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ORIGINAL ARTICLE

# Efficacy of neoadjuvant chemotherapy combined with intraperitoneal hyperthermic chemotherapy in advanced ovarian cancer

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## Summary

***Purpose:*** *To explore the efficacy and safety of neoadjuvant chemotherapy (NAC) combined with cytoreductive surgery (CRS) and postoperative intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of advanced ovarian cancer.*

***Methods:*** *132 patients with advanced ovarian cancer admitted to our hospital from May 2013 to May 2016 were enrolled and randomly divided into control group (n=44), IPHC group (n=44) and NAC+IPHC group (n=44). The patients in the control group underwent CRS and postoperative TP chemotherapy (iv. drip of paclitaxel + peritoneal perfusion of cisplatin), those in IPHC group underwent the CRS and postoperative IPHC+TP chemotherapy, and those in the NAC+IPHC group received two cycles of preoperative NAC and postoperative IPHC+TP chemotherapy. The surgery indexes (operation time, amount of intraoperative bleeding, diameter of tumor and number of metastatic foci) were recorded. The clinical effective rate, changes in levels of serum tumor markers and adverse reactions were evaluated. Moreover, the tumor recurrence and survival of patients after treatment were recorded.*

***Results:*** *In NAC + IPHC group, the operation time, amount of intraoperative bleeding and of ascites, diameter of tumor and number of metastatic foci were all significantly reduced, and the optimal cytoreduction rate was increased compared with IPHC group and control group. The clinical effective rate was 43.2% (19/44), 61.4% (27/44) and 72.7% (32/44), respectively, in the three groups, with significant differences, and the clinical effective rate was obviously higher in NAC+IPHC group than in control group, while it had no significant difference in IPHC group compared with NAC+IPHC group or control group. After treatment, the levels of serum human epididymis protein 4 (HE4) and carbohydrate antigen 125 (CA125) were evidently higher in NAC + IPHC group than in IPHC group, while they were also evidently higher in IPHC group than in control group. According to the follow-up results, the 1-year recurrence rate in NAC+IPHC group was remarkably lower than in control group, and the median progression-free survival in NAC+IPHC group and IPHC group was remarkably longer than in control group, while it had no significant difference between NAC+IPHC group and IPHC group. The median overall survival had no statistically significant differences among the three groups.*

***Conclusions:*** *NAC combined with IPHC can significantly reduce the perioperative risk, increase the optimal cytoreduction rate and raise the clinical effective rate of CRS in the treatment of advanced ovarian cancer. Moreover, patients have good tolerance, and both tumor progression and survival of patients are significantly improved.*

***Key words:*** *ovarian cancer, neoadjuvant chemotherapy, intraperitoneal hyperthermic chemotherapy, efficacy*

## Introduction

Ovarian cancer is a relatively common gynecological malignant tumor, with about 200,000 new cases and up to 125,000 deaths in the world every year, with a mortality rate ranking first among gynecological tumors [1]. The early symptoms are not obvious, and there is a lack of reliable early screen-

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ing methods, so ovarian cancer has been often in the advanced stage when detected [2]. The standard treatment for patients with stage III and IV ovarian cancer is cytoreductive surgery (CRS) combined with postoperative chemotherapy. Intraperitoneal hyperthermic chemotherapy (IPHC) clinically applied in recent years combines thermotherapy and chemotherapy, and studies have shown that postoperative IPHC has a better killing effect on detached tumor cells or residual tumor tissues and micrometastatic foci in ovarian cancer surgery [3,4]. Preoperative neoadjuvant chemotherapy (NAC) combined with CRS has been widely applied, and studies have demonstrated that NAC has a significant therapeutic effect on patients with advanced ovarian cancer, which can significantly reduce the preoperative tumor volume, increase the opportunity of surgical treatment, lower the surgical risk and the incidence rate of postoperative complications, increase the optimal surgical resection rate and reduce the recurrence [5,6]. However, its effect on long-term prognosis remains unclear according to several studies.

The present study aimed to explore the safety and efficacy of NAC combined with CRS and postoperative IPHC in the treatment of advanced ovarian cancer patients, so as to provide references for the treatment of patients.

## Methods

*General materials*

A total of 132 patients diagnosed with advanced ovarian cancer from May 2013 to May 2016 evaluated, and the diagnoses were confirmed by histopathology. The clinical staging criteria were based on the "Staging of Ovarian Carcinoma, Carcinoma of Fallopian Tube and Peritoneal Carcinoma" published by the FIGO in 2013, in which the clinical stage III refers to the invasion of tumor into unilateral or bilateral ovaries accompanied with local lymph node metastasis or extrapelvic peritoneal metastasis, and the clinical stage IV refers to the ovarian cancer accompanied with extraperitoneal distant metastasis [7]. The patients were aged 39-67 years with an average of 55.98±9.17, and the ECOG Performance Status (PS) score was ≤2 points. There were 68 cases of serous adenocarcinoma, 49 cases of mucinous adenocarcinoma, 9 cases of clear cell carcinoma and 6 cases of unclassified carcinoma. Sixty-four cases were in clinical stage III and 24 in stage IV. *Inclusion criteria:* patients with the PS score ≤2 points and expected survival >6 months.

*Exclusion criteria:* patients with severe hepatic or renal dysfunction, heart failure or severe blood system diseases. This study was approved by the Ethics Committee of Yantaishan Hospital, and the patients and their families were informed and signed informed consent.

According to the different therapeutic regimens, the patients were divided into control group (n=44), IPHC group (n=44) and NAC+IPHC group (n=44). There were no statistically significant differences in basic data such as age, clinical stage, histological type and ECOG score among the three groups (p>0.05) (Table 1).

*Treatment methods*

Patients in the control group underwent the CRS of ovarian cancer and postoperative TP chemotherapy (iv. drip of 135 mg/m$^2$ paclitaxel + peritoneal perfusion of 75 mg/m$^2$ cisplatin) once every 3 weeks for ≥3 months. In CRS, the tumor tissues were removed as much as possible, so that the maximum diameter of the residual lesion was ≤2 cm, and the uterus, great omentum and bilateral adnexa were excised, followed by pelvic lymph

**Table 1.** Baseline demographic and clinical characteristics of the studied patients

| *Parameters* | *Control group (n=44) n (%)* | *IPHC group (n=44) n (%)* | *NAC+ IPHC group (n=44) n (%)* | *p value* |
|---|---|---|---|---|
| Age, years | 55.73±10.50 | 58.06±9.81 | 56.80±10.22 | 0.563 |
| Histology | | | | 0.641 |
| Serous carcinoma | 23 (52.3) | 20 (45.5) | 25 (56.8) | |
| Mucinous carcinoma | 16 (36.4) | 17 (38.6) | 16 (36.4) | |
| Clear cell carcinoma | 4 (9.1) | 3 (6.8) | 2 (4.5) | |
| Not classified | 1 (2.2) | 4 (9.1) | 1 (2.2) | |
| FIGO stage | | | | 0.473 |
| III | 30 (68.2) | 34 (77.3) | | |
| IV | 14 (31.8) | 10 (22.7) | | |
| ECOG PS score | | | | 0.472 |
| 0 | 11 (25.0) | 16 (36.4) | | |
| 1 | 27 (61.4) | 24 (54.5) | | |
| 2 | 6 (13.6) | 4 (9.1) | | |

IPHC: intraperitoneal hyperthermic chemotherapy, NAC: neoadjuvant chemotherapy, FIGO: Federation of Gynecology and Obstetrics, ECOG PS: ECOG performance status

node dissection, appendectomy and paraaortic lymph node dissection. Cystectomy and intestinal partial resection could be performed if necessary.

Patients in the IPHC group underwent the CRS of ovarian cancer, and two infusion tubes were placed on the upper left and lower right abdomen and two drainage tubes on the lower left and upper right abdomen before the abdomen was closed. Then IPHC was performed: 2000 mL of normal saline was heated to 45-48°C and perfused with 80 mg of cisplatin, 10 mg of dexamethasone and 10 mg of lidocaine in the abdomen for 1-1.5 h. The operation was repeated after 1 d, and the indwelling components were removed. Postoperative TP chemotherapy was also performed (iv. drip of 150 mg/m$^2$ paclitaxel + peritoneal perfusion of 70 mg/m$^2$ cisplatin) once every 3 weeks for ≥3 months.

Patients in the NAC+IPHC group received two cycles of preoperative NAC (TP regimen), as well as CRS after NAC for 1-2 months based on the condition of chemotherapy. Other operations were the same as those in IPHC group. The IPHC instrument (RB-700) was purchased from Guangzhou Bright Technology Co., Ltd. (Guangzhou, China), and the perfusate was normal saline (42-43°C).

*Observation indexes*

The operation time, amount of intraoperative bleeding, amount of ascites, diameter of tumor, number of metastatic foci, postoperative infection rate and optimal cytoreduction rate were recorded in the three groups. The criterion for optimal cytoreduction was the diameter of postoperative residual tumor <1 cm. After 3 courses of chemotherapy, physical examination was performed, as well as color Doppler ultrasound, CT and MRI for the abdominal and pelvic cavity. Besides, the levels of serum human epididymis protein 4 (HE4) and carbohydrate antigen 125 (CA125) were detected via enzyme-linked immunosorbent assay (ELISA) before and after treatment. The adverse reactions were recorded according to the Common Terminology Criteria Adverse Events 3.0.

After 3 courses of postoperative chemotherapy, the clinical efficacy was evaluated based on the Response Evaluation Criteria In Solid Tumors. Complete response (CR): The tumor completely disappears, and the clinical examination results are normal without new lesions. Partial response (PR): The solid tumor volume shrinks by more than half compared with that before treatment, and metastatic lymph nodes have no changes. Stable disease (SD): The solid tumor volume shrinks by ≤50% or expands by ≤25%. Progressive disease (PD): The solid tumor volume expands by >25% after treatment or new lesion(s) appear. In this study, the effective rate of tumor response was CR+PR cases/total cases.

The patients were followed up till October 31, 2018, and the tumor recurrence, median progression-free survival and median overall survival were recorded.

*Statistics*

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Continuous variables were expressed as mean ± standard deviation, and the variance was homogeneous according to the Levene test. T-test was used for analyzing measurement data. Differences between two groups were analyzed by using the Student's t-test. Comparison between multiple groups was done using one-way ANOVA test followed by *post hoc* test (Least Significant Difference). The sample means at the same time point were compared between two groups through independent-samples t-test, and $x^2$ test was performed for the categorical data. Kaplan-Meier method was used to plot survival curves which were compared with log-rank test. P<0.05 suggested the statistically significant differences.

## Results

*Surgery indexes*

In NAC+IPHC group, the operation time, amount of intraoperative bleeding, amount of ascites, diameter of tumor and number of metastatic foci were all considerably reduced, and the optimal cytoreduction rate was increased compared with those in IPHC group and control group (p<0.05). There were no statistically significant differences in the postoperative fever and pelvic abdominal infection rate among the three groups (p>0.05). The operation time, amount of intraoperative bleeding, amount of ascites, diameter of tumor, number of

**Table 2.** Comparison of perioperative parameters

| *Parameters* | *Control group (n=44)* | *IPHC group (n=44)* | *NAC+ IPHC group (n=44)* | *p value* |
|---|---|---|---|---|
| Operation time (min) | 156.58±36.30[a] | 149.21±29.49[d] | 126.37±34.30 | 0.001 |
| Blood loss (ml) | 587.41±75.46[a] | 575.40±59.26[d] | 521.48±65.20 | 0.001 |
| Ascites volume (ml) | 1203.42±133.13[a] | 1165.98±122.87[d] | 734.33±102.47 | 0.001 |
| Tumor size (cm) | 13.82±2.72[b] | 12.27±2.43[d] | 8.11±2.03 | 0.001 |
| Number of metastasis foci | 4.13±0.74[a] | 3.74±0.86[d] | 2.84±0.69 | 0.001 |
| Ideal tumor reduction rate | 12 (27.3%)[c] | 15 (34.1%) | 21 (47.7%) | 0.127 |
| Postoperative fever | 3 (6.8%) | 4 (9.1%) | 5 (11.4%) | 0.759 |
| Pelvic & peritoneal infection | 13 (29.5%) | 12 (27.3%) | 9 (20.5%) | 0.597 |

IPHC: intraperitoneal hyperthermic chemotherapy, NAC: neoadjuvant chemotherapy, [a]p (Control group *vs.* NAC+ IPHC group) <0.001, [b]p (Control group *vs.* NAC+ IPHC group) =0.006, [c]p (Control group *vs.* NAC+ IPHC group) =0.048, [d]p (IPHC group *vs.* NAC+ IPHC group) <0.001

metastatic foci and optimal cytoreduction rate had no statistically significant differences between IPHC group and control group (p>0.05) (Table 2).

*Clinical effective rate*

The clinical effective rate was 43.2% (19/44), 61.4% (27/44) and 72.7% (32/44), in the three groups respectively, showing statistically significant differences (p=0.017), and the clinical effective rate had a statistically significant difference between NAC + IPHC group and control group (p=0.009), while it had no statistically significant difference in IPHC group compared with that in NAC + IPHC group or control group (p=0.135, p=0.364) (Table 3).

*Comparison of levels of serum tumor markers*

The levels of serum HE4 and CA125 declined from 656.56±76.44 pmol/L and 96.43±15.45 U/mL before treatment to 413.38±83.80 pmol/L and 47.71±9.66 U/mL after treatment in the control group, from 671.24±69.46 pmol/L and 98.80±19.06 U/mL before treatment to 349.91±79.41 pmol/L and 35.49±8.27 U/mL after treatment in the IPHC group, and from 641.17±74.03 pmol/L and 95.08±15.93 U/mL before treatment to 266.37±34.30 pmol/L and 22.38±9.22 U/mL after treatment in the NAC+IPHC group. It can be seen that the levels of serum HE4 and CA125 were significantly lower after treatment than those before treatment in the three groups

**Table 3.** Comparison of clinical efficacy of patients in the two studied patients

| *Parameters* | *Control group (n=44)* *n (%)* | *IPHC group (n=44)* *n (%)* | *NAC+ IPHC group (n=44)* *n (%)* | *p value* |
|---|---|---|---|---|
| CR | 5 (11.4) | 7 (15.9) | 10 (22.7) | |
| PR | 14 (31.8) | 20 (45.5) | 22 (50.0) | |
| SD | 16 (36.4) | 11 (25.0) | 9 (20.5) | |
| PD | 9 (20.4) | 6 (13.6) | 3 (6.8) | |
| CR+PR | 19 (43.2) | 27 (61.4) | 32 (72.7) | 0.017 |

IPHC: intraperitoneal hyperthermic chemotherapy, NAC: neoadjuvant chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

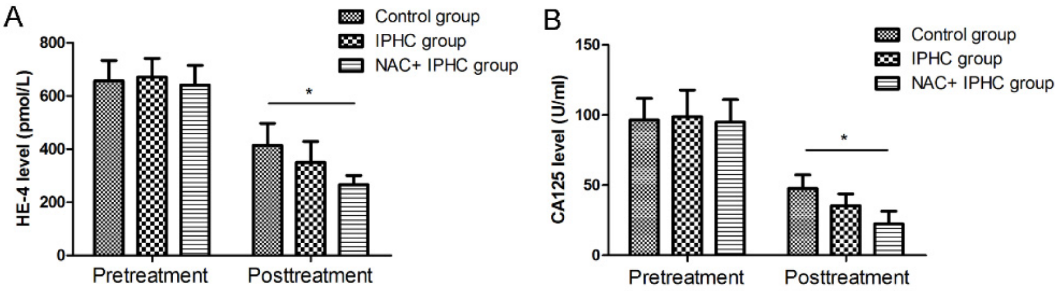


**Figure 1.** The serum level of HE-4 and CA125 were significantly decreased in patients of the three groups (p<0.05). The difference between HE-4 **(A)** and CA125 **(B)** level of patients in the three groups had significant difference (p<0.001). The difference between HE-4 **(A)** and CA125 **(B)** level of patients in the NAC+IPHC group and IPHC group had statistically significant difference, as well as those of IPHC group and control group (p<0.001). * p<0.001.

**Table 4.** Comparison of adverse reactions of patients in the studied groups

| *Parameters* | *Control group (n=44)* *n (%)* | *IPHC group (n=44)* *n (%)* | *NAC+ IPHC group (n=44)* *n (%)* | *p value* |
|---|---|---|---|---|
| Myelosuppression | 13 (29.5) | 14 (31.8) | 21(47.7) | 0.155 |
| Nausea / Vomiting | 37 (84.1) | 38 (86.4) | 43 (97.7) | 0.084 |
| Diarrhea | 3 (6.8) | 3 (6.8) | 5 (11.4) | 0.673 |
| Renal dysfunction | 24 (54.5) | 27 (61.4) | 33 (75.0) | 0.127 |
| Liver dysfunction | 25 (56.8) | 29(65.9) | 35 (79.5) | 0.073 |
| Peripheral neurotoxicity | 17 (38.6) | 21 (47.7) | 26 (59.1) | 0.157 |
| Cardiotoxicity | 20 (45.5) | 19 (43.2) | 29 (65.9) | 0.063 |

IPHC: intraperitoneal hyperthermic chemotherapy, NAC: neoadjuvant chemotherapy

(p<0.05). After treatment, the differences in levels of serum HE4 and CA125 had statistical significant difference among the three groups (p<0.001), and remarkably significant difference between NAC+IPHC group and IPHC group and between IPHC group and control group (p<0.001) (Figure 1).

*Adverse reactions and complications*

The main adverse reactions were peripheral gastrointestinal reaction, myelosuppression, hepatic and renal dysfunction, neurotoxicity and cardiotoxicity in the three groups, without statistically significant differences among the three groups (p>0.05) (Table 4).

*Follow-up results of survival*

All patients were followed up for 7-45 months (median 24). During the 1-year follow-up, the recurrence rate was 29.5% (13/44), 38.6% (17/44) and 52.3% (23/44), respectively, in the NAC+IPHC group, IPHC group and control group, displaying no statistically significant differences (p=0.139), and it was significantly lower in the NAC+IPHC group than in the control group (p=0.040). The median progression-free survival was 13.52±1.34 months, 12.97±1.54 months and 9.41±1.46 months, respectively, in the three groups, showing statistically significant differences (p<0.001), and it was remarkably longer in the NAC+IPHC group and IPHC group than in the control group (p<0.001), while it had no statistically significant difference between NAC+IPHC group and IPHC group (p>0.05). Besides, the median overall survival was 35.03±5.65 months, 32.86±5.93 months and 33.30±6.11 months, respectively, in the three groups, without statistically significant differences among the three groups (p=0.138) and in pairwise comparison (p>0.05). The survival curves of patients (Kaplan-Meier) and the survival time of patients in the three groups showed no statistically significant differences (log-rank, p=0.085). (Figure 2).

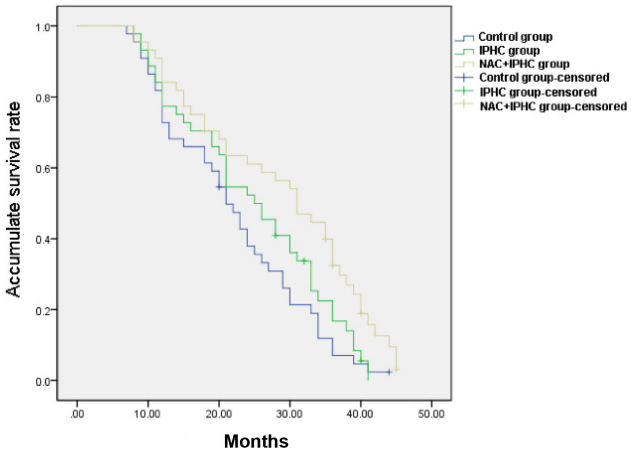


**Figure 2.** Kaplan-Meier survival curve of patients in the three groups. The difference between overall survival rate of patients in the three groups had no statistically significant difference (p=0.085).

## Discussion

In 2014, it was reported in foreign countries that 70% of new cases of ovarian cancers were in advanced stage at the initial diagnosis, and the overall survival rate was about 44% during 5-year follow-up [8]. At present, the clinically recognized therapy is the combined treatment based on CRS supplemented by chemotherapy [8, 9]. The success or failure of primary CRS is closely related to tumor prognosis, and extensive pelvic and abdominal implantation often exists in stage III or IV disease, bringing great difficulty to CRS. The optimal cytoreduction rate was only slightly more than 50% in 2000, and the incomplete primary CRS often makes the patients lose the opportunity of undergoing satisfactory CRS [10,11]. Therefore, the concept of NAC in CRS was proposed by clinical authors. Preoperative NAC can control the clinical symptoms of patients, and reduce the tumor volume, with a high tumor resection rate and a high success rate of CRS, good conditions of operation, fewer postoperative complications and high quality of life. At the same time, it can kill micrometastatic foci in distant organs or lymph nodes, and minimize the risk of tumor recurrence and metastasis [12,13]. IPHC refers to the local hyperthermic perfusion therapy combining thermotherapy and chemotherapy, which can not only maintain the high concentration of chemotherapeutic drugs in the abdominal cavity for a long time, and effectively kill tumor cells through the synergistic effect of thermotherapy and chemotherapy, but also prevent the local tumor spread caused by laparotomy and ascites diffusion [14,15].

In recent years, IPHC has achieved good therapeutic effects in the treatment of ovarian cancer and improved the disease-free survival rate and overall survival of patients, while the overall survival was prolonged more significantly in the treatment of recurrent ovarian cancer [16-18]. In 2010, NAC combined with CRS and direct CRS were prospectively compared in the treatment of advanced ovarian cancer by foreign researchers [9], and it was found that NAC can significantly reduce the tumor cell burden, lower the tumor diameter and increase the surgical satisfaction, but it had no statistically significant difference in the progression-free survival of patients compared with direct tumor excision according to the long-

term survival prognosis, having no significant effect on the prognosis of patients. In the present study, the operation time, amount of intraoperative bleeding, amount of ascites, diameter of tumor and number of metastatic foci in the NAC+IPHC group were all significantly reduced, and the optimal cytoreduction rate was evidently increased compared with those in the IPHC group and control group ($p<0.05$), indicating that NAC can significantly reduce the surgical risk of patients with advanced ovarian cancer and improve the success rate of surgical resection of ovarian tumor, something that is consistent with previous reports. In this study, it was found that the clinical effective rate was significantly higher in the NAC+IPHC group than in the control group ($p=0.009$), while it had no statistically significant difference in the IPHC group compared with NAC+IPHC group or control group ($p=0.135$, $p=0.364$), suggesting that NAC can obviously raise the clinical effective rate of CRS. According to the follow-up results, the 1-year recurrence rate in the NAC+IPHC group was remarkably lower than that in the control group ($p=0.040$), and the median progression-free survival in the NAC+IPHC group and IPHC group was remarkably longer than in the control group ($p<0.001$), while it had no statistically significant difference between NAC+IPHC group and IPHC group ($p>0.05$). The median overall survival had no statistically significant differences among the three groups ($p=0.138$), demonstrating that NAC combined with IPHC can obviously reduce the 1-year recurrence rate and improve the progression-free survival of patients, but it had no significant effect on the overall survival of patients. Besides, preoperative NAC had no marked impact on improving the tumor progression and survival time of patients, consistent with previous research results [19].

HE4 and CA125 are clinically recognized tumor markers for ovarian cancer, having a certain diagnostic value for patients with this disease [19,20]. In this study, the improvement of HE4 and CA125 in the NAC+IPHC group was greater than in the IPHC group and control group, demonstrating that the changes in levels of HE4 and CA125 can serve as indexes for clinical efficacy. In terms of the toxic and side effects of chemotherapy, the incidence rates of adverse reactions had no statistically significant differences among the three groups ($p>0.05$), and neither NAC nor IPHC significantly increased the incidence of adverse reactions.

There are still some limitations in this study. For example, the sample size was small, the follow-up was not comprehensive enough, and the possible influences of combined treatment on the quality of life of patients were not evaluated, so the conclusions made still need further verification via multi-center, large-sample randomized controlled clinical studies.

## Conclusions

NAC combined with IPHC can significantly reduce the perioperative risk, increase the optimal cytoreduction rate and raise the clinical effective rate of CRS in the treatment of advanced ovarian cancer. Moreover, patients have good tolerance, and both tumor progression and survival of patients are significantly improved.

## Conflict of interests

The authors declare no conflict of interests.

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