Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis

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Editor’s key points
- Retrospective analysis of the potential effect of epidural or general anaesthesia/opioid anaesthesia on cancer surgery outcome.
- The outcome measure used was deaths at 3 and 5 yr, not tumour recurrence.
- Better outcome (hazard ratio 1.214) was found in the epidural group.
- Small retrospective study but it provides further evidence of the role of anaesthetic technique.
- The need for large prospective randomized-controlled trials in this important area is emphasized.

Background. Animal studies have shown that regional anaesthesia and analgesia may prevent or attenuate the surgical stress response by preserving immune function and result in better long-term outcome. We have tested the hypothesis that patients with ovarian serous adenocarcinoma who had surgery with epidural anaesthesia and analgesia would have better long-term outcome than those who were given general anaesthesia (GA) and i.v. opioid analgesia.

Methods. A retrospective review of medical records identified 143 patients with ovarian serous adenocarcinoma who underwent surgery between January 1994 and October 2006 at the Sun Yat-sen University Cancer Center. Data in the analysis included age, anaesthesia–analgesia technique, ASA status, blood loss, transfusion, duration of surgery, status of preoperative cancer antigen 125, tumour size, International Federation of Gynecology and Obstetrics stage, histological grade, lymph node status, residual macroscopic tumour, and chemotherapy. Survival analysis was made with the main outcome measure of death.

Results. The 3- and 5-yr overall survival rates were 78% and 61% in the patient group who received epidural anaesthesia and analgesia (Group E, n=106), and 58% and 49% in the patient group who received GA and i.v. opioid analgesia (Group G, n=37), respectively. After adjusting for the other variables, Group G had a hazard ratio of 1.214 (P=0.043) in a multivariable Cox regression model compared with Group E.

Conclusions. This retrospective analysis suggests that epidural anaesthesia and analgesia for ovarian serous adenocarcinoma surgery may reduce mortality during the initial years of follow-up.

Keywords: anaesthetic technique; ovarian serous adenocarcinoma; prognosis

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Methods

This study was approved by the ethics committee of the Sun Yat-sen University Cancer Center (Guangzhou, PR China). The medical records of all patients who underwent ovarian serous adenocarcinoma surgery at the centre, between January 1994 and October 2006, were reviewed. Only the records from newly diagnosed patients were included. Patients who underwent surgery more than once were excluded.

The patients were allocated into two groups. Group E included patients who underwent surgery with epidural anaesthesia and analgesia, and Group G included patients who had GA combined with postoperative i.v. fentanyl analgesia. All patients studied were under the care of the same anaesthetist and surgeon. Although epidural anaesthesia and analgesia was our usual technique, GA was also used for a variety of reasons, including the presence of absolute or relative contraindications, or preference of the anaesthetist, surgeon, or patient.

Group E received midazolam 0.04 mg kg\(^{-1}\) for sedation. The epidural was inserted before operation at T11–T12 or L2–L3, and an initial dose of local anaesthetic (lidocaine 1.5–2.0%) was given before surgical incision. Local anaesthetic (bupivacaine 0.125% or ropivacaine 0.150%) and morphine 6–8 mg were then continued as an infusion for 48 h after surgery. The GA technique for Group G included midazolam 0.04 mg kg\(^{-1}\), fentanyl 3–4 μg kg\(^{-1}\), and propofol 1–2 mg kg\(^{-1}\) (or thiopental 3–5 mg kg\(^{-1}\)) for induction and vecuronium 0.1 mg kg\(^{-1}\) to facilitate tracheal intubation. Anaesthesia was maintained with sevoflurane 2–3% (or isoflurane 1.5–2.5%) in nitrous oxide and oxygen. Patient-controlled analgesia (PCA) was given with a CADD-Legacy ambulatory infusion pump (model number 6300; Deltec Inc., St Paul, MN, USA) and Rhythmic PCA Pump (Micrel

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and operative characteristics for patients receiving epidural anaesthesia (Group E) or GA and opioids (Group G). Data are reported as number (%), mean (range), mean (SD), or median (first, third quartiles). P-values obtained from *the Kruskal–Wallis test or **one-way analysis of variance. CBP, cyclophosphamide, bleomycin, carboplatin/cisplatin; FIGO, International Federation of Gynecology and Obstetrics; TP, paclitaxel, carboplatin/cisplatin</th>
</tr>
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<tbody>
<tr>
<td>ASA</td>
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</tr>
<tr>
<td>I</td>
<td>54 (50.9%)</td>
</tr>
<tr>
<td>II</td>
<td>50 (47.2%)</td>
</tr>
<tr>
<td>III</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45.7 (30–65)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>350.0 (200.0,500.0)</td>
</tr>
<tr>
<td>Transfusion (ml)</td>
<td>100.0 (0,300.0)</td>
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<tr>
<td>Duration of surgery (h)</td>
<td>3.3 (2.7,3.5)</td>
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<tr>
<td>Preoperative CA125 status (μmol)</td>
<td>679.6 (174.8,1858.2)</td>
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<tr>
<td>Chemotherapy received</td>
<td></td>
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<tr>
<td>CBP</td>
<td>54 (51.0%)</td>
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<td>TP</td>
<td>49 (46.2%)</td>
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<td>Others</td>
<td>3 (2.8%)</td>
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<tr>
<td>FIGO stage</td>
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<td>I</td>
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</tr>
<tr>
<td>II</td>
<td>24 (22.6%)</td>
</tr>
<tr>
<td>III</td>
<td>52 (49.1%)</td>
</tr>
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<td>IV</td>
<td>5 (4.7%)</td>
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<tr>
<td>Histological grade</td>
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<td>I</td>
<td>31 (29.2%)</td>
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<tr>
<td>II</td>
<td>46 (43.4%)</td>
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<td>Residual macroscopic tumour</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>62 (58.5%)</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>28 (26.4%)</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>16 (15.1%)</td>
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<td></td>
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<tr>
<td>None</td>
<td>67 (63.2%)</td>
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<td>Systematic lymphadenectomy</td>
<td>30 (28.3%)</td>
</tr>
<tr>
<td>Unsystematic lymphadenectomy</td>
<td>9 (8.5%)</td>
</tr>
</tbody>
</table>
Medical Devices S.A., Greece) programmed to deliver fentanyl boluses of 10 μg with a lockout time of 5 min.

The main outcome measure was death of the patients. The evaluation cut-off time was November 2008 (i.e. follow-up interval of 2.0–14.5 yr). Survival time was defined as the time between surgery and death. The survival time for patients in whom death was not recorded was defined as the time between the date of surgery and the date of last follow-up. Characteristics of the study groups were analysed based on the anaesthesia–analgesia technique, ASA, blood loss, transfusion, duration of surgery, status of preoperative cancer antigen 125 (CA125), tumour size, International Federation of Gynecology and Obstetrics (FIGO) stage, histological grade, lymph node status, and residual macroscopic tumour, whether postoperative or preoperative adjuvant chemotherapy was used, and the current status of patients, determined by the documentation of their follow-up visits to the outpatient clinics.

Exclusion criteria included loss of follow-up and an inadequate or lost documentation of medical records. The groups were compared on potential baseline confounders (Table 1) using χ² test for categorical variables, and either t-test or Wilcoxon’s rank-sum test for continuous variables, as appropriate. Univariate association between overall survival and anaesthetic technique was assessed with the Kaplan–Meier survival estimates; the groups were compared using the log-rank test. In addition, univariate association between overall survival and all potential baseline confounders was assessed using the Cox proportional hazards regression.

For the primary analysis, we compared the survival rate using multivariable Cox’s proportional hazards regression while adjusting for any baseline or intraoperative factors independently related with the outcome. Variables considered included ASA status, tumour size, length of surgery, estimated blood loss, transfusion, FIGO stage, histological grade, lymph node status, preoperative CA125 status, residual macroscopic tumour, and chemotherapy received. We used stepwise regression and a liberal significance criterion of P<0.30 to be confident of having adjusted for any potential confounding of the relation between anaesthetic and survival time among the available baseline factors and to obtain a more precise estimate of hazard ratio (HR) for anaesthetic treatment.

The proportional hazards assumption of the Cox regression model was assessed graphically by plotting the log(–log (survival)) against log(time). The predictive value of the multivariable model with the c-index was assessed. This summary measure gives the proportion of all usable pairs in which predicted and actual survival times are concordant, such that a patient with a longer survival time than another is also predicted as such by the model. However, the c-index is a less informative measure of predictive ability when a significant proportion of the data are censored. The linearity of the relation between continuous and ordinal variables and recurrence was assessed graphically. We also used propensity score matching to assess the robustness of our primary analysis results between the type of anaesthesia–analgesia and survival rate.

Fig 1 Consort style flow diagram.
The significance level for all hypotheses was 0.05. A Bonferroni correction to the significance criterion for multiple comparisons was applied where appropriate. SPSS (Chicago, IL, USA) software version 16.0 was used for all analyses.

### Results

The medical records of 143 patients who underwent ovarian serous adenocarcinoma surgery between January 1994 and...
October 2006, and who matched the inclusion criteria, were reviewed (Fig. 1). Cause of death was established by the Follow-up Service in our centre which was blinded to the type of anaesthesia–analgesia administered. Out of 143 patients, 106 underwent surgery with epidural anaesthesia and analgesia (Group E) and 37 had GA combined with post-operative i.v. opioid analgesia (Group G). The follow-up interval was 2.0–14.5 yr. Group E tended to have slightly shorter surgeries ($P=0.06$), more complications ($P=0.07$), and slightly better FIGO stage ($P=0.111$) than Group G but these were not statistically significant (Table 1). Complications included postoperative bleeding, pneumonia or other respiratory tract infection, and urinary tract infection. These factors were thus prime candidates for inclusion in our multivariable model.

Univariable Cox’s regression model results for each baseline and intraoperative factor are shown in Table 2. Without adjusting for potential confounders (i.e. univariably), Group G had a significantly higher estimated risk of death compared with Group E, with an HR of 1.818 [95% confidence interval (CI), 1.048–3.153]. The duration of surgery, preoperative CA125 status, FIGO stage, histological grade, residual macroscopic tumour, and lymphatic metastasis were also significantly associated with the overall survival rate in univariable analysis. The Kaplan–Meier survival rate estimates and 95% CIs at landmark follow-up times showed that Group E seemed to have a higher overall survival rate than Group G. The 1-, 3-, and 5-yr overall survival rates were 96% (95% CI, 92–99%), 78% (95% CI, 70–86%), and 61% (95% CI, 52–71%) in Group E, whereas 78% (95% CI, 64–91%), 58% (95% CI, 42–74%), and 49% (95% CI, 32–65%) in Group G, respectively (Table 3 and Fig. 2).

After adjusting for preoperative CA125 status, FIGO stage, histological grade, residual macroscopic tumour, and lymphatic metastasis, Group G had an estimated 21.4% (95% CI, 7.5–43.1%) increased mortality rate compared with Group E, with a corresponding HR of 1.214 (95% CI, 1.075–1.431, $P=0.043$) in our multivariable Cox regression model (Table 4).

As a sensitivity analysis to explore the potential for bias due to censoring, the association between the anaesthetic group and overall survival rate was assessed using only the first 5 yr of data for each patient. Univariable and multivariable associations were similar to the full-data results, with $P=0.034$ and 0.045, respectively.

Propensity score matching was used to assess the association between the type of anaesthesia–analgesia and survival rate. Propensity scores were created for all 135 patients who had non-missing data for all baseline and intraoperative potential confounding variables (Table 5). Before matching, patients in Group E and Group G differed significantly on the propensity score, with smaller differences in other variables. Twenty-nine matched pairs were obtained ($n=58$ patients); matching was successful in improving the balance between groups (Table 5). We then assessed the association between

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**Table 4** Multivariable association with survival rate: Cox’s regression model. CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CA125, cancer antigen 125

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group E</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group G</td>
<td>1.214 (1.075–1.431)</td>
<td>0.043</td>
</tr>
<tr>
<td>Preoperative CA125 status (per $\mu$mol)</td>
<td>1.107 (1.054–1.189)</td>
<td>0.032</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>II</td>
<td>2.197 (1.001–5.298)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>3.276 (1.906–6.517)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV</td>
<td>5.432 (2.274–12.669)</td>
<td>&lt;0.001</td>
</tr>
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<td>Histological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>1.325 (1.152–1.691)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>1.360 (1.212–1.612)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residual macroscopic tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$&lt;2$ cm</td>
<td>1.221 (1.115–1.426)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\geq 2$ cm</td>
<td>2.554 (1.297–4.835)</td>
<td>&lt;0.001</td>
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<tr>
<td>Lymphatic metastasis</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>1</td>
<td>0.029</td>
</tr>
<tr>
<td>Systematic lymphadenectomy</td>
<td>1.213 (1.102–1.476)</td>
<td></td>
</tr>
<tr>
<td>Unsystematic lymphadenectomy</td>
<td>1.528 (1.053–2.502)</td>
<td></td>
</tr>
</tbody>
</table>

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![Fig 2 Survival curves of Group E and Group G.](image)
different anaesthesia–analgesia type and survival rate on the propensity-matched pairs using Cox’s regression. Group G had a univariable HR of 1.322 (95% CI, 1.083–1.697, \( P = 0.039 \)) compared with Group E (Table 6). A multivariable Cox regression analysis on the propensity-matched patients (Table 6) resulted in an HR of 1.201 (95% CI, 1.015–1.502, \( P = 0.042 \)).

**Discussion**

We have evaluated survival rate in patients undergoing ovarian serous adenocarcinoma surgery. The 3- and 5-yr overall survival rates were 78% and 61% in Group E, and 58% and 49% in Group G, respectively. After adjusting for tumour size, FIGO stage, histological grade, lymph node status, preoperative CA125 status, residual macroscopic tumour, and chemotherapy, Group G has a corresponding HR of 1.214 (\( P = 0.043 \)) in a multivariable Cox regression model compared with Group E. These results suggest that patients who underwent surgery for ovarian serous adenocarcinoma with epidural anaesthesia and analgesia had a better clinical outcome than patients who had GA and postoperative i.v. opioid analgesia.

These results may be consistent with the theory that there is suppression of immune defence mechanisms during surgery and in the postoperative period. Such immune compromise could affect the postoperative infection rate, healing, and rate and extent of tumour dissemination.

### Table 5  Perioperative variables before and after propensity score matching. Data are reported as mean (range), mean (SD), median (quartiles), or per cent. *All factors in Table 5 except propensity score were used to create the propensity scores. †Propensity score (PS) = predicted probability patient receives general anesthesia given baseline variable; matching on PS achieved balance on the other variables in the table used to create the PS. FIGO, International Federation of Gynecology and Obstetrics; CA125, cancer antigen 125; CBP, cyclophosphamide, bleomycin, carboplatin/cisplatin; TP, paclitaxel, carboplatin/cisplatin

<table>
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<th>Factor*</th>
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<th>After matching</th>
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<td>Group G (n = 34)</td>
</tr>
<tr>
<td>PS†</td>
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<td>0.42 (0.10)</td>
</tr>
<tr>
<td>ASA</td>
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<td>Age (yr)</td>
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<td>47.8 (31–68)</td>
</tr>
<tr>
<td>Tumour size (cm³)</td>
<td>712.8 (239.4, 2123.2)</td>
<td>982.1 (243.6, 1939.5)</td>
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<td>Duration of surgery (h)</td>
<td>3.4 (2.8, 3.7)</td>
<td>3.5 (3.1, 3.8)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>355.0 (200.0, 500.0)</td>
<td>370.0 (200.0, 500.0)</td>
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<tr>
<td>Transfusion (ml)</td>
<td>100.0 (0, 300.0)</td>
<td>150 (0, 375.0)</td>
</tr>
<tr>
<td>Preoperative CA125 status (µmol)</td>
<td>679.6 (174.8, 1858.2)</td>
<td>705.3 (185.7, 2497.7)</td>
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<td>FIGO stage</td>
<td>2.3 (0.6)</td>
<td>2.9 (0.8)</td>
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<td>Year of surgery (%)</td>
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<td>1996</td>
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<td>2006</td>
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<td>Residual macroscopic tumour (%)</td>
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<tr>
<td>0</td>
<td>56.4</td>
<td>52.9</td>
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<td>&lt; 2 cm</td>
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<td>32.4</td>
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<td>14.7</td>
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<tr>
<td>Chemotherapy received (%)</td>
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<tr>
<td>CBP</td>
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<td>TP</td>
<td>39.6</td>
<td>44.1</td>
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<tr>
<td>Others</td>
<td>9.9</td>
<td>8.8</td>
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can suppress immune function. An animal study has shown that ketamine, thiopental, and halothane suppressed NK cell activity, and thus promoted metastasis. Volatile anaesthetics can impair NK cell function by as much as 90%. Halothane and isoflurane comparably reduce neutrophil motility, whereas sevoflurane impairs T lymphocyte activity. A significant decrease in NK cell activity after surgery was found in mothers who received GA. GA can induce a reduction in NK cell activity, and this may increase the susceptibility to infection or the risk of tumour dissemination. In our experience, sevoflurane seemed to be a contributory factor, and, in a previous study where sevoflurane was not used, the reduction in NK activity was less marked.

This suppression could be attributed, at least in part, to opioids which are known to suppress immune function, particularly NK cell activity. The immune modulatory effects of opioids may depend on the interaction between the dose and time of administration. Morphine has also been shown to decrease the survival of rats inoculated with tumour cells. Morphine, fentanyl, and sufentanil all suppress NK cell activity. High- and low-dose fentanyl anaesthesia has been shown to produce similar suppression of NK cell activity, with a peak effect of 24 h after surgery, but there was a difference in the rate of recovery of NK cell activity. On the second postoperative day, NK cell activity had returned to control values in the low-dose fentanyl patients, but was still significantly suppressed after high-dose fentanyl.

On the other hand, regional anaesthesia and analgesia may play an important role in preserving immune function by attenuating or preventing the immunosuppressive effect. The proposed mechanism is that regional anaesthesia modulates the neuroendocrine stress response by blocking afferent neural transmission from reaching the central nervous system to activate the stress response and by blocking descending efferent activation of the sympathetic nervous system. An animal study showed that intrathecal local anaesthetic combined with morphine in rats provided significant protection against the tumour-enhancing effects of surgery and resulted in better tumour outcome than a single preoperative systemic dose of morphine. One large retrospective analysis found that GA for excision of primary melanoma was associated with a decrease in the survival rate (relative risk of 1.46) compared with local anaesthesia.

On the basis of the mechanisms discussed above, we speculate that at least two factors might account for the results of our study. First, the immunosuppressive effects of GA were not present in Group E. Secondly, the amount of opioids used in Group E was much lower than in Group G, where a dose almost 10 times larger was used. Both of these could lead to a lesser suppression of the NK cell activity, and thus prevent tumour dissemination.

There are several important limitations in this retrospective study. The patients were not randomized, and clinical care was not standardized, so that selection bias and the effects of unmeasured confounding variables cannot be excluded. The sample size of the two groups differed greatly. The results of our study show that Group G has a corresponding HR of 1.214 (95% CI, 1.075–1.431) in a multivariable Cox regression model with a P-value of 0.043 compared with that of Group E.

This study, like most retrospective analyses, identifies testable possibility. Our findings prompt further questions that would be best addressed by a well-conducted prospective randomized-controlled trial comparing the effect of epidural anaesthesia–analgesia on ovarian cancer outcome. For future studies, it is also necessary to evaluate the effect of

<p>| Table 6 Univariable and multivariable models comparing propensity-matched groups (n=58). *Variables other than Group G included if significant at P&lt;0.05 in stepwise selection; all variables in Table 5 other than PS were considered for this model. CI, confidence interval; CA125, cancer antigen 125 |
|---------------------------------|-----------|-----------|-----------|</p>
<table>
<thead>
<tr>
<th>Variables*</th>
<th>Reference or units</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
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<td>Group E</td>
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<td>0.039</td>
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<tr>
<td>Multivariable*</td>
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<td>Group G</td>
<td>Group E</td>
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<td>0.042</td>
</tr>
<tr>
<td>Preoperative CA125 status</td>
<td>1</td>
<td>1.112 (1.076–1.201)</td>
<td>0.023</td>
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<td>1.991 (0.998–4.201)</td>
<td>&lt;0.001</td>
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<td>1.330 (1.103–1.894)</td>
<td>&lt;0.001</td>
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<tr>
<td>Residual macroscopic tumor</td>
<td>0</td>
<td>1.865 (1.315–2.743)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

during surgery. Anaesthesia and surgical procedures have been reported to suppress natural killer (NK) activity and other immune functions for a couple of days. Surgery-induced immunosuppression is also associated with increased risk of tumour development and metastasis. Several clinical studies have shown that the reduction in the immunosuppressive effects of surgery not only plays an important role in preventing tumour development, but also has a beneficial effect on overall survival of cancer patients. Higher numbers of NK cells before surgery have a beneficial effect on overall survival of gastric and colorectal stage III cancer patients, whereas suppression of NK cell activity may contribute to the increased tumour metastases and worse clinical outcome.

Preservation of immune function has become a strategy to improve outcome. Recent studies suggest that choosing therapeutic agents or methods that produce a sustained increase, or do not decrease, in the immunological function, would result in a better clinical outcome.

Postoperative immunosuppression is partly ascribed to the effects of anaesthesia and may compromise patients’ resistance to cancer metastasis. Both surgical stress and GA suppress immune function, especially NK cell activity. Recent studies have shown that several anaesthetic agents can suppress immune function. An animal study has shown that ketamine, thiopental, and halothane suppressed NK cell activity, and thus promoted metastasis. Volatile anaesthetics can impair NK cell function by as much as 90%. Halothane and isoflurane comparably reduce neutrophil motility, whereas sevoflurane impairs T lymphocyte activity. A significant decrease in NK cell activity after surgery was found in mothers who received GA. GA can induce a reduction in NK cell activity, and this may increase the susceptibility to infection or the risk of tumour dissemination.
different anaesthetic techniques on the patients’ immune function after ovarian serous adenocarcinoma surgery.

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Conflict of interest

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