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ORIGINAL REPORT

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欧文凯泽永久欧文医疗中心德万苏·特瓦里；加州旧金山加州大学加州分校太平洋/帕洛阿尔托医学基金会/萨特研究所的陈约翰；纽约州布法罗市罗斯威尔公园癌症研究所妇科肿瘤组统计和数据中心的詹姆斯·j·爪哇；哥伦布俄亥俄州立大学韦克斯纳医学中心里图·萨拉尼；俄亥俄州辛辛那提市辛辛那提大学托马斯·赫尔佐格；约翰·霍普斯金大学医学院西德尼·金梅尔综合癌症中心，医学博士；美国癌症治疗中心东部区域医疗中心的莫里·马克曼，宾夕法尼亚州费城；布拉德利·蒙克，克雷顿大学医学院，亚利桑那州凤凰城。

Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

晚期卵巢癌腹腔化疗的长期生存优势和预后因素：一项妇科肿瘤组研究

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Purpose

目的

To determine long-term survival and associated prognostic factors after intraperitoneal (IP)

确定腹腔注射后的长期生存率和相关预后因素

chemotherapy in patients with advanced ovarian cancer.

晚期卵巢癌患者的化疗。

Patients and Methods

患者和方法

Data from Gynecologic Oncology Group protocols 114 and 172 were retrospectively analyzed. Cox

对妇科肿瘤组方案 114 和 172 的数据进行回顾性分析。艇长

proportional hazards regression models were used for statistical analyses.

比例风险回归模型用于统计分析。

Results

结果

In 876 patients, median follow-up was 10.7 years. Median survival with IP therapy was 61.8

在 876 名患者中，中位随访时间为 10.7 年。IP 治疗的中位生存期为 61.8

months (95% CI, 55.5 to 69.5), compared with 51.4 months (95% CI, 46.0 to 58.2) for intravenous therapy. IP therapy was associated with a 23% decreased risk of death (adjusted hazard ratio [AHR], 0.77; 95% CI, 0.65 to 0.90; $P = .002$). IP therapy improved survival of those with gross

月 (95% 可信区间，55.5 至 69.5)，而静脉注射治疗为 51.4 个月 (95% 可信区间，46.0 至 58.2)。IP 治疗与死亡风险降低 23% 相关 (调整后的危险比 [AHR]，0.77；95% 置信区间，0.65 至 0.90；P = .002)。IP 疗法提高了患有严重

residual (≤ 1 cm) disease (AHR, 0.75; 95% CI, 0.62 to 0.92; $P = .006$). Risk of death decreased

残留 (≤ 1 cm) 疾病 (AHR, 0.75；95% 置信区间，0.62 至 0.92；P = .006)。死亡风险降低

by 12% for each cycle of IP chemotherapy completed (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Factors associated with poorer survival included: clear/mucinous versus serous histology (AHR,

IP 化疗每个周期完成 12% (AHR, 0.88；95% 置信区间，0.83 至 0.94；P < .001)。与较差生存率相关的因素包括：透明/粘液性与浆液性组织学 (AHR,

2.79; 95% CI, 1.83 to 4.24; $P < .001$), gross residual versus no visible disease (AHR, 1.89; 95% CI, 1.48 to 2.43; $P < .001$), and fewer versus more cycles of IP chemotherapy (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Younger patients were more likely to complete the IP regimen, with a 5% decrease in probability of completion with each year of age (odds ratio, 0.95; 95% CI, 0.93

2.79；95% 置信区间，1.83 至 4.24；P < .001)，总残留对无可见疾病 (AHR, 1.89；95% 置信区间，1.48 至 2.43；P < .001)，并且 IP 化疗周期更少与更多 (AHR, 0.88；95% 置信区间，0.83 至 0.94；P < .001)。年轻患者更有可能完成 IP 方案，完成的概率随着年龄的增长而降低 5%(优势比，0.95；95% 置信区间，0.93

to 0.96; $P < .001$).

至 0.96；P < .001)。

Conclusion

结论

The advantage of IP over intravenous chemotherapy extends beyond 10 years. IP therapy

IP 相对于静脉化疗的优势超过了 10 年。知识产权疗法

enhanced survival of those with gross residual disease. Survival improved with increasing number of IP cycles.

严重残留疾病患者的存活率提高。存活率随着 IP 周期数的增加而提高。

ing local therapies. Prior studies

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have
the
advantage
delivering

Epithelial ovarian carcinoma is the leading cause of gynecologic cancer mortality in the United States, with an associated 15,500 deaths in 2012.[1,2] Most patients with advanced-stage cancer will eventually experience recurrence and die as a result of the dis- ease.[3] Therefore, more effective therapies are needed in the treatment of this aggressive cancer.

当地疗法。先前的研究报道了递送顺铂的药理学优势

上皮性卵巢癌是美国妇科癌症死亡的主要原因，2012 年有 15，500 人死亡。[1,2] [3]

The peritoneum serves as the primary site of spread and failure in most cases of advanced can- cers. Even in the relapsed setting, the disease is typically confined to the peritoneal cavity. Thus, this region provides a sanctuary site for develop-

在大多数晚期癌症病例中，腹膜是扩散和衰竭的主要部位。即使在复发的情况下，该疾病也通常局限于腹膜腔。因此，这个地区为发展提供了一个避难所

intraperitoneally (IP), with a 20-fold higher concentration in the IP space compared with that measured in plasma after intravenous (IV) administration.[4-6] Likewise, IP paclitaxel can achieve a 1,000-fold greater concentration compared with IV administration.[7-12] In addition, IP therapy allows for continuous and pro- longed exposure of high drug concentrations with lower peak plasma levels over time.[13]

腹膜内给药，与静脉内给药后在血浆中测得的浓度相比，腹腔内给药的浓度高 20 倍。[4671213]

Three intergroup trials have demonstrated the survival benefit associated with IP over IV therapy in advanced, low-volume ovarian cancer.[14-16] Despite the positive clinical trial results and a subsequent

三项组间试验已经证明了晚期低体积卵巢癌与静脉注射治疗相关的生存益处。[1416]

National Cancer Institute alert, IP treatment has not been widely accepted as the standard of care in the United States and is infrequently used in Europe.[13,17] The hesitancy of clinicians to use IP therapy is likely attributed to higher toxicity, inconvenience, catheter complica- tions, and uncertain long-term benefits.[18] In the most recent trial, the majority of patients did not complete the proposed experimental IP regimen because of toxicity and other related complications.[14] Thus, it is unclear if a therapeutic advantage to increasing the number of IP cycles exists. Conversely, it is not known if there is a minimum num- ber of cycles of IP treatment needed to achieve the pharmacologic advantage and thus avoid unnecessary toxicity. In addition, there are no studies that have identified demographic and clinicopathologic characteristics of patients who may not tolerate or benefit from IP therapy, such as older patients with poor performance status or those with macroscopic residual disease. Most importantly, it is uncertain if the benefit of IP therapy persists over an extended period.

国家癌症研究所提醒，IP 治疗在美国尚未被广泛接受为护理标准，在欧洲也很少使用。[1317 18 14]

As such, we report this exploratory analysis of two Gynecologic

因此，我们报告了两个妇科的探索性分析

Oncology Group (GOG) randomized phase III clinical trials to inves- tigate the 10-year survival outcomes of those who underwent IP versus IV chemotherapy. We also evaluated factors associated with survival after IP therapy, including the extent of residual disease and number of cycles of IP therapy.

肿瘤学小组 (GOG) 进行了随机三期临床试验，以研究接受静脉化疗和静脉化疗患者的 10 年生存率。我们还评估了与 IP 治疗后生存率相关的因素，包括残余疾病的程度和 IP 治疗的周期数。

Our study was a posthoc analysis using pooled data from all patients enrolled onto GOG protocols 114 and 172 (Fig 1).[15,16] Eligibility criteria included stage III epithelial ovarian or peritoneal carcinoma with no residual disease > 1 cm in diameter after surgery. All patients had a GOG performance status of 0 to 2. Patients enrolled onto GOG 114 were randomly assigned to two different

我们的研究是一项事后分析，使用了 GOG 方案 114 和 172 中登记的所有患者的汇总数据 (Fig 1[1516])

treatment arms. Patients received either IV paclitaxel 135 mg/m^2 followed by IV cisplatin 75 mg/m^2 for six courses or the study arm of IV carboplatin for two

治疗武器。患者接受紫杉醇静脉注射 135 毫克/平方米，然后顺铂静

脉注射 75 毫克/平方米，共六个疗程，或者接受卡铂静脉注射两个疗程

Enrolled onto (N = 1,018) trials
GOG-0114 (n = 589)
GOG-0172 (n = 429)

Excluded (n = 142)
Did not meet (n = 76) inclusion criteria
Discontinued arm (n = 66) of GOG-

Retrospectively eligible 0114 and randomly assigned to IV or IP chemotherapy treatment (n = 876)

Assigned to IV chemotherapy treatment (n = 436)

Assigned to IP chemotherapy treatment (n = 440)

Continued to receive IV IP chemotherapy treatment (n = 346)

Crossed over to chemotherapy treatment (n = 94)

参加 (N = 1，018) 次试验
GOG-0114 (n = 589)
GOG-0172 (n = 429) 除外 (n = 142)
不符合纳入标准 (n = 76)
停产臂 (n = 66)
GOG-0114 回顾性合格，随机分配
转静脉或静脉注射化疗
治疗
(n = 876)

分配给分配给
静脉化疗 IP 化疗治疗
(n = 436) (n = 440)
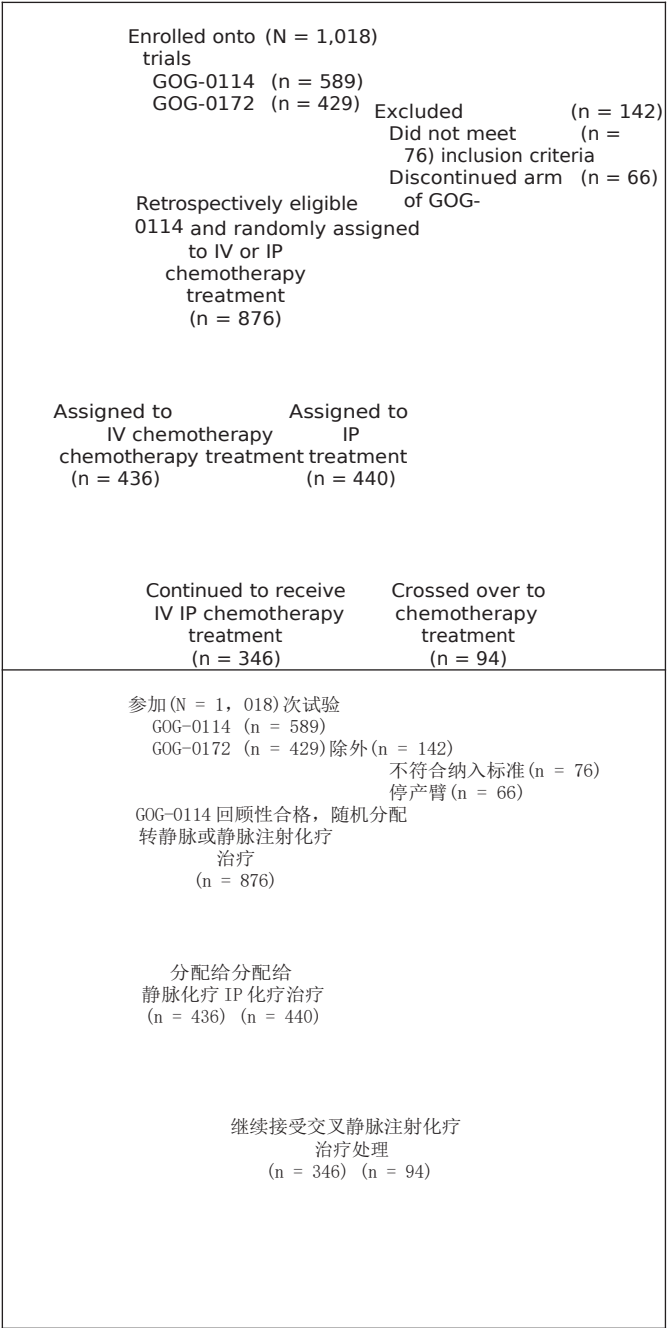
继续接受交叉静脉注射化疗
治疗处理
(n = 346) (n = 94)

Fig 1. CONSORT diagram. GOG, Gynecologic Oncology Group; IP, intraperi- toneal; IV, intravenous.

图 1。CONSORT 图。GOG，妇科肿瘤集团；内部知识产权；四、静脉注射。

courses followed by IV paclitaxel 135 mg/m² on day 1 and IP cisplatin 100 mg/m² on day 8 for six courses. IV cisplatin was substituted for IP cisplatin for catheter-related malfunctions. In GOG 172, patients received 135 mg/m² IV paclitaxel followed by either 75 mg/m² IV cisplatin on day 2 (IV group) or 100 mg/m² of IP cisplatin on day 2 and 60 mg/m² of IP paclitaxel on day 8 (IP group) for six cycles. If IP cisplatin could not be administered secondary to toxicity or catheter-related issues, substitution with IV carboplatin was per- mitted. Patients who were treated provided signed informed consent consis- tent with all regulatory requirements.

疗程后，第 1 天静脉注射紫杉醇 135 mg/m2，第 8 天静脉注射顺铂 100 mg/m2，共 6 个疗程。静脉注射顺铂代替静脉注射顺铂治疗导管相关故障。在 GOG 172，患者接受 135 毫克/平方米的静脉注射紫杉醇，然后在第 2 天接受 75 毫克/平方米的静脉注射顺铂（静脉注射组），或在第 2 天接受 100 毫克/平方米的静脉注射顺铂，在第 8 天接受 60 毫克/平方米的静脉注射紫杉醇（静脉注射组），共 6 个周期。如果顺铂不能继发于毒性或导管相关问题，建议用静脉注射卡铂替代。接受治疗的患者提供了符合所有监管要求的签署的知情同意书。

We compared baseline patient characteristics within and between the GOG studies using Pearson's y^2 test to examine relationships between cate- gorical variables and the Wilcoxon Mann-Whitney test for continuous vari- ables.[19,20] Potential heterogeneity in treatment effect by prognostic factor subgroups was evaluated using likelihood ratio tests of subgroup-by-treatment interaction in models fitted to both the subgroups themselves and to the entire population. Kaplan-Meier estimates of survival functions included all-cause mortality and were compared using a two-sided log-rank test.[21] Hazard ratios (HRs) and CIs were estimated with Cox proportional hazards regression models to assess the relationship of treatment modality and survival outcomes adjusted for baseline demographic and clinicopathologic fac- tors.[22,23] Overall significance of factors included in the Cox models was eval- uated with Wald tests.[24] The number of total deaths resulting from nondisease causes was low for the patient sample (44 [5%] of 876). As a preliminary step in deciding whether competing-risk analyses were warranted, we censored non- disease deaths in the multivariable Cox models. Because results of the disease- specific models were not appreciably different from those of the all-cause models, competing-risk analyses were not performed. In addition, because this analysis was exploratory and hypothesis generating, no adjustments for mul- tiple comparisons were made. All statistical analyses were performed with R software (version 2.14.2; http://www.r-project.org).

我们使用皮尔逊 y2 检验比较了 GOG 研究内部和之间的基线患者特征，以检验类别变量和连续变量的威尔科克森-惠特尼检验之间的关系。[19][20][21][22][23] [24] http://www.r-project.org

Characteristics of 876 patients included in the study are listed in Table

研究中包括的 876 名患者的特征列于 Table

1. Demographic and clinicopathologic characteristics of patients in the two protocols were similar (Appendix Table A1, online only). Overall median follow-up was 10.7 years (GOG 114: median, 13.8 years; GOG 172: median, 9.7 years). In the overall study group, me- dian progression-free survival (PFS) was 25 and 20 months for the IP

1。两个方案中患者的人口统计学和临床病理特征相似（附录 Table A1

and IV arms (P = .019), with corresponding overall survival (OS) of

和第四臂（P = .019），相应的总生存率为

3

61.8 versus 51.4 months, respectively (*P* = .042; Table 2; Fig 2). More

分别为 61.8 个月和 51.4 个月（P = .042Table 2Fig 2

specifically, IP therapy was associated with a 21% decreased risk of progression (adjusted HR [AHR], 0.79; 95% CI, 0.67 to 0.92; *P* = .003) and 23% decreased risk of death, with an AHR of 0.77 (95% CI, 0.65 to 0.90; *P* = .002) after adjusting for age, performance status, cell type, tumor grade, and residual disease (Table 2). Long-term survival rates

具体而言，IP 治疗与进展风险降低 21%相关（调整后的 HR [AHR]，0.79；95%置信区间，0.67 至 0.92；P = .003），死亡风险降低 23%，AHR 值为 0.77（95%置信区间，0.65–0.90；P = .002）在对年龄、表现状态、细胞类型、肿瘤分级和残留疾病（Table 2

after IV versus IP therapy based on protocols 114 and 172 are listed in Appendix Table A2 and Fig A1 (online only). We evaluated factors associated with long-term survival after IP therapy (Table 3). Clear- cell/mucinous versus serous histology (AHR, 2.79; 95% CI, 1.83 to

附录中列出了基于方案 114 和 172 的静脉注射与静脉注射治疗后的情况 Table A2 Fig A1 Table 3

4.24; *P* < .001), gross residual (≤ 1 cm) versus no visible disease (AHR, 1.89; 95% CI, 1.48 to 2.43; *P* < .001), and fewer cycles of IP chemotherapy with crossover to IV therapy (AHR, 1.43; 95% CI, 1.02 to 2.01; *P* = .041) were prognostic factors associated with poorer long-term survival after IP therapy.

4.24;P < .001），总残留（≤ 1 厘米）对比无可见疾病（AHR， 1.89； 95% 置信区间，1.48 至 2.43；P < .001），并且 IP 化疗与 IV 治疗交叉的周期更少（AHR，1.43；95%置信区间，1.02 至 2.01；P = .041）是与 IP 治疗后长期生存率较差相关的预后因素。

We then evaluated surgical factors that may predict for more benefit associated with IP therapy. Specifically, we proposed to deter- mine whether IP therapy benefits those with gross residual disease (≤ 1 cm) in addition to those with no visible disease. Our data showed that IP therapy also improved the survival of those with gross residual

然后，我们评估了手术因素，这些因素可以预测 IP 治疗的更多益处。具体来说，我们建议确定除了没有明显疾病的患者外，IP 治疗是否对严重残留疾病（≤ 1 cm）的患者有益。我们的数据显示，IP 治疗也提高了总残留患者的存活率

Table 1. Overall Patient Characteristics (N = 876)		
Characteristic	No.	%
Age, years		
Median		48.6
Range		48.6-65.6
≤ 55.0	391	44.6
≥ 55.0	485	55.4
Race/ethnicity		
White	798	90.2
Black	41	4.7
Hispanic	28	3.2
Asian	16	1.8
Other	1	0.1
BMI, kg/m²		
Median		24.7
Range		21.8-29.1
Performance status		
Normal, fully ambulatory	419	47.8
Symptomatic, ambulatory	387	44.2
Symptomatic, in bed ≤ 50%	70	8.0
FIGO stage III	876	100
Tumor grade		
1	336	38.4
2	440	50.2
3	336	38.4
Histology		
Serous	635	72.5
Endometrioid	83	9.5
Clear cell	35	4.0
Mucinous	16	1.8
Other	107	12.2
Gross residual disease (≤ 1 cm)		
Yes	560	63.9
No	316	36.1
Treatment		
Intravenous	436	49.8
Intraperitoneal	440	50.2
GOG protocol		
172	414	47.3
114	462	52.7

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group.

No. at risk

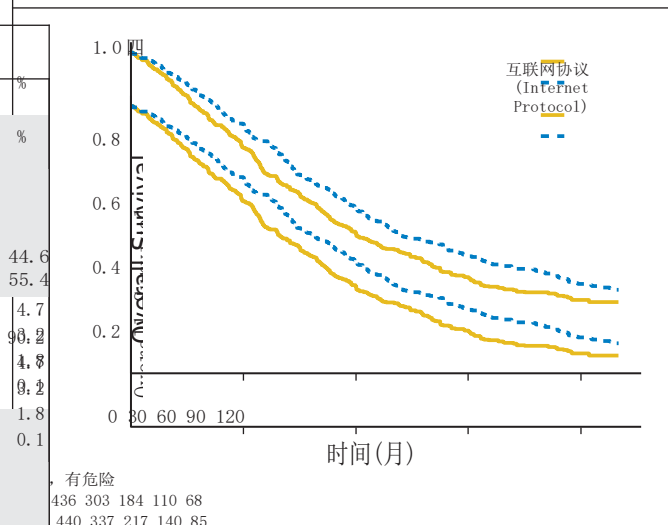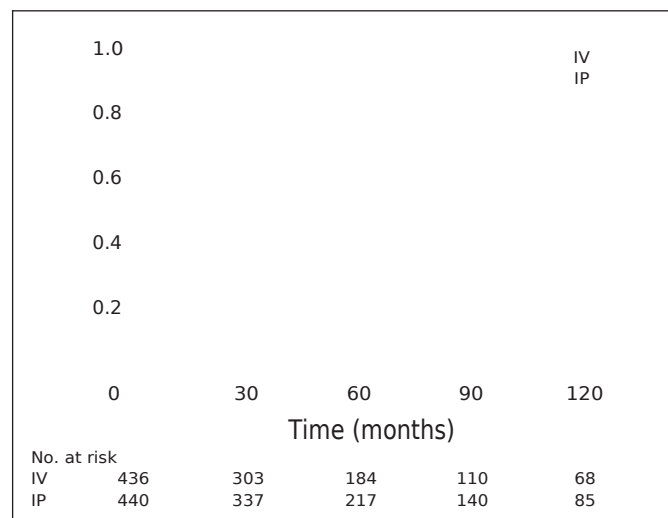|					
IV	436	303	184	110	68
IP	440	337	217	140	85

Time (months)

互联网协议 (Internet Protocol)

时间(月)

Fig 2. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy (*P* = .04).

图 2。静脉(静脉)化疗与腹腔(静脉)化疗患者的长期总生存期(*P* = .04)。

disease (AHR, 0.75; 95% CI, 0.62 to 0.92; P = .006; Fig 3). Neverthe- less, it is important to note that those with gross residual disease had a 1.89-fold increase in risk of death (95% CI, 1.48 to 2.43; P < .001) compared with patients with no visible disease.

疾病（AHR，0.75；95% 置信区间，0.62 至 0.92；P = .006Fig 3

The overall study group of both trials showed 50% of patients in the IP arm completed six cycles of IP therapy required by the proto- cols. Because only a fraction of patients was able to complete the planned treatment, we considered the effect of treatment completion on survival. To account for the changing risk associated with chemo- therapy over time, the number of cycles of chemotherapy completed was entered into the Cox proportional hazards model as a time- varying covariate. In our analysis, risk of death decreased by 12% for each cycle of IP chemotherapy completed by any patient (AHR, 0.88; 95% CI, 0.83 to 0.94; P < .001). The survival rates of subgroups of patients in GOG 0172 who completed all six cycles of chemotherapy are shown in Figure 4. Of these patients, completion of six cycles of IP chemotherapy was associated with better survival compared with three cycles of IP followed by three cycles of IV treatment (P = .032). Because those who completed more cycles of IP therapy had a lower risk of death, we also evaluated the demographic and clinico- pathologic factors associated with completing all six cycles of IP che- motherapy and found that younger age was associated with a higher likelihood of completing IP therapy. More specifically, the odds of completing IP therapy decreased approximately 5% for each increas- ing year of age at enrollment (odds ratio, 0.95; 95% CI, 0.93 to 0.96; P < .001). Other demographic and clinicopathologic factors, includ- ing performance status, were not prognostic of completing IP therapy.

两项试验的总体研究组显示，IP 组中 50%的患者完成了原型组所需的六个周期的 IP 治疗。因为只有一小部分患者能够完成计划的治疗，我们考虑了治疗完成对生存率的影响。为了说明随着时间的推移化疗相关风险的变化，已完成化疗的周期数作为时变协变量被输入 Cox 比例风险模型。

在我们的分析中，任何患者完成的 IP 化疗每个周期的死亡风险降低了 12%（AHR，0.88；95%置信区间，0.83 至 0.94；P < .001）。GOG 0172 患者亚组中完成所有六个化疗周期的生存率如所示 Figure 4

Table 2. Long-Term PFS and OS of Patients After IV Versus IP Therapy (N = 876) PFS						OS				
Therapy Type	Median (months)	Range (months)	AHR	95% CI	P	Median (months)	Range (months)	AHR	95% CI	P
IV	20	17.7-23.5	Referent		—	51.4	46.0-58.2	Referent		—
IP	25	23.0-29.0	0.79	0.67 to 0.92	.003*	61.8	55.5-69.5	0.76	0.65 to 0.90	.002*
All	23	21.8-24.5	—		.019†	56.3	52.4-60.7	—		.042†

Abbreviations: AHR, adjusted hazard ratio; IP, intraperitoneal; IV, intravenous; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Wald test.

表 2。静脉注射与静脉注射治疗后患者的长期全氟辛烷磺酸和 OS（N = 876）

治疗类型	中位数（月）	范围中位数范围（月）AHR 95%置信区间 P（月）（月）						AHR 操作系统	95%置信区间	P
注入静脉的	20	17.7-23.5	指示物		—	51.4	46.0-58.2	指示物		—
互联网协议（Internet Protocol）	25	23.0-29.0	0.79	0.67 至 0.92	.003*	61.8	55.5-69.5	0.76	0.65 至 0.90	.002*
全部	23	21.8-24.5	—		.019†	56.3	52.4-60.7	—		.042†

缩写：AHR，调整后的危险比率；腹腔注射；四、静脉注射；OS，整体生存；PFS，无进展生存期。
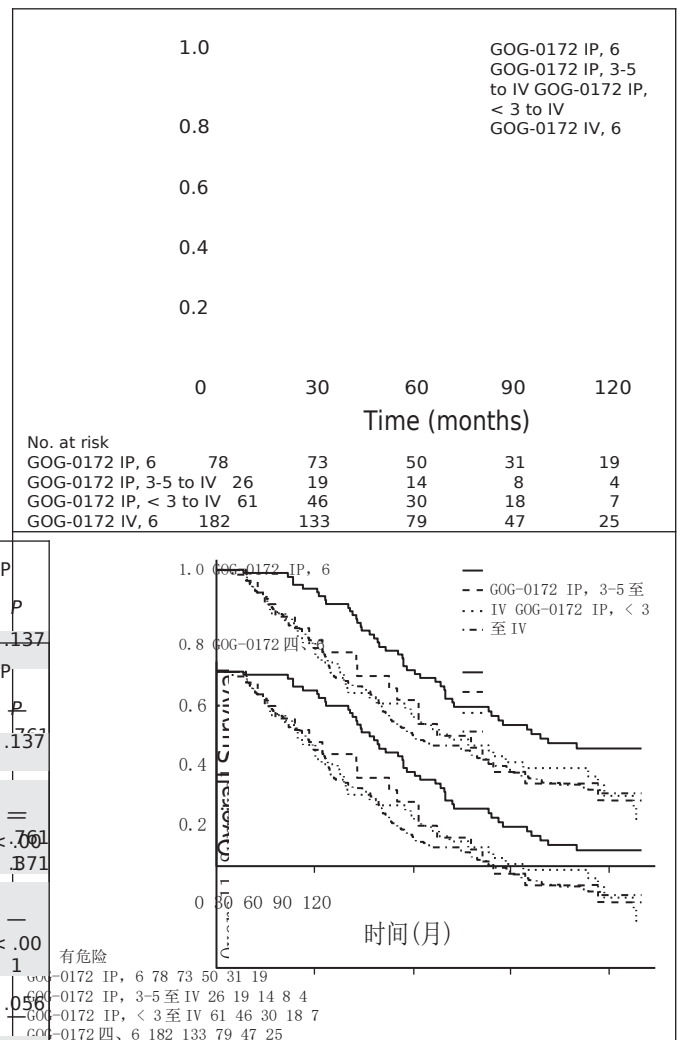*对数秩检验。
沃尔德测试。

Fig 4. Long-term overall survival based on number of cycles of intraperitoneal (IP) therapy (P = .03). Analysis restricted to patients in Gynecologic Oncology Group (GOG) -0172 who completed all six cycles of chemotherapy (both IP and intravenous [IV] arms).

图 4。基于腹膜内治疗周期数的长期总生存率（P = .03）。分析仅限于妇科肿瘤（GOG）-0172 名完成所有六个周期化疗（静脉注射和静脉注射）的患者。

Legend: GOG-0172 IP, 6 / GOG-0172 IP, 3-5 to IV GOG-0172 IP, < 3 to IV / GOG-0172 IV, 6

No. at risk

GOG-0172 IP, 6	78	73	50	31	19
GOG-0172 IP, 3-5 to IV	26	19	14	8	4
GOG-0172 IP, < 3 to IV	61	46	30	18	7
GOG-0172 IV, 6	182	133	79	47	25

Table 3. Factors Associated With Long-Term Survival After IP Therapy

Therapy Factor	AHR	95% CI	P
Age, years	1.01	1.00 to 1.02	.137
GOG performance status			
0 (normal, asymptomatic)	1.00	Referent	—
1 (symptomatic, ambulatory)	0.96	0.75 to 1.24	.762
5 (symptomatic, in bed ≤ 50%)	1.20	0.80 to 1.81	.371
Histology			
Serous, other	1.00	Referent	—
Clear cell or mucinous	2.79	1.83 to 4.24	< .001
Tumor grade	1.48	0.99 to 2.25	.056
1	1.00	Referent	
Gross residual disease*			
No	1.00	Referent	—
Yes	1.89	1.48 to 2.43	< .001
Cycles of IP chemotherapy (zero to six)	0.88	0.83 to 0.94	< .001
IV crossover†			
No	1.00	Referent	—
Yes	1.43	1.02 to 2.01	.041

has not been widely adopted. GOG protocol 104 did show an IP survival advantage; however, cyclophosphamide was used rather than paclitaxel.[15] In GOG 114, investigators used paclitaxel, but OS was not statistically significant, and the IP arm included intensive IV carboplatin, which may have confounded the results.[16] The GOG 172 trial demonstrated that

尽管试验显示了生存益处，但是 IP 疗法还没有被广泛采用。GOG 协议 104 确实显示了 IP 生存优势；然而，使用的是环磷酰胺而不是紫杉醇。[15] [16]

Despite trials showing survival benefit, IP therapy

IV paclitaxel plus IP cisplatin and IP paclitaxel improved survival over IV paclitaxel and IV cisplatin. However, nearly half of the patients did not complete the IP regimen because of reported toxicity or associated complications. Furthermore, inferential data using cross-trial com- parisons suggested that IV carboplatin may be slightly better than IV cisplatin, and the weekly schedule in the IP arm may have partially explained the survival advantage. This suggests that the magnitude of clinical benefit with IP therapy may not have been as prominent if the control arm of GOG 172 had included carboplatin and/or weekly dosing. On the contrary, two large meta-analyses combining multiple randomized trials showed the incorporation of an IP cisplatin regimen improved the survival of patients with advanced ovarian cancer.[25,26]
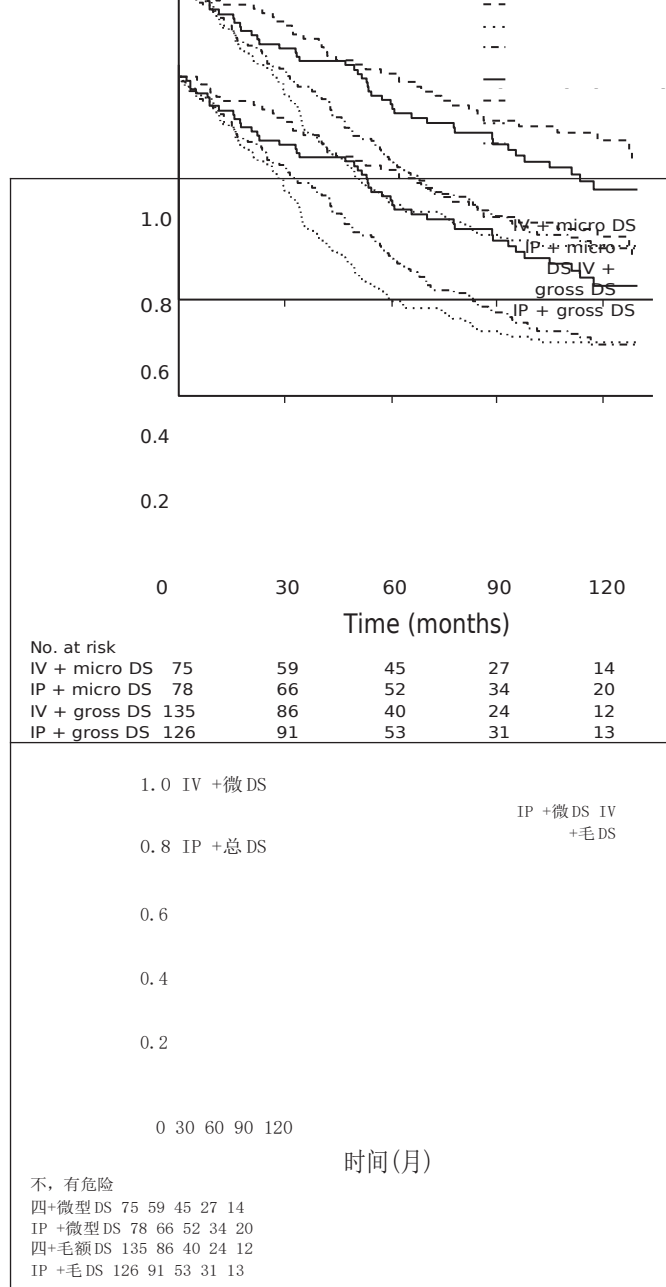

Fig 3. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy based on extent of residual disease (DS; *P* < .001). NOTE. Gross residual defined as ≤ 1 cm; micro residual defined as no visible disease.

图 3。根据残留疾病的程度，静脉（静脉）化疗与腹腔（腹腔）化疗患者的长期总生存率；P＜.001）。注。总残留定义为≤ 1 厘米；微残留定义为无可见疾病。

与静脉注射紫杉醇和静脉注射顺铂相比，静脉注射紫杉醇加静脉注射顺铂和静脉注射紫杉醇提高了生存率。然而，由于报告的毒性或相关并发症，近一半的患者没有完成 IP 方案。此外，使用交叉试验比较的推断数据表明，静脉注射卡铂可能略好于静脉注射顺铂，静脉注射组的每周时间表可能部分解释了生存优势。这表明，如果 GOG 172 的控制组包括卡铂和/或每周给药，IP 疗法的临床益处可能没有那么显著。相反，两项结合多项随机试验的大型荟萃分析显示，联合应用顺铂方案可提高晚期卵巢癌患者的生存率。[2526]

Additional concerns regarding IP therapy include: increased tox- icity, multiday scheduling, lack of familiarity with catheter placement, and IP drug administration. More importantly, because median du- ration of follow-up was < 4.5 years in GOG 172, it is unknown if these

关于静脉注射治疗的其他问题包括：毒性增加、多日计划、不熟悉导管放置和静脉注射给药。更重要的是，因为 GOG 172 的中位随访时间< 4.5 年，所以这些是否

results are sustainable after extended follow-up > 10 years. Our report

延长随访> 10 年，结果可持续。我们的报告

provides 10-year data demonstrating the long- term survival advan- tage of IP over IV therapy. More specifically, IP treatment was associ- ated with a 23% decreased risk of death that remained consistent after adjusting for age, performance status, cell type, tumor grade, and residual disease.

提供了 10 年的数据来证明静脉注射治疗比静脉注射治疗的长期生存优势。更具体地说，IP 治疗与死亡风险降低 23%相关，在调整年龄、表现状态、细胞类型、肿瘤分级和残留疾病后，死亡风险保持一致。

Additional advantages of IP therapy relate to a several-fold in- crease in drug concentration in the abdominopelvic cavity compared with systemic administration.[27,28] Despite this regional advantage, penetration into larger tumor burden may be limited; early animal studies showed that the penetration of IP drugs was limited to the superficial cell layer. Thus, IP therapy may not provide any advantage over IV treatment in patients with macroscopic residual disease.[10,11] Most clinical investigations of IP therapy have been confined to small- volume residual disease.[12,29-32] However, others have shown that pro- longed drug exposure resulting from slow absorption from the peritoneum may contribute to an IP advantage. However, it is unclear if this pharmacokinetic advantage would benefit those with gross residual disease. In our analysis, we showed a survival advantage of IP

与全身给药相比，腹腔注射疗法的其他优点涉及腹腔内药物浓度的几倍增加。[27281011122932]

over IV therapy in patients with both gross residual (≤ 1 cm) and no visible disease. In a prior phase II trial, investigators evaluated the efficacy of IP therapy in women with large-volume residual disease and found a PFS of 25 months versus 20 months in IP- versus IV-treated patients.[33] A potential explanation for why IP therapy is effec- tive even in large-volume residual disease is that multiple regimens of both IV and IP chemotherapies are administered over time. It is possible that the first few cycles of treatment depend on the delivery of platinum via capillary flow to reduce the size of larger residual tu- mors.[16,34] Subsequent IP treatments delivered regionally are more effective in small residual tumors.

总残留（≤ 1 cm）且无可见疾病的患者进行静脉注射治疗。在之前的一项二期试验中，研究人员评估了 IP 疗法在患有大体积残留疾病的女性中的疗效，发现 IP 与静脉注射治疗的患者的 PFS 分别为 25 个月和 20 个月。[33] [1634]

These data are reassuring, because the most recent IP trial, GOG 252 (ClinicalTrials.gov identifier, NCT00951496), allowed for the en- rollment of patients with larger-volume residual disease. If the long- term results from our report are confirmed, more patients might be candidates for IP treatment. It is important to note that those with gross residual disease had a 1.89-fold increase in risk of death com- pared with those with no visible residual disease. Our data confirmed a prior report on GOG trials 111, 132, 152, and 162 showing that those with microscopic residual disease or no gross residual disease had superior outcomes.[35-38] Our results confirm reports using data from two large prospective randomized trials and highlight the importance of complete cytoreductive surgery while suggesting a clinical benefit of IP therapy among those with gross residual disease.

这些数据令人放心，因为最近的知识产权审判，GOG 252（ClinicalTrials.gov [3538]

Given that fewer than half of patients in the GOG 172 IP arm com-
考虑到在 GOG 172 IP 分支机构中不到一半的患者

pleted the proposed therapy, and yet there was an OS advantage, some may suggest that it is not necessary to complete all six cycles of IP therapy. However, there are no studies that have evaluated the number of cycles of therapy needed to obtain the IP advantage. Our data showed that those who completed more cycles of IP therapy had superior survival. Recent studies have shown that dose-dense therapy is associated with improved outcomes. The Japanese GOG study found that dose-dense therapy

with paclitaxel improved OS, with a median follow-up of 6.4 years.[39] In con- trast, aprior GOG study showed that doubling the dose of IV cisplatin and cyclophosphamide did not improve survival.[40] In fact, the strategy of increasing the dose density or dose-intensity of IV platinum agents re- sulted in significant nonhematologic toxicity related to cisplatin and thrombocytopenia resulting from carboplatin. The data from our report suggest that those who complete up to six cycles of IP therapy experience the most benefit. To achieve this, collaboration with a team of gynecologic oncologists, medical oncologists, and nursing professionals experienced in IP therapy may be required. We acknowledge that these findings may be confounded by the selection of patients who had better prognostic factors, leading to a higher likelihood of completing six cycles of chemo- therapy with better outcomes. Nevertheless, these data on improved out- come associated with more cycles of IP chemotherapy remained significant after adjusting for demographic and clinical factors including age and performance status using multivariable analysis.

完成了建议的治疗，但仍有操作系统优势，有些人可能会建议没有必要完成所有六个周期的 IP 治疗。然而，没有研究评估获得 IP 优势所需的治疗周期数。我们的数据显示，完成更多周期 IP 治疗的患者存活率更高。最近的研究表明，剂量密集疗法与改善结果相关。日本 GOG 的研究发现，紫杉醇的剂量密集疗法改善了 OS，中位随访时间为 6.4 年。[39] [40]

Because our data showed that it is important to receive six cycles
因为我们的数据显示，接受六个周期很重要

of IP therapy, we performed an analysis to identify factors associated with completing the IP regimen. These findings may allow the clini- cian to better individualize IP therapy for those who will most likely complete and benefit from IP treatment and prevent unnecessary toxicity for those who will not tolerate this intensive regimen. Our data suggest that younger patients are more likely to complete six cycles of treatment. Prior studies have also shown that although younger pa- tients are more likely to tolerate more intensive treatment, they also

在 IP 治疗中，我们进行了一项分析，以确定与完成 IP 方案相关的因素。这些发现可能允许临床医生对最有可能完成 IP 治疗并从中获益的患者进行更好的个体化 IP 治疗，并防止那些不能耐受这种强化治疗的患者出现不必要的毒性反应。我们的数据表明，年轻患者更有可能完成六个周期的治疗。先前的研究也表明，尽管年轻患者更有可能耐受更强化的治疗，但他们也

have better survival compared with older women after adjusting for extent of cytoreductive surgery and cycles of chemotherapy.[41]

调整细胞减灭术的范围和化疗周期后，与老年妇女相比有更好的存活率。[41]

The long-term results of these trials are encouraging and provide additional support on the benefit of IP therapy while demonstrating that long-term survival end points are achievable in advanced ovarian cancer. Clinical trial investigators suggest it is challenging to demonstrate long-term survival in cancers with an extended survival after progression. This may be explained by the significant treatment ad- vances in salvage therapies, where variability in survival after progres- sion dilutes the OS comparison for the initial treatment.[42] Some investigators have suggested that OS not be used as a primary end

这些试验的长期结果令人鼓舞，并为 IP 治疗的益处提供了额外的支持，同时表明晚期卵巢癌可以实现长期生存终点。临床试验研究人员认为，在进展后生存期延长的癌症中，维持长期生存期具有挑战性。这可能是由于挽救疗法的显著治疗进展，进展后存活率的可变性稀释了初始治疗的 OS 比较。[42]

point when median survival after progression is > 12 months, but

进展后中位生存期> 12 个月，但是

long-term OS results reported in our analysis suggest the contrary. We performed additional analyses in an attempt to determine the reason why IP chemotherapy prolonged OS. It is possible that IP therapy may not only extend the time to initial recurrence but also enhance re- sponse to subsequent treatment on relapse, resulting in better long- term survival. In our exploratory analyses, we found both an extension in PFS with updated follow-up data and longer survival after treat- ment for recurrence in the IP compared with IV patients. However, given the exploratory nature of this subset analysis, with a lower number of patients remaining in follow-up beyond 5 to 10 years after censoring, these findings should be interpreted with caution. Further- more, it is possible that long-term survival results may have been affected by the differences in treatment of recurrent disease, which were not controlled for in these patients.

我们分析中报告的长期 OS 结果表明情况恰恰相反。我们进行了额外的分析，试图确定 IP 化疗延长 OS 的原因。有可能 IP 治疗不仅可以延长初始复发的时间，还可以增强复发后对后续治疗的反应，从而获得更好的长期生存率。在我们的探索性分析中，我们发现，与静脉注射患者相比，静脉注射患者的随访数据更新，肿瘤复发治疗后生存期延长。然而，考虑到这种子集分析的探索性，在审查后 5 到 10 年的随访中，患者数量较少，这些发现应谨慎解释。此外，长期生存结果可能受到复发疾病治疗差异的影响，这些患者的复发疾病未得到控制。

In conclusion, to our knowledge, this report provides the first

总之，据我们所知，这份报告提供了第一个

updated results of GOG IP chemotherapy trials, showing long-term survival benefit extending

beyond 10 years. Future results of the fourth phase III trial in GOG 252 will yield additional information regarding the incorporation of different approaches to IP therapy, including: dose-dense paclitaxel, antivascular targeted therapy, and maintenance therapy. Converting IP therapy into clinical practice based on the results of positive clinical trials is challenging. The long-term survival benefits described in this report may encourage more clinicians to adopt IP chemotherapy in the community. In addition, IP therapy may be implemented as a quality measure at institutions with the expertise and support teams necessary to administer IP treatment. Clinicians should support patients through the IP regimen, particu- larly if there are no significant or excessive toxicities. Lastly, the ability to better select patients who are more likely to complete IP therapy with better outcomes and less toxicity warrants further investigation as we move toward individualizing therapies.

GOG IP 化疗试验的最新结果，显示长期生存获益超过 10 年。在 GOG 252 的第四个三期试验的未来结果将产生关于整合不同 IP 治疗方法的额外信息，包括：剂量密集紫杉醇、抗血管靶向治疗和维持治疗。将 IP 疗法转化为基于阳性临床试验结果的临床实践具有挑战性。本报告中描述的长期生存益处可能会鼓励更多的临床医生在社区中采用 IP 化疗。此外，知识产权治疗可以作为一种质量措施在具有管理知识产权治疗所需的专业知识和支持团队的机构中实施。临床医生应通过 IP 方案支持患者，尤其是在没有明显或过度毒性的情况下。最后，随着我们向个体化治疗迈进，更好地选择更有可能完成 IP 治疗且结果更好、毒性更小的患者的能力值得进一步研究。

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（四）在卵巢上皮性癌或原发性癌周原发性去肿块手术后伴有肿块残留疾病的患者中，卡铂联合紫杉醇静脉注射：三凯妇科研究小组（SGSG）的一项研究。《临床肿瘤》25:294，2007（增刊；abstr 5584）

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Appendix

附录

The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California at Los Angeles, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group, University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St Luke's Medical Center, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, Southwestern Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Columbus Cancer Council, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Eastern Collaborative Oncology Group, Thomas Jefferson University Hospital, Case Western Reserve University, Tampa Bay Cancer Consortium, North Shore University Hospital, Gynecologic Oncology Network, Ellis Fischel Cancer Center, and Fletcher Allen Health Care.

以下妇科肿瘤组成员机构参加了初级治疗研究：阿拉巴马大学伯明翰分校、俄勒冈健康科学大学、杜克大学医学中心、阿宾顿纪念医院、罗切斯特大学医学中心、沃尔特·里德陆军医学中心、韦恩州立大学、明尼苏达大学医学院、南加州大学洛杉矶分校、密西西比大学医学中心、科罗拉多妇科肿瘤组、加州大学洛杉矶分校、华盛顿大学、宾夕法尼亚大学癌症中心、 迈阿密大学医学院、米尔顿·s·好时医学中心、乔治敦大学医院、辛辛那提大学、北卡罗来纳大学医学院、爱荷华大学医院和诊所、德克萨斯大学达拉斯西南医学中心、印第安纳大学医学院、威克森林大学医学院、奥尔巴尼医学院、加州大学欧文分校医学中心、塔夫茨-新英格兰医学中心、拉什-长老会-圣卢克医学中心、肯塔基大学东弗吉尼亚医学院、克利夫兰诊所基金会、约翰·霍普金斯肿瘤中心、 纽约州州立大学东宾夕法尼亚州立大学石溪分校 GYN/ONC 中心、西南肿瘤学集团、华盛顿大学医学院、纪念斯隆-凯特琳癌症中心、哥伦布癌症理事会、麻省大学医学院、福克斯蔡斯癌症中心、南卡罗来纳医科大学、妇女癌症中心、俄克拉荷马大学、弗吉尼亚大学健康科学中心、芝加哥大学、亚利桑那大学健康科学中心、塔科马总医院、东部协作肿瘤学集团、托马斯·杰斐逊大学医院、凯斯西储大学、坦帕湾癌症联盟、北岸大学医院、妇科肿瘤学网络、埃利斯·菲舍尔癌症中心、

Table A1. Demographic and Clinicopathologic Characteristics of Patients in GOG Protocols 114 and 172 (N = 876) GOG 114 (n = 462)			GOG 172 (n = 172)		
Characteristic	No.	%	No.	%	P
Age, years					.047˙
Media		56.6		57.5	
n		47.4-		49.5-	
Range		64.9		66.8	
Age, years					.289†
< 55.0	214	46.3	177	42.8	
≥ 55.0	248	53.7	237	57.2	
Race/ethnicity					.003†
White	418	90.5	372	89.9	
Black	30	6.5	11	2.7	
Hispanic	10	2.2	18	4.3	
Asian	4	0.9	12	2.9	
Other	0	0.0	1	0.2	
BMI, kg/m²‡					.445˙
Median		24.5		25	
Range		21.7-		21.9-	
		28.8		29.3	
Performance status					.027†
Normal, asymptomatic	206	44.6	181	43.7	
Symptomatic, ambulatory	209	45.2	210	50.7	
Symptomatic, in bed < 50%	47	10.2	23	5.6	
Tumor grade (differentiation)					.417†
1	57	12.3	43	10.4	
2	182	39.4	154	37.2	
3	223	48.3	217	52.4	
Histology					< .001†
Serous	308	66.7	327	79.0	
Endometrioid	54	11.7	29	7.0	
Mucinous	13	2.8	3	0.7	
Clear cell	15	3.2	20	4.8	
Other	72	15.6	35	8.5	
Gross residual disease					.606†
No	163	35.3	153	37.0	
Yes	299	64.7	261	63.0	
Treatment					.593†
IV	226	48.9	210	50.7	
IP	236	51.1	204	49.3	

Abbreviations: BMI, body mass index; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous.
˙Wilcoxon test;
†Pearson's test.
‡Because of missing values, n = 873.

表 A1。GOG 方案 114 和 172 （N = 876） GOG 方案 114 （n = 462） GOG 方案 172 （n = 172）患者的人口统计学和临床病理特征					
特征号%号% P					
年龄，年份					.047*
中位数		56.6		57.5	
范围		47.4–		49.5–	
		64.9		66.8	
年龄，年份					
< 55.0	214	46.3	177	42.8	.289†
≥ 55.0	248	53.7	237	57.2	
种族/民族					.003†
怀特（姓氏）	418	90.5	372	89.9	
黑色	30	6.5	11	2.7	
西班牙的	10	2.2	18	4.3	
亚洲的	四	0.9	12	2.9	
其他的	0	0.0	一	0.2	
身体质量指数，千克/平方米					.445*
中位数		24.5		25	
范围		21.7–		21.9–	

	28.8			29.3	
性能状态					.027†
正常，无症状	206	44.6	181	43.7	
有症状的，可走动的	209	45.2	210	50.7	
有症状，卧床 < 50%	47	10.2	23	5.6	
肿瘤分级(分化)					.417†
一	57	12.3	43	10.4	
2	182	39.4	154	37.2	
3	223	48.3	217	52.4	
组织学					< .001†
浆液的	308	66.7	327	79.0	
子宫内膜样的	54	11.7	29	7.0	
黏液的	13	2.8	3	0.7	
透明细胞	15	3.2	20	4.8	
其他的	72	15.6	35	8.5	
严重残留疾病					.606†
不	163	35.3	153	37.0	
是	299	64.7	261	63.0	
处理					.593†
注入静脉的	226	48.9	210	50.7	
互联网协议(Internet Protocol)	236	51.1	204	49.3	

简称:身体质量指数，体重指数；GOG，妇科肿瘤集团；腹腔注射；四、静脉注射。
*威尔科克森试验。
皮尔逊检验。
因为缺少值，n = 873。

Table A2. Long-Term PFS and OS After IV Versus IP Therapy for Patients in GOG Protocols

GOG Protocol Arm	No. of Patients	No. of Events	Median (months)	Range (months)	P*	AHR	95% CI	P†	No. of Events	Median (months)	Range (months)	P†	AHR	95% CI
					114 and 172 PFS					OS				
114-IV	226	191	22.2	17.8-25.1	.131	Referent	—		174	52.4	45.1-63.8	.216	Referent	—
172-IV	210	173	18.3	15.6-23.3		1.09	0.88 to 1.34	0.44	155	50.4	43.2-58.6		1.07	0.85 to 1.33	0.57
114-IP	236	197	27.3	23.4-30.7		0.83	0.68 to 1.01	0.06	176	59.6	52.3-69.5		0.87	0.71 to 1.08	0.21
172-IP	204	160	23.8	20.7-29.0		0.87	0.70 to 1.07	0.18	141	65.6	57.1-81.4		0.83	0.66 to 1.04	0.10

Abbreviations: AHR, adjusted hazard ratio; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Wald test.

表 A2。GOG 方案 114 和 172 患者静脉注射与静脉注射治疗后的长期全氟辛烷磺酸和全氟辛烷磺酸

手臂患者事件(月)(月)P*						AHR 95%置信区间 P 事件(月)(月)P*						AHR 95%置信区间		
114-四	226	191	22.2	17.8-25.1	.131	指示物	—	174	52.4	45.1-63.8	.216	指示物	—
172-四	210	173	18.3	15.6-23.3	1.09	0.88 至 1.34	0.44	155	50.4	43.2-58.6	1.07	0.85 至 1.33	0.57
114-IP	236	197	27.3	23.4-30.7	0.83	0.68 至 1.01	0.06	176	59.6	52.3-69.5	0.87	0.71 至 1.08	0.21
172-IP	204	160	23.8	20.7-29.0	0.87	0.70 至 1.07	0.18	141	65.6	57.1-81.4	0.83	0.66 至 1.04	0.10

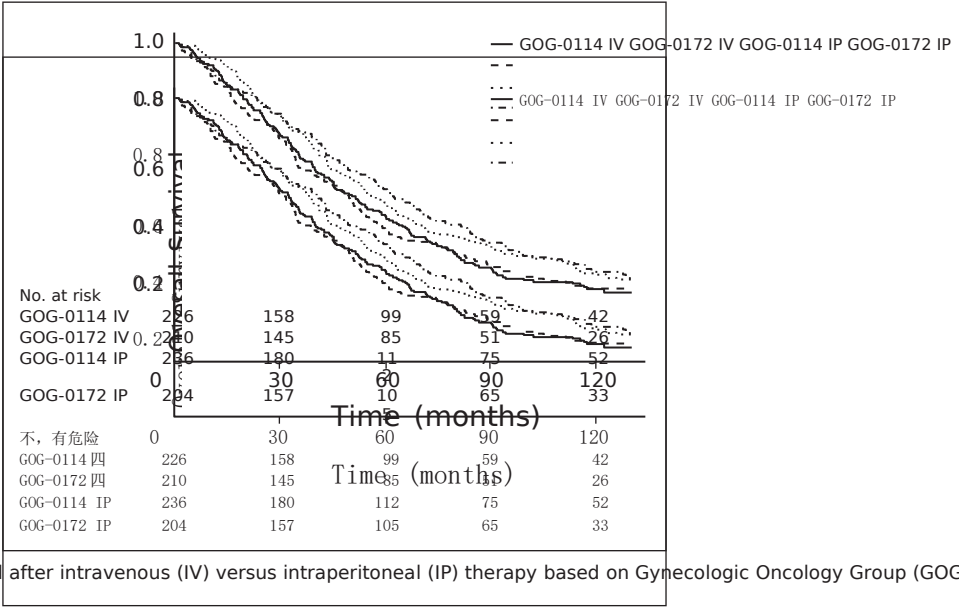缩写:AHR，调整后的危险比率；GOG，妇科肿瘤集团；腹腔注射；四、静脉注射；OS，整体生存；PFS，无进展生存。
*对数秩检验。
沃尔德测试。

Fig A1. Long-term overall survival after intravenous (IV) versus intraperitoneal (IP) therapy based on Gynecologic Oncology Group (GOG) protocols 0114 and 0172.

图 A1。根据妇科肿瘤组(GOG)方案 0114 和 0172，静脉(静脉)与腹腔(静脉)治疗后的长期总生存率。