dose-dense regimen group (n=147)	Conventional regimen group (n=135)	p value
Complete response	29 (20%)	21 (16%)	0·44
Partial response	53 (36%)	51 (38%)	0·81
Stable disease	43 (29%)	42 (31%)	0·80
Progressive disease	4 (3%)	9 (7%)	0·16
Not evaluable	18 (12%)	12 (9%)	0·44

See Methods section for definitions of responses.

Table 2: **Clinical response in patients with measurable lesions**

	Dose-dense regimen group (n=312)	Conventional regimen group (n=314)	p value
Neutropenia	286 (92%)	276 (88%)	0·15
Thrombocytopenia	136 (44%)	120 (38%)	0·19
Anaemia	214 (69%)	137 (44%)	<0·0001
Febrile neutropenia	29 (9%)	29 (9%)	1·00
Nausea	32 (10%)	36 (11%)	0·70
Vomiting	9 (3%)	11 (4%)	0·82
Diarrhoea	10 (3%)	8 (3%)	0·64
Fatigue	15 (5%)	8 (3%)	0·14
Arthralgia	3 (1%)	5 (2%)	0·72
Myalgia	2 (1%)	4 (1%)	0·69
Neuropathy (motor)	15 (5%)	12 (4%)	0·56
Neuropathy (sensory)	21 (7%)	20 (6%)	0·87

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[14]

Table 3: **Frequency of grade 3 or 4 adverse events**

Discussion

Our study showed that compared with a conventional regimen, dose-dense treatment with paclitaxel and carboplatin improved progression-free survival in women with newly diagnosed, stage II to IV ovarian cancer. Women assigned to dose-dense paclitaxel and carboplatin had a 29% lower risk of disease progression and a 25% lower risk of death than did patients assigned to the conventional regimen. Benefits of this magnitude have been rare in women with advanced ovarian cancer, including those with suboptimally debulked stage III and IV disease, since the approval of paclitaxel for the indication of ovarian cancer.

The concept of dose density is based on the hypothesis that a shorter interval between doses of cytotoxic therapy would more effectively reduce tumour burden than would dose escalation.[17] In breast cancer, recently published phase 3 trials have shown that paclitaxel given every week improves response and survival.[18,19] Consistent with these findings, our study showed that progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group. Increased doses of paclitaxel of 225 mg/m² or 250 mg/m² given every 3 weeks have been compared with the standard dose (ie, 175 mg/m²) in women with ovarian cancer, but showed no benefit in survival.[20,21] Our study showed a survival advantage with an increased total dose of 240 mg/m², given in three divided doses during a 21-day cycle, suggesting that dose density is more important than increased dose intensity.

There was greater haematological toxicity in the dose-dense treatment group than in the conventional treatment group, which resulted in more delays and dose modifications. The optimum dose and schedule of dose-dense paclitaxel and carboplatin have not yet been established. Rose and colleagues[8] reported that weekly paclitaxel at a dose of 60 mg/m² in combination with carboplatin at an AUC of 5 mg/mL per min was tolerated and active in patients with recurrent ovarian cancer. An alternative schedule of dose-dense treatment is to give both paclitaxel and carboplatin every week. Sehouli and co-workers[7] showed that weekly paclitaxel at a dose of 100 mg/m² and weekly carboplatin at an AUC of 2 mg/mL per min showed substantial activity and tolerability in patients with primary ovarian cancer. A treatment delay occurred in only 2·8% of cycles and the frequency of grade 3 neurotoxicity (2% [three of 129 patients]) was lower than that reported in our study. Additionally, weekly carboplatin of AUC 2 mg/mL per min and weekly paclitaxel of 60 mg/m² on days 1, 8, and

15 every 4 weeks showed a favourable toxicity profile in elderly ovarian cancer patients.[22]

The response rate did not differ between groups. Virtually all previous randomised trials in ovarian cancer that showed an improvement in progression-free survival and overall survival also had a higher response rate for the more effective treatment. A lower dose of paclitaxel had antiangiogenic activity in a xenograft model.[23] Antiangiogenic agents might promote tumour dormancy by maintaining tumour size and preventing outgrowth.[24] Vascular endothelial growth factor (VEGF) is frequently expressed in ovarian cancer, and might be an important therapeutic target. Longer survival in the dose-dense regimen group without an improved response rate might be attributed to the antiangiogenic effect of paclitaxel. Anti-VEGF agents such as bevacizumab combined with the dose-dense treatment will be assessed in future trials.

Neurotoxicity is the adverse reaction of greatest concern in patients who receive a combination of paclitaxel and carboplatin. In breast cancer trials, the incidence of neurotoxicity was higher in patients given paclitaxel every week than in patients given paclitaxel every 3 weeks.[19] In our study, however, the frequency of neurotoxicity was similar in both groups. This finding might be because patients in the dose-dense treatment group discontinued treatment more often than did those in the conventional treatment group.

Fewer than half the patients assigned to the dose-dense regimen completed treatment according to the study protocol. When designing the protocol, we debated whether patients who responded to six cycles of chemotherapy should receive three more cycles. However, this study was not designed to assess the relation between the duration of treatment and clinical outcomes, and there is little evidence to suggest that more than six cycles of chemotherapy would prolong survival. About 60% of patients in the dose-dense regimen group received six or more cycles of chemotherapy. Treatment cycles were more frequently delayed in the dose-dense treatment group than in the conventional treatment group, mainly because of neutropenia.

Clear-cell and mucinous adenocarcinoma of the ovary is associated with low sensitivity to chemotherapy and poor survival.[25,26] In our study, neither dose-dense nor conventional treatment seemed effective against clear-cell or mucinous ovarian carcinoma, which suggests that other treatment strategies are needed.

Thus, our study showed that a dose-dense regimen of paclitaxel once a week plus carboplatin every 3 weeks is associated with longer progression-free and overall survival than a conventional regimen of paclitaxel and carboplatin given every 3 weeks in women with advanced epithelial ovarian cancer.

Contributors

NK, MY, FT, SI, TS, EK, and KO conceived and designed the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator for the study. NK and FT analysed and interpreted the results. NK drafted the report. KN was responsible for the overall planning and conduct of the study. NK, MY, SI, TJ, DA, HT, TS, SK, EK, and KO were involved in the provision of study material or patients, or data acquisition. NK, MY, TS, EK, and KO were members of the steering committee. All authors were involved in writing the report and approved the final version of the manuscript.

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Conflicts of interest

SI and DA have received honoraria from Bristol-Myers Squibb. DA and HT have received grant support from Bristol-Myers Squibb. All other authors declare that they have no conflicts of interest.

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SPECIAL ARTICLE

Evidence-based guidelines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (JSGO) 2009 edition

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Abstract Endometrial carcinoma is one of the most common gynecologic malignancies in Japan and its incidence has increased recently. Although surgery is the cornerstone of the management of patients with endometrial cancer, there is significant variation in Japan with regard to the type of hysterectomy employed. Additionally, it remains controversial whether full nodal staging is required in all patients. Furthermore, adjuvant therapy differs between Japan and Western countries. To delineate clearly the standard of care for endometrial cancer treatment in Japan, the guidelines for the treatment of endometrial cancer were published in 2006 and revised in 2009. The 2009 edition included topics not addressed in the previous edition including the treatment of mesenchymal tumors, for example

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leiomyosarcoma, and sections covering the treatment of serous and clear-cell adenocarcinoma. These guidelines are composed of nine chapters and include nine algorithms. The guidelines also contain fifty-one clinical questions (CQs) and each CQ consists of recommendations, background, explanations, and references. The treatment recommendations herein are tailored to reflect current Japanese clinical practice and ensure equitable care for all Japanese women diagnosed with endometrial cancer.

Keywords Endometrial cancer · Clinical practice guidelines · Surgery · Chemotherapy · Irradiation

Introduction

Endometrial carcinoma is one of the most common malignancies of the female genital tract. In Japan, the age-adjusted incidence rate of endometrial cancer was 6.5 (per 100,000 women) in 2004, indicative of a four to fivefold increase over the last three decades [1]. To treat endometrial cancer, surgery, chemotherapy, radiation, and hormone therapy are used either alone or sequentially. Surgery is the cornerstone of the management of patients with endometrial cancer. When the disease is limited to the uterus, hysterectomy and bilateral salpingo-oophorectomy, and pelvic/para-aortic lymph node dissection are recommended by The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [2]. There is, however, significant variability with regard to the type of hysterectomy performed for endometrial cancer in Japan [3]. Additionally, it remains controversial whether all patients require full nodal staging [4, 5]. Furthermore, there are differences with regard to the adjuvant therapies employed in Japan and in Western countries. In Western countries, radiotherapy is the mainstay of postoperative adjuvant therapy whereas in Japan it is more frequently chemotherapy. These differences are one reason why evidence from Western countries cannot be applied directly to developing recommendations for Japanese patients. To delineate clearly the standard of care for endometrial cancer treatment in Japan, the guidelines for the treatment of endometrial cancer were published in 2006 for the first time, and revised in 2009. The revision contains two new sections. The first is a chapter addressing the treatment of mesenchymal tumors, for example leiomyosarcoma. The second is a section addressing the treatment of serous and clear-cell adenocarcinoma. The treatment recommendations herein are tailored to reflect current Japanese clinical practices and ensure equitable care for all Japanese women diagnosed with endometrial cancer.

Basic policies in creating the guidelines

To create these guidelines, the Guidelines Formulation Committee and Evaluation Committee were independently established within the Committee for Treatment Guidelines for Uterine Body Neoplasms. The initial draft was created after a thorough evaluation. Opinions from within and outside the Japan Society of Gynecologic Oncology (JSGO) were incorporated into the final draft. The guidelines were published after their approval by the JSGO. These guidelines were created in accordance with the principles of "Evidence-Based Medicine", considered to be the international standard for creating clinical practice guidelines. Searches were performed of data

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and literature published up until October 2008 and included Japanese and non-Japanese studies in Japan and overseas. The surgical staging criteria described in the 2009 edition were based on the surgical staging system developed in 1988 by the International Federation of Gynecology and Obstetrics.

Much of the evidence that formed the basis for the Japanese guidelines was obtained from clinical trials in Western countries. However, given the differences between practice in Japan and other countries, the consensus clinical practice in Japan took priority in the event of discrepancies. Wherever possible, high-level Japanese evidence was utilized to formulate these guidelines. Finally, these guidelines are not intended to restrict the use of treatments not mentioned in this text.

Evidence levels and the grade of recommendation

The collected evidence was evaluated for quality using the criteria of the Japan Society of Clinical Oncology and its Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents (Table 1). The grades of the recommendations in our guidelines were also determined according to the Medical Information Network Distribution Service as shown in Table 2.

Table 1 Evidence quality evaluation criteria (levels)

I	Evidence from meta-analyses of multiple randomized controlled trials
II	Evidence from at least one randomized controlled trial, or evidence from multiple well-designed controlled studies without randomization
III	Evidence obtained from at least one other type of well-designed quasi-experimental study, or evidence obtained from well-designed, non-experimental descriptive studies, for example comparative studies, correlation studies, and case studies
IV	Expert committee reports, or opinions and/or clinical experiences of respected authorities

Table 2 Grades of recommendation

A	Can be strongly recommended that clinicians provide the intervention to eligible patients. There is evidence from at least one level I quality study to indicate efficacy
B	Recommended that clinicians provide to eligible patients. There is evidence from at least one level II quality study to support efficacy
C1	There is insufficient evidence to make a recommendation; however, clinicians may use their discretion to provide this intervention to eligible patients. There is evidence from more than one level III quality study suggesting efficacy
C2	There is insufficient evidence to recommend the intervention for routine practice
D	The intervention is not recommended as there is a possibility that its benefits are outweighed by its harm

Algorithms

These guidelines contain the following nine algorithms:

1. Initial Treatment: Clinical Stages I and II (Fig. 1).
2. Initial Treatment: Clinical Stages III and IV (Fig. 2).
3. Postoperative Adjuvant Therapy for Endometrial Cancer (Fig. 3; Table 3).
4. Treatment of Recurrent Endometrial Cancer (Fig. 4).
5. Strategies for Fertility-Preserving Treatment: Atypical Endometrial Hyperplasia and Endometrioid Adenocarcinoma of Grade 1 (Fig. 5).
6. Initial Treatment and Postoperative Adjuvant Therapy for Serous or Clear-Cell Adenocarcinoma (Fig. 6).
7. Treatment of Recurrent Serous or Clear-Cell Adenocarcinoma (Fig. 6).
8. Treatment for Carcinosarcoma (Fig. 7).
9. Treatment for Uterine Sarcoma (Leiomyosarcoma, Endometrial Stromal Sarcoma) (Fig. 8).

Summary of recommendations

In general, each chapter consists of a clinical question (CQ), recommendations, background, objectives, explanations, and references. This article summarizes these guidelines in a question and answer format. Recommendations from each chapter are listed below under their respective chapter titles. References in each chapter are available through the JSGO web site (http://www.jsgo.gr.jp/).

Chapter 1: Overview of guidelines

Chapter 2: Initial treatment

CQ01 Which surgical techniques for hysterectomy are recommended for clinical stage I?

Recommendations:

1. Abdominal total hysterectomy (extrafascial technique) is recommended (Grade B).
2. Modified radical (extended) hysterectomy is also an option (Grade C1).

CQ02 Which surgical techniques of hysterectomy are recommended for clinical stage II?

Recommendations: It is advisable to employ either radical hysterectomy or modified radical hysterectomy for patients with clinically apparent cervical involvement (Grade C1).

CQ03 What are the benefits of pelvic lymphadenectomy?

Recommendations: Pelvic lymphadenectomy is critical for accurate surgical staging, which has implications

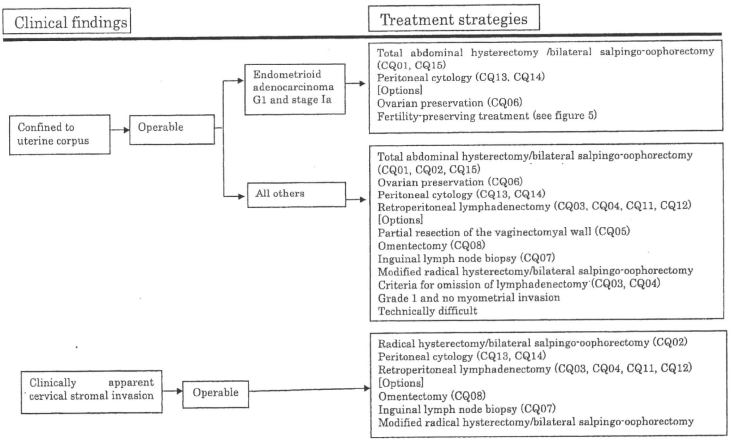

Fig. 1 Initial treatment for clinical stages I and II. Staging is based on clinical findings. Radiotherapy or chemotherapy is performed for inoperable patients. *CQ* indicates a clinical question

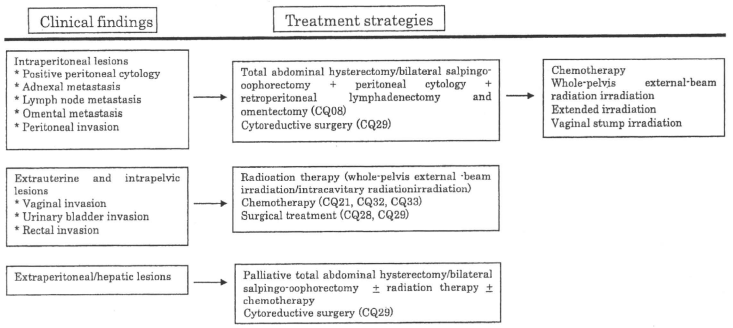

Fig. 2 Initial treatment for clinical stage III–IV. Patients with extraperitoneal/hepatic lesions can present with symptoms such as hemorrhage. Accordingly, palliative total abdominal hysterectomy is sometimes performed

for prognosis. There are, however, no therapeutic benefits of pelvic lymphadenectomy demonstrated thus far (Grade C1).

CQ04 What are the benefits of para-aortic lymphadenectomy in addition to pelvic lymphadenectomy?

Recommendations: Para-aortic lymphadenectomy enables accurate surgical staging, although there still remain controversies regarding therapeutic benefit of para-aortic lymphadenectomy (Grade C1).

CQ05 What are the clinical benefits of partial vaginectomy?

Recommendations: Partial vaginectomy might be performed to reduce vaginal stump recurrence, although the benefit of partial vaginectomy has not been demonstrated (Grade C1).

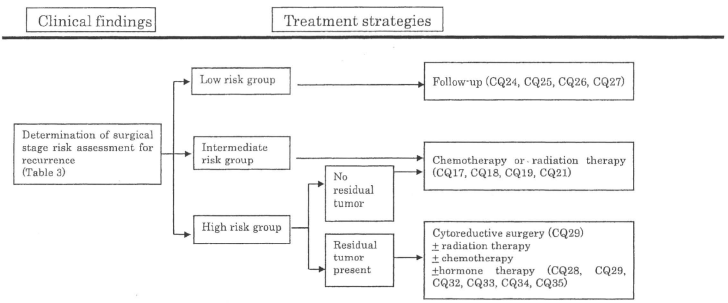

Fig. 3 Postoperative adjuvant therapy for endometrial cancer (endometrioid adenocarcinoma). Patients with positive peritoneal cytology are classified as stage IIIa in the surgical staging. However, if there are no predictive factors associated with a poor prognosis other than positive peritoneal cytology, or there are no findings of extrauterine spread, it has been reported that positive peritoneal cytology is not a predictive factor associated with a poor prognosis. If there are predictive factors associated with a poor prognosis other than positive peritoneal cytology or spread to an extrauterine site, in addition to positive peritoneal cytology, the appropriate postoperative treatment is recommended. Radiotherapy and chemotherapy are often performed as adjuvant therapy for the intermediate risk group. However, there is insufficient evidence for their utility. Therefore additional clinical trials need to be performed. See CQ17, CQ18, CQ19, and CQ21

Table 3 Classification of postoperative recurrence risk of uterine body cancer

Low-risk group
Endometrioid adenocarcinoma G1 or G2 and ≤1/2 myometrial invasion
No cervical invasion
Negative peritoneal cytology
No venous or lymphatic invasion
No distant metastasis
Intermediate-risk group
Endometrioid adenocarcinoma G3 and ≤1/2 myometrial invasion
Endometrioid adenocarcinoma and >1/2 myometrial invasion
Cervical invasion
Positive peritoneal cytology (see CQ12)
Venous or lymphatic invasion
Serous adenocarcinoma, clear-cell adenocarcinoma, or undifferentiated carcinoma
No distant metastasis
High-risk group
Spread to the uterine adnexae, serosa, or cardinal ligament
Invasion of the vaginal wall
Pelvic or para-aortic lymph node metastasis
Vesical or rectal invasion
Peritoneal dissemination
Distant metastasis

Extracted from reference [6] (with some modifications)

CQ06 Are young patients candidates for ovarian preservation?

Recommendations: Caution should be exercised with regard to ovarian preservation, even in young patients (Grade C1).

CQ07 In the surgical staging guidelines, inguinal lymph node metastases are considered for staging. Is an inguinal lymph node biopsy necessary?

Recommendations:

1. If an enlarged inguinal lymph node is detected in preoperative imaging, for example CT scanning, then biopsy is recommended to determine the surgical stage (Grade B).
2. If an enlarged inguinal lymph node is not detected, the benefits of biopsy are not evident. Therefore, routine inguinal lymph node biopsy is not recommended (Grade C2).

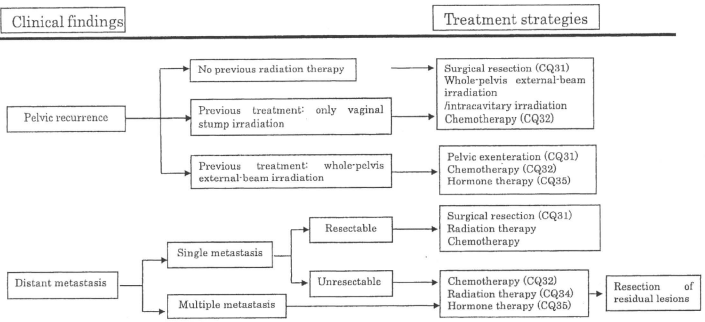

Fig. 4 Treatment of recurrent endometrial cancer. Surgical resection is sometimes performed for patients with multiple resectable metastases

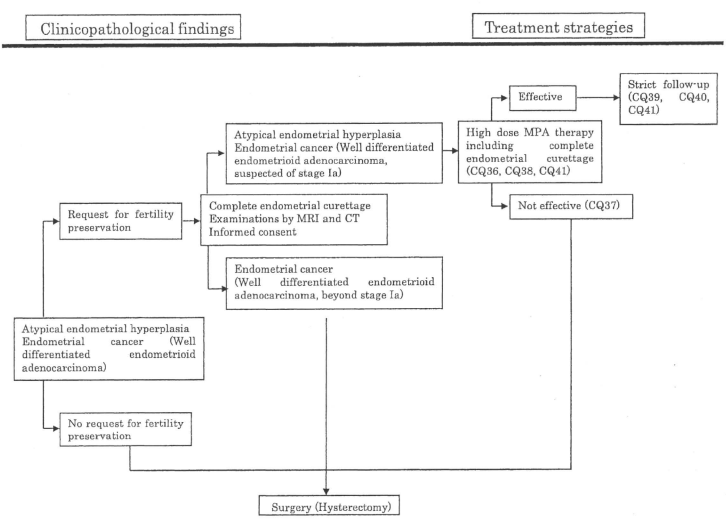

Fig. 5 Strategies for fertility preservation in the treatment of atypical endometrial hyperplasia and well differentiated endometrioid adenocarcinoma (G1)

CQ08 Is omentectomy necessary?

Recommendations: Omentectomy is useful to determine metastatic involvement in the setting of visible macroscopic intrapelvic or peritoneal dissemination, or if the pathological diagnosis is serous adenocarcinoma or clear-cell adenocarcinoma (Grade C1).

CQ09 Is preoperative diagnostic imaging necessary for surgical planning?

Recommendations:

1. It is advisable to evaluate for myometrial invasion and cervical invasion by preoperative MRI (Grade C1).

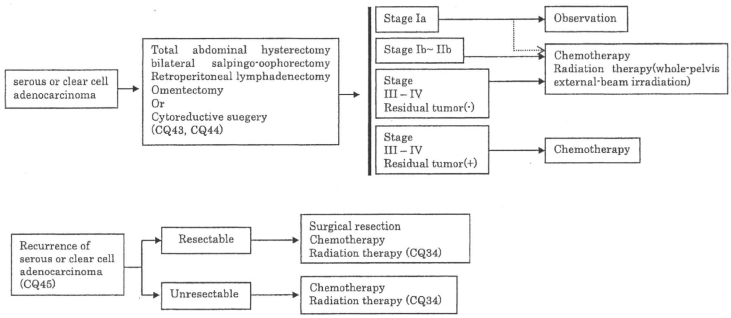

Fig. 6 Initial treatment and postoperative adjuvant therapy for serous/clear-cell adenocarcinoma and recurrent tumors

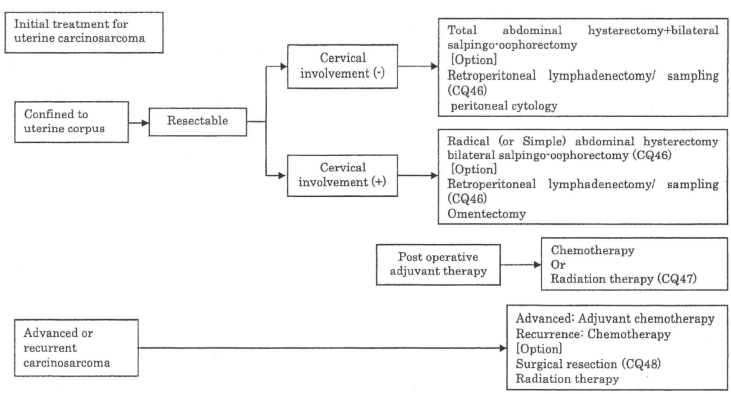

Fig. 7 Treatment for carcinosarcoma. Radiotherapy or chemotherapy is performed for inoperable patients with advanced disease

2. It is advisable to evaluate for lymph node metastases or distant metastases by preoperative imaging (Grade C1).

CQ10 Is intraoperative frozen-section diagnosis useful for the determination of histological type, degree of differentiation, and degree of myometrial invasion?

Recommendations: Intraoperative frozen-section diagnosis is useful for predicting high-risk disease for which pelvic and para-aortic lymphadenectomy or omentectomy would be appropriate (Grade C1).

CQ11 Should intraoperative frozen-section diagnosis be performed to detect lymph node metastases?

Recommendations: There is insufficient evidence to recommend modification of the surgical technique on the basis of the status of lymph node metastases assessed with intraoperative frozen-section. It is not recommended in daily practice (Grade C2).

CQ12 Can lymphadenectomy be omitted if a sentinel node biopsy is performed?

Recommendations: There is insufficient evidence to omit retroperitoneal lymphadenectomy on the basis of sentinel lymph node status. It is not recommended in daily practice (Grade C2).

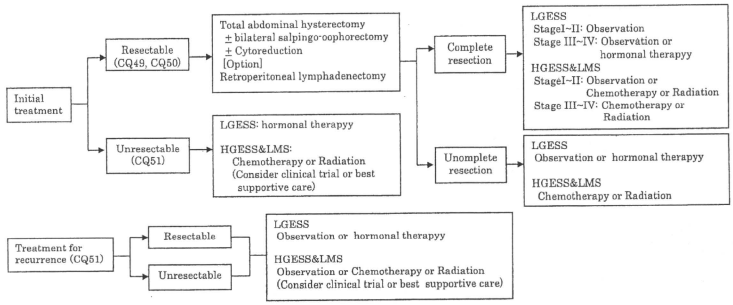

Fig. 8 Treatment for uterine sarcoma (leiomyosarcoma, endometrial stromal sarcoma). *LGESS* Low-grade endometrial stromal sarcoma, *HGESS* high-grade endometrial stromal sarcoma, *LMS* uterine leiomyosarcoma

CQ13 Should peritoneal cytology be used to determine the surgical approach?

Recommendations: Positive peritoneal cytology is not an independent factor for poor prognosis, if it is an isolated finding during complete surgical staging and if there is no other evidence of extrauterine spread. Peritoneal cytology is, however, a required component of complete surgical staging in accordance with the recent General Rules for Clinical and Pathological Management of Uterine Corpus Cancer (2nd edition) in Japan (Grade A).

CQ14 Is rapid intraoperative peritoneal cytology necessary for determination of the surgical technique?

Recommendations: There is insufficient evidence to support basing the surgical technique on the results of rapid intraoperative peritoneal cytology. It is not recommended in daily practice (Grade C2).

CQ15 Will endoscopic surgery become the standard surgical technique?

Recommendations: At present, endoscopic surgery has not been established as the standard surgical technique, and is not recommended in daily practice (Grade C2).

CQ16 Is radiotherapy recommended for patients who are poor surgical candidates?

Recommendations: Radiotherapy is recommended for these patients (Grade B).

Chapter 3: Postoperative adjuvant therapy

I. Radiotherapy

CQ17 What are the indications for postoperative whole-pelvis external-beam irradiation?

Recommendations:

1. Postoperative whole-pelvis external-beam irradiation might be useful for patients with multiple risk factors for recurrence (Grade C1).
2. Postoperative whole-pelvis external-beam irradiation is not recommended for patients without risk factors for recurrence (Grade D).

CQ18 Is postoperative vaginal brachytherapy useful?

Recommendations: Postoperative vaginal brachytherapy might be performed to reduce the vaginal recurrence rate, although it is unclear whether it prolongs overall survival (Grade C1).

CQ19 Is postoperative irradiation of the para-aortic lymph node region and whole abdominal irradiation useful?

Recommendations:

1. Postoperative irradiation of the para-aortic lymph node region may be considered, although there is insufficient clinical evidence to demonstrate its benefits (Grade C1).
2. Postoperative whole abdominal irradiation is not clearly beneficial, and is not recommended in daily practice (Grade C2).

CQ20 Are there contraindications for postoperative radiotherapy?

Recommendations:

1. Postoperative radiotherapy is contraindicated in patients with previous radiotherapy to the pelvis (Grade A).
2. Postoperative radiotherapy may be considered for patients with concurrent rheumatic diseases or concurrent inflammatory bowel diseases if the patients are

deemed to be at high risk of recurrence. These patients must be closely monitored for adverse radiation effects (Grade B).

II. Chemotherapy and hormone therapy

CQ21 Has the efficacy of postoperative adjuvant chemotherapy been established?

Recommendations:

1. Postoperative adjuvant chemotherapy is recommended for high-risk patients with residual tumor smaller than 2 cm (Grade B).
2. Postoperative adjuvant chemotherapy may improve the prognosis for intermediate-risk patients (Grade C1).
3. Postoperative adjuvant chemotherapy is not recommended for low-risk patients (Grade D).

CQ22 Which drugs are recommended for postoperative adjuvant chemotherapy?

Recommendations:

1. Regimens including anthracyclines and platinum-based drugs are recommended (Grade B).
2. Taxanes may also be used in combination with the above, although there is insufficient evidence to recommend this (Grade C1).

CQ23 Is hormone therapy recommended as a postoperative adjuvant therapy?

Recommendations: Postoperative high-dose progesterone therapy is not recommended for patients with a low risk of recurrence (Grade D).

Chapter 4: Post-treatment follow-up

CQ24 What intervals are recommended for post-treatment follow-up?

Recommendations: Standard intervals between routine follow-up appointments are as shown below (Grade C1):

1. Every 1–3 months for the first 1–3 years after treatment;
2. Every 6 months for the fourth and fifth years after treatment;
3. Annually from the sixth year after treatment.

CQ25 Should serum tumor markers be measured in post-treatment follow-up?

Recommendations: CA-125 or CA19-9 may be measured in post-treatment follow-up, although the merits of measuring tumor markers have not been established (Grade C1).

CQ26 Are a pelvic examination and vaginal vault smears useful in post-treatment follow-up?

Recommendations:

1. Because pelvic recurrences account for 30–65% of recurrences, pelvic examination is useful (Grade B).
2. Vaginal vault smears may be useful for detecting vaginal stump recurrences (Grade C1).

CQ27 How often should chest X-rays and other diagnostic imaging methods be performed in post-treatment follow-up?

Recommendations:

1. It is advisable to perform a chest X-ray annually or biannually for early detection of recurrence (Grade C1).
2. Diagnostic imaging methods other than chest X-ray are useful as a method to confirm recurrence which is clinically suspected (Grade B).

Chapter 5: Treatment of advanced and recurrent cancer

CQ28 What is the indication for surgery for clinical stages III and IVa?

Recommendations: It is advisable to choose surgery whenever a hysterectomy and cytoreduction are possible (Grade C1).

CQ29 What are the therapeutic benefits of cytoreductive surgery for patients with macroscopic extrapelvic and intra-abdominal spread?

Recommendations: The prognosis may be improved by cytoreductive surgery (Grade C1).

CQ30 Are neoadjuvant chemotherapy and preoperative radiotherapy useful for advanced cancer?

Recommendations:

1. The benefits of preoperative chemotherapy are not evident; it is, therefore, not recommended for routine practice (Grade C2).
2. Preoperative radiotherapy may be used for patients with cervical invasion and enlargement; however, it is not commonly practiced in Japan (Grade C2).

CQ31 What are the indications for surgery for recurrent cancer?

Recommendations:

1. Surgical resection is considered for all operable patients without obvious distant metastasis (Grade C1).
2. Partial resection of the lung is considered for patients with lung metastases smaller than 4 cm (Grade C1).

CQ32 Is chemotherapy useful for advanced and recurrent cancer?

Recommendations: Chemotherapy is useful for patients with incompletely resected advanced cancer (stages III and IVa), distant metastasis (stage IVb), or recurrent cancer (Grade B).

CQ33 Which regimens are recommended for chemotherapy in advanced and recurrent cancer?

Recommendations: Platinum-based drugs in combination with anthracyclines or taxanes are recommended (Grade B).

CQ34 Is radiotherapy useful for recurrent and inoperable advanced cancer?

Recommendations:

1. Radiotherapy is useful for patients with recurrence at the vaginal cuff (Grade B).
2. Radiotherapy is a palliative option for advanced and recurrent cancer (Grade C1).

CQ35 Is progesterone therapy useful for advanced and recurrent cancer?

Recommendations: Progesterone therapy is useful for patients with well-differentiated endometrioid adenocarcinoma and advanced or recurrent cancer with positive progesterone receptors (Grade B).

Chapter 6: Fertility-preserving treatment

CQ36 Is progesterone therapy useful for patients with well-differentiated endometrioid adenocarcinoma who desire fertility preservation?

Recommendations: Progesterone therapy might be useful as a fertility-preserving treatment for patients with well-differentiated endometrioid adenocarcinoma suspected to be confined to the endometrium (Grade C1).

CQ37 What treatments are recommended for recurrent cases of well-differentiated endometrioid adenocarcinoma after fertility preservation therapy?

Recommendations:

1. The effectiveness of retreatment with progesterone has not been established in patients with recurrent disease. Retreatment with progesterone is not recommended for routine practice (Grade C2).
2. Total hysterectomy is recommended for patients with recurrent disease, an incomplete response, or progressive disease (Grade B).

CQ38 What are the adverse effects of progesterone therapy and their associated risk factors?

Recommendations: Thrombosis is a serious adverse reaction associated with progesterone therapy. Use of progesterone should be avoided in patients with a high risk of thrombosis (Grade D).

CQ39 Is ovulation induction permissible in patients who have preserved fertility?

Recommendations: Induction of ovulation is not contraindicated, because there is no evidence that it negatively affects prognosis (Grade C1).

CQ40 What are suitable follow-up periods and examinations?

Recommendations: It is advisable to perform a complete endometrial curettage and transvaginal ultrasonography every 3 months after completion of medroxyprogesterone acetate (MPA) therapy (Grade C1).

Chapter 7: Atypical endometrial hyperplasia

CQ41 What are the benefits of progesterone therapy if fertility-preserving treatment is used for atypical endometrial hyperplasia?

Recommendations: Progesterone therapy is useful in patients who desire fertility preservation. In this setting, it is advisable to perform a complete endometrial curettage and transvaginal ultrasonography at intervals of 3–6 months (Grade C1).

CQ42 Is endometrial biopsy alone sufficient for diagnosing atypical endometrial hyperplasia?

Recommendations: Even if endometrial atypical hyperplasia is diagnosed by endometrial biopsy, a complete endometrial curettage is recommended because of the high rate of concomitant cancer (Grade A).

Chapter 8: Non endometrioid types

CQ43 What surgical technique is recommended for serous adenocarcinoma and clear-cell adenocarcinoma?

Recommendations:

1. Total hysterectomy with bilateral salpingo-oophorectomy is employed to determine the accurate surgical stage (Grade B).
2. It is advisable to perform pelvic and para aortic lymphadenectomy/lymph nodes biopsy (Grade C1).
3. Omentectomy is useful to assess spread (Grade C1).

CQ44 What postoperative adjuvant therapy is recommended for surgical stage I and II serous and clear-cell adenocarcinoma?