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Perioperative epidural use and survival outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer

Jill H Tseng, MD¹, Renee A Cowan, MD¹, Anoushka M Afonso, MD², Qin Zhou, MS³, Alexia Iasonos, PhD³, Narisha Ali, MS¹, Errika Thompson, BS¹, Yukio Sonoda, MD^{1,4}, Roisin E O’Cearbhaill, MD^{5,6}, Dennis S Chi, MD^{1,4}, Nadeem R Abu-Rustum, MD^{1,4}, and Kara Long Roche, MD^{1,4}

¹Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

²Departments of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering, New York, N.Y

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

⁴Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY

⁵Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

⁶Department of Medicine, Weill Cornell Medical College, New York, NY

Abstract

Objective: Epidurals are associated with improved outcomes in some solid tumors, presumably due to its effect on surgical stress response. There are limited data on the prognostic significance of epidural anesthesia in patients undergoing primary debulking surgery (PDS) for advanced ovarian cancer. We sought to assess the impact of epidural anesthesia on the survival outcomes of patients undergoing PDS for advanced ovarian cancer.

Corresponding author: Kara Long Roche, MD, Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 Tel. 212-639-7043, longrock@mskcc.org.

Author Contributions

Conception and design: Tseng JH, Cowan RA, Afonso AM, Abu-Rustum NR, Long Roche K

Acquisition of data: Tseng JH, Cowan RA, Ali N, Thompson E, Long Roche K

Analysis and interpretation of data: Tseng JH, Afonso AM, Zhou Z, Iasonos A, Sonoda Y, O’Cearbhaill RE, Chi DS, Abu-Rustum NR, Long Roche K

Drafting the article or revising it critically for important intellectual content: Tseng JH, Cowan RA, Afonso AM, Zhou Z, Iasonos A, Ali N, Thompson E, Sonoda Y, O’Cearbhaill RE, Chi DS, Abu-Rustum NR, Long Roche K

Final approval of the version to be published: Tseng JH, Cowan RA, Afonso AM, Zhou Z, Iasonos A, Ali N, Thompson E, Sonoda Y, O’Cearbhaill RE, Chi DS, Abu-Rustum NR, Long Roche K

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Methods: In this retrospective study, consecutive patients with stage IIIB-IV epithelial ovarian, fallopian tube, or peritoneal carcinoma who underwent PDS at our institution from 01/2005–12/2013 were identified. Progression-free survival (PFS) and overall survival (OS) with regard to epidural use were analyzed.

Results: Of 648 patients, 435 received an epidural and 213 did not. Patients in the former group were more likely to have higher stage disease (stage IV disease, 26% vs. 16%, respectively; $P=.005$), carcinomatosis (87% vs. 80%, respectively; $P=.027$), and bulky upper abdominal disease (66% vs. 58%, respectively; $P=.046$). Complete gross resection was achieved in 48% and 32%, respectively ($P<.001$). For the epidural vs. non-epidural groups, median PFS was 20.8 months and 13.9 months, respectively ($P=.021$); median OS was 62.4 months and 41.9 months, respectively ($P<.001$). After controlling for confounding factors, including residual disease, epidural use was independently associated with a decreased risk of progression (HR=1.327; 95% CI, 1.066–1.653) and death (HR=1.588; 95% CI, 1.224–2.06).

Conclusions: Perioperative epidural use was independently associated with improved PFS and OS in these patients. Epidural anesthesia at the time of PDS may be warranted in this setting.

Keywords

ovarian cancer; epidural anesthesia; primary debulking surgery; residual disease; survival

Introduction

Primary debulking surgery (PDS) with maximal tumor cytoreduction remains the cornerstone of treatment for advanced epithelial ovarian cancer. For patients diagnosed with advanced-stage disease, 5-year survival is only 30% [1]. Several prognostic factors have been identified [2–5]. Yet, the only well-established, modifiable factors for survival are residual disease at the time of PDS and postoperative chemotherapy regimen [6–8].

Perioperative epidural use has emerged as a potential prognostic factor in solid tumor malignancies. The proposed theory behind this relates to the surgical stress response and the immune system. Surgery has been shown to promote micrometastasis through tumor disruption, suppression of anti-angiogenic factors, and release of growth factors [9,10]. Cell-mediated immunity (CMI) plays a crucial role in preventing tumor metastasis by recognizing and responding to foreign antigens, including tumor cells [11]. However, surgical stress inhibits CMI through the release of anti-CMI cytokines and catecholamines. General anesthesia and systemic opioid use also suppress CMI [9]. Perioperative epidural use is thought to blunt the surgical stress response, leading to decreased pro-tumorigenic cytokine and catecholamine release while promoting anti-tumorigenic cell-signaling mechanisms [11]. Epidural anesthesia also reduces the need for general anesthesia and systemic opioid administration, thereby counteracting surgery-induced CMI inhibition.

Several retrospective studies have demonstrated prolonged survival with the use of epidural anesthesia during oncologic surgery [12–17], although findings in the published literature have been inconsistent [18–21]. Only a few studies, with conflicting results, have investigated the impact of epidural anesthesia on ovarian cancer survival [22–26]. We,

therefore, sought to evaluate the effects of epidural use on survival in patients undergoing PDS for advanced ovarian, fallopian tube, or primary peritoneal carcinoma. We hypothesized that perioperative epidural use would be associated with improved survival outcomes.

Methods

This single-institution, retrospective cohort study was approved by the Institutional Review Board (IRB) of Memorial Sloan Kettering Cancer Center (MSK). We identified all patients diagnosed with stage IIIB to IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who had undergone PDS at our institution between January 1, 2005 and December 31, 2013. Staging was based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system. Patients were only included if there was clear documentation of whether or not epidural anesthesia was used. Since advanced ovarian cancer often requires significant tumor cytoreduction, which may lead to greater tumor disruption and surgical stress compared to the surgical treatment of early ovarian cancer, we limited our study to patients with stage IIIB to IV disease.

Individual medical records were reviewed, and demographic and clinical variables were abstracted. Patients with no visible disease remaining at the end of the surgical procedure were considered to have undergone a complete gross resection (CGR). Those who had one or more tumor nodules measuring 1–10 mm in greatest diameter at the completion of surgery were considered to have undergone an optimal resection. Those with any remaining tumor nodule measuring >1 cm in greatest diameter at the completion of surgery were considered to have had a suboptimal resection. Bulky upper abdominal (UAB) disease was defined as tumor implants ≥1 cm cephalad to the greater omentum. The presence of peritoneal carcinomatosis was determined according to the attending surgeon's operative note. If not stated in the operative note, carcinomatosis was defined as the presence of ≥20 tumor implants within the abdominal cavity. Complications occurring within 30 days of surgery were prospectively captured and graded according to the MSK institutional surgical secondary events grading system [27].

Patients were divided into two groups: those who received epidural anesthesia (epidural group) and those who did not (non-epidural group). For those who did not receive an epidural, postoperative pain management consisted of narcotic-containing intravenous patient-controlled analgesia (IV PCA). All patients received intraoperative general anesthesia with volatile anesthetics (most commonly isoflurane or sevoflurane), regardless of epidural use.

The decision to place an epidural catheter was made by the attending surgeon and the attending anesthesiologist, with consideration of the patient's preference. Patients with a preoperative platelet count <100,000 per mcL or requiring therapeutic anticoagulation were ineligible for epidural placement. Epidurals were infused with 0.05% bupivacaine with or without hydromorphone, fentanyl, or morphine. They were set at a continuous dose of 3 mL/h and a patient-initiated demand dose of 3 mL every 30 min. All epidurals were placed preoperatively and were started either intraoperatively or immediately postoperatively at the

discretion of the attending anesthesiologist. Placement and management of epidural catheters were performed by the Acute Pain Service of the Department of Anesthesiology. Epidurals were discontinued with the consensus of the surgical and acute pain teams, generally based upon a patient's readiness to transition to oral pain medication, inadequate pain control requiring an alternate method of analgesia, malfunction, or duration of use exceeding 14 days.

Patients were treated with postoperative platinum and taxane-based chemotherapy. The use of intraperitoneal (IP) chemotherapy was defined as the administration of 1 or more cycles of IP treatment [28]. Those without evidence of disease at the completion of chemotherapy were followed every 3 months for the first 2 years, every 6 months for the following 3 years, and yearly after the fifth year. Serum CA-125 levels were routinely drawn at follow-up visits, and imaging was performed as clinically indicated. Recurrence/progression was defined as one or more new or enlarging lesions on imaging resulting in surgical resection, initiation of chemotherapy, or a change in current chemotherapy regimen.

Statistical analysis

To compare the epidural versus non-epidural groups, categorical variables were analyzed using the Fisher exact test, and continuous variables were analyzed using the Wilcoxon-rank sum test. Progression-free survival (PFS) was defined as the time from the date of PDS to the date of progression, death, or last follow-up. Both progression and death were considered as events in the PFS analysis. Overall survival (OS) was defined as the time from the date of PDS to the date of death or last follow-up. The Kaplan-Meier method was used to estimate median PFS and OS. For the univariate analysis, the log-rank test was used to compare PFS and OS for all categorical variables except epidural use and IP chemotherapy. The Wald test, based on the Cox proportional hazards (PH) model, was applied to continuous variables to obtain P values. Epidural use was tested by fitting a marginal Cox PH model that included surgeon as a cluster effect [29]. The P value for IP chemotherapy was obtained by including IP chemotherapy (yes/no) as a time-dependent covariate in the Cox PH model. All variables with a P value <0.05 on univariate analysis were included in the multivariable model except for *BRCA* status, as this variable was mostly documented as unknown. The multivariable Cox PH models were fit controlling for surgeons as a clustering effect [29]. All tests were 2-sided, and P values <0.05 were considered significant. Analyses were performed using SAS 9.4 (SAS Institute Inc.).

Results

We identified 724 consecutive patients with stage IIIB-IV ovarian, fallopian tube, or primary peritoneal carcinoma (based on the 2009 FIGO staging system) who had undergone PDS at our institution between 1/1/2005 and 12/31/2013. Seventy-six patients were excluded due to a lack of documentation regarding the presence or absence of epidural use. Our final cohort was composed of 648 patients (Figure 1). Demographic and clinical characteristics are summarized in Table 1. The median age was 62 years (range, 19–88 years). Three hundred thirty-eight patients (53%) had an American Society of Anesthesiologists (ASA) physical status classification score of 3–4, and 94 (15%) had a known deleterious germline *BRCA*

mutation. Most patients were diagnosed with stage IIIB-C disease (n=499, 77%) and had disease of serous histology (n=588, 91%). Carcinomatosis and bulky UAB disease were found in 547 (85%) and 410 (63%) of patients, respectively. Two hundred seventy-seven patients (43%) achieved a CGR, 234 (36%) underwent optimal debulking, and 137 (21%) underwent suboptimal debulking. The median length of postoperative hospital stay was 8 days (range, 1–86 days), and the rate of major complications was 17% (n=108). Almost all patients were treated with postoperative chemotherapy (99.1%, n=631), and 284 patients (45%) received at least 1 cycle of postoperative IP chemotherapy.

Among the 648 patients, 435 (67%) received epidural anesthesia (epidural group) and 213 (33%) did not (non-epidural group). Comparisons of baseline characteristics between the groups are shown in Table 1. Patients in the epidural group, compared with the non-epidural group, had significantly higher stage disease (stage IV, 26% vs. 16%, $P=.005$), higher rates of carcinomatosis (87% vs. 80%, $P=.027$) and bulky UAB disease (66% vs. 58%, $P=.046$), and longer median operative times (319 min vs. 239 min, $P<.001$). A CGR was achieved in 48% of patients in the epidural group compared to 31% in the non-epidural group, while more patients in the non-epidural group underwent suboptimal debulking (30% vs. 17%; $P<.001$). There was no difference in age, body mass index (BMI), ASA score, or *BRCA* mutation status among those who underwent genetic testing, histology, major complication rate, or rate of postoperative chemotherapy use between the groups.

Of the 434 patients with documented intraoperative or postoperative epidural use, epidural anesthesia was started intraoperatively in 385 (89%) and immediately postoperatively in 49 (11%). The median duration of use was 5 days (range, 0–13 days). There was no significant difference in the duration of use between those started intraoperatively (median, 5 days; range, 0–13 days) and those started postoperatively (median, 4 days; range, 0–13 days; $P=.64$).

Median follow-up for the 107 progression-free survivors was 70.8 months (range, 1.3–143.5 months), and median follow-up for the 250 survivors was 68.8 months (range, 1.3–152.7 months). Survival statistics are shown in Table 2. For the entire cohort, median PFS was 18.3 months (95% CI, 17.0–19.5) and median OS was 57.3 months (95% CI, 52.1–63.1). Overall, 504 patients had documented recurrences and 398 died during the study period. Among those who died, 238 were in the epidural group and 160 were in the non-epidural group. Kaplan-Meier curves for PFS and OS, stratified by epidural use, are shown in Figure 2. Patients in the epidural group had a significantly longer median PFS (20.8 months; 95% CI, 18.7–22.9) compared to those in the non-epidural group (13.9 months; 95% CI, 12.9–15.0; $P=.021$). Similarly, median OS was significantly longer in the epidural group compared to the non-epidural group (62.4 months; 95% CI, 57.5–77.8 vs. 41.9 months; 95% CI, 37.5–51.7, respectively; $P<.001$).

Risk factors associated with PFS and OS on univariate analysis are shown in Table 3. Older age, stage IV compared to stage III disease, optimal and suboptimal debulking compared to CGR, presence of carcinomatosis or bulky UAB disease, and no epidural compared to epidural use were significantly associated with a higher risk of recurrence/progression and death. No epidural use remained significantly associated with a higher risk of recurrence/

progression and death after controlling for surgeon clustering effect (PFS, HR 1.33; 95% CI, 1.11–1.59; OS, HR 1.67; 95% CI, 1.36–2.04). There was no significant difference in recurrence/progression or death between patients whose epidural was started postoperatively versus intraoperatively (intraoperative, reference; postoperative: PFS, HR 1.14; 95% CI, 0.83–1.57; postoperative: OS, HR 1.31; 95% CI, 0.91–1.89).

Multivariable Cox PH models were used to examine variables independently associated with survival outcomes. These data are presented in Table 4. After accounting for surgeon clustering effect and controlling for potentially confounding factors, bulky UAB disease (HR, 1.51; 95% CI, 1.23–1.86) and optimal (HR 1.71; 95% CI, 1.45–2.01) or suboptimal debulking (HR 1.99; 95% CI, 1.63–2.44) were significantly associated with an increased risk of recurrence/progression, while IP chemotherapy was associated with a decreased risk of recurrence/progression (HR 0.63; 95% CI 0.55–0.72). Compared to epidural anesthesia, no epidural anesthesia was independently associated with a 33% increased risk of recurrence/progression (HR 1.33; 95% CI, 1.07–1.65).

Similar results were observed for factors associated with OS. On multivariable analysis, increasing age (HR 1.01; 95% CI, 1.00–1.02), bulky UAB disease (HR 1.46; 95% CI, 1.12–1.90), as well as optimal (HR 1.52; 95% CI, 1.25–1.84) and suboptimal debulking (HR 1.52; 95% CI, 1.25–1.85) compared to CGR, were significantly associated with an increased risk of death. IP chemotherapy administration was significantly associated with a decreased risk of death (HR 0.48; 95% CI, 0.40–0.57). Lack of epidural use independently conferred a 59% increased risk of death compared to epidural use (HR 1.59; 95% CI, 1.22–2.06).

Discussion

This is one of the largest studies examining the association between perioperative epidural use and oncologic outcomes among solid tumor malignancies. We demonstrate a survival advantage in patients who received epidural anesthesia during PDS for advanced ovarian cancer compared to those who did not. Median PFS and OS were prolonged by 7 months and 20 months, respectively, with epidural use. Although the CGR rate was higher in the epidural group, epidural utilization was still found to be independently associated with a decreased risk of recurrence/progression and death after controlling for residual disease and other confounding factors on multivariable analysis.

Surgical stress stimulates the release of anti-CMI cytokines while decreasing systemic levels of pro-CMI cytokines [30,31]. Perioperative interventions, including general anesthesia and systemic opioids, may also suppress CMI [32,33]. Multiple studies have demonstrated that epidural anesthesia diminishes the surgical stress response and decreases suppression of CMI inhibition [34–36]. In one study, 61 patients with ovarian cancer scheduled to undergo debulking surgery were randomized to combined general and epidural anesthesia or general anesthesia alone. Increased levels of NK cell activity and antitumorigenic cytokines were observed in the combined general and epidural anesthesia group compared to the general anesthesia group [34]. All of the aforementioned evidence supports the hypothesis that epidural use during primary tumor resection is associated with improved survival. There are limited retrospective data regarding epidural use and oncologic outcomes in ovarian cancer.

Three published reports show similar findings to those of our current study. In 2011, Lin et al. analyzed OS in 106 patients with ovarian cancer who received epidurals during PDS compared to 35 patients who did not [23]. The 5-year OS rate was significantly improved in those who received epidurals (61% vs. 49%, respectively), and patients who received postoperative IV opioid analgesia without epidural anesthesia had a higher risk of death (HR, 1.21; 95% CI, 1.08–1.43). de Olivera et al. evaluated the recurrence-free survival of 182 patients with ovarian cancer who underwent optimal primary debulking [22]. Intraoperative epidural use was significantly associated with a decreased risk of recurrence and a PFS benefit of 35 months compared to no epidural use. A study by Elias et al. also demonstrated an association between improved PFS and epidural use [26]. Two other studies, however, reported conflicting results [24,25]. Both studies had small sample sizes, possibly affecting their ability to detect survival differences between epidural and non-epidural groups. Additionally, one of these studies included patients who underwent PDS or neoadjuvant chemotherapy followed by interval debulking surgery; they also limited their analysis to only those who had a CGR of all visible disease [24].

Prospective studies to investigate the effects of perioperative epidural use on ovarian cancer survival are warranted. Until such data are available, results from large retrospective studies, such as the current one, may help in guiding patient care.

Physiologic stress is highest at the time of surgery. It thus seems logical that intraoperative combined with postoperative epidural use, as opposed to solely postoperative epidural use, would have the greatest potential for preserving immune function. In our study, there was no difference in risk of recurrence/progression or death when comparing intraoperative versus postoperative initiation of epidural anesthesia. In the study by de Olivera et al., intraoperative epidural use significantly increased the time to recurrence, while postoperative-only and no-epidural use did not [22]. Continued investigation of immune function during the perioperative timeline will be important in determining whether the timing of epidural initiation affects tumor metastasis and survival, and what the optimal timing of epidural use is.

Study limitations include the biases associated with its retrospective nature. The timing of intraoperative epidural initiation lacked standardization; thus, some patients received epidural anesthesia throughout their surgery, while others did not receive epidural anesthesia until the middle or end of their surgery. Additionally, the platinum/taxane-based postoperative chemotherapy regimens were variable in a minority of patients. Our study, however, is the largest study regarding epidural use in ovarian cancer. The single-institution design allowed patients in both epidural and non-epidural groups to receive the same pre- and postoperative care. We had a robust follow-up period of almost 7 years. We also performed a thorough multivariable analysis, controlling for well-established prognostic factors in ovarian cancer.

Perioperative epidural use appears to be significantly associated with improved PFS and OS in patients with ovarian cancer undergoing PDS. With the limited number of modifiable prognostic factors for ovarian cancer, it is important to invest in all interventions that may confer a survival advantage in these patients. Further prospective trials to delineate the

specific oncologic benefits related to epidural anesthesia are necessary, and the PDS perioperative period provides a rich investigatory milieu to further our understanding of immune function and tumor metastasis in this disease.

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References

1. Noone AM, Howlader N, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975–2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, 4 2018.
2. Winter WE, 3rd, Maxwell GL, Tian C, et al.; Gynecologic Oncology Group. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25:3621–3627. [PubMed: 17704411]
3. Winter WE, 3rd, Maxwell GL, Tian C, et al.; Gynecologic Oncology Group. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2008;26:83–89. [PubMed: 18025437]
4. Zhong Q, Peng HL, Zhang L, et al. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. *Clin Cancer Res*. 2015;21:211–220. [PubMed: 25348513]
5. Landrum LM, Java J, Mathews CA, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013;130:12–18. [PubMed: 23578540]
6. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol*. 2002;20:1248–1259. [PubMed: 11870167]
7. Chang SJ, Hodeib M, Chang J, et al. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. *Gynecol Oncol*. 2013;130:493–498. [PubMed: 23747291]
8. Bookman MA. First-line chemotherapy in epithelial ovarian cancer. *Clin Obstet Gynecol*. 2012;55:96113.
9. Ben-Eliyahu S The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. *Brain Behav Immun*. 2003;17 Suppl 1:S27–36. [PubMed: 12615183]
10. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? *Ann Surg Oncol*. 2003;10:972–992. [PubMed: 14527919]
11. Smyth MJ, Godfrey DI, Trapani JA. A fresh look at tumor immunosurveillance and immunotherapy. *Nat Immunol*. 2001;2:293–299. [PubMed: 11276199]
12. Merquiol F, Montelimard AS, Nourissat A, et al. Cervical epidural anesthesia is associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer surgery: a retrospective propensity-matched analysis. *Reg Anesth Pain Med*. 2013;38:398–402. [PubMed: 23881179]
13. Cummings KC, 3rd, Xu F, Cummings LC, et al. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116:797–806. [PubMed: 22273991]
14. Lee BM, Singh Ghotra V, et al. Regional anesthesia/analgesia and the risk of cancer recurrence and mortality after prostatectomy: a meta-analysis. *Pain Manag*. 2015;5:387–395. [PubMed: 26250850]

15. Scavonetto F, Yeoh TY, Umbreit EC, et al. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. *Br J Anaesth*. 2014;113 Suppl 1:i95–102. [PubMed: 24346021]
16. Chen WK, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. *PLoS One*. 2013;8:e56540. [PubMed: 23437162]
17. Weng M, Chen W, Hou W, et al. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. *Oncotarget*. 2016;7:15262–15273. [PubMed: 26918830]
18. Myles PS, Peyton P, Silbert B, et al.; ANZCA Trials Group Investigators. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. *BMJ*. 2011;342:d1491. [PubMed: 21447587]
19. Pei L, Tan G, Wang L, et al. Comparison of combined general-epidural anesthesia with general anesthesia effects on survival and cancer recurrence: a meta-analysis of retrospective and prospective studies. *PLoS One*. 2014;9:e114667. [PubMed: 25548913]
20. Binczak M, Tournay E, Billard V, et al. Major abdominal surgery for cancer: does epidural analgesia have a long-term effect on recurrence-free and overall survival? *Ann Fr Anesth Reanim*. 2013;32:e81–8. [PubMed: 23618609]
21. Cakmakaya OS, Kolodzie K, Apfel CC, et al. Anaesthetic techniques for risk of malignant tumour recurrence. *Cochrane Database Syst Rev*. 2014;(11):CD008877. [PubMed: 25379840]
22. de Oliveira GS, Jr, Ahmad S, Schink JC, et al. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med*. 2011;36(3):271–277. [PubMed: 21519312]
23. Lin L, Liu C, Tan H, et al. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. *Br J Anaesth*. 2011;106:814–822. [PubMed: 21436156]
24. Capmas P, Billard V, Gouy S, et al. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. *Anticancer Res*. 2012;32:1537–1542. [PubMed: 22493398]
25. Lacassie HJ, Cartagena J, Brañes J, et al. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the Chilean population. *Anesth Analg*. 2013;117:653–660. [PubMed: 23868889]
26. Elias KM, Kang S, Liu X, et al. Anesthetic selection and disease-free survival following optimal primary cytoreductive surgery for stage III epithelial ovarian cancer. *Ann Surg Oncol*. 2015;22:1341–1348. [PubMed: 25287437]
27. Strong VE, Selby LV, Sovel M, et al. Development and assessment of Memorial Sloan Kettering Cancer Center's Surgical Secondary Events grading System. *Ann Surg Oncol*. 2015;22:1061–1067. [PubMed: 25319579]
28. Suidan RS, Zhou Q, Iasonos A, et al. Prognostic Significance of the Number of Postoperative Intraperitoneal Chemotherapy Cycles for Patients with Advanced Epithelial Ovarian Cancer. *Int J Gynecol Cancer*. 2015;25:599–606. [PubMed: 25664437]
29. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariable incomplete failure time data by using the marginal distributions. *J Am Stat Assoc*. 1989;84:1065–1073.
30. Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. *World J Surg*. 1996;20:454–459. [PubMed: 8662134]
31. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127:117–126. [PubMed: 10686974]
32. Galley HF, DiMatteo MA, Webster NR. Immunomodulation by anaesthetic, sedative and analgesic agents: does it matter? *Intensive Care Med*. 2000;26:267–274. [PubMed: 10823382]
33. Carr DJ, Serou M. Exogenous and endogenous opioids as biological response modifiers. *Immunopharmacology*. 1995;31:59–71. [PubMed: 8655291]
34. Dong H, Zhang Y, Xi H. The effects of epidural anaesthesia and analgesia on natural killer cell cytotoxicity and cytokine response in patients with epithelial ovarian cancer undergoing radical resection. *J Int Med Res*. 2012;40:1822–1829. [PubMed: 23206463]

35. Li JM, Shao JL, Zeng WJ, et al. General/epidural anesthesia in combination preserves NK cell activity and affects cytokine response in cervical carcinoma patients undergoing radical resection: a cohort prospective study. *Eur J Gynaecol Oncol.* 2015;36:703–707. [PubMed: 26775356]
36. Kun L, Tang L, Wang J, et al. Effect of Combined General/Epidural Anesthesia on Postoperative NK Cell Activity and Cytokine Response in Gastric Cancer Patients Undergoing Radical Resection. *Hepatogastroenterology.* 2014;61:1142–1147. [PubMed: 26158178]

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Highlights

- Epidural use significantly improved progression-free and overall survival in patients undergoing surgery for ovarian cancer
- Epidural use was also found to be independently associated with progression-free and overall survival
- Perioperative epidural use in patients undergoing primary debulking surgery for advanced ovarian cancer may be warranted

Figure 1. Study design

Patients with stage IIIB-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who underwent primary debulking surgery (PDS) at our institution between January 2005 and December 2013 were identified. Those with a lack of documentation regarding epidural use were excluded. The remaining patients were placed into one of the following two groups: those who received perioperative epidural anesthesia and those who did not.

Figure 2. Progression-Free and Overall Survival by Epidural Use

A, Progression-free survival for epidural vs non-epidural groups. B, Overall survival for epidural vs nonepidural groups.

*P value after controlling for surgeon clustering effect.

Table 1.

Demographic and clinical characteristics

Characteristic	All patients (N=648)		Epidural use				P
			Epidural (N=435)		Non-epidural (N=213)		
	N	%	N	%	N	%	
Age, years Median Range	62 19–88		62 19–88		61 30–86		.76
BMI, kg/m ² Median Range	25.9 16.3–58.5		25.7 16.3–58.5		26 17.7–54.6		.74
ASA score (n=642) 1–2 3–4	304 338	47 53	194 236	45 55	110 102	52 48	.11
BRCA status Negative Positive Unknown BRCA status (unk excluded) Negative Positive	240 94	94 28	177 65	41 27	63 29	30 32	.009 .42
Stage IIIB-C IV	499 149	77 23	321 114	74 26	178 35	84 16	.005
Histology Serous Other	588 60	91 9	398 37	91 9	190 23	89 11	.23
Carcinomatosis (n=646) No Yes	99 547	15 85	57 378	13 87	42 169	20 80	.027
Bulky UAB disease No Yes	238 410	37 63	148 287	34 66	90 123	42 58	.046
Operative time, min Median Range	301 36–893		319 44–893		239 36–857		<.001
Length of hospital stay, days Median Range	8 1–86		8 1–58		8 1–86		.76
Major (G3–5) complication No Yes	540 108	83 17	355 80	82 18	185 28	87 13	.086
Residual disease CGR Optimal (1–10 mm) Suboptimal (>10 mm)	277 234 137	43 36 21	210 152 73	48 35 17	67 82 64	31 39 30	<.001
Postoperative chemotherapy (n=637) No Yes	6 631	1 99	4 427	1 99	2 204	1 99	>.99
IP chemotherapy (n=634) No Yes	350 284	55 45	225 204	52 48	125 80	61 39	.05

BMI, body mass index; ASA, American Society of Anesthesiologists; unk, unknown; UAB, upper abdominal; G; grade; CGR, complete gross resection; IP, intraperitoneal

Table 2.

Progression-free and overall survival

	Progression-free survival			Overall survival		
	Median PFS	95% CI	P	Median OS	95% CI	P
Entire cohort	18.3 months	17.0–20.5	--	57.3 months	52.1–63.1	--
Epidural	20.8 months	18.7–22.9	.021*	62.4 months	57.5–77.8	<.001*
Non-epidural	13.9 months	12.9–15.0		41.9 months	37.5–51.7	

PFS, progression-free survival; OS, overall survival; CI, confidence interval

* P value after controlling for surgeon clustering effect

Table 3.

Univariate analysis of factors associated with progression-free and overall survival

Variables	Progression-free survival			Overall survival		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.01	1.00–1.02	.016	1.02	1.01–1.03	.001
BMI, kg/m ²	1.00	0.99–1.01	.98	1.00	0.98–1.01	.62
ASA score 1–2 3–4	Reference 0.98	-- 0.83–1.16	.82	Reference 1.08	-- 0.89–1.32	.42
BRCA status Negative Positive Unknown	Reference 0.79 1.32	-- 0.6–1.04 1.1–1.58	<.001	Reference 1.00 1.84	-- 0.72–1.4 1.48–2.29	<.001
Stage IIIB–C IV	Reference 1.43	-- 1.18–1.74	<.001	Reference 1.42	-- 1.13–1.78	.003
Residual disease CGR Optimal (1–10 mm) Suboptimal (> 10 mm)	Reference 1.91 3.00	-- 1.57–2.31 2.4–3.76	<.001	Reference 1.77 2.81	-- 1.4–2.24 2.18–3.63	<.001
Carcinomatosis No Yes	Reference 1.38	-- 1.08–1.76	.009	Reference 1.37	-- 1.02–1.84	.034
Bulky UAB disease No Yes	Reference 1.82	-- 1.52–2.19	<.001	Reference 1.73	-- 1.39–2.14	<.001
Epidural use Yes No	Reference 1.33	-- 1.11–1.59	.021 *	Reference 1.67	-- 1.36–2.04	<.001 *
Epidural use Intraoperative start Postoperative start No epidural	Reference 1.14 1.34	-- 0.83–1.57 1.12–1.61	<.001 *	Reference 1.31 1.72	-- 0.91–1.89 1.4–2.12	<.001 *
Operative time, min	1.00	1.00–1.00	.35	1.00	1.00–1.00	.76
IP chemotherapy No Yes	Reference 0.50	-- 0.42–0.60	<.001	Reference 0.39	-- 0.32–0.48	<.001

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; CGR, complete gross resection; UAB, upper abdominal; IP, intraperitoneal;

* P value after controlling for surgeon clustering effect

Table 4.

Multivariable Cox proportional hazards analysis of factors associated with progression-free and overall survival (after controlling for surgeon clustering effect)

Variables	Progression-free survival			Overall survival		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.00	0.99–1.01	.12	1.01	1.00–1.02	.027
Stage IIIB-C IV	Reference 1.13	-- 0.90–1.41	.30	Reference 1.10	-- 0.83–1.46	.50
Carcinomatosis No Yes	Reference 0.94	-- 0.72–1.23	.65	Reference 1.00	-- 0.71–1.38	.99
Bulky UAB disease No Yes	Reference 1.51	-- 1.23–1.86	<.001	Reference 1.46	-- 1.12–1.90	.005
Residual disease CGR Optimal (1–10 mm) Suboptimal (> 10 mm)	Reference 1.71 1.99	-- 1.45–2.01 1.63–2.44	<.001	Reference 1.52 1.52	-- 1.25–1.84 1.25–1.85	<.001
Epidural use Yes No	Reference 1.33	-- 1.07–1.65	.012	Reference 1.59	-- 1.22–2.06	<.001
IP chemotherapy* No Yes	Reference 0.63	-- 0.55–0.72	<.001	Reference 0.48	-- 0.40–0.57	<.001

HR, hazard ratio; CI, confidence interval; CGR, complete gross resection; UAB, upper abdominal; IP, intraperitoneal;

* Analysis performed using time dependent coding