The Role of Secondary Cytoreductive Surgery in Patients with Recurrent Epithelial Ovarian, Tubal, and Peritoneal Cancers: A Comparative Effectiveness Analysis

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ABSTRACT

Background. All published reports concerning secondary cytoreductive surgery for relapsed ovarian cancer have essentially been observational studies. However, the validity of observational studies is usually threatened from confounding by indication. We sought to address this issue by using comparative effectiveness methods to adjust for confounding.

Methods. Using a prospectively collected administrative health care database in a single institution, we identified 1,124 patients diagnosed with recurrent epithelial, tubal, and peritoneal cancers between 1990 and 2009. Effectiveness of secondary cytoreductive surgery using the conventional Cox proportional hazard model, propensity score, and instrumental variable were compared. Sensitivity analyses for residual confounding were explored using an array approach.

Results. Secondary cytoreductive surgery prolonged

overall survival with a hazard ratio (95% confidence interval) of 0.76 (range 0.66–0.87), using the Cox proportional hazard model. Propensity score methods produced comparable results: 0.75 (range 0.64–0.86) by nearest matching, 0.73 (0.65–0.82) by quintile stratification, 0.71 (0.65–0.77) by weighting, and 0.72 (0.63–0.83) by covariate adjustment. The instrumental variable method also produced a comparable estimate: 0.75 (range 0.65–0.86). Sensitivity analyses revealed that the true treatment effects may approach the null hypothesis if the association between unmeasured confounders and disease outcome is high.

Conclusions. This comparative effectiveness study provides supportive evidence for previous reports that secondary cytoreductive surgery may increase overall survival for patients with recurrent epithelial, tubal, and peritoneal cancers. *The Oncologist* 2012;17:847–855

INTRODUCTION

In 2010, more than 21,000 women in the United States were diagnosed with ovarian cancer; two-thirds of these women died from this disease, which ranked as the most common cause of death among gynecologic malignancies [1]. A complete clinical remission can be achieved in nearly 70%–80% of these patients with the use of maximal primary cytoreductive

surgery followed by platinum-based combination chemotherapy. Unfortunately, more than 75% of clinically complete responders develop recurrent disease [2].

In situations of recurrent disease, it may be possible to improve the chance of a complete response and/or a longer duration of second remission by using secondary cytoreductive surgery with chemotherapy. Berek et al. initially defined sec-

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ondary cytoreductive surgery as a surgical procedure carried out on patients with persistent or recurrent disease after completion of a full planned course of chemotherapy [3]. The randomized clinical trial set the standard for clinical research [4]. Currently, there are two ongoing clinical trials evaluating the efficacy of secondary cytoreductive surgery [5, 6]. To date, although published reports concerning secondary cytoreductive surgery show a certain positive significance, all are essentially observational studies [7–17].

Observational studies can generate credible evidence of intervention effects. They are more clinically relevant than randomized trials, with better generalizability and applicability in routine clinical scenarios. However, the major drawback of an observational study is that its validity is threatened by confounding by indication [18, 19]. Confounding by indication (also known as channeling bias) is a form of selection bias, which occurs when treatments are preferentially prescribed to groups of patients based on their underlying risk profile [20]. Conventional statistical methods used to adjust for confounding, such as matching and multivariable regression, result in possible residual confounding due to unmeasured factors [21]. Comparative effectiveness analyses, such as the propensity score and instrumental variable approach for observational studies, have become increasingly popular, with the goal of addressing residual confounding problems by mimicking a randomized trial [22].

In the current study, we used comparative effectiveness techniques, including the propensity score and instrumental variable approach, to explore the therapeutic effects of secondary cytoreductive surgery on overall survival rates for patients with recurrent epithelial ovarian, tubal, and peritoneal cancers using an administrative health care database.

METHODS

Study Population

The study entailed a retrospective analysis of prospectively collected demographic, tumor profile, treatment, and comorbidity data, linking electronic data sources, including the cancer registry, administrative and clinical databases, and surgery records of 1,268 consecutive patients with recurrent epithelial ovarian, tubal, and peritoneal cancers between January 1990 and December 2009. This study was approved by the institutional review board of Taipei Veterans General Hospital. The procedures used in this study were in accordance with the guidelines of the Declaration of Helsinki on human experimentation.

Patients had to meet one of two criteria to be defined as recurrent cases. Firstly, patients had to be in complete clinical remission for at least 6 months with normal CA-125 and negative image studies (by either computerized tomography [CT] or magnetic resonance imaging [MRI]) during or after first-line chemotherapy. Secondly, after completion of first-line chemotherapy, patients were followed up regularly or underwent consolidation chemotherapy at the provider's discretion. During the follow-up period, the patient was defined as having recurrent disease if the patient's CA-125 exceeded twice the upper normal limit or the patient had measurable disease, de-

fined as at least one lesion that could be accurately measured in at least one dimension. Each lesion had to be ≥ 20 mm when measured by conventional techniques (including ultrasonography, CT, and MRI) or ≥ 10 mm when measured by spiral CT.

Once recurrent disease was confirmed, patients either (a) were treated with single or multiple regimens of second-line chemotherapy and then followed up until death or end of study or (b) underwent secondary cytoreductive surgery before initiation of second-line chemotherapy or during second-line chemotherapy treatment, as decided by multidisciplinary team discussion.

Secondary Cytoreductive Surgery

Once secondary cytoreductive surgery was considered appropriate after a multidisciplinary team discussion, the gynecologic oncologist took responsibility for the initial step of surgery, with the aim of removing all resectable tumors. Peritoneal stripping was performed at each gynecologic oncologist's own discretion, if extensive peritoneal tumor dissemination was found. An ad-hoc general surgeon or colorectal surgical specialist team was consulted once bowel, liver, spleen, or pancreas surgery was deemed necessary. Commonly consulted surgeries that were performed included resection of a tumor-containing bowel with reanastomosis (end-to-end or end-to-side), ileostomy, jejunostomy, colostomy, segmental resection of the liver, splenectomy, partial or total gastrectomy, and partial pancreatectomy, as appropriate. If the patient had undergone any stomy procedure, a special stomy care team provided nursing and educational support. Surgical findings and residual tumor status were recorded after completion of surgery. Operations that were symptom oriented only and for strictly palliative purposes or surgeries within the context of primary therapy (e.g., second-look laparotomy or interval cytoreductive surgery) were excluded from the definition of secondary cytoreductive surgery. All relevant surgical specimens were reviewed by a central pathologist (C.R.L.).

Approximately 2 weeks to 1 month after secondary cytoreductive surgery, a multidisciplinary team evaluated the patient's performance status and clinical parameters to decide whether and when to initiate second-line chemotherapy.

Statistical Analysis

The primary endpoint of this study was overall survival, which was defined as time from first diagnosis to death from any cause; survivors were censored on the date they were last known to be alive. Continuous variables are presented as means ($\pm$ standard deviations) and were compared using Student's unpaired *t* test. Categorical variables are presented as counts and percentages and were compared with the χ^2 test when appropriate (expected frequency > 5). Otherwise, Fisher's exact test was used. Overall survival duration was calculated from disease diagnosis to disease-specific death or last follow-up. Multivariate Cox proportional hazards models were fit to test the relationship between survival time and clinicopathological parameters. The assumption of the proportional hazard was verified by a visual examination of the log minus log curves, and the linearity assumption was assessed by plot-

Table 1. Clinical characteristics of eligible patients before ($n = 1,124$) and after propensity score matching ($n = 742$)^a

	Before matching			After matching		
	No SCS ($n = 634$)	SCS ($n = 490$)	<i>p</i> value	No SCS ($n = 371$)	SCS ($n = 371$)	<i>p</i> value
Age (mean $\pm$ SD)	50.7 $\pm$ 4.6	51.5 $\pm$ 5.6	.004	51.2 $\pm$ 4.7	51.2 $\pm$ 5.6	.83
Body mass index (%)			.001			.25
≤ 18.5	43 (6.8)	29 (5.9)		16 (4.3)	24 (6.5)	
18.6–24.9	434 (68.4)	378 (77.1)		279 (75.2)	278 (75.0)	
25.0–29.9	143 (22.6)	67 (13.6)		69 (18.6)	57 (15.4)	
≥ 30.0	14 (2.2)	16 (3.3)		7 (1.9)	12 (3.2)	
GOG performance (%)			.97			.83
0 or 1	534 (84.2)	413 (84.3)		318 (85.7)	316 (85.2)	
≥ 2	100 (15.8)	77 (15.7)		53 (14.3)	55 (14.8)	
Stage (%)			.006			.07
I	54 (8.5)	48 (9.8)		31 (8.3)	39 (10.5)	
II	67 (10.8)	84 (17.1)		33 (8.9)	49 (13.2)	
III	428 (67.5)	287 (58.8)		254 (68.5)	221 (59.8)	
IV	85 (13.4)	71 (14.5)		53 (14.3)	62 (16.7)	
Grade (%)			.005			.25
1	29 (4.6)	6 (1.2)		8 (2.1)	6 (1.6)	
2	538 (84.9)	427 (87.1)		327 (88.1)	315 (84.9)	
3	67 (10.6)	57 (11.6)		36 (9.7)	50 (13.5)	
Histology (%)			.57			.99
Serous	288 (45.4)	238 (48.6)		175 (47.2)	171 (46.1)	
Mucinous	113 (17.8)	92 (18.8)		72 (19.4)	74 (19.9)	
Endometrioid	88 (13.9)	67 (13.7)		51 (13.7)	50 (13.5)	
Clear cell	89 (14.1)	60 (12.3)		44 (11.9)	45 (12.1)	
Mixed type	56 (8.8)	33 (6.7)		24 (7.2)	31 (8.4)	
Residual tumor after primary cytoreductive surgery (%)			<.001			.47
No gross residual	282 (44.5)	282 (57.6)		176 (47.4)	188 (50.7)	
≤ 1 cm	284 (44.8)	149 (30.4)		148 (39.9)	132 (35.6)	
> 1 cm	68 (10.7)	59 (12.0)		47 (12.7)	51 (13.8)	
Front-line regimen (%)			<.001			.52
Not paclitaxel based	153 (24.1)	191 (38.9)		108 (29.1)	116 (31.2)	
Paclitaxel based	481 (75.9)	299 (61.0)		263 (70.9)	255 (68.7)	
Route of front-line regimen (%)			<.001			.38
Intravenous	558 (88.0)	349 (71.2)		320 (86.2)	328 (88.4)	
Intraperitoneal	76 (12.0)	141 (28.8)		51 (13.7)	43 (11.6)	
Consolidation chemotherapy (%)			<.001			.29
No	534 (84.2)	353 (72.0)		299 (80.6)	310 (83.6)	
Yes	100 (15.8)	137 (27.9)		72 (19.4)	61 (16.4)	
Recurrence interval (%)			.25			.99
< 12 months	67 (10.6)	64 (13.1)		43 (11.6)	42 (11.3)	
12–24 months	517 (81.6)	380 (77.6)		297 (80.1)	297 (80.1)	
> 24 months	50 (7.9)	46 (9.4)		31 (8.4)	32 (8.6)	

(continued)

Table 1. (Continued)

	Before matching			After matching		
	No SCS (n = 634)	SCS (n = 490)	p value	No SCS (n = 371)	SCS (n = 371)	p value
Number of second-line chemotherapy (%) ^b			.74			.73
0	86 (13.6)	59 (12.0)		41 (12.4)	43 (12.9)	
1	378 (59.6)	295 (60.2)		201 (60.5)	191 (57.5)	
≥2	170 (26.8)	136 (27.7)		90 (27.1)	98 (29.5)	
Bowel obstruction (%) ^c			.95			.66
No	561 (88.5)	433 (88.3)		305 (91.8)	308 (92.7)	
Yes	73 (11.5)	57 (11.6)		27 (8.1)	24 (7.2)	
Charlson comorbidity index (%)			.29			.59
0	569 (89.6)	430 (87.8)		330 (87.5)	325 (86.2)	
≥1	65 (10.2)	60 (12.2)		47 (12.5)	52 (13.8)	
Tumor burden at recurrence (%) ^d			.02			.83
Single	114 (17.9)	62 (12.7)		52 (14.0)	49 (13.2)	
Multiple/carcinomatosis	520 (82.0)	428 (87.3)		319 (86.0)	322 (86.8)	

^aUsed nearest one-to-one matching with caliper = 0.25σ as a matching scheme.
^bAdjusted as conditioning variable during propensity score analysis.
^cDiagnosed within 1 month before secondary cytoreductive surgery.
^dTumor burden was defined by surgical findings (SCS group) or by image studies (no SCS group).
Abbreviation: SCS, secondary cytoreductive surgery.

ting the Martingale residuals against continuous covariates [23].

The propensity score method was used to reduce selection bias and make causal inference. The propensity score is a summary confounder score that is modeled using the exposure or treatment as the dependent variable [24]. We applied four methods including matching, stratification, covariate adjustment, and weighting for the adjustment of the propensity score.

For the matching adjustment, we conducted a three-step analysis. At step 1, we used 15 conditioning variables (Table 1) to develop propensity scores. At step 2, we used an algorithm of greedy matching (including nearest neighbor matching within caliper and Mahalanobis metric matching with or without propensity scores) to create various matched samples [25]. At step 3, we compared the hazard ratio-treated group (patients who received secondary cytoreductive surgery) and the control group (patients who did not receive secondary cytoreductive surgery) using the Cox proportional hazard model.

For stratification adjustment, patients were stratified into quintiles according to their predicted propensity score. Rosenbaum and Rubin concluded that stratifying on the quintiles of the propensity score could be expected to eliminate approximately 90% of the bias to an imbalance in the confounding variable between two groups [26]. The hazard ratio was calculated within each quintile and was then pooled across strata to obtain an overall effect. Stratification approximates matching without running the risk of losing unmatched patients because

balance in the proportions of experimental and control patients within each stratum is not required.

For covariate adjustment using the propensity score, the predicted propensity score was used as a covariate combined with the treatment variable to be fitted in the Cox proportional model to hazard ratio. This method assumes that treated and control patients with the same propensity score have the same distribution of measured baseline characteristics [27].

For the weighting adjustment, the inverse probability of treatment weighting method was applied by using the propensity score to assign individual weights to all observations, resulting in an altered composition of the study population [28]. With this approach, the contributions of the study subjects are weighted by 1 / (propensity score) for experimental patients and by 1 / (1 – propensity score) for control patients. The changed study composition was then analyzed using the Cox proportional hazard model with the treatment variable as the only covariate. Furthermore, stabilized weights that take the marginal prevalence of the treatment variable into account were used to maximize efficiency and to obtain a reweighted population composition of equal size [29].

For the instrumental variable analysis, we used the gynecologic oncologist's preference of performing secondary cytoreductive surgery as an instrumental variable, under the assumption that, on average, patient outcomes do not vary systematically from one oncologist to another in a manner that is related to the surgeon's performing patterns [30]. For the estimate of the hazard ratio, we performed a two-stage regression

in which the treatment was predicted as a function of the instrumental variable and the confounders using a logistic model, and the outcome was predicted using Cox proportional hazards regression as a function of the predicted treatment and the confounders [31]. To test for strength of association, we examined the partial F test from the first-stage regression model, which predicts treatment as a function of instrument and covariates. The partial F test has the null hypothesis that the coefficient for effect of the instrument in the first-stage regression model is 0 [32], and the partial F statistic in the current research was 15.2, indicating that the instrumental variable is not weak.

The estimated hazard ratio for the overall effect of secondary cytoreductive surgery using the Cox proportional model, propensity score, and instrumental variable analysis was derived from the antilog of the pooled log hazard ratio, which was calculated as the average of the log hazard ratio from each analysis weighted by the inverse of its variance.

All analyses were performed using STATA SE version 11 (Stata Corp, College Station, TX); $p < .05$ was considered statistically significant.

Residual Confounding and Sensitivity Analysis

To address the issue of residual confounding, we conducted a sensitivity analysis using an array approach to measure how the strength of an unmeasured confounder and imbalance between treatment groups (patients who received vs. patients who did not receive secondary cytoreductive surgery) affects the observed hazard ratio [33]. The observed hazard ratio was set at 0.72 (using the results of meta-analysis, as seen in Figure 2). Prevalence of the unmeasured confounder in the control group (not receiving surgery) was set at 0.3. Two factors were varied: the strength of the unmeasured confounder-outcome association (1.0–5.5) and the prevalence of the unmeasured confounder in the treatment group who received surgery (0.0–0.5). A three-dimensional mesh plot was constructed to check the impacts on the fully adjusted hazard ratio by varied unmeasured confounder settings.

RESULTS

A total of 1,124 patients were recruited for analysis. The patients' baseline clinical characteristics are summarized in Table 1. There were significant differences in age, body mass index, stage, tumor grade, residual tumor size after primary cytoreductive surgery, regimen of first-line chemotherapy, route of chemotherapy, and performance of consolidation. After nearest neighbor one-to-one matching, all 15 conditioning variables were comparable, with 371 patients receiving and 371 patients not receiving secondary cytoreductive surgery.

Figure 1 shows the Kaplan-Meier survival plot using the propensity score approach, including nearest one-to-one matching (caliper = 0.25σ ; $p = .001$, log-rank test; Fig. 1A), Mahalanobis metric matching without the propensity score ($p < .001$, log-rank test; Fig. 1B), and Mahalanobis metric matching with the propensity score ($p < .001$, log-rank test; Fig. 1C). These plots all show a survival advantage for patients

Figure 1. Kaplan-Meier plot for overall survival using different propensity score strategies. (A) Nearest neighbor one-to-one matching (caliper = 0.25σ ; $p = .001$, log-rank test). (B) Mahalanobis metric matching without propensity score ($p < .001$, log-rank test). (C) Mahalanobis metric matching with propensity score ($p < .001$, log-rank test).

who underwent secondary cytoreductive surgery compared to those patients who did not.

Table 2 lists Cox proportional analyses using different propensity scores and instrumental approach strategies. Using the

Table 2. Hazard ratio using different strategies of propensity score and instrumental variables

Scheme	Description	<i>n</i>		Hazard ratio	95% CI
		SCS	No SCS		
Unadjusted		490	634	0.69	0.61–0.78
Multivariable Cox proportional hazard model ^a		490	634	0.76	0.66–0.87
Propensity score adjustment ^b					
Matching					
Nearest neighbor (caliper = 0.25 σ) ^c	Nearest 1:1 using caliper = 0.65 (0.25 σ)	371	371	0.75	0.64–0.86
Nearest neighbor (caliper = 0.1)	Nearest 1:1 using caliper = 0.1	318	318	0.77	0.65–0.90
Mahalanobis without <i>p</i> score added	Calculation of Mahalanobis distance	459	459	0.64	0.55–0.74
Mahalanobis with <i>p</i> score added	Calculation of Mahalanobis distance with <i>p</i> score added	459	459	0.63	0.53–0.74
Stratification quintile		490	634	0.73	0.65–0.82
Weighting					
IPTW	Inverse probability of treatment weighting using unstabilized weight	490	634	0.71	0.65–0.77
Stabilized IPTW ^d	Inverse probability of treatment weighting using stabilized weight	490	634	0.71	0.65–0.77
Covariate adjustment	Using <i>p</i> score for regression	490	634	0.72	0.63–0.83
Instrumental variable adjustment ^e	Two-stage regression model	490	634	0.75	0.65–0.86

^aAdjusted for age, body mass index, GOG performance, stage, grading, histology, residual tumor after primary cytoreductive surgery, regimen of front-line chemotherapy, and recurrence interval.
^bPropensity scores are calculated based on the 14 conditioning variables listed in Table 1.
^c σ = standard deviation of calculated propensity scores.
^dThe marginal prevalence of the secondary cytoreductive surgery was taken into account to maximize efficiency.
^eGynecologic oncologist's preference of performing secondary cytoreductive surgery was used as an instrumental variable.
Abbreviations: CI, confidence interval; GOG, gynecologic oncology group; IPTW, inverse probability of treatment weighted; *p* score, propensity score; SCS, secondary cytoreductive surgery.

different propensity score approach strategies (including matching, quintile stratification, weighting, and covariate adjustment), the hazard ratios of patients who underwent secondary cytoreductive surgery ranged from 0.63 to 0.77, compared with patients without secondary cytoreductive surgery. Using the instrumental variable approach to mitigate unmeasured confounders, the patients who underwent secondary cytoreductive surgery also had a comparable hazard ratio of 0.75 (95% CI: 0.65–0.86), compared with the propensity score method and conventional Cox proportional hazard model.

The pooled effect estimate revealed homogenous effects (heterogeneity test: Q value = 5.64, p = .82) with a hazard ratio of 0.72 (95% CI: 0.69–0.76) for patients who underwent secondary cytoreductive surgery compared with patients who did not receive secondary cytoreductive surgery (Fig. 2).

Sensitivity analysis for residual confounding using the array approach demonstrated a curved surface representing the “true” or fully adjusted hazard ratio for patients who underwent secondary cytoreductive surgery, assuming an observed hazard ratio of 0.72 and a prevalence of an unmeasured confounder of 0.3 (P_{Co}) in the no-surgery group. The prevalence of the unmeasured confounder in the surgery group (P_{Ci}) varied

between 0.0 and 0.5 on the x -axis. The strength of the confounder-outcome association (HR_{CD}) varied between 1.0 and 5.5 on the z -axis. The curved surface shows that when P_{Ci} is low (i.e., ≤ 0.1) and HR_{CD} is high (i.e., ≥ 3.5), then the true hazard ratio would approach the null hypothesis (i.e., secondary cytoreductive surgery had no effect). However, most of the adjusted hazard ratios were < 1 in different settings, indicating that in most scenarios secondary cytoreductive surgery did confer an overall survival benefit (Fig. 3).

DISCUSSION

In a randomized trial, the randomization of participants to different treatments guarantees that on average there should be no systematic differences in measured or unmeasured covariates (i.e., bias) between treatment groups. However, in a nonrandomized observational study, investigators have no control over the treatment assignment; therefore, direct comparisons of outcomes from the treatment groups may be misleading [34]. Traditional methods of adjustment (matching, stratification, and covariance adjustment) are often limited because they can only use a limited number of measured covariates for adjustment. The value of secondary cytoreductive surgery has

Figure 2. Forest plot of the hazard ratio of overall survival with secondary cytoreductive surgery versus without secondary cytoreductive surgery. The estimate of the hazard ratio of each study corresponds to the middle of the squares and the horizontal line gives the 95% confidence interval (CI). The closed diamond shows the pooled total hazard ratio with its 95% CI. A test of heterogeneity by Q-statistic between the studies is given below the summary statistic.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighted.

Figure 3. Sensitivity analysis using an array approach. The observed hazard ratio was set at 0.72 (from pooled results of Fig. 2). Prevalence of unmeasured confounders in the control group (not receiving surgery) was set at 0.3. Two factors were varied: the strength of the unmeasured confounder-outcome association (1.0–5.5) and the prevalence of the unmeasured confounder in the treatment group (received surgery, 0.0–0.5). A three-dimensional mesh plot was constructed to check the impacts on the fully adjusted hazard ratio by varied unmeasured confounder settings.

Abbreviation: HR, hazard ratio.

long been discussed in the literature, but these reports are all essentially retrospective or prospective observational studies. These reports use traditional adjustment methods to measure treatment effects, which implies that the reports

may potentially introduce biased estimates. Many more variables need to be adjusted for secondary cytoreductive surgery than for primary cytoreductive surgery. However, if too many variables need to be included in a model relative to

the number of events, the estimates from these models can be incorrect [35, 36].

In the current study, we used the propensity score and instrumental variable to mitigate the problem of confounding by indication. In the analysis, the propensity score and instrumental variable method produced relatively homogenous outcome results, with hazard ratios ranging from 0.65 to 0.77, which were comparable to those of conventional Cox proportional hazard analysis. The value of our study is that it strengthened the findings of previous observational studies; that is, if secondary cytoreductive surgery is well-planned and a multidisciplinary team approach is used, this second-line surgical intervention prolongs overall survival for patients with recurrent epithelial ovarian, tubal, and peritoneal cancers. A potential reason why secondary cytoreductive surgery benefits survival is the contribution of the surgical procedures, including bowel decompression or stomy constructions, used to maintain normal bowel movements. Indeed, the authors noted 5 of 24 (20.8%) patients with symptoms of bowel obstruction survived for >3 years after bowel decompression or stomy procedures. This rate was hardly achieved for patients with the same symptoms who received chemotherapy only.

Propensity scores estimate the predicted probability (propensity) of use of a given therapy or intervention in a particular subject, based on the conditioning variables when the treatment is chosen. Subjects with the same propensity score should have the same chance of receiving treatment. Therefore, propensity scores are often conceptualized as simulating randomized trials, although they do so only with respect to confounders that have been adequately measured. Furthermore, propensity scores allow simultaneous control for confounding by several variables in situations where conventional multivariable models might not be appropriate, owing to the small number of outcomes or events.

If potentially important covariates are not measured, the propensity score may not be robust [37]. We used the instrumental variable approach to address the issue of potential unmeasured confounders. Instrumental variable methods are used to estimate the effects of receiving treatment or exposure to a risk factor on outcome when there is unmeasured confounding in medical research, such as in clinical trials with nonadherence to treatment or with observational studies [22, 38]. Comparable results gained by the instrumental variable method imply that there may be no overt hidden bias in the current study.

The present study has several limitations. First, the composition of the study cohort may be influenced by referral bias because of the monocentric design. The index hospital is a tertiary care center with more patients with comorbidities. Thus,

the results of the present study may not be generalizable to the general population. Second, limitations in patient-level data collection were also present. Socioeconomic factors have been found to be associated with cancer mortality [39]; nonetheless, our database did not capture relevant socioeconomic factors, which potentially affects the reliability of Cox proportional hazard and propensity score modeling. Third, the protocol of follow-up was not strictly defined; therefore, progression-free survival or survival duration between tumor recurrence and death could not be accurately measured.

CONCLUSION

In conclusion, results from this comparative effectiveness study provide supportive evidence for previous relevant reports finding that secondary cytoreductive surgery could increase overall survival for patients with recurrent epithelial, tubal, and peritoneal cancers, providing that the surgery is well planned, uses a multidisciplinary team approach, and has the aim of maximal cytoreduction. Increased survival rates provide these patients with better chances of receiving novel therapeutic modalities as they emerge [40]. However, meticulous preoperative evaluation is mandatory for the implementation of secondary cytoreductive surgery, as carelessly performed surgery may even decrease the expected survival of these patients. We propose that referral of patients with recurrent epithelial ovarian, tubal, and peritoneal cancers to a focused-care institute is imperative. Although this study adds supporting evidence that secondary cytoreductive surgery confers survival benefit, we should await the results of two relevant ongoing clinical trials to confirm its real value.

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