Archives of Anesthesiology and Critical Care (Spring 2023); 9(2): 107-115.

Available online at http://aacc.tums.ac.ir

Research Article

Association of Perioperative Use of Epidural Analgesia with Disease Free Survival in Epithelial Ovarian Cancer: A Retrospective Cohort Observational Study with Propensity Score Matched Analysis

Kalpana Balakrishnan[1], Punitha Chockalingam[1], Thendral Ramasamy[1], Meenakshi Venkateswaran[1], Madhupriya Sundaram[2], Veluswami Sridevi[2]*

[1]*Department of Anesthesiology Cancer Institute (WIA), Adyar Chennai, India.*

[2]*Department of Surgical Oncology Cancer Institute (WIA), Adyar Chennai, India.*

ARTICLE INFO

Article history:
Received 12 May 2022
Revised 02 Jun 2022
Accepted 16 Jun 2022

Keywords:
Disease free survival;
Epidural analgesia;
Epithelial ovarian cancer;
General anesthesia;
Survival analysis

ABSTRACT

Background: Recurrence is common after surgery for epithelial ovarian cancer and is multifactorial. Perioperative factors affecting stress and inflammation have an influence on immunity and thus cancer recurrence. The effect of peri-operative epidural anesthesia has been quoted to be beneficial by decreasing stress. A retrospective analysis of perioperative Epidural analgesia use (EA) was compared to general anesthesia (GA) without epidural, with disease free survival (DFS)as the outcome.

Methods: We did a retrospective observational study of patients with epithelial ovarian malignancy who had undergone surgery between 2013 and 2017. Cohorts were primarily divided based on receipt of epidural analgesia. Perioperative patient, anesthetic, and tumor related data were collected. The aim was to estimate the association of epidural analgesia with disease free survival (DFS). To prevent bias due to skewed covariate distribution propensity score match was done matching all covariates.

Results: We had 312 patients with age ranging from 18 to 77. The median DFS in months was 32.73±25.6 for the entire cohort while it was 54.81±28.69 for the GA group and 27.23±21.84 for EA group. After PSM median DFS was 35.33 for the full cohort and it was 46 and 34 months for the GA and EA groups, respectively. Multivariate Cox regression analysis demonstrated that only patients who were undergoing primary surgery had survival advantage (P<0.013). Perioperative epidural analgesia was not associated with survival benefit (P=0.480).

Conclusion: Perioperative use of epidural analgesia did not offer survival benefit in epithelial ovarian cancer as measured by disease free survival.

Cancer is the second most common cause of death across the world and metastasis from cancer causes 90% of these deaths [1]. Metastasis can be multifactorial and occurs when cancer cells are able to evade the immune system due to perioperative immune suppression and continue to proliferate [2-3]. Normally cell mediated immunity recognizes foreign tumor cells and prevents metastasis. However the perioperative period is tumorigenic with various factors like the stress and inflammation associated with surgery and perioperative medications and transfusions producing a state of relative immunosuppression [4]. The immunosuppression is due to stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and

The authors declare no conflicts of interest.
*Corresponding author.
E-mail address: kalpana.balakrishnan@gmail.com

sympathetic nervous system [5] with secretion of cytokines and catecholamines. Perioperative factors modulating stress and inflammation can in effect be associated with recurrence and multiple anesthetic agents [6] such as intravenous induction agents like propofol, volatile anesthetics [7] analgesics both opioids and non-steroidal anti-inflammatory drugs [8] have been implicated on this premise. Perioperative epidural use has emerged as an important factor in solid tumor malignancies, it acts by decreasing the surgical stress response, leading to decreased pro-tumorigenic cytokine release [9].

Ovarian cancer is a highly fatal malignant neoplasm with few modifiable risk factors, Epidural was not routinely used at our institute for ovarian cytoreductive surgery however we have started using it much more frequently after reports of its benefit in both early post-operative outcomes and in recurrence rates. To gain clarity on association of peri-operative epidural use with cancer recurrence we decided to retrospectively analyze data from our cohort of epithelial ovarian cancers (EOC). We also decided to account for all peri anesthetic factors affecting recurrence. Our hypothesis was that epidural by decreasing the stress response to surgery will be beneficial and will improve survival. Our aim was to look for the association between use of peri-operative epidural analgesia and disease-free survival (DFS).

Methods

A retrospective observational study of patients with EOC who underwent surgery between 2013 and 2017 in a tertiary referral cancer hospital in India. Ethical committee approval was obtained before the commencement of data collection. As the study was observational and patients had surgery much before commencement of study, informed consent was not obtained. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for the cohort study.

Patients: Data were collected for patients from tumor registry by scrutinizing the files and electronic medical records, Raw data were cleaned before analysis. Clearly erroneous values were backchecked with the original data and corrected. Missing data that could not be corrected were coded as a dummy missing variable and were removed from the analysis.

Inclusion criteria were age>18years, ASA 1, 2 or 3, histology of epithelial ovarian tumors and patients who had elective optimal cytoreduction. Other histology, patients≤18 and emergency surgery were excluded from the study. Patients who received hyperthermic intra peritoneal chemotherapy (HIPEC) after cytoreduction were excluded from the study. Patients who met the inclusion criteria were divided into those that had received Epidural with General anesthesia (EA) and others who had received only General anesthesia (GA).

Data collected included demography, histological staging, co-morbidity, preoperative chemotherapy, type of anesthesia if only general or if epidural was also placed, type of inhalation agent used, non-steroidal anti-inflammatory drugs (NSAID) if used, blood transfusion if given, type of surgery (primary staging or optimal interval cytoreduction (OIC)), duration of surgery and date of recurrence.

All our patients had received general anesthesia (GA), induction had been with intravenous (IV) propofol and maintenance with nitrous oxide and an inhalation agent either sevoflurane, isoflurane or desflurane, with analgesia achieved with IV opioids (fentanyl). Post-operative pain management had been with IV paracetamol and tramadol. Some of the patients had received supplemental epidural analgesia perioperatively at the discretion of the anesthesiologists, while some had also received non-steroidal anti-inflammatory drugs (NSAIDs). Epidurals had been at lower thoracic levels and all patients in EA had received epidural local anesthetic bupivacaine 0.1 to 0.125% with morphine intra and post -operatively for 72 hrs. adjusted to pain score of <4/10 on the numerical rating scale. All patients had been warmed by forced air patient warming system intraoperatively to maintain normothermia. Blood had been transfused as needed, based on the departmental transfusion trigger.

Patients had been taken up for either primary debulking surgery or interval cytoreduction after chemotherapy. Patients had been treated with pre and postoperative platinum and taxane based chemotherapy. Those without evidence of disease at the completion of treatment protocol had been followed every 3 months for the first 3 years, every 6 months for the following 2 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. Documentation of recurrence in medical record based on an increase in CA-125 or presence of a new lesion radiologically was noted as the date of recurrence. Disease free survival (DFS) was computed as the time between date of surgery and anesthesia (considered as the intervention) and the date of occurrence. For those without either event of cancer recurrence or death, their DFS was regarded as the corresponding censored observations with the last visit date used as the censored date.

The data were analyzed using SPSS statistics for windows Version 25.0 Armonk, NY: IBM Corp. Descriptive statistics was used for demographic variables and is presented as numbers and percentage for categorical variables and median and range for continuous variables for the full cohort and after dividing into EA and GA groups. Patient specific, disease specific and anesthetic variables were included in the survival analysis. Survival analysis was done using Kaplan-Meier estimator with differences between groups assessed with log rank test. and p value less than 0.05 was considered significant. Cox regression both univariate and adjusted

were done to elicit significant factors associated with DFS.

As the demographic characteristics were significantly different between the EA and GA groups Propensity score-matching (PSM) was used to match the groups and simulate a randomized controlled trial. Matched pairs were formed by using nearest neighbor matching thus minimizing the difference between the propensity scores of the paired patients The groups were matched for age, co-morbidity, tumor staging, type of surgery, use of NSAIDS, blood transfusion and duration of surgery. Kaplan Meier curve with log rank was computed for GA and EA groups after PSM. Univariate cox regression was done after PSM and variables which were significant with P<0.05 were included in the multivariate regression to elicit independent prognostic factor after adjusting for co-variates.

Results

We had a total of 374 patients who underwent surgery for ovarian cancer between 2013 to 2017, 48 did not meet the inclusion criteria, data were missing in 33 and 14 were lost to follow up thus we analyzed 312 patients (Figure1). Over 46% of the patients had some co-morbidity, only 36.5% had primary surgery,72.3% of patients had stage 3 to 4 disease (Table1).

We had placed an epidural in 62.9% patients while others received only general anesthesia with opioid analgesia, of the inhalation agents used most had received sevoflurane (n=194; 62.17 %) Surgery had lasted a mean of 245 minutes and 102 (32.69%) had received blood transfusion while 72 (23.07%) had received NSAIDS. The median DFS in months was 32.73±25.6 for the entire cohort while it was 54.81±28.69 for the GA group and 27.23±21.84 for EA group. After propensity matching cohorts (75 in each) were well matched for all the covariates.

The Kaplan Meier curves with log rank for the entire cohort for different covariates like age, co-morbidities, tumor staging, type of surgery, anesthesia, transfusion, NSAID use, and duration of surgery are in (Figure 2).

All covariates were found to be significantly associated with DFS. GA was associated with significantly better median DFS compared to EA with P =0.035. before PSM. However multivariate regression showed that only age (P=0.004, HR 1.025 (95% CI =1.008-1.042)) and type of surgery {(p=0.004), HR = 2.942, 95%CI 1.757-4.927)} were significantly associated with DFS (Table2).

After PSM age (P=0.042), Tumor staging (P<0.001) and type of surgery(P<0.001) were statistically significant in univariate regression (Table3). Multivariate regression showed only primary surgery was associated with improved survival, {P=0.013 (HR=2.406,95% CI1.205-4.801)}. Kaplan Meier curve for type of anesthesia after PSM had log rank of P=0.480 (Figure 3) Median DFS after PSM was 46 months for the GA group and 34 months for the EA group.

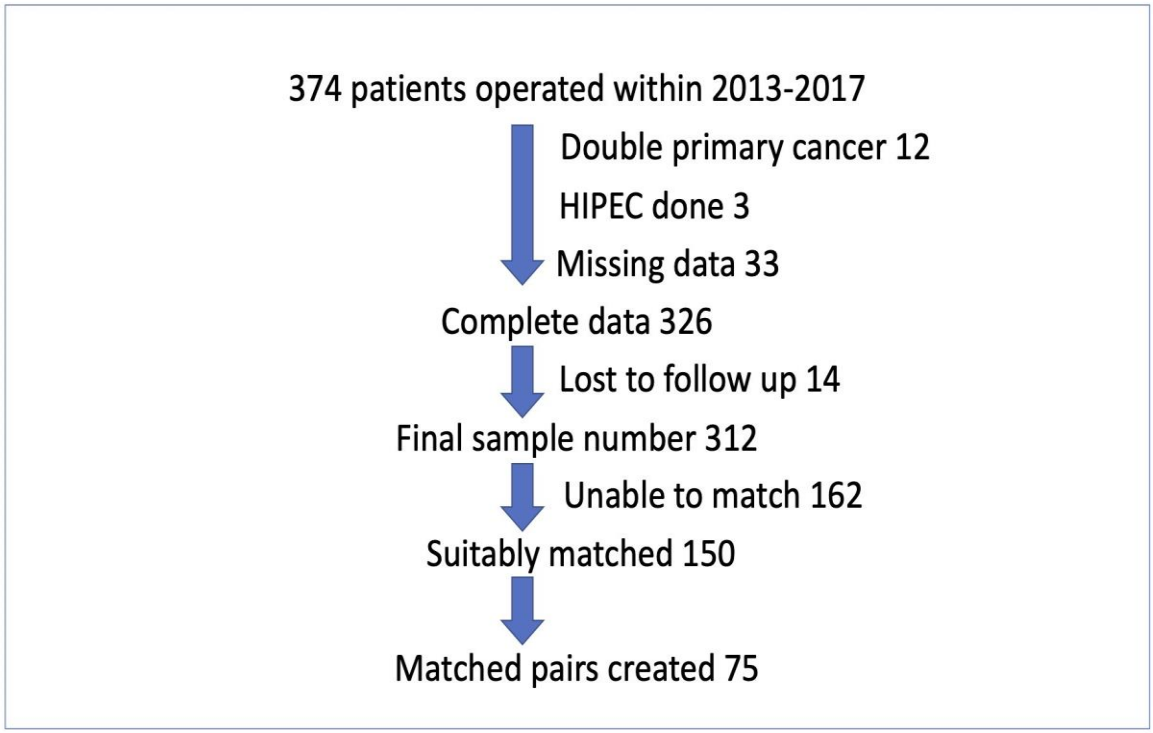

Figure 1- Cohort diagram of the study patients

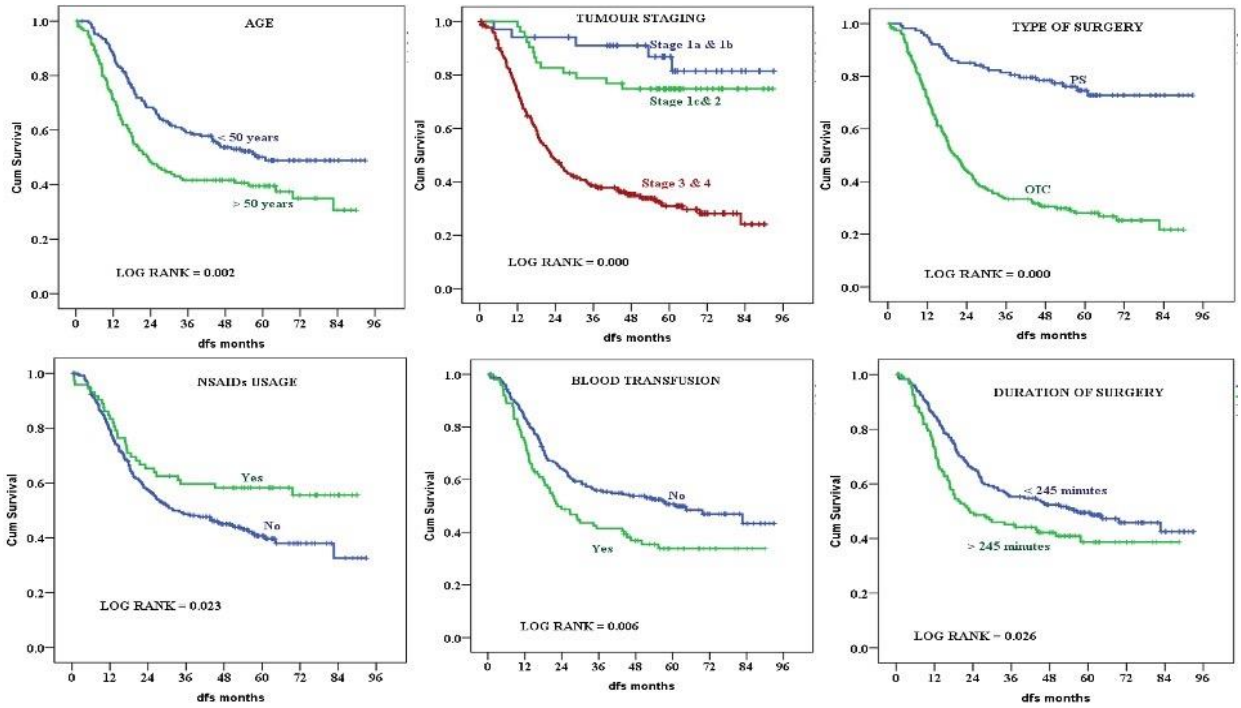

Figure 2- Kaplan Meier curves with log rank for age, Tumor staging, Type of surgery, NSAID usage, Transfusion and Duration of surgery

Table 1- Patient, Anaesthetic and surgical details for the full cohort and after dividing into EA and GA groups before and after PSM

	Total n=312	**GA n=116(37.1 %)**	**GA+ EA n=196(62.9%)**	**Chi - square (χ^2)**	**After PSM n=150**	**GA n=75**	**GA+ EA n=75**	**Chi - square (χ^2)**
Age (yrs) -median	49±10.82	48	49	0.784	48.5±13	48	49	0.567
< 50yrs	169 (54.2%)	64(55.2%)	105(53.6%)		84(56%)	42	42	
≥ 50yrs	143(45.8%)	52(44.8%)	91(46.4%)		66(44%)	33	33	
Comorbidity				0.087				0.627
Yes	146(46.8%)	47(40.5%)	99(50.5%)		69(46%)	33	36	
No	166(53.2%)	69(59.5%)	97(49.5%)		81(54%)	42	39	
Tumor Staging	(n=311)			0.011				0.963
Stage 1	34(10.9%)	15(12.9%)	19(9.7%)		15(10%)	8(10.7%)	7(9.3%)	
Stage 2	52(16.7%)	28(24.1%)	24(12.3%)		28(18.7%)	14(18.7%)	14(18.7%)	
Stage 3	225(72.3%)	73(62.9%)	152(77.9%)		107(71.3%)	53(70.7%)	54(72%)	
Type of surgery	(n=312)							
Primary staging	114(36.5%)	50(43.5%)	64(32.7%)	0.056	75(50%)	27(36%)	29(38.7%)	0.736
OIC*	198(63.5%)	66(56.9%)	132(67.3%)		75(50%)	48(64%)	46(61.3%)	
Agents				0.000				
Desflurane	73(23.4%)	15(12.9%)	58(29.6%)		22(14.7%)	8	14	
Isoflurane	45(14.4%)	35(30.2%)	10(5.1%)		33(22%)	26	7	
Sevoflurane	194(62.2%)	66(56.9%)	128(65.3%)		95(63.3%)	41	54	
Intra-op use of NSAIDs†				0.000				0.570
Yes	72(23.1%)	51(44%)	21(10.7%)		37(24.7%)	17	20	
No	240(76.9%)	65(56%)	175(89.3%)		113(75.3%)	58	55	
Intra-op transfusion				0.001				0.352
Yes	102(32.7%)	25(21.6%)	77(39.3%)		39(26%)	17	22	

No	210(67.3%)	91(78.4%)	119(60.7%)		111(74%)	58	53	
Mean (n=308)				0.000				0.550
duration of surgery (mins)	245±114.05	191.28	277.06		195	180	205	
< 245 mins	182(58.3%)	96(82.8%)	86(43.9%)		111(74)	57(76)	54(72)	
≥ 245 mins	126(40.4%)	19(16.4%)	107(54.6%)		39(26)	18(24)	21(28)	
DFS‡ Median (months)	32.73±25.6	54.81±28.69	27.23±21.84		35.33	46	34	

* = Optimal interval cytoreduction †= Non steroidal anti-inflammatory drugs. ‡= Disease free survival

Table 2- Univariate & Multivariate Cox Regression analysis before PSM N=326

Variables	**Unadjusted Values**				**Adjusted Values**			
	B	**Sig**	**Exp(B)**	**95% CI**	**B**	**Sig**	**Exp(B)**	**95% CI**
Age	0.026	0.000	1.026	1.012-1.040	0.024	0.004	1.025	1.008-1.042
Tumor Staging								
1	Reference							
2	0.567	0.282	1.762	0.628-4.944	0.507	0.382	1.660	0.533-5.170
3	1.995	0.000	7.355	3.012-17.962	1.049	0.065	2.854	0.937-8.692
Type of surgery								
Primary staging	Reference							
OIC	1.514	0.000	4.546	3.022-6.838	1.079	0.000	2.942	1.757-4.927
Anaesthesia								
GA	Reference							
GA+EA	0.347	0.035	1.415	1.025-1.953	0.77	0.683	1.080	0.747-1.561
NSAIDs								
Not received	Reference							
Received	-0.450	0.025	0.638	0.431-0.944	0.263	0.229	0.769	0.501-1.180
Transfusion								
No	Reference							
Yes	0.432	0.007	1.541	1.127-2.106	0.170	0.338	1.185	0.837-1.667
Duration of surgery	0.002	0.002	1.002	1.001-1.003	0.001	0.069	1.001	1.000-1.003
Comorbidity								
No	Reference							
Yes	0.289	0.063	1.335	0.985-1.809				
Agents								
Desflurane	Reference							
Isoflurane	0.152	0.562	1.165	0.695-1.951				
Sevoflurane	0.269	0.176	1.309	0.886-1.934				

Table 3- Univariate & Multivariate Cox Regression analysis. (After PSM) N= 150

	DFS							
Variables	**Unadjusted Values**				**Adjusted Values**			
	B	**Sig**	**Exp(B)**	**95% CI**	**B**	**Sig**	**Exp(B)**	**95% CI**
Age	0.020	0.042	1.020	1.001-1.040	-0.009	0.445	0.991	0.967-1.015
Tumor Staging								
1	Reference							
2	0.451	0.505	1.570	0.416-5.920	0.323	0.638	1.381	0.359-5.311
3	1.799	0.002	6.042	1.902-19.20	1.186	0.087	3.273	0.843-12.710
Type of surgery								
Primary staging	Reference							
OIC	1.400	0.000	4.055	2.353-6.987	0.878	0.013	2.406	1.205-4.801
Anesthesia								
GA	Reference							
GA+EA	0.152	0.481	1.164	0.764-1.773				
NSAIDs								
Not received	Reference							
Received	-2.83	0.285	0.753	0.448-1.266				

Transfusion				
No	Reference			
Yes	0.075	0.814	1.059	0.658-1.704
Duration of surgery				
<245 mins	Reference			
≥ 245 mins	0.001	0.417	1.001	0.999-1.003
Comorbidity				
No	Reference			
Yes	0.080	0.708	1.084	0.713-1.647

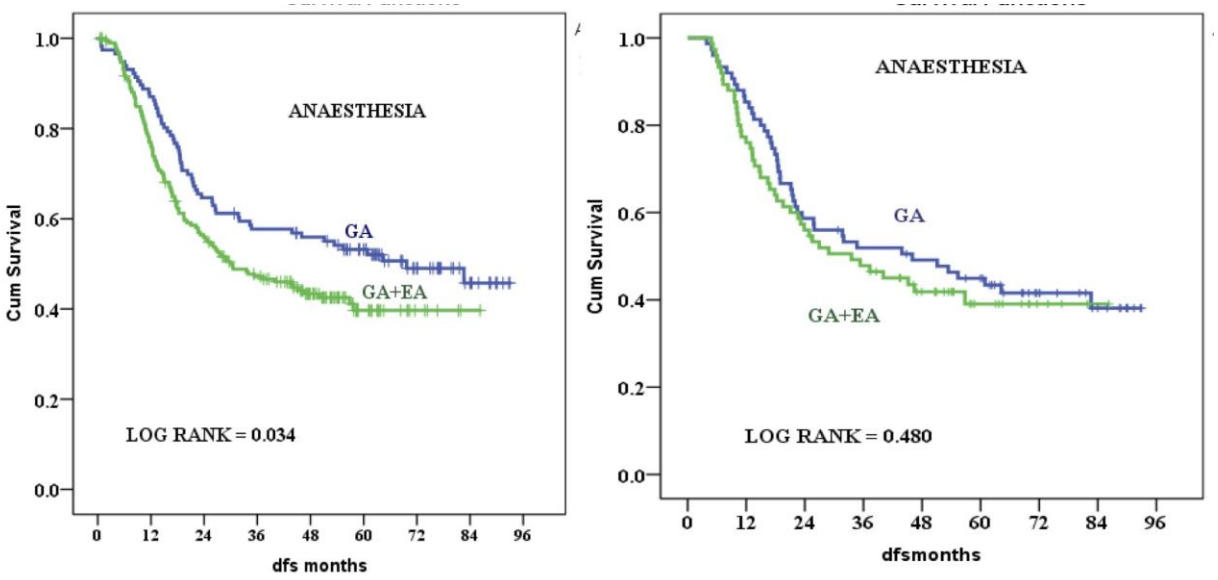

Figure 3- Kaplan Meier curves for Anesthesia (EA and GA groups) before and after PSM

Discussion

Our retrospective analysis of perioperative epidural analgesia in epithelial ovarian cancer showed that EA did not confer survival advantage compared with GA without epidural both before and after PSM. Patients who were younger, underwent primary surgery, had received only GA with NSAIDS and had not received blood transfusion and when surgery lasted <245 minutes had better DFS before PSM.

We tried to account for other peri-anesthetic factors that could affect recurrence rates Nonsteroidal anti-inflammatory (NSAIDS) drugs seem to give some protection against metastasis when used during cancer surgery and improves survival [10]. In our cohort, out of the 72 patients who received NSAIDS, 41(56.9%) did not have recurrence and 33 of these were in the GA group. As EA was being used for perioperative analgesia only a small percentage of patients (29%) in EA group received NSAIDs. Merritt and co-workers in their cohort study found that those taking NSAIDS had improved ovarian cancer specific survival [11].

Perioperative blood transfusion has been propounded as a cause for metastasis, a recent Cochrane review including 12,127 patients confirmed the association of blood transfusion with recurrence [12] yielding an OR of 1.42 (95% CI, 1.20 to 1.67) against transfusion. In our cohort of the 102 who received transfusion, 77(75.4%%) were in the EA group. We also found transfusion to be associated with poor DFS (p<0.022).

To account for these baseline differences, we did PSM and matched all covariates and found that EA did not offer any statistically significant survival advantage. Epidural analgesia by decreasing the stress response [13] to surgery is considered to have beneficial effects on recurrence however multiple studies and metanalysis [14] have been conflicting regarding the efficacy of regional anesthesia use for cancer recurrence. In ovarian cancer, Lin and co- workers found epidural combined with GA to have a survival advantage in their retrospective analysis with hazard ratio of 1.214 in the GA group [15]. In another study intraoperative use of epidural analgesia was associated with an increased time to tumor recurrence after surgery compared to only postoperative use [16]. In a recent study by Tseng and co-workers median overall survival 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) [17] however in our cohort the GA group had clinical survival advantage with the median survival for GA group being 46 months and for EA 34 months .They had selected only primary debulking surgery while our cohort had both primary debulking and interval cytoreduction and the outcome was not statistically significant.

There are studies which found no benefit with epidural in overall survival [18] and others that found no benefit both in overall survival and time to recurrence in advanced ovarian malignancy with the median survival time of 3.3 and 2.7 years for the EA and no EA groups, respectively (P = 0.37) [19] mimicking our study, A few recent meta-analysis on this subject concluded that regional anesthesia was not associated with improved survival [20-21]. A Cochrane review has opined those studies on regional anesthesia benefitting recurrence had serious inconsistency and risk of bias and that evidence for the benefit was inconsistent.

Most studies on recurrence with regional analgesia have been retrospective or observational, the first prospective study on breast cancer surgeries failed to show any benefit with regional analgesia and was stopped after a futility boundary that was a part of the methods was crossed [22]. A recent randomized controlled study in lung cancer surgery [23] and the long term follow up of a randomized controlled study in colorectal cancer also concluded that epidural analgesia did not improve cancer-specific long-term mortality [24]. In our cohort while the effect of anesthesia on DFS was not statistically significant after PSM, the life table seemed to indicate some clinical benefit for GA group between 40 to 60 months as seen from the KM curves, further robust data are needed to declare any advantage.

Even after PSM, the unadjusted regression showed older age and type of surgery (interval cytoreduction) and higher stage of disease to be associated with early recurrence. May and co-workers [25] have found that primary surgery gives better survival advantage mimicking our results. Older age and higher FIGO stage have been associated with early recurrence in multiple studies, including the recent Nigerian analysis [26-27]. In our cohort, multivariate regression after PSM showed only primary surgery to be associated with survival advantage {P=0.013). Studies from Egypt on Stage 3 EOC (p = 0.017, HR 1.5; 95% CI 1.10 - 1.70) [28] and from India too found that primary surgery is associated with better survival (59 months versus 38 months, p = 0.001) [29].

As elegantly put in a recent editorial [30], use of regional analgesia should be for stress-response reduction, opioid-sparing, and postoperative analgesia rather than for improved outcomes after cancer surgery - at least till more data are available.

One of the strengths of the present report is that all patients had epithelial ovarian cancers and multiple malignancies were not compared, but epithelial ovarian cancer is not a single diseasebut a diverse group of tumors with distinctive morphologic and molecular genetic features which may confound the results. We have tried to account for all likely confounders with respect to peri-anesthetic care and matched them with PSM thus making the results more robust.

The limitations of the study are, as commonly found in single-center retrospective observational studies, selection bias may exist along with a possible lack of generalizability of the results even after PSM. Being retrospective, the indication for EA was influenced by anesthesiologists' preference, baseline characteristics, and practice pattern at that time. Our patient cohort had diverse surgeries both primary debulking and interval cytoreduction and comparing outcomes in similar surgeries may have yielded different results. Including patients after neoadjuvant chemotherapy may have changed their immune status thus making the effect of epidural analgesia difficult to discern. While all patients received epidural bupivacaine with morphine, in the GA group some had received IV tramadol and a few even IV morphine we did not have full details of opioid consumption amongst our patients and this could have skewed our analysis. Results of ongoing prospective trials and further randomized control trials on use of epidural along with GA in primary surgeries are needed to have more clarity on the practice of routine use of epidural anesthesia as one of the strategies in oncological anesthesia with the intent of improving survival.

Conclusion

In this retrospective propensity matched cohort study on epithelial ovarian cancer, we report that cancer recurrence as measured by disease free survival was not positively influenced by epidural analgesia when used as an adjunct to general anesthesia.

Acknowledgements

Arya .C Soman, Biostatistician Clinical Trials research unit at Cancer Institute (WIA) helped with statistical analysis.

References

[1] Mehlen P, Puisieux A. Metastasis: a question of life or death. Nat Rev Cancer. 2006; 6(6):449-58.

[2] Divatia JV, Ambulkar R. Anesthesia and cancer recurrence: What is the evidence? J Anaesthesiol Clin Pharmacol. 2014; 30(2):147-50.

[3] Jain P, Balkrishanan K, Nayak S, Gupta N, Shah S. Onco-Anaesthesiology and palliative medicine: Opportunities and challenges. Indian J Anaesth. 2021; 65(1):29-34.

[4] Anesthesia and cancer recurrence - UpToDate [Internet]. Available from: https://www.uptodate.com/contents/anesthesia-and-cancer-recurrence
[5] Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med. 2018;16(1):8.
[6] Das J, Kumar S, Khanna S, Mehta Y. Are we causing the recurrence-impact of perioperative period on long-term cancer prognosis: Review of current evidence and practice. J Anaesthesiol Clin Pharmacol. 2014; 30(2):153-9.
[7] Elias KM, Kang S, Liu X, Horowitz NS, Berkowitz RS, Frendl G. Anesthetic Selection and Disease-Free Survival Following Optimal Primary Cytoreductive Surgery for Stage III Epithelial Ovarian Cancer. Ann Surg Oncol. 2015; 22(4):1341-8.
[8] Kuo CN, Pan JJ, Huang YW, Tsai HJ, Chang WC. Association between nonsteroidal anti-inflammatory drugs and colorectal cancer: A population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2018; 27(7):737-745.
[9] Smyth MJ, Godfrey DI, Trapani JA. A fresh look at tumor immunosurveillance and immunotherapy. Nat Immunol. 2001; 2(4):293-9.
[10] Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth. 2014; 113 Suppl:i82-7.
[11] Merritt MA, Rice MS, Barnard ME, Hankinson SE, Matulonis UA, Poole EM, et al. Pre-diagnosis and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a cohort study. Lancet Oncol. 2018; 19(8):1107–16.
[12] Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev. 2006; 2006(1):CD005033.
[13] Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. Oncotarget. 2016; 7(12):15262–73.
[14] Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, 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(12):e114667.
[15] Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth. 2011; 106(6):814–22.
[16] de Oliveira GSJ, Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. 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):271–7.
[17] Tseng JH, Cowan RA, Afonso AM, Zhou Q, Iasonos A, Ali N, et al. Perioperative epidural use and survival outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer. Gynecol Oncol. 2018; 151(2):287–93.
[18] Capmas P, Billard V, Gouy S, Lhommé C, Pautier P, Morice P, et al. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. Anticancer Res. 2012; 32(4):1537–42.
[19] Lacassie HJ, Cartagena J, Brañes J, Assel M, Echevarría GC. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the Chilean population. Anesth Analg. 2013; 117(3):653–60.
[20] Grandhi RK, Lee S, Abd-Elsayed A. The Relationship Between Regional Anesthesia and Cancer: A Metaanalysis. Ochsner J. 2017;17(4):345–61.
[21] Lee ZX, Ng KT, Ang E, Wang CY, Binti Shariffuddin II. Effect of perioperative regional anesthesia on cancer recurrence: A meta-analysis of randomized controlled trials. Int J Surg. 2020; 82:192-199.
[22] Sessler DI, Ben-Eliyahu S, Mascha EJ, Parat M-O, Buggy DJ. Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp Clin Trials. 2008; 29(4):517–26.
[23] Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anesthesia–Analgesia and Recurrence-free Survival after Lung Cancer Surgery: A Randomized Trial. Anesthesiology. 2021; 135(3):419-432.
[24] Du Y-T, Li Y-W, Zhao B-J, Guo X-Y, Feng Y, Zuo M-Z, et al. Long-term Survival after Combined Epidural–General Anesthesia or General Anesthesia Alone: Follow-up of a Randomized Trial. Anesthesiology. 2021; 135(2):233-245.
[25] May T, Comeau R, Sun P, Kotsopoulos J, Narod SA, Rosen B, et al. A Comparison of Survival Outcomes in Advanced Serous Ovarian Cancer Patients Treated with Primary Debulking Surgery Versus Neoadjuvant Chemotherapy. Int J Gynecol Cancer. 2017; 27(4):668-674.
[26] Ditto A, Leone Roberti Maggiore U, Bogani G, Martinelli F, Chiappa V, Evangelista MT, et al. Predictive factors of recurrence in patients with early-stage epithelial ovarian cancer. Int J Gynaecol Obstet. 2019; 145(1):28–33.
[27] Okunade KS, Adejimi AA, Ohazurike EO, Salako O, Osunwusi B, Adenekan MA, et al. Predictors of Survival Outcomes After Primary Treatment of Epithelial Ovarian Cancer in Lagos, Nigeria. JCO Glob Oncol. 2021; 7:89–98.

[28] Amin AT, Ahmed BM, Refaat A, Sileem SA, Khallaf SM, Amin AT, et al. Primary Debulking Surgery for Stage III Epithelial Ovarian Cancer Has a Better Outcome Than Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery. J Cancer Therapy. 2020;11(3):142–53.

[29] Georgeena P, Rajanbabu A, Vijaykumar DK, Pavithran K, Sundaram KR, Deepak KS, et al. Surgical treatment pattern and outcomes in epithelial ovarian cancer patients from a cancer institute in Kerala, India. Ecancermedicalscience. 2016; 10:619.

[30] Buggy DJ, Riedel B, Sessler DI. Can anaesthetic technique influence cancer outcome? The next steps…. Br J Anaesth. 2021; 127(1):5-7.