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Original Paper

Outcome of Epithelial Ovarian Cancer in Women under 40 years of Age Treated with Platinum-based Chemotherapy

C.K. Lee,[1] M. Pires de Miranda,[1] J.A. Ledermann,[1] M.-C. Ruiz de Elvira,[1] A.E. Nelstrop,[2] H.E. Lambert,[3] G.J.S. Rustin[2] and C.W.L. Trask[4]

[1]Department of Oncology, UCL Medical School, 91 Riding House Street, London, W1P 8BT; [2]Department of Medical Oncology, Mount Vernon Hospital, Northwood; [3]Department of Clinical Oncology, Hammersmith Hospital, London; and [4]Department of Oncology, Southend Hospital, Southend, U.K.

We retrospectively investigated the outcome of ovarian cancer in women aged less than 40 years treated in three randomised phase III studies of platinum-based chemotherapy. 624 patients had invasive epithelial ovarian cancer. A Cox proportional hazard model was used to study prognostic variables. 29 women (5%) were under 40 years of age. Stage, histological grade and amount of residual disease were significantly worse in women aged ≥40 years. Median follow-up was 66.7 months. At 5 years 65% of women below 40 years of age were alive compared with 20% of older women (95% confidence interval (CI) of the difference 27.1–63.0). The progression-free interval was 59% versus 16% (95% CI 24.3–60.8). No patient under 40 years of age relapsed after 18 months. Age ≥40 years was a poor prognostic variable, particularly for serous tumours, the commonest subtype in younger women (hazard ratio (HR): 3.33). Other prognostic factors were Eastern Cooperative Oncology Group (ECOG) performance status (HR: 1.25), presence of residual disease (HR: 1.43), histological grade (HR: 1.36) and International Federation of Gynaecology and Obstetrics (FIGO) stage (HR: 1.47). These results suggest that there are biological differences in the behaviour of serous carcinoma of the ovary in women of reproductive age compared with older women.

Key words: epithelial ovarian cancer, ovarian carcinoma, prognostic factors, multivariate analysis, carboplatin, platinum chemotherapy
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INTRODUCTION

EPITHELIAL OVARIAN cancer is the most common fatal gynaecological cancer and accounts for approximately 6% of all cancer-related deaths in women [1]. International Federation of Gynaecology and Obstetrics (FIGO) stage I ovarian cancer may be cured by surgery alone but the majority of patients present with advanced disease and require a combination of surgery and chemotherapy. Chemotherapy with cisplatin and paclitaxel produces the highest tumour response rate and is now used in all first-line chemotherapy regimens for advanced ovarian cancer [2, 3]. Before the introduction of taxanes, there have been many randomised trials with platinum-based chemotherapy and there has been no clear indication that any one regimen using standard doses is superior [4].

Correspondence to J.A. Ledermann, e-mail: j.ledermann@ucl.ac.uk
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Three prospective platinum-based chemotherapy trials which form the basis of this report have failed to show any difference between the type of platinum used, the number of cycles of treatment, or the use of chemotherapy alone or with whole abdominal radiation [5–7]. The effect of a number of prognostic variables can be investigated better by combining the data sets of these three independently conducted randomised clinical trials. Previous studies have demonstrated that FIGO stage, histology, tumour grade, performance status and amount of residual disease are important independent predictors of outcome [8–14].

It has been suggested that age at presentation may also affect outcome although much of the data have arisen from registry and population statistics [15–19]. Several studies have identified age as a univariate prognostic factor and young patients often have lower grade and earlier stage tumours [13, 19]. In this study, we performed a multivariate

analysis of many variables and in particular, investigated whether reproductive age (defined as under 40 years) is an independent prognostic factor.

PATIENTS AND METHODS

Three phase III randomised controlled trials of platinum-based chemotherapy for epithelial ovarian cancer conducted between 1984 and 1994 were retrospectively analysed. The results have been previously published [5–7]: the North Thames Ovary Trial 3 compared five courses of carboplatin (400 mg/m^2) followed by whole abdominal irradiation or five further courses of carboplatin [5]; the North Thames Ovary Trial 4 compared five versus eight courses of cisplatin (75 mg/m^2) or carboplatin (400 mg/m^2) [6]; and the third compared carboplatin (400 mg/m^2) versus iproplatin (300 mg/m^2) [7].

The data were retrieved from all the enrolled patients in the studies. The individual records of patients and histology were reviewed. Only patients with invasive epithelial ovarian cancer (i.e. of serous, mucinous, endometrioid, clear cell histology or undifferentiated types) were included in the analysis. Staging was performed according to the FIGO classification. ECOG (Eastern Cooperative Oncology Group) performance status was recorded immediately before the start of chemotherapy. The amount of residual disease was assessed by surgeons during the operation and supplemented by imaging results before chemotherapy.

An event was defined as death or clinical progression supported by imaging results and/or rising serum CA 125. Overall survival and progression-free interval (PFI) were calculated from the start of chemotherapy.

Statistical methods

Patient characteristics were compared using the Mann–Whitney, chi-square or Fisher's exact test as appropriate. Survival curves were estimated by the Kaplan–Meier method, using the log-rank test for differences between curves. Multivariate analyses were made using the Cox proportional hazard model. All variables recorded at diagnosis were used for the multivariate analyses, following a stepwise procedure. The proportionality assumption was tested graphically using standard methods [20]. Tests were considered significant at an alpha value of 0.05. Although the analyses are shown with 95% confidence interval (CI) which assume two-tailed tests, in most cases concerning prognostic variables in multivariate analyses one-tailed tests would have been appropriate; when deemed necessary this has been noted in the tables.

RESULTS

Characteristics of all patients from the three studies

624 out of the total of 652 patients were included. 28 patients were excluded because of adenocarcinoma of uncertain origin ($n = 13$), borderline carcinoma of ovary ($n = 9$) or müllerian tumours ($n = 6$). Four of the 28 women excluded from the study were under 40 years leaving 29 women aged under 40 years in the analysis.

The median age of the whole group was 59 years with 5% younger than 40 years. 94% of all patients had ECOG 0 or 1 (61% and 33%, respectively). Serous histology was present in 49% of patients and 49% of the tumours were classified as poorly differentiated (Table 1).

Most women presented with advanced disease at the time of diagnosis (71% FIGO stage III and 14% FIGO stage IV diseases). Most of the 'early stage' patients had positive peritoneal washings. More than half of the patients (56%) had significant residual disease (i.e. disease more than 2 cm diameter) assessed by their surgical records and computerised tomographic imaging. Survival of patients in the three trials was not significantly different.

The median age of the 29 women aged less than 40 years was 34 years (range: 17–39). They were not different from those ≥40 years with respect to the histology, positivity of peritoneal washings or performance status (Table 1). However, the distribution of tumour grade was different between younger and older women. In women under 40 years of age, well, moderately or poorly differentiated tumours were found in 41%, 24% and 28%, respectively, in contrast to 8%, 36% and 50%, respectively, in women ≥40 years of age (chi-square, $P < 0.001$). 31% of younger patients had more than 2 cm of residual disease after initial surgery in comparison with 57% among older patients (chi-square, $P = 0.02$). Women under 40 years of age tended to have less advanced disease. 31% of younger women presented with FIGO I or II stages whilst only 14% of older women did so (chi-square $P = 0.02$).

Relapse and survival analyses

The median follow-up was 66.7 months with no differences between age groups. Overall survival was significantly better in women under 40 years of age (Figure 1a, $P < 0.0001$). Median survival was 22.4 months in older women, whilst more than 60% of women below 40 years of age were still alive at the last recorded time (116.5 months).

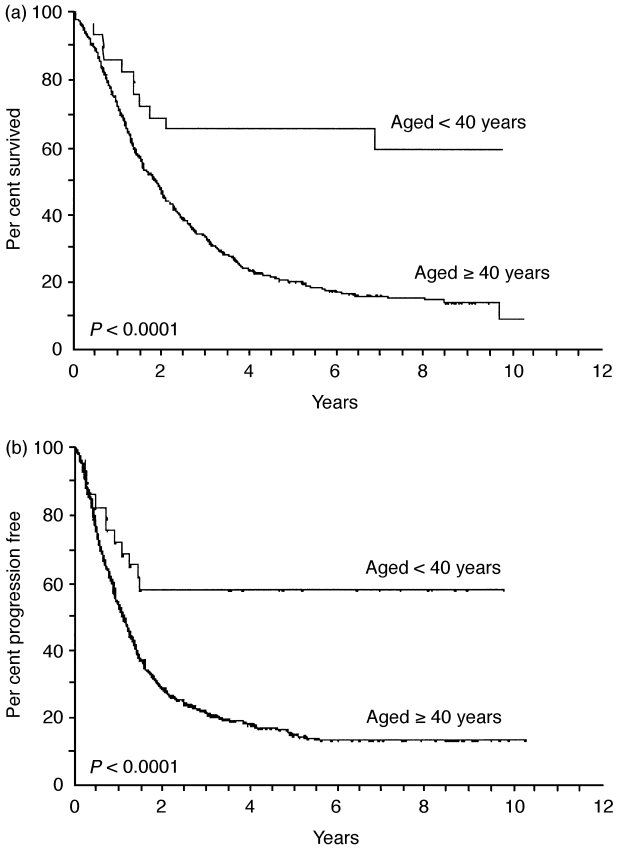

Figure 1. (a) Overall survival; (b) progression-free interval of all patients above ($n = 595$) or below ($n = 29$) 40 years.

Table 1. *Clinical and histopathological characteristics of women aged under and over* 40 *years with epithelial ovarian cancer*

	Age < 40 years ($n = 29$)	Age ≥ 40 years ($n = 595$)	Total ($n = 624$)	P value
Median age	34 (17–39) years	60 (40–79) years	59 (17–79) years	
ECOG performance status				
0	19 (66%)	363 (61%)	382 (61%)	
1	10 (34%)	195 (33%)	205 (33%)	
2 +	–	37 (6%)	37 (6%)	
Histology				
Serous	18 (62%)	286 (48%)	304 (49%)	
Mucinous	3 (10%)	38 (6%)	41 (7%)	
Endometrioid	3 (10%)	77 (13%)	80 (13%)	
Clear cell	1 (3%)	36 (6%)	37 (6%)	
Mixed/undifferentiated	4 (14%)	158 (27%)	162 (26%)	
Tumour grade				< 0.001
Well differentiated	12 (41%)	50 (8%)	62 (10%)	
Moderate differentiation	7 (24%)	212 (36%)	219 (35%)	
Poor differentiation	8 (28%)	299 (50%)	307 (49%)	
Not reported	2 (7%)	34 (6%)	36 (6%)	
Peritoneal cytology				
Positive	27 (93%)	546 (92%)	573 (92%)	
Negative	1 (3%)	20 (3%)	21 (3%)	
Not available	1 (3%)	29 (5%)	30 (5%)	
Residual disease after surgery				0.02
None	5 (17%)	61 (10%)	66 (11%)	
< 2 cm	15 (52%)	192 (32%)	207 (33%)	
≥ 2 cm	9 (31%)	342 (57%)	351 (56%)	
FIGO stage				0.02
I + II	9 (31%)	82 (14%)	91 (15)	
III	19 (66%)	426 (72%)	445 (71%)	
IV	1 (3%)	87 (15%)	88 (14%)	

P values less than 0.05 indicate a significant difference in the distribution between older and younger women.

There was a significant survival difference at 5 years (95% confidence interval (CI) 27.1–63.0), with 65% of women aged below 40 years alive compared with only 20% of older women.

PFI was also significantly better in women aged less than 40 years (Figure 1b, $P < 0.0001$). The median PFI was 13.3 months in older women, whilst more than 58% of women below 40 years of age were still disease-free at the last recorded time (116.5 months). There was a significant difference in PFI at 5 years (95% CI 24.3–60.8), with 59% of women aged below 40 years disease-free compared with only 16% of older women. No women below 40 years of age relapsed after 18 months.

Serous histology was the only group which contained a sufficient number of younger women to allow an independent analysis. In all other histologies, the number of women less than 40 years was represented by three or less individuals making comparisons between different histological subtypes impossible. For serous histology only, we obtained similar results. A significant survival advantage was seen in women below 40 years of age. The median survival was 24.0 months for older women whilst more than 60% of women aged below 40 years were alive at the last recorded time (106.4 months). Survival at 5 years for younger women was 78% versus 17% for older women (95% CI of the difference: 41.1%–80.5%). The results for PFI were similar, with a median progression-free interval of 14.4 months for older women, whilst over 58% of women aged below 40 years were disease-free at the last recorded time (106.4 months).

Although the grouping together of all other histologies may not seem appropriate, we repeated the analyses for all non-serous histologies in an attempt to see whether age was still a relevant variable. The results indicated that there are no significant differences between women below 40 years of age and older women either for survival ($P = 0.061$) or for PFI ($P > 0.1$). Median overall survival and PFI for women below 40 years with non-serous histology was 20.4 and 10.7 months, respectively, whilst for older women it was 18.6 and 11.9 months. The trend for improvement in overall survival for younger women completely disappeared if women with endometrioid cancer were removed from the analysis ($P > 0.1$).

Multivariate analyses

Multivariate analyses were performed using all variables recorded at randomisation with the original codes, leaving age as a continuous variable and stratifying by whether the histology was serous or non-serous. Age, stage, ECOG performance status and residual disease had an effect on survival and PFI (Table 2). In addition, the stratifying variable showed a significant effect demonstrating that there were differences in survival and PFI between serous and non-serous histologies in the multivariate setting. These observations in addition to those made earlier when analysing the survival curves persuaded us to analyse serous and non-serous histology separately.

Proportionality of hazard

Proportionality of hazard tests were run for all variables, and a certain amount of recoding was performed. For age,

Table 2. Cox regression showing the prognostic factors affecting overall survival for all patients using original codes, age as a continuous variable and stratified between serous and non-serous histology

$n = 624$	Coefficient	Hazard ratio	95% CI
Age	0.020	1.02	1.01–1.03
ECOG	0.327	1.39	1.18–1.62
Residual disease	0.257	1.29	1.10–1.51
Stage	0.492	1.63	1.40–1.91

CI, confidence interval.

proportionality was tested by subdividing the patients by decades with the first group encompassing all patients below 30 years of age, the next one all patients older than 29 years and younger than 40 years, etc., until the last group which was formed by all patients older than 69 years. It was found that all patients above 39 years could be grouped together with similar overall survival (Figure 2). The same was true for both groups below 40 years, although there was a trend for patients younger than 30 years to have a better survival. The lack of numbers prevented us from analysing this group separately. The proportionality between women aged below 40 years and older women was good.

Patients with no residual disease or residual disease less than 2 cm were grouped together for serous histology; this was suggested by the proportionality test and the low number of patients with no residual disease. Recoding was not done for non-serous histology.

There were only two patients with ECOG performance status 3 so these were grouped together with ECOG performance status 2 and there was good proportionality. Stage also showed good proportionality, although we had to group patients with stages I and II due to the few numbers available. Grade showed good proportionality and was not recoded any further.

Serous histology

Age, stage, ECOG performance status, grade and residual disease at randomisation all had an independent effect on overall survival in patients with serous histology (Table 3). The same prognostic factors with the exception of residual disease also had an effect on PFI.

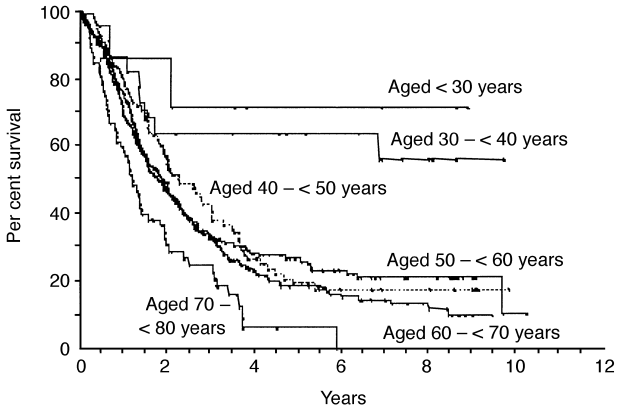

Figure 2. Survival of patients by decade from age <30 years (n=7), 30–<40 years (n=22), 40–<50 years (n=99), 50–<60 years (n=195), 60–<70 years (n=229), 70–<80 years (n=72).

Non-serous histology

This was a heterogeneous group with only a small number of patients aged less than 40 years in each histological group. Stage, residual disease and ECOG performance status at randomisation all had independent effects on overall survival and PFI in patients with non-serous histology (Table 4). Age and grade had no effect. Survival in those aged under and over 40 years is shown in Figure 3. The differences in survival of patients with serous or non-serous histology in the under 40 years age group contrasts with the absence of a difference in the survival of the older patients.

DISCUSSION

The survival of patients enrolled into the three randomised trials used in our analysis was similar. In order to study the prognostic factors affecting outcome we combined the data of 624 women who had been followed-up for a median of more than 5 years. In particular we examined outcome in women of reproductive age (defined as less than 40 years). In most previous studies, the under 40 years age group has been heterogeneous. Women with tumours of borderline malignancy were often included, or reports were from a series of patients seen in a single institution. In many publications analyses were performed on registry data [15, 17–19]. The patients in this report are a more homogeneous group in which the effect of age and other prognostic variables can be studied.

Table 3. Cox regression showing the prognostic factors affecting overall survival and PFI for patients with serous histology

$n = 294$	Coefficient	Hazard ratio	95% CI
Overall survival			
Age (1 = below 40 years; 2 = 40 years or older)	1.20	3.33	1.23–8.24
Stage (1 = I or II; 2 = III; 3 = IV)	0.385	1.47	1.08–2.00
Grade (not recoded)	0.307	1.36	1.09–1.69
Residual disease (1 = none or less than 5 cm; 2 = 5 cm or more)	0.355	1.43	1.06–1.92
ECOG performance status (not recoded)	0.223	1.25	0.99–1.58*
Progression-free interval (PFI)			
Age (1 = below 40 years; 2 = 40 years or older)	1.341	3.82	1.55–9.44
Stage (1 = I or II; 2 = III; 3 = IV)	0.419	1.52	1.15–2.01
Grade (not recoded)	0.296	1.34	1.14–1.65
ECOG performance status (not recoded)	0.262	1.30	1.04–1.63

CI, confidence interval. *Significant in a one-tailed test.

Table 4. Cox regression showing the prognostic factors affecting overall survival and PFI for patients with non-serous histology

$n = 319$	Coefficient	Hazard ratio	95% CI
Overall survival			
Residual disease (not recoded)	0.239	1.27	1.00–1.61
Stage (1 = I or II; 2 = III; 3 = IV)	0.636	1.89	1.45–2.47
ECOG performance status (0 = 0, 1 = 1, 2 = 2 or 3)	0.463	1.59	1.27–1.98
Progression-free interval (PFI)			
Residual disease (not recoded)	0.210	1.23	0.98–1.56*
Stage (1 = I or II; 2 = III; 3 = IV)	0.628	1.87	1.44–2.44
ECOG performance status (0 = 0, 1 = 1, 2 = 2 or 3)	0.437	1.55	1.24–1.93

CI, confidence interval. *Significant in a one-tailed test.

Epithelial ovarian cancer is uncommon in young women; only 5% of our group were under 40 years. The true incidence is almost certainly an underestimate as some women with early stage disease are not offered chemotherapy or are given chemotherapy but not entered into clinical trials. The overall results of treatment in each of the three trials are consistent with those of previously published trials (data not shown) [4, 12, 21]. However, we found that women aged under 40 years had a significantly better PFI and overall survival compared with older women. Ten-year survival in women under 40 years was 59%.

Although younger women had a greater proportion of moderately or well differentiated tumours, age was an independent prognostic factor in the multivariate analysis. The PFI and overall survival were also adversely affected by pretreatment poor performance status, advanced stage of disease (i.e. FIGO stage III or IV) and residual disease when all histologies were grouped. Most of the patients in the under 40 years age group had papillary serous tumours. The patients with non-serous tumours were a more heterogeneous group. In patients with serous histology the effect of age was even more striking and tumour grade was also an important prognostic variable.

Several studies have reported advanced age as a poor prognostic factor with a tendency for younger women to live longer even with same stage of disease. Bjorkholm and colleagues [21] showed increasing age was associated with a poorer prognosis in a series of 2412 women with ovarian cancer between 1958 and 1973. Subsequently, Thigpen and associates [14] summarised six Gynecologic Oncology Group trials from 1976 to 1990 and concluded that age, in addition to volume of residual disease and performance status, were the major prognostic factors in 2123 patients. Poor outcome in older women (greater than 69 years) was not due to modification of the drugs or schedules.

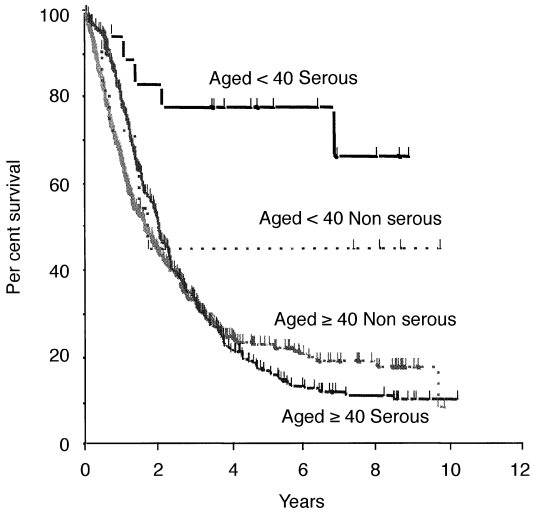

Figure 3. Survival of patients with serous or non-serous histology aged under 40 years or over 40 years.

Two large population analyses have suggested a better outcome in women aged under 45 years [17] or under 35 years [19]. It is unclear whether patients with tumours of low malignant potential were excluded from the analyses. A high proportion of patients with tumours of low malignant potential could explain the better prognosis in women of reproductive age. Massi and colleagues [18] reported in a series of 74 patients from a single institution that tumours of low malignant potential occurred in 37.5% of cases, twice as frequently as in women over 30 years of age. In another series, tumours of low malignant potential accounted for 30% of cases under 30 years but only 4% of patients between 30 and 39 years [15]. In a very large series spanning 14 years, improvements in survival were greater in younger patients. The proportion of patients who received combined surgery and chemotherapy with respect to time was higher in younger women and the older age group showed much less of a change [17]. The reason suggested by Gloeckler Ries and others [19, 22] was that fewer older women with ovarian cancer were treated by surgery and chemotherapy because tumours were more likely to be inoperable either due to advanced stage or overriding comorbid conditions.

Our results differ from previous reports in two important respects. Firstly, patients with tumours of low malignant potential were excluded, and secondly, the type of treatment given to younger and older women was the same as patients were in randomised trials. The intensity and dose of chemotherapy were not significantly different in the two groups.

Some studies have not found age to be a prognostic factor. Redman and colleagues [11] studied a group of 89 women with advanced epithelial ovarian cancer receiving combination chemotherapy with or without cisplatin and found a significantly better survival for those with no or minimal residual disease and less advanced stage but not those of a younger age. Marsoni and colleagues [10] retrospectively reviewed the results of four randomised trials that included 852 patients with epithelial ovarian cancer mostly treated with platinum-based chemotherapy. In their multivariate analyses of 721 women with known performance status, tumour size more than 5 cm, histology other than serous type and FIGO stage were associated with worse outcome. There was no significant difference in outcome in patients above or below the

age of 50 years; the proportion under 40 years was not given. Our analysis suggests that there are few differences in survival between the fifth to eighth decades (Figure 3) so that comparisons which include patients aged between 40 and 50 years in the younger age group may mask an effect of age.

We found that age under 40 years was an independent prognostic variable and we suggest that particularly in serous tumours the clinical behaviour of epithelial ovarian cancer in young women is different. The underlying mechanism for this is unclear. Early onset ovarian cancer is more likely to have an heritable cause than cancer in older women. It has recently been reported that patients with ovarian cancer who have a germ-line mutation in *BRCA1* have a more favourable clinical outcome [23]. Mutations of *p53* are associated with a poorer prognosis and their frequency increases with the stage of the disease [24]. The likelihood of acquiring *p53* mutations appears to be related to the number of lifetime ovulatory cycles [25]. This is one possible explanation for the more favourable prognosis in patients aged less than 40 years, although an analysis for the presence of p53 protein has not been performed in our patients.

In conclusion, multivariate analysis of a group of 624 women with epithelial ovarian cancer treated in randomised trials with platinum-based chemotherapy demonstrated that poor performance status, advanced FIGO stage, and residual disease > 2 cm are associated with a worse survival. In addition, age was an independent variable and we suggest that the biology of serous tumours in younger women may be different. Further work is required to explore the underlying mechanism.

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