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Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence

A Retrospective Analysis

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Background: **Regional anesthesia and analgesia attenuate or prevent perioperative factors that favor minimal residual disease after removal of the primary carcinoma. Therefore, the authors evaluated prostate cancer recurrence in patients who received either general anesthesia with epidural anesthesia/analgesia or general anesthesia with postoperative opioid analgesia.**

Methods: **In a retrospective review of medical records, patients with invasive prostatic carcinoma who underwent open radical prostatectomy between January 1994 and December 2003 and had either general anesthesia–epidural analgesia or general anesthesia–opioid analgesia were evaluated through October 2006. The endpoint was an increase in postoperative prostate-specific antigen.**

Results: **After adjusting for tumor size, Gleason score, preoperative prostate-specific antigen, margin, and date of surgery, the epidural plus general anesthesia group had an estimated 57% (95% confidence interval, 17–78%) lower risk of recurrence compared with the general anesthesia plus opioids group, with a corresponding hazard ratio of 0.43 (95% confidence interval, 0.22–0.83; $P = 0.012$) in a multivariable Cox regression model. Gleason score and tumor size (percent of prostate involved) were also independent predictors of recurrence (hazards ratios of 1.19 [1.08, 1.52], $P = 0.004$, and 1.17 [1.03, 1.34] for 10% size difference, $P = 0.01$, respectively). A similar association between epidural use and recurrence was obtained by comparing patients matched on the propensity to receive epidural *versus* general anesthesia.**

Conclusions: **Open prostatectomy surgery with general anesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence. Prospective randomized trials to evaluate this association seem warranted.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

PROSTATE cancer is the most common malignancy in men; it is a major cause of morbidity and kills approximately 27,000 people per year in the United States alone.** Although there are various treatment options for prostate cancer, control of advanced disease often hinges on effective surgical removal of the primary tumor. Unfortunately, recurrence occurs in a significant fraction of patients, perhaps in part because even with the best technique, tumor surgery is usually associated with release of tumor cells into the lymphatic and blood streams. Furthermore, many patients already harbor micrometastases and scattered tumor cells at the time of surgery.[1–3]

Whether this minimal residual disease results in local or metastatic recurrence is thought to depend largely on the efficacy of host defenses, especially natural killer (NK) cells, which are the primary defense against cancer.[4,5] At least three perioperative factors shift the balance toward progression of minimal residual disease:

- The first is surgery *per se*, which releases tumor cells into the circulation,[1–3] depresses cell-mediated immunity including cytotoxic T-cell and NK cell functions,[6–8] reduces circulating concentrations of tumor-related antiangiogenic factors (*e.g.*, angiostatin and endostatin),[9–12] increases concentrations of proangiogenic factors such as vascular endothelial growth factor,[13,14] and releases growth factors that promote local and distant growth of malignant tissue.[15]
- The second factor is anesthesia *per se*, which impairs numerous immune functions including neutrophil, macrophage, dendritic cell, T-cell, and NK cell functions.[16–19]
- The third is opioids, which are given to control surgical pain. Opioids inhibit both cellular and humoral immune function in humans.[16,20,21] Furthermore, morphine is proangiogenic and promotes breast tumor growth in rodents.[22] Consequently, nonopioid analgesia helps to preserve NK cell function in animals and humans and reduces metastatic spread of cancer in rodents.[23]

Regional anesthesia and analgesia attenuates or prevents each of these adverse effects. For example, regional anesthesia moderates the neuroendocrine stress response to surgery by blocking afferent neural transmis-

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** American Cancer Society: Cancer Facts & Figures 2007. Available at: http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf. Accessed May 2, 2007.

sion from reaching the central nervous system and activating the stress response, and by blocking descending efferent activation of the sympathetic nervous system.[24–26] Consequently, NK cell function is better preserved and metastatic load to the lungs is reduced in a rat model of cancer metastasis.[6]

When regional anesthesia and general anesthesia are combined, the amount of general anesthetic required is much reduced—as is, presumably, immune suppression. Furthermore, regional analgesia provides superb pain relief, essentially obviating the need for postoperative opioids and the consequent adverse effects on immune function and of tumor growth.[16,21,26] Regional analgesia also reduces release of endogenous opioids.[27]

Available animal data thus suggest that regional anesthesia and analgesia help to preserve effective defenses against tumor progression by attenuating the surgical stress response, by reducing general anesthesia requirements, and by sparing postoperative opioids. Limited retrospective data in humans are also consistent with this theory: Paravertebral anesthesia and analgesia for breast cancer surgery was associated with an approximate fourfold reduced risk of recurrence or metastasis during a 2.5- to 4-yr follow-up period (95% confidence interval [CI] of estimated hazard ratio is 0.71–0.06).[28] However, other results in humans have yet to be reported. Therefore, we evaluated recurrence of prostate cancer after open radical prostatectomy in patients who received either general anesthesia combined with epidural analgesia or general anesthesia and postoperative opioid analgesia. Specifically, we tested the hypothesis that recurrence of prostate cancer is less common with combined general anesthesia and epidural analgesia than with general anesthesia alone.

Materials and Methods

After approval by the ethics committee of the Mater Misericordiae University Hospital (Dublin, Ireland), we reviewed the medical records of all patients who underwent radical prostatectomy in Mater Misericordiae University Hospital and the Mater Private Hospital between January 1994 and December 2003. Only the records from patients with invasive prostatic carcinoma where radical prostatectomy was indicated were included. We excluded patients who presented only for transurethral prostatic resection or patients diagnosed with prostate cancer who did not have an open radical prostatectomy.

Protocol

All patients undergoing radical prostate surgery at the Mater Misericordiae University Hospital are given balanced general anesthesia. Most typically, this includes 1–2 μg/kg fentanyl and 1–2 mg/kg propofol for induction, and neuromuscular antagonism to facilitate tracheal intubation with 0.5 mg/kg atracurium. Anesthesia was maintained with nitrous oxide in oxygen, with a fraction of inspired oxygen of 0.3–0.5 at the anesthesiologist's discretion. Nonsteroidal antiinflammatory drugs, *e.g.*, 75–100 mg diclofenac, and 0.1–0.15 mg/kg morphine were given for postoperative analgesia.

Epidural anesthesia and analgesia has been an integral part of the Mater Hospital's acute pain service since 1990. Typically, it is offered in combination with general anesthesia to patients undergoing radical prostatectomy. When an epidural is used, it is usually inserted preoperatively at a low thoracic level (*e.g.*, T11–T12), and a preemptive dose of local anesthetic is given before the surgical incision. Local anesthetic administration is then continued as an infusion for 48–72 h after surgery. However, a sizeable minority of patients for this procedure did not receive epidural anesthesia and analgesia for a variety of reasons, including the presence of absolute or relative contraindications, or by preference of the anesthetist, surgeon, or patient. These patients received postoperative patient-controlled morphine analgesia. Patient-controlled analgesia was administered *via* a CADD-Legacy ambulatory infusion pump (model number 6300; Deltec Inc., St. Paul, MN) programmed to deliver morphine boluses of 1 mg with a lockout time of 6 min.

Our primary outcome measure was the incidence of "biochemical recurrence," *i.e.*, increase in prostate-specific antigen (PSA) after radical prostatectomy compared with its immediate postoperative nadir, which prompted the clinician to instigate adjuvant treatment (radiation therapy, endocrine therapy, or chemotherapy). Post-prostatectomy increase in PSA is indicative of metastatic spread or local cancer recurrence. The time epoch evaluated ended October 2006 (*i.e.*, follow-up interval of 2.8–12.8 yr). Recurrence-free time was defined as the time between the date of surgery and the date of the last PSA, which was at or below the early postoperative nadir. Biochemical recurrence was in turn defined as an increase in PSA above the early postoperative nadir value, which prompted adjunctive therapy (chemotherapy or endocrine therapy or radiation therapy). Recurrence-free time for those patients without a recorded recurrence was defined as the time between the date of surgery and the date of last follow-up.

The following data were obtained from medical records: demographic characteristics; tumor size, grade, and type; PSA status; extent of inguinal nodal disease; whether postoperative or preoperative adjuvant chemotherapy, endocrine therapy, or radiation therapy was used; and each patient's current status as determined by documentation of follow-up visits to the hospital's outpatient clinic or general practitioner. In addition, we recorded the histologic tumor margins and whether the tumor was androgen receptive positive. If the most recent follow-up documentation in the hospital records exceeded 3 months from the date of our assessment, we contacted the patient's general practitioner by telephone to ensure that no consultation had occurred in the interim. This occurred in nine cases: six patients who received general anesthesia alone and three patients who received combined general–epidural anesthesia. In all cases, this clarified whether the patient had contacted his or her general practitioner regarding prostate cancer recurrence.

Data Analysis

A total of six patients who received an epidural had documented administration of intramuscular morphine at some point in the first 36 h postoperatively, indicating either epidural failure or inadequate block needing rescue analgesia. These patients were included in the general anesthesia plus epidural group, according to intention-to-treat analysis. Reasons for censoring data included loss to follow-up or inadequate or lost documentation in the medical records.

The anesthetic groups were compared on potential baseline confounders (table 1) using chi-square tests for categorical variables and either *t* tests or Wilcoxon rank sum test for continuous variables, as appropriate. Univariable association between recurrence-free survival and anesthetic technique was assessed with Kaplan-Meier survival estimates, and the groups were compared with the log-rank test.[29] In addition, univariable association between recurrence and all potential baseline confounders was assessed using Cox proportional hazards regression.

Table 1. Demographic, Morphometric, and Operative Characteristics for Radical Prostatectomy Cancer Patients Undergoing General Anesthesia and Postoperative Opioid Analgesia (General–Opioid) or General Anesthesia with Epidural Anesthesia and Analgesia (Epidural–General)

	General–Opioid (n = 123)	Epidural–General (n = 102)	*P* Value
ASA physical status			0.11*
I	58 (47)	39 (38)	
II	62 (50)	55 (54)	
III	3 (2)	8 (8)	
Margins clear	64 (52)	40 (39)	0.06†
Age, yr	62 ± 6	63 ± 5	0.34‡
Gleason score	6.1 ± 1.5	5.9 ± 1.3	0.42‡
Tumor size, % of prostate	30 [10, 50]	20 [10, 40]	0.19*
Preoperative PSA status	8.7 [6.4, 12.2]	8 [6, 13.6]	0.77*
Duration of surgery, h	2.0 ± 0.5	1.8 ± 0.4	0.06‡
Blood loss, mL	990 [600, 1,350]	805 [500, 1,500]	0.61*
Transfusion	13 (11)	10 (10)	0.85†

Data are reported as number (%), mean ± SD, or median [first, third quartiles]. Gleason scoresrange from 2 (least likely to spread) to 10 (more likely to spread).

P values obtained from * Wilcoxon rank sum test, † Pearson chi-square test, or ‡ Student *t* test.

ASA = American Society of Anesthesiologists; PSA = prostate-specific antigen.

For the primary analysis, we compared the anesthetic technique groups on recurrence-free survival using multivariable Cox proportional hazards regression while adjusting for any baseline or intraoperative factors independently related with the outcome. Variables considered were American Society of Anesthesiologists physical status, tumor size, length of surgery, Gleason score, margin (yes/no), preoperative PSA, estimated blood loss, transfusion (yes/no), and date of surgery. 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 anesthetic and recurrence among the available baseline factors, as well as to obtain a more precise estimate of hazard ratio for anesthetic treatment.

We assessed the proportion hazards assumption of the Cox regression model graphically by plotting the log [−log (survival)] against log (time). We assessed the predictive ability of the multivariable model with the *c* index.[30] This summary measure gives the proportion of all usable pairs in which predicted and actual survival times are concordant, such that a patient surviving longer than another is also predicted by the model to survive longer. 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.

To assess the robustness of our primary analysis results, we also used propensity score matching to assess the association between type of anesthesia and cancer recurrence. A propensity score, defined as the probability of receiving regional anesthesia as predicted from all available baseline and intraoperative variables (same variables as previously listed in primary analysis), was calculated for each patient using logistic regression. No significance criterion was used to remove variables; all were retained. A greedy matching algorithm[31] was used to match pairs of regional and general anesthesia patients to within 0.05 on the propensity score scale. Then, to assess association with outcome, the matched groups were compared on cancer recurrence using Cox proportional hazards regression—both univariably, and multivariably using a significance criterion of 0.05 to adjust for any residual confounding.

The significance level for all hypotheses was 0.05. A Bonferroni correction to the significance criterion for multiple comparisons was applied where appropriate. SAS software version 9.1 (SAS Institute, Cary, NC) and R software version 2.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses.

Results

The groups were not perfectly balanced: The epidural–general patients seemed to have had slightly worse

Table 2. Univariable Association with Cancer Recurrence: Cox Regression Results

	n*	Hazard Ratio (95% CI)	P Value†
Anesthesia group			
General–opioid	123	1.0	<0.001
Epidural–general	102	0.34 (0.19–0.61)	
ASA physical status			
I	97	1.0	0.77
II	117	0.92 (0.54–1.55)	
III	11	0.60 (0.14–2.54)	
Margin			
No	121	1.0	<0.001
Yes	104	2.88 (1.66–4.99)	
Yes	23	1.01 (0.46–2.24)	
Yes	43	1.00 (0.54–1.86)	
Age			
Per 5 yr	225	1.02 (0.80–1.30)	0.89
Gleason score			
Per unit	225	1.53 (1.29–1.80)	<0.001
Tumor size			
Per 10% of prostate	224	1.25 (1.13–1.38)	<0.001
Preoperative PSA status			
Per unit	225	1.01 (1.00–1.03)	0.03
Duration of surgery			
Per 1 h	225	1.79 (1.09–2.92)	0.02
Blood loss			
Per 250 ml	225	0.99 (0.89–1.10)	0.86
Transfusion			
No	202	1.0	0.98
Yes	23	1.01 (0.46–2.24)	

Gleason scores range from 2 (least likely to spread) to 10 (more likely to spread).

* Number of observations. † *P* value obtained from univariable Cox proportional hazard regression testing hazard ratio = 1.

ASA = American Society of Anesthesiologists; CI = confidence interval; PSA = prostate-specific antigen.

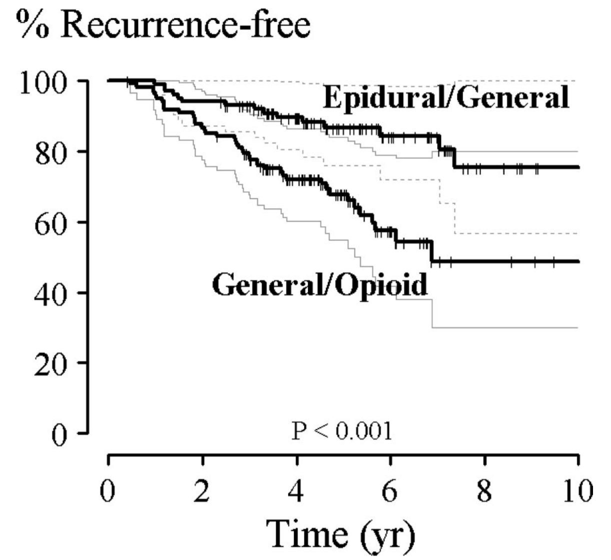

Fig. 1. Kaplan-Meier recurrence-free survival estimates for 123 patients given general anesthesia and postoperative opioids (general–opioid) and for 102 patients given general anesthesia combined with epidural analgesia (epidural–general) during radical prostatectomy for prostate cancer; univariable *P* < 0.001. *Vertical tick marks* represent censored values. *Light dashed lines* show 95% confidence intervals for the epidural–general group; *light solid lines* show 95% confidence intervals for the general–opioid group.

American Society of Anesthesiologists physical status ($P = 0.11$), more complications ($P = 0.05$), and slightly shorter surgeries ($P = 0.06$) than the general–opioid patients (table 1). Complications were postoperative bleeding, pneumonia or other respiratory tract infection, and urinary tract infection. In addition, the epidural–general patients had a smaller fraction of patients with clear surgical margins ($P = 0.06$). These factors were thus prime candidates for inclusion in our multivariable model.

Table 2 contains univariable Cox regression model results for each baseline and intraoperative factor. Without adjusting for potential confounders (*i.e.*, univariably), patients treated with a combination of epidural and general anesthesia had a significantly lower estimated risk of recurrence compared with the general anesthesia and postoperative opioid group, with hazard ratio of 0.34 (95% CI, 0.19–0.61). Margin, Gleason score, preoperative PSA, tumor size, and duration of operation were also significantly associated with recurrence in univariable analysis. Kaplan-Meier recurrence-free survival estimates and 95% CIs at landmark follow-up times for each anesthesia group are in table 3, with the survival curves plotted in figure 1.

After adjusting for tumor size, Gleason score, preoperative PSA, margin, and date of surgery, the epidural plus general anesthesia group had an estimated 57% (95% CI, 17–78%) lower risk of recurrence compared with the general anesthesia plus opioids group, with a corresponding hazard ratio of 0.43 (95% CI, 0.22–0.83; $P =$

Table 3. Kaplan-Meier Recurrence-free Survival Estimates According to Anesthesia Regimen

	General–Opioid				Epidural–General			
Time	Survival (95% CI)*	No. Events	No. Censored	No. Left	Survival (95% CI)*	No. Events	No. Censored	No. Left
At treatment	100	0	0	123	100	0	0	102
1 yr	97 (94–100)	4	1	118	99 (97–100)	1	0	101
3 yr	78 (70–85)	27	4	92	93 (88–98)	7	7	88
5 yr	68 (59–77)	36	47	40	87 (79–94)	12	43	47
7 yr	49 (34–64)	43	72	8	84 (76–93)	13	65	24
9 yr	49 (34–64)	43	76	4	76 (62–89)	15	81	6
Final observation	49 (34–64)	43	80	0	76 (62–89)	15	87	0

* Pointwise 95% confidence interval (CI).

Table 4. Multivariable Association with Recurrence: Cox Regression Model

Model Factor*	Reference or Units	Hazard Ratio (95% CI)	*P* Value
Epidural–general	General–opioids	0.43 (0.22–0.83)	0.012
Tumor size	Per 10 percent of prostate	1.17 (1.03–1.34)	0.01
Gleason score	1	1.19 (1.08–1.52)	0.004
Margin = yes	No	1.49 (0.77–2.87)	0.24
Preoperative PSA status	1	1.02 (1.00–1.04)	0.054
Date of surgery	NA	NA	0.28

* In addition to the listed factors, other factors considered for this model were American Society of Anesthesiologists physical status, transfusion (yes/no), and age.

CI = confidence interval; NA = hazard ratio not meaningful for surgical dates; PSA = prostate-specific antigen.

0.012) in our multivariable Cox regression model (table 4). Gleason score and baseline PSA were strongly associated with recurrence independent of the other model factors. An additional model where all preoperative and intraoperative factors were forced into the regression model gave similar results, with hazard ratio of 0.42 (95% CI, 0.21–0.94; $P = 0.014$).

There was no evidence of nonproportionality in the hazards for the two groups, and the *c* index for the final model was estimated at 0.91, suggesting excellent predictive ability. Although only 64% of the possible pairs were usable because of heavy censoring after 4 yr, the *c* index is reliable here because a large fraction of prostate cancer recurrences are expected before 4 yr and little loss to follow-up occurred before then.[2] As a sensitivity analysis to explore the potential for bias due to censoring, we assessed the association between anesthetic group and recurrence using only the first 3 yr of data for each patient. Using data through 3 yr, before which only 8% of patients were censored, univariable and multivariable associations were similar to the full data results, with $P = 0.012$ and $P = 0.033$, respectively.

We also assessed the association between anesthesia technique and cancer recurrence using propensity score matching. Propensity scores were created (see Materials and Methods) for all 200 patients who had nonmissing data for all baseline and intraoperative potential confounding variables (table 5). Before matching, epidural and general anesthesia patients differed significantly on the propensity score and length of surgery, with smaller differences on other variables. Seventy-one matched pairs were obtained (n = 142 patients); matching was successful in improving the balance between groups (table 5). Length of hospital stay is shown in table 5 for informational purposes but was not included in the formation of the propensity scores or in the assessment of association with recurrence.

Table 5. Perioperative Variables before and after Propensity Score Matching

	Before Matching			After Matching		
Factor*	Gen (n = 109) Statistics	Epi (n = 91) Statistics	*P* Value	Gen (n = 71) Statistics	Epi (n = 71) Statistics	*P* Value
PS†	0.41 (0.15)	0.51 (0.16)	<0.001	0.47 (0.14)	0.47 (0.14)	0.98
ASA physical status	1.6 (0.55)	1.7 (0.62)	0.14	1.6 (0.6)	1.6 (0.6)	0.89
Tumor size, % prostate	30.0 [10, 40]	20.0 [10, 30]	0.11	28.3 (22.5)	27.4 (21.7)	0.82
Surgery, h	2.0 [1.5, 2.5]	1.5 [1.5, 2.0]	0.009	1.8 (0.4)	1.8 (0.4)	0.81
Gleason score	6.0 (1.5)	5.9 (1.3)	0.34	5.9 (1.5)	6.0 (1.2)	0.68
Margin, % yes	50	37	0.08	44	44	0.99
Preoperative PSA status	8.7 [6, 12]	8.1 [6, 14]	0.67	9.8 (5.1)	10.3 (5.8)	0.55
Year of surgery			0.33			0.53
1994	1.8	2.2		1.4	1.4	
1995	1.8	4.4		2.8	1.4	
1996	0	3.3		0	2.8	
1997	1.8	8.8		2.8	5.6	
1998	3.7	7.7		4.2	8.5	
1999	6.4	12.1		7.0	11.3	
2000	20.2	7.7		19.7	9.9	
2001	28.4	15.4		29.6	15.5	
2002	19.3	17.6		19.7	18.3	
2003	16.5	20.9		12.7	25.4	
EBL, l	0.95 [0.60, 1.3]	0.8 [0.5, 1.5]	0.82	0.80 [0.6, 1.2]	0.80 [0.5, 1.3]	0.90
Transfusion, % yes	31	24	0.56	21	23	0.91
Hospital LOS*	9.0 [8, 10]	12.0 [9, 15]	<0.001	9 [8, 10]	12 [9, 14]	<0.001

Data are reported as mean (SD), median [quartiles], or percent.

* All factors in table 5 except hospital length of stay (and propensity score, of course) were used to create the propensity scores. † Propensity score (PS) = predicted probability patient receives epidural anesthesia given baseline variable: Matching on PS achieved balance on the other variables in the table used to create the PS.

ASA = American Society of Anesthesiologists; EBL = estimated blood loss; Epi = epidural; Gen = general anesthesia; LOS = length of stay; PSA = prostate-specific antigen.

Table 6. Univariable and Multivariable Models Comparing Propensity-matched Groups (n = 142)

Model Parameter	Reference or Units	Hazard Ratio (95% CI)	*P* Value
Univariable			
Epidural–general	General–opioids	0.48 (0.23–1.00)	0.049
Multivariable*			
Epidural–general	General–opioids	0.51 (0.25–1.06)	0.07
Gleason score	1	1.4 (1.1–1.7)	0.005
Margin = yes	No	2.2 (1.04–4.7)	0.039
Preoperative PSA status	1	1.06 (1.01–1.13)	0.032

* Variables other than epidural–general included if significant at $P < 0.05$ in stepwise selection; all variables in table 5 other than hospital length of stay were considered for this model.

CI = confidence interval; PSA = prostate-specific antigen.

Association between epidural and general anesthesia on cancer recurrence was then assessed on the propensity-matched pairs using Cox regression. Epidural patients were an estimated 52% less likely (0–77%) to recur at any given time compared with general anesthesia patients, with a univariable hazard ratio of 0.48 (95% CI, 0.23–1.00; $P = 0.049$). Although unnecessary because of excellent matching, a multivariable Cox regression analysis on the propensity-matched patients (table 6) resulted in a hazard ratio of 0.51 (95% CI, 0.25–1.06; $P = 0.07$). Our propensity-matched analysis results are thus quite similar to our unmatched multivariable model (table 4).

Discussion

We evaluated cancer recurrence in men undergoing radical prostatectomy. After adjustment for confounding factors, patients who received general anesthesia combined with epidural analgesia had a 57% (95% CI, 17–78%) lower risk of cancer recurrence than patients who had general anesthesia and postoperative opioids. A propensity-matched analysis on a subset of the data gave a similar result: Epidural analgesia had a 52% (95% CI, 0–77%) lower risk of cancer recurrence. These results are strikingly similar to our previous report in women undergoing breast cancer surgery in which disease-free survival was 94% (95% CI, 87–100%) and 82% (74–91%) at 24 months, and 94% (87–100%) and 77% (68–87%) at 36 months in the paravertebral and general anesthesia patients, respectively ($P = 0.012$).

Both results are consistent with a "decisive period" during and after cancer surgery during which minimal residual disease is either controlled by host defense (presumably largely by NK cells) or is retained in the body—eventually becoming clinically apparent as local recurrence or metastasis. Considerable *in vitro* and animal data support this theory and suggest that, unlikely as it might thus initially seem, use of regional analgesia may reduce the risk of recurrence after major cancer surgery.

Natural killer cells, the primary host defense against cancer, are a subpopulation of lymphoid cells that spontaneously recognize and kill a variety of tumor cells *in vitro* and *in vivo* [4] and are known to play a determinant role in controlling tumor development—and especially the metastatic process.[5] We did not evaluate NK cell function in our patients, but much previous work indicates that suppression of NK cell activity occurs within hours of surgery, lasts a few days, and is proportional to the invasiveness of the surgery.[17,32] Tissue damage, inflammation, pain, anesthetic and analgesic compounds, and psychological stress all contribute to NK cell suppression and the tumor-promoting effects of surgery[33–36]—and all are moderated by regional analgesia.

Ketamine, thiopental, and halothane have each been shown to suppress NK cell activity and promote metastasis in an animal model.[37] Other volatile anesthetics also impair NK cell function[17] by as much as 90%.[18] Halothane and isoflurane comparably reduce neutrophil motility,[38] and sevoflurane impairs T lymphocytes.[39] Although the immune effects of other volatile anesthetics differ somwhat,[40,41] most—including isoflurane and sevoflurane, which were used in our patients—seem to substantially inhibit various immune functions. We were unable to determine the amount of volatile anesthetic given to our patients. However, it is highly plausible that patients in the epidural group—who were routinely given a preemptive dose of local anesthetic—required considerably less volatile anesthetic than those given general anesthesia alone.

Acute and chronic administration of opioids inhibits components of the cellular and humoral immune function, including antibody production, NK cell activity, cytokine secretion, lymphocyte proliferative responses to mitogens, and phagocytic activity.[42,43] The immunosuppressive effects of morphine are best studied[21,44]; however, other opioids, including fentanyl[20,45] and subtype-specific opioid receptor agonists,[46] produce comparable immune suppression in most studies.[47] Inhibition seems to be dose dependent.[20] Endogenous and exogenous opioids bind three major types of receptors: the μ-, δ-, and κ-opioid receptors that have been identified not only in peripheral sensory neurons and the central nervous system, but also in cells of the immune system such as polymorphonuclear leukocytes, macrophages, T lymphocytes, splenocytes, and macrophage-like and T cell–like cell lines.[43] Although we were unable to quantify opioid use in our two patient groups, those given epidural analgesia presumably required little opioid, whereas those given general anesthesia alone surely required considerable amounts of opioid for analgesia after open radical prostatectomy, which is a large and painful procedure.

Several important limitations are inherent in this study's retrospective, observational design. Patients were not randomized and clinical care was not standardized, so that selection bias and the effects of unmeasured confounding variables cannot be excluded. Although our sample size was large enough to detect a strong association, our estimation was rather imprecise, evidenced by wide CIs. And as with most observational studies, even a propensity analysis was not able to completely balance the anesthetic groups on all potential confounders.

There was no significant alteration in clinical practice in the center in question in the relevant time epoch of the study. Laparoscopic or robotic prostate surgery was not introduced, nor were there substantial changes in the frequency of use of epidural analgesia for this type of surgery.

This study, like most retrospective analyses, should be viewed as generating a hypothesis and an estimated effect size for future large randomized controlled trials. (Two are already in progress [ClinicalTrials.gov identifiers NCT00418457 and NCT00531349], and others, including one to evaluate the effect of anesthesia on outcome after radical prostatectomy, will start soon.) Although these studies will require many years of enrollment and follow-up, even a smaller effect size would be clinically important, making the relation between anesthetic technique and cancer recurrence an important hypothesis to pursue, especially given its biologic plausibility.

After primary treatment for clinically localized prostate cancer, including radical prostatectomy, biochemical recurrence (defined as an increase in PSA above its posttreatment nadir) is usually the first evidence of either local recurrence or metastatic progression.[48] Radical prostatectomy has been shown to provide high 10-yr PSA recurrence-free survival regardless of whether the prostate tumor involves one or both lobes of the gland, once the tumor is histologically confined within the gland.[49] Others have used either PSA doubling time or any increase in PSA above the posttreatment nadir value as indicative of recurrence.[50]

In summary, cancer surgery releases tumor cells into surrounding healthy tissue and into the systemic circulation. We speculate that whether this minimal residual disease becomes established as recurrent cancer or metastases depends on immune competence in the immediate perioperative period. Regional anesthesia and analgesia may help to preserve immune function by attenuating the surgical stress response, decreasing anesthetic requirement, and diminishing the need for opioids. Consistent with this theory, radical prostatectomy with epidural analgesia was associated with a substantial and statistically significant reduction in biochemical evidence of cancer recurrence. Although limited by its retrospective design, our study suggests that prospective trials evaluating the effects of regional analgesia and opioid sparing on cancer recurrence are warranted.

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