Outcome at second-look laparotomy: Anaesthesia related risk factors

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Summary

Purpose of investigation: To identify anaesthesia related risk factors associated with positive second-look laparotomy (SLL) findings in patients with epithelial ovarian carcinoma who had previous optimal cytoreduction surgery under general anaesthesia.

Methods: A retrospective review of the anaesthesia and medical records of patients with epithelial ovarian cancer who underwent SLL at our institution and analysis of patient related (age, haemoglobin, albumin), anaesthesia related (duration of anaesthesia, anaesthetics and dosages, transfusion of blood products), tumour related (stage, grade, presence of ascites, adhesion, histological type, capsule penetration and CA-125) data and outcome of SLL was undertaken.

Results: The patients had SLL 305 ± 215 days after the first operation. Of the 83 patients 28 (33.7%) were SLL (+). SLL (+) patients were significantly more likely to have a mucinous histological subtype, required intraoperative packed red blood cell (PRBC) transfusion and longer anaesthesia duration ($p < 0.05$). Type of induction agent, whether narcotics were used or not, type of volatile agent used, dosages of induction agents and dosages of narcotic and muscle relaxants did not vary significantly between the patients with and without cancer recurrence ($p > 0.05$). Duration of anaesthesia (OR, 1.03; CI, 1-1.05, $p = 0.031$) and histological subtype (OR, 16.1; CI, 1.8-141.7, $p = 0.012$), were the independent variables predicting cancer recurrence in the multivariate logistic regression.

Conclusion: We emphasize that duration of anaesthesia and histological subtype are risk factors for cancer recurrence in early stage ovarian carcinoma. From our data it seems that interventions to shorten the duration of general anaesthesia or reversing immunosuppression induced by anaesthesia and surgery must be carefully considered.

Key words: Anaesthesia; Ovarian carcinoma; Recurrence; Immune Function; Multivariate analysis.

Introduction

Anaesthesia itself or perioperative interventions by the anaesthesiologist such as blood transfusion may substantially alter immune function with a potential impact on the postoperative course in cancer patients. However, previous studies have not included anaesthesia as a risk factor for cancer recurrence although extensive data have shown the immunosuppressive effects of anaesthetics [1]. Anaesthetics may either modulate the host defense indirectly by affecting afferent neuronal input from the operative site, thus affecting the neurohumoral response to injury, or directly act on immunocompetent cells [2, 3]. Animal data indicates that certain anaesthetic agents may enhance tumour metastasis [4].

The purpose of the study was to identify anaesthesia related risk factors (anaesthetics and transfusion of blood products) associated with positive second-look laparotomy (SLL) findings in patients who had had previous surgery for ovarian carcinoma.

Materials and Methods

After institutional approval, we retrospectively reviewed the medical records of patients who had epithelial ovarian carcinoma and second-look laparotomy (SLL) by the same surgeon in our institution since 1990. During this period, our routine anaesthesia practice was anaesthesia induction with an intravenous anaesthetic (thiopental, propofol, etomidate), opioids (fentanyl) and a muscle relaxant (succinylcholine, vecuronium, atracurium, rocuronium), anaesthesia maintenance with volatile agents (halothane, isoflurane, sevoflurane) supplemented with opioids.

Management of early ovarian cancer patients in our institution during this period was as follows: The same surgeon did accurate and comprehensive surgical staging with a vertical incision sufficient to explore the entire abdomen and pelvis. The ovarian tumour was removed intact, along with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial infracolic omentectomy. Pelvic, iliac, and paraaortic lymph nodes were sampled. Selected peritoneal and diaphragmatic biopsies were performed. Any ascitic fluid was removed, or if none was present, washing was done for cytology. Patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IA or Stage IB and well-differentiated histology did not receive any adjuvant therapy. In contrast, patients with poor prognostic features including Stage IC and II disease, poorly differentiated histology, massive ascites, clear-cell histology, and dense adhesions received platinum-based combination chemotherapy [5]. The same surgeon also performed the second-look laparotomy.

The variables examined include those previously reported risk factors for positive SLL findings in ovarian cancer patients together with anaesthesia related factors: [6-8] patient related (age, preoperative haemoglobin, preoperative haematocrit, preoperative albumin), anaesthesia related (duration of anaesthesia, anaesthetics and dosages, transfusion of blood products), tumour related (FIGO stage, grade, presence of ascites, adhe-

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sion, histological type, capsule penetration and CA-125) [9]. Preoperative and intraoperative data were collected from the anaesthesia forms while postoperative data were collected from the hospital medical records of the patients and from the comprehensive database of the gynaecological oncology department records. All data were verified by one of the investigators both before and after entry into our computerized database.

The end-point of the study was the outcome of SLL (positive versus negative SLL findings). Both the surgical diagnosis and pathological confirmation of recurrence were required to be classified as positive SLL.

Univariate analyses were performed to determine the potential risk factors associated with SLL outcome examined. Differences in proportions were determined by chi-square tests. Parametric results were generally reported by using mean ± SD as the measure of central tendency and analysed by the t-test. Median (range) was used as the measure of central tendency for the nonparametric results and nonparametric data was analysed by the Mann-Whitney U test. Univariate predictor variables with $p < 0.05$ were included in the multivariate analysis. The results were reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). For stepwise backward multiple logistic regression analysis, no transformations of variables were used and the significance level for removal from the model was set as 0.2. All analyses were performed with SPSS 10.0 for windows statistical package.

Results

The patients had SLL 305 ± 215 days after the first operation. Of the 83 patients 28 (33.7%) were SLL (+). Only two patients were Stage IA and did not receive any adjuvant therapy. Both of those patients were SLL (-). All the other patients received platinum-based combination chemotherapy before SLL. We first analysed SLL outcome by a univariate approach to determine which values were associated with positive findings in SLL (Tables 1 and 2).

As can be seen from Tables 1 and 2, SLL (+) patients were significantly more likely to have a mucinous histological subtype, required intraoperative packed red blood cell (PRBC) transfusion and longer anaesthesia duration ($p < 0.05$). Potentially important variables such as age, preoperative haemoglobin, albumin, tumour stage, tumour grade, presence of ascites, capsule penetration, dense adherence, rupture and CA-125 levels did not vary between the patients with and without cancer recurrence.

Because we were particularly interested in the role anaesthetics might play in causing cancer recurrence, we searched for a possible association between anaesthetics and SLL outcome. Anaesthesia was induced with thiopental in 24 (29%) patients, propofol in 55 (66%) patients, and etomidate (20 mg) in four (5%) patients for the primary cancer cytoreduction surgery. The median (minimum-maximum) dose of thiopental, and propofol was 500 (200-500) mg and 200 (180-200) mg, respectively. Fentanyl with a median dose of 100 μg (100-1000) was the narcotic used in 62 (75%) patients during primary cancer cytoreduction surgery. Halothane (0.5-2 MAC) in 17 patients (20.5%), isoflurane (0.5-2 MAC) in 56 patients (67.5%), sevoflurane (0.5-2 MAC) in ten patients (12%) and N_2O (2-4 l/min) in all patients were the volatile agents used during primary cancer cytoreduction surgery. Vecuronium (mean ± SD: 6.7 ± 1 mg) in 70 patients (84.1%), atracurium (65±15 mg) in 11 patients (13.5%), rocuronium (50 mg) in one patient (1.2%) and succinylcholine (550 mg) in one patient (1.2%) were the neuromuscular blocking agents. Type of induction agent, whether narcotics were used or not, type of volatile agent used, dosages of induction agents and dosages of narcotic and muscle relaxants did not vary significantly between the patients with and without cancer recurrence ($p > 0.05$).

Table 1. — *Patient characteristics and outcome of second-look laparotomy (SLL).*

Variables	SLL (–) (n = 55)	SLL (+) (n = 28)	p value
Age (year) (mean ± SD)	47 ± 17	50 ± 14	0.398
FIGO Stage IA	7	1	0.572
FIGO Stage IB	7	6	
FIGO Stage IC	11	4	
FIGO Stage IIA	2	3	
FIGO Stage IIB	7	2	
FIGO Stage IIC	6	2	
Histologic subtype: Serous	22	5	0.015*
Histologic subtype: Mucinous	9	8	
Histologic subtype: Endometrioid		1	
Grade 1 (well-differentiated)	8	1	0.291
Grade 2 (moderately-differentiated)	7	2	
Grade 3 (poorly-differentiated)	10	5	
Grade 4 (undifferentiated)	5	2	
Presence of ascites	32	18	0.498
Dense adherence	20	12	0.396
Capsular penetration	6	4	0.675
Rupture and tumour spillage	0	1	0.273
CA-125 Uml^{-1}	416 ± 226	1627 ± 618	0.235
Preoperative haemoglobin ($g\ dl^{-1}$) (mean ± SD)	11.7 ± 1.5	12.2±1.5	0.179
Preoperative albumin ($g\ dl^{-1}$) (mean ± SD)	3.8 ± 0.6	3.9 ± 0.6	0.910
Intraoperative packed red blood cells transfusion (n)	21	18	0.007*
Intraoperative packed red blood cells transfusion (units)	0 (0-4)	1 (0-4)	0.019*
Intraoperative fresh frozen plasma transfusion (n)	46	24	0.377
Intraoperative fresh frozen plasma transfusion (units)	2 (0-4)	2 (0-4)	0.203
Postoperative haemoglobin ($g\ dl^{-1}$) (mean ± SD)	11 ± 1.7	11.4 ± 1.8	0.363

Mean ± SD, median (range); *p < 0.05; FIGO: International Federation of Gynecology and Obstetrics.

Table 2. — *Anaesthetics used for primary ovarian cancer cytoreduction surgery and SLL outcome.*

	SLL (–) (n = 55)	SLL (+) (n = 28)	p value
Duration of anaesthesia (min)	115 ± 40	134 ± 41	0.040*
Thiopental (n)	15	9	0.515
Propofol (n)	36	19	
Etomidate (n)	2	2	
Narcotics used (n)	41	21	0.593
Halothane (n)	11	6	0.334
Isoflurane (n)	40	16	
Sevoflurane (n)	4	6	

n = number of patients; mean ± SD; min = minute; PRBC = packed red blood cells; FFP = fresh frozen plasma; *p < 0.05.

In multivariate logistic regression we included histological type, duration of anaesthesia and intraoperative PRBC transfusion. Duration of anaesthesia, (OR, 1.03; CI, 1-1.05, p = 0.031) and histological type, (OR, 16.1; CI, 1.8-141.7, p = 0.012) were the independent variables predicting cancer recurrence.

Discussion

In this study duration of anaesthesia and histological subtype were found to be risk factors for cancer recurrence in early stage ovarian carcinoma.

Either the bigger or more complicated tumours necessitating longer anaesthesia or direct immunosupressive effects of the surgery and anesthetics may explain the association between longer duration of anaesthesia and poor SLL outcome. Multiple operations and anaesthesia enhance tumour implantation and growth of metastases in rats [10]. Immune suppression associated with surgical stress results from the combined effects of surgical trauma, endocrine changes, and anaesthetics used during the perioperative period. There has been extensive research about the effects of anaesthesia and surgery on the immune response. Both cellular (natural killer cells, lymphocytes) and humoral (cytokines, antibodies) components of the immune system are affected by the surgery and anaesthesia.

There are clinically important implications of knowing that longer anaesthesia increases cancer recurrence. For example, immunotherapies can be tailored to reverse the type of immunosuppression induced by anaesthesia and surgery. Natural Killer (NK) cells are an important component of the anticancer immune system because of their cytotoxic action against tumour cells and their ability to produce a variety of regulatory cytokines. NK cytotoxicity is inhibited by anaesthesia for at least 11 days postoperatively [11, 12]. NK activity can be restored to presurgery levels by interferon-α. Perioperative administration of interferon-a has been associated with decreased lung metastases after tumour resection in mice [13]. Thus, neoadjuvant therapy with interferon-α in ovarian cancer patients with microscopic residual disease may have value after clinical relevance is determined by well-controlled (for both tumour and anaesthesia related factors) studies [14]. Another implication of knowing that longer general anaesthesia is a risk factor for cancer recurrence, would be limiting general anaesthesia duration either by the surgical technique or using epidural anaesthesia. It is valuable to ask if cancer patients would benefit from epidural anaesthesia instead of general anaesthesia, as epidural anaesthesia does not decrease NK cytotoxicity [15].

The choice of the anaesthetic agent during cytoreduction surgery in our study was not an independent risk factor for positive second-look findings in early stage ovarian carcinoma patients. A type II error could not be excluded due to the size of this study but no clinically relevant adverse actions on the immune system have ever been identified in short-term anaesthesia with any substance before, although differential effects of different anaesthetics on the immune system have been found. Anaesthetics, such as etomidate, propofol, or thiopentone and opioid analgesics may directly affect the function of immune competent cells [1]. However, these actions may only be apparent with high or supraclinical concentrations and/or long-term exposure such as in long-term sedation in intensive care units [1, 16]. In clinically employed concentrations these negative effects seem to be rapidly and completely reversible. For example, although initially both small dose (5 ug/kg) and large dose (75-100 ug/kg) fentanyl anaesthesia cause suppression of NK cell cytotoxicity with a peak effect 24 hours after surgery, the two types of anaesthesia, nonetheless, differ in the rate of recovery of NK cell function. By the second day NK cell function returns to control values in small-dose fentanyl anaesthesia patients whereas NK cell cytotoxicity is prolonged in large-dose fentanyl anaesthesia [17]. In our patients we used fentanyl in 75% of patients in small doses.

The association between homologous blood transfusion and cancer recurrence has been repeatedly reported in different types of cancers such as colorectal, breast, lung, prostate, gastric, kidney, cervix, vulva, liver, bone, head and neck cancers [18-20]. Our SLL (+) patients were more likely (64%) to have received intraoperative PRBC transfusion compared to SLL (-) patients (38%). SLL (+) patients also received more units (median of 1 unit more) of PRBC compared to SLL (-) patients. However PRBC transfusion was not an independent factor predicting SLL outcome in multivariate analysis. Preoperative haemoglobin, haematocrit, stage and grade of tumour were similar between the patients who did and who did not receive PRBC. Patients who received PRBC had longer duration of anaesthesia (mean 138 ± 46 minutes) compared to patients who did not receive any PRBC (mean 101 ± 26 minutes) ($p < 0.05$). Duration of anaesthesia was more important in predicting the SLL outcome and PRBC transfusion was not an independent factor.

In our study SLL was more likely to be positive (47%) in patients with mucinous type epithelial ovarian carcinoma compared to the serous subtype (23%). Preoperative haemoglobin, haematocrit, duration of anaesthesia, type of anaesthetics used, use of blood products, stage and grade of tumour were similar between the patients with serous- or mucinous-type tumours. Previously, it was believed that serous tumours were more aggressive, and mucinous tumours had more favourable prognoses as mucinous tumours were commonly confined to the ovary at initial diagnosis [6]. However when grade and stage are considered together with the histological subtype, five-year survival of patients has been recently reported to be lower in patients with mucinous-type compared to the serous-type histology in ovarian cancer [21].

Conclusion

Although this study has limitations due to its retrospective nature and the small sample size, we believe it

will reassure anaesthesiologists and surgeons that the types and dosages of the anaesthetics used do not seem to change cancer recurrence rates clinically. We emphasize that duration of anaesthesia and the histological subtype are risk factors for cancer recurrence in early stage ovarian carcinoma. From our data it seems interventions to shorten the duration of general anaesthesia or reversing immunosuppression induced by anaesthesia and surgery must be carefully considered.

References

[1] Bauer M., Rensing H., Ziegenfuss T.: "Anesthesia and perioperative immune function". *Anaesthetist.,* 1998, *47* (7), 538.

[2] Tonessen E., Wahlgreen C.: "Influence of extradural or general anaesthesia on natural killer cell activity and lymphocyte subpopulations in-patients undergoing hysterectomy". *Br. J. Anaesth.,* 1988, *60,* 500.

[3] Crozier T.A., Müller J.E., Quittkat D., Sydow M., Wuttke W., Kettler F.D.: "Effect of anaesthesia on the cytokine responses to abdominal surgery". *Br. J. Anaesth.,* 1994, *72,* 280.

[4] Moudgil G.C., Singal D.P.: "Halothane and isoflurane enhance melanoma tumour metastasis in mice". *Can. J. Anaesth.,* 1997, *44,* 90.

[5] Young R.C., Pecorelli S.: "Management of early ovarian cancer". *Semin. Oncol.*, 1998, *25*, 335.

[6] Friedlander M.L.: "Prognostic factors in ovarian cancer". *Semin. Oncol.,* 1998, *25,* 305.

[7] Vanbelle S.J., Cocquyt V.: "Impact of haemoglobin levels on the outcome of cancers treated with chemotherapy". *Crit. Rev. Oncol./Hematol.,* 2003, *47*, 1.

[8] Obermair A., Petru E., Windbichler G. *et al.*: "Significance of pretreatment serum hemoglobin and survival in epithelial ovarian cancer". *Oncol. Rep.,* 2000, *7,* 639.

[9] Chen V.W., Ruiz B., Killen J.L., Cote T.R., Wu X.C., Correa C.N.: "Pathology and classification of ovarian tumors". *Cancer,* 2003, *97,* 2631.

[10] Weese J.L., Ottery F.D., Emoto S.E.: "Do operations facilitate tumor growth? An experimental model in rats". *Surgery,* 1986, *100,* 273.

[11] Markovic S.N., Knight P.R., Murasko D.M.: "Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane". *Anesthesiology,* 1993, *78*, 700.

[12] Kutza J., Gratz I., Afshar M., Murasko D.M.: "The effects of general anesthesia and surgery on basal and interferon stimulated natural killer cell activity of humans". *Anesth. Analg.,* 1997, *85*, 918.

[13] Markovic S.N., Murasko D.M.: "Neoadjuvant immunotherapy with interferon of the spontaneously metastasizing murine B16F10L melanoma". *Int. J. Cancer,* 1990, *45,* 788.

[14] Bookman M.A.: "Biological therapy of ovarian cancer". *Semin. Oncol.*, 1998, *25,* 381.

[15] Ryhanen P., Jouppila R., lanning M., Jouppila P., Hollmen A.: "Natural killer cell activity after elective cesarean section under general and epidural anesthesia in healthy parturients and their newborns". *Gynecol. Obstet. Invest.,* 1985, *19,* 139.

[16] Helmy S.A.K., Al-Attiyah R.J.: "The immunomodulatory effects of prolonged intravenous infusion of propofol versus midazolam in critically ill surgical patients". *Anaesthesia*, 2001, *56,* 4.

[17] Beilin B., Shavit Y., Hart J., Mordashow B., Cohn S., Notti I., Bessler H.: "Effects of anaesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period". *Anesth. Analg.,* 1996, *82*, 492.

[18] Blumberg N., Heal J.M.: "Murphy Perioperative blood transfusion and colorectal cancer recurrence". *Transfusion,* 1994, *34* (5), 450.

[19] Petranyl G.G., Reti M., Harsanyl V., Szabo J.: "Immunologic consequences of blood transfusion and their clinical manifestations". *Int. Arch. Allergy Immunol.,* 1997, *114,* 303.

[20] Vamvakas E., Moore S.B.: "Perioperative blood transfusion and colorectal cancer recurrence: a qualitative statistical overview and meta- analysis". *Transfusion,* 1993, *33,* 754.

[21] Ishioka S., Sagae S., Terasawa K. *et al.*: "Comparison of usefulness between a new universal grading system for epithelial ovarian cancer and FIGO grading system". *Gynecol. Oncol.,* 2003, *89*, 447.

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