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Impact of pattern of recurrence on clinical outcome of ovarian cancer patients: Clinical considerations

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ABSTRACT

Recurrence of disease represents a clinical challenge in ovarian cancer patients. The aim of this study was to analyse the distribution and pattern of recurrence and their association with clinical outcome in a large series of ovarian cancer patients.

This study was conducted on 328 primary untreated ovarian cancer patients. For each relapse, information on date of clinical/instrumental recurrence, and pattern of disease presentation were retrieved.

In stage III–IV cases ($n = 270$), diffuse abdominal carcinomatosis occurred in 62.1% of cases, while recurrences presented as a single lesion or multiple nodules occurred in 9.9% and 26.7% of cases, respectively. Pattern of recurrence as carcinomatosis was shown to be associated with unfavourable outcome even when stratified according to platinum free interval (PFI) duration. In multivariate analysis, pattern of recurrence and PFI duration retained an independent prognostic role for post-relapse survival.

Duration of PFI and type of recurrence may independently influence post-relapse survival in ovarian cancer patients.

1. Introduction

Ovarian cancer is the most lethal gynaecological malignancy in adult women, with an estimated 5-year survival rate of 39%.[1] At diagnosis, the majority of epithelial ovarian cancer patients have progressed to stage III or IV, which results in poor long-term survival and quality of life.[2] Although standard treatments including cytoreductive surgery followed by systemic platinum–paclitaxel chemotherapy[3–5] have improved response rates and survival times, most patients with advanced epithelial ovarian cancer will ultimately recur and succumb to the disease.[6,7] Indeed, the major determinants of clinical outcome are represented by both residual tumour at first surgery and sensitivity to platinum-based chemotherapy defined on the basis of the interval between completion of first line chemotherapy and recurrence of disease.[8]

Standard treatment of recurrence is still poorly defined: as far as medical treatment is concerned. In patients recurring within 6 months from the completion of first line treatment, salvage chemotherapy with non-platinum agents often results in short lived response duration and survival,[9–11] while in patients considered platinum sensitive, the median survival with platinum or platinum/paclitaxel re-challenge has been reported to range from 24 to 42 months.[12–15]

Recently, much attention has been focused on the role of surgery in the management of ovarian cancer recurrence.[16] Indeed, in most of the studies, surgery has been acknowledged

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to be possibly beneficial only in selected patients presenting with a single recurrence after a platinum free interval (PFI) longer than 6/12 months, and likely to be optimally cytoreduced to no visible tumour, although definitive conclusions are far from being reached.[16]

The controversies about this issue have to be found in the heterogeneity of the series and selection bias,[16,17] but most importantly, in the lack of knowledge of the natural history of the recurrence according to the pattern of disease presentation: indeed, it is still not clear whether the duration of PFI or presentation of recurrence as a discrete lesion versus diffuse abdominal carcinomatosis, or site/size of recurrence might differently impact on patient clinical outcome.

Moreover, the investigation of whether all these variables are interrelated, and to what extent, could provide additional information to help modelling a panel of recurrence characteristics to be taken into account in the choice of treatment options.

The aim of this study was to analyse the distribution and pattern of recurrence according to clinico-pathological features in a large single institution series of consecutively accrued ovarian cancer patients. The analysis of clinico-pathological parameters predicting the pattern of recurrence and the association between pattern of recurrence presentation and clinical outcome has been performed.

2. Patients and methods

This study was conducted on 328 primary untreated ovarian cancer patients consecutively admitted to the Gynaecologic Oncology Unit, Catholic University of Rome, from January 1995 to December 2004. Clinico-pathological characteristics of the whole series are summarised in Table 1. All patients underwent exploratory laparotomy with a cytoreductive intent. Surgery was performed by the same gynaecologic oncology team. In stage III–IV ovarian cancer, infiltration of the upper gastrointestinal tract and/or the major vessels and agglutinated bowel/mesentery[18] precluded primary cytoreduction in 139 (51.4%) patients, in which only multiple biopsies were performed to obtain the pathologic diagnosis. In 131 cases it was possible to proceed to surgical removal of tumour masses along with total abdominal hysterectomy, adnexectomy, radical omentectomy and appendicectomy. Additional surgery (diaphragm stripping, intestinal resection, posterior pelvic exenteration and low rectal anastomosis) was required in 37 patients. Radical pelvic and aortic lymphadenectomy was performed in cases who were left with no visible residual disease, or in cases of grossly involved lymph nodes. Cytoreduction to a residual tumour less than 0.5 cm was achieved in 60 (22.2%) of cases, while suboptimal (residual tumour = 0.5–2.0 cm) cytoreduction was accomplished in 71 (26.3%) of cases.

Within 2–3 weeks after surgery, 89/306 patients (29.1%) underwent six cycles of cisplatin-based (75–100 mg/m^2 for each cycle), or platinum/paclitaxel containing (175 mg/m^2 for each cycle) chemotherapy (n = 217/306, 70.9%). Response to chemotherapy was assessed by gynaecological examination, CT scan, ultrasound examination, analysis of CA125 levels, and was recorded according to World Health Organisation (WHO) criteria.[19]

Table 1 – Clinical and pathological characteristics of ovarian cancer patients at diagnosis

Characteristics	No. of patients (%)
All cases	328
Age (years)	
⩽65	234 (71.3)
>65	94 (28.6)
FIGO stage	
I–II	58 (17.7)
III	226 (68.9)
IV	44 (13.4)
Ascites	
No	136 (41.5)
Yes	192 (58.5)
Histotype	
Serous	220 (67.1)
Mucinous	10 (3.0)
Endometrioid	48 (14.6)
Undifferentiated	27 (8.2)
Other	23 (7.0)
Grade	
G1–2	70 (21.3)
G3	215 (65.5)
n.a.	43 (13.1)
Carcinomatosis	
No	125 (38.1)
Yes	203 (61.9)
Residual tumour at 1st surgery[a]	
<0.5 cm	60 (22.2)
0.5–2.0 cm	71 (26.3)
Exploratory laparotomy	139 (51.5)
Residual tumour at IDS[b]	
<0.5 cm	57 (66.3)
0.5–2.0 cm	29 (33.7)

a Calculated in stage III–IV ovarian cancer patients (n = 270).
b Only in initially unresectable cases undergoing successful interval debulking surgery (IDS).

In patients with initially unresectable disease who achieved clinical response to chemotherapy, a second attempt of cytoreduction (interval debulking surgery – IDS) was performed and residual tumour was recorded.

For each relapse, information on date of recurrence as assessed by CT scan and CA125, and pattern of disease presentation (discrete lesions versus diffuse carcinomatosis, site and size, duration of PFI) were retrieved and entered into a computerised database. Clinical relapse, i.e. physical evidence of cancer upon examination or imaging, was used so as to be consistent with the literature which uses this end point, not serologic relapse, as the basis for the time-oriented definitions of 'sensitive/resistant/refractory' relapse.[8] Relapse was classified as single nodule, multiple (up to three nodules at one or more sites) and diffuse abdominal carcinomatosis for descriptive purposes and in two categories (discrete nodules versus diffuse carcinomatosis) for statistical analysis. Duration of PFI was classified in four categories (⩽6, 7–12, 13–24, >24 months) for descriptive purposes, and in two subgroups (⩽12, >12 months) for statistical analysis.

2.1. Statistical analysis

Fisher's exact test or χ^2 test were used to analyse the distribution of recurrences according to clinico-pathological features. Post-relapse survival was recorded from the date of clinical relapse/progression of disease to the date of death or date last seen. Survival probabilities were estimated according to the method of Kaplan and Meier and compared by the log rank test.[20,21]

Cox's regression model with stepwise variable selection[22] was used to analyse the role of clinico-pathological parameters, PFI duration and type of recurrence as prognostic factors for post-relapse survival. Statistical analysis was carried out using SOLO (BMDP Statistical Software, Los Angeles, CA) and Statview survival tools (Abacus Concepts- Inc- Berkeley CA).

3. Results

With a median follow up of 30 months (range 1–122), 210 recurrences/progression of disease (63.4%) were observed. Recurrence of disease was observed in 11/58 (18.9%) stage I–II patients and were represented by a single lesion (pelvis: $n = 4$; retroperitoneum: $n = 1$), multiple lesions ($n = 5$), and one case of diffuse abdominal carcinomatosis.

Table 2 shows the characteristics of recurrences in stage III–IV cases undergoing cytoreduction at first or secondary surgery.

Diffuse abdominal carcinomatosis represented the prevalent pattern of recurrence presentation in 100/161 (62.1%) cases, while recurrences presented as a single lesion or multiple nodules in 16 (9.9%) and 43 (26.7%) cases, respectively. In case of discrete nodules the maximum diameter of the largest lesion ranged from 0.8 to 12.0 cm (median 3.0 cm).

In 52.8% of cases, recurrence/progression of disease occurred after a PFI $\leqslant$12 months. The vast majority (146/161, 90.7%) of recurrent patients underwent chemotherapy: in particular, 97 patients (60.2%) were re-challenged with platinum-based regimen and 64 (39.8%) patients received non platinum agents. Only in 15 cases (9.3%) was cytoreductive surgery performed and followed by chemotherapy.

In order to better characterise the pattern of recurrence and identify parameters able to predict the characteristics of recurrence presentation, a separate analysis of stage III–IV patients was performed according to the extent of cytoreduction at first or secondary surgery (Table 3).

In patients left with microscopic residual disease at first surgery 35 (58.3%) recurrences were observed. Diffuse abdominal carcinomatosis represented the prevalent pattern of recurrence presentation in 18 (51.4%) cases, while recurrences presented as a single lesion or multiple nodules in six (17.1%) and 11 (31.4%) cases, respectively. In this subset of patients there was no correlation between the pattern of recurrence (discrete lesions versus diffuse abdominal carcinomatosis) and duration of PFI (Table 4): in particular, recurrence as diffuse abdominal carcinomatosis was observed in six out of 13 (46.1%) cases with PFI $\leqslant$12 months with respect to 12/22 (54.5%) cases with a PFI >12 months (p value = 0.73). We could not identify any clinical or pathological parameter at diagnosis able to predict the pattern of recurrence (data not shown).

Table 2 – Characteristics of ovarian cancer recurrences in stage III–IV cases submitted to cyoreduction at first or secondary surgery

Characteristics	Stage III–IV No. of cases (%)
Recurrences	161
Type of recurrence	
Single nodule	16 (9.9)
Multiple nodules	43 (26.7)
Diffuse abdominal carcinomatosis	100 (62.1)
Not specified	2
Size of the largest lesion[a] (cm)	
Median (range)	3.0 (0.8–12.0)
PFI (months)	
⩽6	33 (20.5)
7–12	52 (32.3)
13–24	47 (29.2)
>24	29 (18.0)
Site[a]	
Single	
Pelvic	5
Brain	3
Liver	3
Lymphnodes	4
Spleen	1
Multiple (one site)	
Brain	3
Liver	4
Lymphnodes	14
Spleen	1
Ileum	1
Multiple (more-sites)	20
Treatment	
Chemotherapy	146 (90.7)
Surgery + chemotherapy	15 (9.3)

PFI = platinum-free interval.
a Only for discrete lesions.

In patients left with residual tumor 0.5–2 cm at first surgery, 54 recurrences (76.0%) were observed. Diffuse abdominal carcinomatosis represented the prevalent pattern of recurrence presentation in 36 (66.7%) cases, while recurrences presented as a single lesion or multiple nodules in four (7.4%) and 14 (25.9%) cases, respectively. In this subset of patients we found a statistically significant correlation between the pattern of recurrence (discrete versus diffuse abdominal carcinomatosis) and duration of PFI (Table 4). In particular, recurrence as diffuse abdominal carcinomatosis was observed in 27 out of 34 (79.4%) cases with PFI $\leqslant$12 months with respect to 9/20 (45.0%) cases with PFI >12 months (p value = 0.013). Among clinical and pathological parameters only the presence of carcinomatosis at diagnosis was associated with a higher probability of recurring as diffuse abdominal carcinomatosis (data not shown).

When considering the subgroup of patients optimally cytoreduced at IDS, 44 (74.6%) recurrences were observed. Recurrence of disease presented as peritoneal diffuse

Table 3 – Characteristics of ovarian cancer recurrences in stage III–IV cases

Characteristics	Residual tumour at first surgery		Residual tumour at IDS	
	<0.5 cm	0.5–2.0 cm	<0.5 cm	0.5–2.0 cm
	No. cases (%)	No. cases (%)	No. cases (%)	No. cases (%)
Cases	60	71	59	29
Recurrences	35	54	44	28
Type of recurrence				
Single nodule	6 (17.1)	4 (7.4)	3[b] (6.8)	3 (10.7)
Multiple nodules	11 (31.4)	14 (25.9)	13 (29.5)	5 (17.8)
Diffuse carcinomatosis	18 (51.4)	36 (66.7)	26 (59.0)	20 (71.4)
Diameter-of-the-largest lesion[a] (cm)				
Median (range)	3.0 (1.0–10.0)	2.5 (0.9–8.0)	2.5 (0.9–8.0)	2.7 (1.5–7.5)
PFI (months)				
⩽12	13 (37.1)	34 (61.1)	28 (43.2)	18 (71.4)
>12	22 (62.9)	20 (38.9)	31 (56.8)	11 (28.6)
Site[a]				
Single				
Pelvic	4	1	–	–
Brain	1	–	2	–
Liver	1	–	–	2
Lymphnodes	–	3	–	1
Spleen	–	–	1	–
Multiple (one site)				
Brain	–	1	1	1
Liver	–	3	–	1
Lymphnodes	3	3	7	1
Spleen	1	–	–	–
Ileum	1	–	–	–
Multiple (more–sites)	6	7	5	2
Treatment				
Chemotherapy	26	51	42	27
Surgery + chemotherapy	9	3	2	1

a Only for discrete lesions.
b 2 cases missing.

Table 4 – Distribution of type of recurrence according to duration of PFI and residual tumour at first surgery in stage III–IV cases

Type-of recurrence	Residual tumour <0.5 cm			Residual tumour 0.5–2 cm		
	Discrete lesions	Carcinomatosis	*P* value	Discrete lesions	Carcinomatosis	*P* value
PFI						
⩽12 months	7	6 (46.1)		7	27 (79.4)	
>12 months	10	12 (54.5)	0.73	11	9 (45.0)	0.013

carcinomatosis in 26 (59.1%) cases, and as a single lesion or multiple nodules in three (6.8%) and 13 (29.5%) cases, respectively. In two cases, type of recurrence was unknown. There was no correlation between the pattern of recurrence (single/discrete versus peritoneal carcinomatosis) and duration of PFI (Table 5): in particular, recurrence as diffuse abdominal carcinomatosis was observed in 14 out of 21 (66.7%) cases with PFI ⩽12 months with respect to 12/21 (57.2%) cases with PFI >12 months (p value = 0.75). We could not identify any clinical or pathological parameter at diagnosis able to predict the pattern of recurrence (data not shown).

Almost all cases in the group of patients suboptimally cytoreduced at IDS experienced recurrence/progression of disease. Diffuse abdominal carcinomatosis was found in 20 (71.4%) cases, and as a single lesion or multiple nodules in three (10.7%) and five (17.8%) cases, respectively. As expected, a strong correlation between the presence of carcinomatosis at diagnosis and the recurrence as carcinomatosis was observed (p value = 0.011) (Table 5).

Table 5 – Distribution of type of recurrence according to duration of PFI and residual tumour at IDS in stage III–IV cases

Type-of recurrences	Residual tumour <0.5 cm			Residual tumour 0.5–2 cm		
	Discrete lesions	Carcinomatosis	P value	Discrete lesions	Carcinomatosis	P value
PFI						
⩽12 months	7	14 (66.7)		2 (11.1)	16 (88.9)	
>12 months	9	12 (57.1)	0.75	6 (60.0)	4 (40.0)	0.011

3.1. *Survival analysis*

In the overall series of stage III–IV ovarian cancer patients, median post relapse survival was 18 months. The prognostic value of pattern of recurrence and PFI duration in the group of patients cytoreduced to residual tumour <2 cm at first or secondary surgery is shown in Fig. 1. In the group of patients with discrete lesions, a better overall survival (OS) was observed in patients recurring after a PFI >12 months (Group A) with respect to patients recurring with a PFI ⩽12 months (Group B) (p value = 0.013). Similarly, in the group of patients recurring as diffuse abdominal carcinomatosis, a better OS was observed in patients with a PFI >12 months (Group C) with respect to patients recurring at a PFI ⩽12 months (p value = 0.04).

There was no difference in the clinical outcome of patients recurring as a discrete lesion with a PFI <12 months (Group B) with respect to patients recurring as diffuse abdominal carcinomatosis after a PFI >12 months (Group C) (p value = 0.7) The exclusion of cases with recurrence undergoing surgical removal did not lead to any modification of survival results (data not shown).

In multivariate analysis assessing the impact of several clinico-pathological factors, only type of recurrence and PFI duration retained an independent prognostic role for post-relapse survival (Table 6).

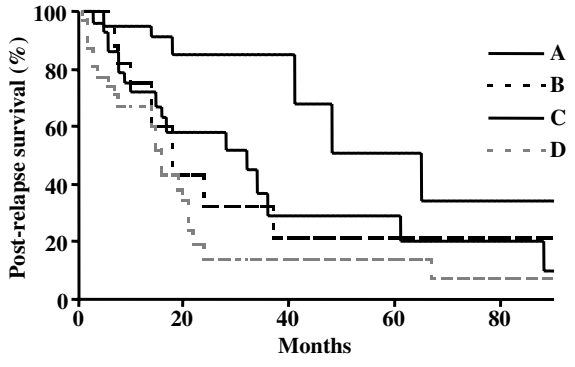

Fig. 1 – Post-relapse survival in recurrent ovarian cancer patients according to type of recurrence and duration of PFI, in stage III–IV ovarian cancer patients undergoing cytoreduction to residual tumour <2 cm at primary or secondary surgery. Discrete lesions, PFI >12 months (Group A), Discrete lesions, PFI ⩽12 months (Group B), Carcinomatosis, PFI >12 months (Group C), Carcinomatosis, PFI ⩽12 months (Group D) Group A versus B: p value = 0.013; Group C versus D: p value = 0.04; Group B versus C: p value = 0.7.

4. Discussion

We reported for the first time in multivariate analysis that pattern of recurrence might play a role in determining a different clinical outcome in ovarian cancer patients: in particular, ovarian cancer patients suffering from recurrence with a prevalent pattern of diffuse abdominal carcinomatosis showed an unfavourable prognosis with respect to cases presenting with discrete lesions. This observation is not biased by the type of relapse treatment since (i) only 9.3% of cases in our series underwent surgical removal of recurrence, and (ii) their exclusion did not have any impact on survival analysis.

As already reported for the differences in gene expression profiles of primary versus secondary ovarian cancer localisation,[23] it is possible to hypothesise that differences in the biology and natural history of discrete versus diffuse abdominal lesions might play a role in sustaining a different clinical outcome. In this context, the molecular characterisation of recurrent ovarian cancer tissues could be of utmost importance in order to attempt explaining the intrinsic attitude of ovarian cancer cells giving rise to diffuse peritoneal involvement to exhibit a more aggressive behaviour, with possible implications for the understanding of ovarian cancer pathogenesis.

Several studies have addressed the issue of the impact of clinical and pathological factors on response and survival after relapse/progression of disease in advanced epithelial ovarian cancer[7,24–26]: in particular, besides time from initial diagnosis to recurrence, other parameters have been considered, such as initial performance status, grade,[7] as well as the number and size of recurrences, and histology.[25,26] While confirming that duration of PFI is predictive of post-relapse, we showed for the first time in multivariate analysis, that duration of PFI has a prognostic value regardless of pattern of relapse presentation, so that patients with recurrence taking place after a PFI >12 months benefit from a more favourable prognosis than cases recurring within 12 months from completion of chemotherapy, both in cases of diffuse abdominal carcinomatosis or discrete lesions.

It has to be taken into account that survival was calculated since the first clinical or instrumental evidence of recurrence, thus abolishing the bias deriving from the analysis of the time since diagnosis. Therefore, with the limits inherent to the sample size, these observations suggest that in the context of each type of recurrence, the chemoresponsiveness/chemoresistance profile, as indirectly represented by PFI duration, may influence the clinical outcome of recurrent ovarian cancer patients. Whether the duration of PFI entirely represents tumour resistance at cellular level, or is also a marker of other biological characteristics of tumour aggressiveness, such as a

Table 6 – Univariate and multivariate analysis of clinico-pathological parameters as prognostic factors for post-relapse survival in stage III–IV ovarian cancer patients

Variable	Univariate			Multivariate[a]		
	RR1	χ^2	p value	RR2	χ^2	p value
Age (years)						
⩽65	1^0					
>65	1.6	2.5	0.11	–	–	–
Stage						
III	1^0					
IV	1.4	0.6	0.4	–	–	–
Ascites						
No	1^0					
Yes	0.9	0.04	0.8	–	–	–
Extent of residual tumor[b]						
<0.5 cm	1^0					
0.5–2 cm	1.2					
Exploratory laparotomy	2.0	5.1	0.023	–	–	–
Type of recurrence						
Discrete	1^0			1^0		
Diffuse abdominal carcinomatosis	2.2	8.1	0.043	2.0	6.4	0.011
Duration of PFI						
⩽12 months	1^0			1^0		
>12 months	2.3	9.6	0.002	2.1	7.7	0.005

RR1 = unadjusted relative risk.
RR2 = relative risk after adjusting for all the factors listed.
1^0 = reference category.
χ^2 of the model = 16.5, p value = 0.0003.
a Only variables with p value <0.10 in the univariate analysis were included in the multivariate model.
b Obtained at primary surgery.

faster kinetics or enhanced angiogenesis, should be investigated.

While the association between a short duration of PFI and recurrence as diffuse carcinomatosis, as well as between the presence of carcinomatosis at time of diagnosis and at recurrence, could have been intuitively expected in patients left with macroscopic residual disease at primary or secondary surgery, it remains to be explained why these correlations are lacking in cases optimally cytoreduced at primary or secondary surgery. It is conceivable that surgical achievement of microscopic residual disease, which potentiates the chances of chemotherapy success, maximizes tumour cell eradication to such extent that subsequent relapse may behave as a disease completely independent of the characteristics at initial presentation: in this case, recurrence would have the same chances of presenting early or late as well as a discrete nodule or diffuse lesion.

Anyway, these findings raise the issue of the need to search, in primary tumours, for the expression of molecules likely to be more strictly related to tumour cell biology which could, therefore, be potentially helpful in modelling a profile predictive of pattern of relapse: this could be of clinical value in optimally cytoreduced patients, nonetheless considered at high risk of relapse as diffuse abdominal carcinomatosis, in light of the growing interest raised by the use of intraperitoneal chemotherapy in different clinical settings of ovarian cancer patient management[27–29] and of novel multimodal approaches such as chemotherapy plus hyperthermia.[30,31]

We found no difference in the survival of cases presenting with early (PFI ⩽12 months) discrete nodule recurrence versus late (PFI >12 months) recurrence as diffuse abdominal carcinomatosis: possible therapeutic alternatives aimed at improving the clinical outcome of these 'intermediate prognosis' groups could be represented, in case of discrete lesions by surgical removal plus chemotherapy, although there is no general agreement on the duration of PFI (6 versus 12 months) which should be taken into consideration in the prediction of survival benefit from surgery. On the other side, in cases of late (PFI >12 months) recurrence as diffuse carcinomatosis, a more aggressive multimodal approach combining peritonectomy and chemotherapy could be explored.[32]

In conclusion, not only the duration of PFI, but also the type of recurrence, may independently influence post-relapse survival in ovarian cancer patients, and both should therefore be taken into great consideration when evaluating the treatment options in the salvage treatment of recurrent patients.

Finally, an important implication of our findings is that, beside the classical clinico-pathological features and PFI duration, the pattern of relapse presentation should also be considered because of its clinical relevance among the randomisation criteria of clinical trials aimed at assessing the efficacy of second line treatments in recurrent ovarian cancer patients.

Conflict of interest statement

None declared.

REFERENCES

1. Jemal A, Murray T, Samuels A, Ghafoor A, Word E, Thun M. Cancer statistics, 2003. *CA Cancer J Clin* 2003;**53**:5–26.
2. Berkenblit A, Cannistra SA. Advances in the management of epithelial ovarian cancer. *J Reprod Med* 2005;**50**:426–38.
3. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Eng J Med* 1996;**334**:1–6.
4. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;**21**:3194–200.
5. Salzberg M, Thurlimann B, Bonnefois H, et al. Current concepts of treatment strategies in advanced or recurrent ovarian cancer. *Oncology* 2005;**68**:293–8.
6. Eisenkop S, Spirtos NM, Friedman RL, Michael Lin WC, Pisani S, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. *Gynecol Oncol* 2003;**90**:390–6.
7. Hoskins PJ, Eisenhauer EA, van Glabbeke M, Vermorken J, Tu K, James K. Predicting outcome after initial relapse of epithelial ovarian cancer: can we identify patients who will not benefit from further therapy? *CME J Gynecol Oncol* 1999;**4**:64–9.
8. Markman M. Recurrence within 6 months of platinum therapy: an adequate definition of 'platinum-refractory' ovarian cancer? *Gynecol Oncol* 1998;**69**:91–2.
9. Harries M, Gore M. Chemotherapy for epithelial ovarian cancer: treatment of recurrent disease. *Lancet Oncology* 2002;**3**:537–45.
10. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian Carcinoma: a randomised phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;**19**:3312–22.
11. D'Agostino G, Amant F, Berteloot P, Scambia G, Vergote I. Phase II study of gemcitabine in recurrent platinum- and paclitaxel resistant ovarian cancer. *Gynecol Oncol* 2003;**88**:266–9.
12. Cannistra SA. Is there a 'best' choice of second line agent in the treatment of recurrent, potentially platinum-sensitive ovarian cancer? *J Clin Oncol* 2002;**20**:1158–60.
13. The ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;**361**:2099–106.
14. Gonzalez-Martin AJ, Calvo E, Bover I, et al. Randomized phase II trial of carboplatin versus aclitaxel and carboplatin in platinum-sensitive recurrent ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. *Ann Oncol* 2005;**16**:749–55.
15. Dizon DS, Dupont J, Anderson S, et al. Treatment of recurrent ovarian cancer: a retrospective analysis of women treated with single agent carboplatin originally treated with carboplatin and paclitaxel. The Memorial Sloan-Kettering Cancer Center experience. *Gynecol Oncol* 2003;**91**:584–90.
16. Harter P, du Bois A. The role of surgery in ovarian cancer with special emphasis on cytoreductive surgery for recurrence. *Curr Opin Oncol* 2005;**17**:505–14.
17. Gungor M, Ortac F, Arvas M, Kosebay D, Sonmezer M, Kose K. The role of secondary cytoreductive surgery for recurrent ovarian cancer. *Gynecol Oncol* 2005;**97**:74–9.
18. Fanfani F, Ferrandina G, Corrado G, et al. Impact of interval debulking surgery on clinical outcome in primary unresectable FIGO stage IIIc ovarian cancer patients. *Oncology* 2003;**65**:316–22.
19. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: WHO; Offset publication 1979; no. **48**:16-21.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;**53**:457–81.
21. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;**50**:163–70.
22. Cox DR. Regression models and life tables. *J Royal Statist Soc* 1972;**34**:197–220.
23. Fishman A, Shalom-Paz E, Fejgin M, Gaber E, Altaras M, Amiel A. Comparing the genetic changes detected in the primary and secondary tumor sites of ovarian cancer using comparative genomic hybridization. *Int J Gynecol Cancer* 2005;**15**:261–6.
24. Markman M, Markman J, Webster K, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. *J Clin Oncol* 2004;**22**:3120–5.
25. Eisenhauer EA, Gore M, Neijt JP. Ovarian cancer: should we be managing patients with good and bad prognostic factors in the same manner? *Annals of Oncology* 1999;**10**(suppl. 1):S9–S15.
26. Eisenhauer EA, Vermorken JB, van Glabbeke M. Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer : a multivariate analysis of 704 patients. *Annals of Oncology* 1997;**8**:963–8.
27. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;**335**:1950–5.
28. Markman M, Bundy BN, Alberts DS, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. *J Clin Oncol* 2001;**19**:1001–7.
29. Armstrong D, Bundy BN, Wenzel L, et al. Phase III randomized trial of intravenous cisplatin and paclitaxel versus an intensive regimen of intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in stage III ovarian cancer: a Gynecologic Oncology Group Study. *New Engl J Med* 2006;**354**:34–43.
30. Gori J, Castano R, Toziano M, et al. Intraperitoneal hyperthermic chemotherapy in ovarian cancer. *Int J Gynecol Cancer* 2005;**15**:233–9.
31. Yoshida Y, Sasaki H, Kurokawa T, et al. Efficacy of intraperitoneal continuous hyperthermic chemotherapy as consolidation therapy in patients with advanced epithelial ovarian cancer: a long-term follow up. *Oncol Rep* 2005;**13**:121–5.
32. Zanon C, Clara R, Chiappino I, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. *World J Surg* 2004;**28**:1040–5.