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REPORTS OF ORIGINAL INVESTIGATIONS

# Association of anesthesia technique for radical prostatectomy with biochemical recurrence: a retrospective cohort study

# Association entre techniques anesthésiques pour la prostatectomie radicale et récidive biochimique: une étude rétrospective de cohorte

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**Abstract**

**Introduction** *Anesthesia technique has been associated with cancer outcomes after radical prostatectomy (RP). These studies are limited by variability in surgeon experience, bias in patient selection, and in some cases, sample size. We evaluated the impact of anesthesia technique for RP on biochemical recurrence (BCR) using a large cohort of patients operated on by a single experienced surgeon.*

**Methods** *We retrospectively reviewed data from a prospective institutional oncologic database on 929 patients treated with RP by a single surgeon from 1999-2008. Spinal anesthesia was used for patients from 2002-2006. We compared outcomes of these patients ($n = 264$) with outcomes of patients who underwent general anesthesia ($n = 665$) at Memorial Sloan-Kettering Cancer Center from 1999-2001 and 2006-2008. Cox proportional hazards regression was used to assess differences in BCR rates between the anesthesia groups adjusting for differences in postoperative factors related to anesthetic technique and tumour pathologic characteristics associated with BCR after RP.*

**Results** *Median follow-up among patients free from BCR was 4.6 yr. On multivariable analysis, spinal anesthesia did not independently predict the rate of BCR (hazard ratio = 1.10; 95% confidence interval 0.7 to 1.74; $P = 0.7$). Independent predictors of BCR were preoperative prostate-specific antigen (PSA), pathologic Gleason grade, extracapsular extension, and seminal vesicle invasion.*

**Conclusions** *We did not find an association between anesthesia technique and disease recurrence in men with prostate cancer treated with RP. Anesthesia technique is unlikely to alter disease recurrence following RP independent of surgical and pathological factors.*

**Résumé**

**Introduction** *La technique d'anesthésie a été associée aux aboutissements du traitement du cancer après prostatectomie radicale (PR). Ces études sont limitées par la variabilité de certains facteurs tels que l'expérience du chirurgien, les biais de sélections des patients et, dans certains cas, la taille de l'échantillon. Nous avons évalué l'impact de la technique d'anesthésie pour RP sur la récidive biochimique (RBC) à partir d'une grande cohorte de patients opérés par un seul et unique chirurgien expérimenté.*

**Author contributions** *Behfar Ehdaie*, *Daniel D. Sjoberg*, *Paul H. Dalecki*, *Peter T. Scardino*, *James Eastham*, and *David Amar* have contributed equally to the study design, conduct of the study, data collection, data analysis, and manuscript preparation. *Behfar Ehdaie*, *Daniel D. Sjoberg,* and *David Amar* have reviewed the original study data and data analysis and attest to the integrity of the original data and the analysis reported in this manuscript. *Behfar Ehdaie* and *Daniel D. Sjoberg* are the archival authors who are responsible for maintaining the study records.

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**Méthodes** *Nous avons réexaminé de façon rétrospective les données d'une base de données oncologiques institutionnelle portant sur 929 patients traités pour PR par un seul chirurgien entre 1999 et 2008. Une rachianesthésie a été utilisée pour les patients de 2002 à 2006. Nous avons comparé les résultats de ces patients (n = 264) avec les résultats de patients ayant bénéficié d'une anesthésie générale (n = 665) au Memorial Sloan-Kettering Cancer Center de 1999 à 2001 et de 2006 à 2008. Le modèle de régression des risques proportionnels de Cox a servi à évaluer les taux de RBC entre les groupes d'anesthésie avec un ajustement pour les différences entre les facteurs postopératoires liés à la technique anesthésique et les caractéristiques pathologiques de la tumeur associées à la RBC après PR.*

**Résultats** *Le suivi médian pour les patients sans RBC a été de 4,6 ans. À l'analyse multivariée, la rachianesthésie n'a pas prédit de façon indépendante le taux de RBC (rapport de risque = 1,10; intervalle de confiance à 95 %: 0,7 à 1,74; P = 0,7). Les éléments prédictifs de RBC étaient le taux préopératoire de l'antigène spécifique de la prostate (PAS), le stade du score de Gleason, l'extension extracapsulaire et l'invasion des vésicules séminales.*

**Conclusions** *Nous n'avons pas trouvé d'association entre la technique d'anesthésie et la récidive de la maladie chez les hommes atteints de cancer de la prostate et traités par PR. Il est peu probable que la technique d'anesthésie influence les récidives après PR, indépendamment des facteurs chirurgicaux et pathologiques.*

Prostate cancer is the most common malignancy in men.[1] Despite an increasing understanding of the indolent natural history of some forms of prostate cancer, radical prostatectomy is an effective curative treatment for higher grade and advanced stage disease.[2] Numerous clinical and pathological characteristics have been traditionally associated with tumour recurrence after radical prostatectomy (RP), including prostate-specific antigen (PSA), Gleason grade, and pathologic stage.[3] Additionally, factors associated with surgical technique, including surgeon experience, have been associated with disease recurrence.[4,5] Despite the effectiveness of RP as a primary treatment for prostate cancer, disease recurrence, defined by an elevation in serum PSA, is seen in 35% of patients within 15 years after RP.[6] Oftentimes, the final pathologic assessment for these cases shows favourable tumour characteristics and negative surgical margins, which suggests that residual disease in the form of tumour spillage, scattered micrometastases, or circulating tumour cells is unavoidable.[7] Nevertheless, the clinical significance of this minimal disease is unknown and depends on a balance of host immunity and tumour aggressiveness. Recent studies suggest that intraoperative factors related to anesthetic technique can shift the balance towards disease progression.[8–14]

Clinical studies evaluating anesthesia technique on cancer recurrence rates have been small retrospective studies that showed large differences, suggesting a significant impact from unmeasured confounders. Two retrospective studies used statistical methods to account for differences between patients who received epidural anesthesia or epidural and general anesthesia and those who received general anesthesia alone. Results of the two studies showed a 55% reduction in the progression of clinical cancer and a 57% lower risk of biochemical recurrence (BCR) in 261 and 225 patients, respectively.[8,12] In both studies, the authors acknowledged significant limitations, including selection bias, small sample size, and multiple surgeons.[10,14] Specifically, studies have previously reported that surgeon experience is associated with the risk of disease recurrence. If experience or other surgeon factors are correlated with preference for anesthesia technique, then disease recurrence may incorrectly appear to be associated with anesthesia technique.

We examined prospectively collected data from patients with prostate cancer during a time period when anesthesia technique was changed from general anesthesia to spinal anesthesia for RP (due to surgeon preference) and when the technique was changed back to general anesthesia (due to standardization of open and minimally invasive RP clinical pathways). Our objective was to assess the association of anesthesia technique with the risk of BCR among 1,087 prostate cancer patients treated with RP by a single high-volume surgeon.

## Methods

### Patient selection

The oncologic data used in this study were collected from an ongoing prospective database of patients with prostate cancer and were registered with the Institutional Review Board (IRB) of Memorial Sloan-Kettering Cancer Center (MSKCC). The IRB granted a Waiver of Authorization for this study as it was determined to be exempt from requiring consent for research in human subjects. We identified a cohort of 1,087 men who underwent RP by a single high-volume surgeon (P.T.S.) from 1999-2008. We chose the beginning of the study at a time when our institution initiated a prospective data collection system for prostate

cancer surgical outcomes. Importantly, there were no significant changes in surgical technique during the timespan of this study. In 1999, when the surgeon (P.T.S.) joined our staff, the standard of care at our institution was general anesthesia for RP. The surgeon (P.T.S.) preferred spinal anesthesia for use in RP, which was employed from 2002-2006 for his patients. The contraindications to receiving spinal anesthesia were primarily determined by anesthesiology staff. In 2006, the urology service at MSKCC standardized RP care, and general anesthesia became the preferred method, thereby returning to the standard anesthesia technique used from 1999-2002. We retrospectively reviewed the anesthesia records of the study patients.

General anesthesia consisted of premedication with midazolam 2 mg and fentanyl 0.5-2 $\mu g \cdot kg^{-1}$ as needed, induction with propofol 1-2 $mg \cdot kg^{-1}$, and rocuronium or vecuronium to facilitate endotracheal intubation and muscle relaxation during the operation. Maintenance of anesthesia consisted of isoflurane and/or sevoflurane in air and oxygen with fentanyl analgesia (typically 200-400 μg) during the operation. Morphine or hydromorphone were titrated as needed at the conclusion of surgery only in patients receiving general anesthesia. The technique for spinal anesthesia involved inserting a 25G pencil-tip needle in the L3/4- or L4/5 interspace and administering 0.5% bupivacaine 10 mg with epinephrine 0.1 mL 1:200,000. A T6-8 level anesthesia was attained to light touch. During surgery, a continuous infusion of propofol was used for sedation in all cases with minimal use of fentanyl (typically 25-50 μg). No patient required conversion to general anesthesia due to inadequate spinal anesthesia. In all patients, postoperative care was guided by standardized clinical pathways that consisted of patient-controlled opioid analgesia on the first postoperative day, followed by oral opioid therapy on the second postoperative day. Specifically, all patients received a morphine sulfate intravenous patient-controlled analgesia with an opioid concentration of 1 $mg \cdot mL^{-1}$ (with no basal rate, demand dose of 0.5 mg, and lockout of ten minutes) for 24 hr postoperatively and oxycodone/acetaminophen five 325-mg tablets every six hours beginning on the second postoperative day. Ketorolac (15 mg every six hours for eight doses) was administered intravenously as a scheduled medication. No blood conservation strategy, such as intravenous iron or erythropoietin, was used for patients during the study period. Patients with missing data regarding preoperative PSA ($n = 2$), seminal vesicle invasion (SVI) ($n = 5$), extracapsular extension (ECE) ($n = 6$), lymph node involvement (LNI) ($n = 70$), pathologic Gleason grade ($n = 23$), and no follow-up after RP ($n = 52$) were excluded from the analyses, leaving 929 patients in the final cohort.

## Data collection

Data from patients undergoing RP for prostate cancer at MSKCC have been collected and entered prospectively into an institutional database since 1999. Patients' preoperative oncologic data and demographics are captured and entered into the database before surgery, and operative details are added immediately following RP. Biochemical outcome data are routinely collected and added to the database. Patients who do not receive their postoperative care at MSKCC are encouraged to have their biochemical data sent to MSKCC, and when received, the data are entered into the database.

## Follow-up regimen

Patients were seen every three months for the first year after RP, every six months for the second year, and annually thereafter. Follow-up consisted of history, physical examination, and serum PSA. Disease recurrence was defined by an elevation of serum-PSA level of $\geq 0.1$ $ng \cdot mL^{-1}$ with one confirmatory rise of detectable PSA starting six weeks after RP.[15]

## Statistical analysis

The two anesthetic groups were compared on potential baseline confounders using Chi square test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. We evaluated the impact of anesthesia technique on BCR using Cox proportional hazards regression. The regression model was adjusted for known clinical and pathological confounders, including preoperative PSA, pathologic Gleason grade, SVI, LNI, ECE, and whether patients received a blood transfusion, a factor suspected to affect oncologic outcomes. Linearity of PSA was assessed using restricted cubic splines with knots at the tertiles, and non-linearity was tested. In addition, no patient received pre- or postoperative adjuvant hormone treatment or radiation therapy.

It has been shown previously that BCR rates for a surgeon improve as their operative volume increases, and the rates of BCR continue to improve through the first 200 and 300 RPs performed.[16] We did not expect this to have an impact on our results, as P.T.S. had performed more than 1,000 surgeries by 1999, when the first patients in this series were treated. Nevertheless, we confirmed that expected differences observed between anesthesia types would be independent of learning curve by testing the trend in BCR compared with surgery number. We did this by adding a variable to our model that indicated surgery number and used Cox proportional hazards regression to determine the independent association of this variable with

**Table 1** Patient characteristics

| | General Anesthesia ($n = 665$) | Spinal Anesthesia ($n = 264$) | $P$ value* |
|---|---|---|---|
| Age (yr) | 59 (54, 64) | 59 (54, 64) | 0.7 |
| ASA score | | | |
| I/II | 495 (90%) | 188 (92%) | 0.4 |
| III | 54 (10%) | 16 (8%) | |
| Surgical time (min) | 225 [195, 242] | 226 [210, 250] | 0.017 |
| Preoperative PSA | 5 [4,7] | 6 [4,9] | 0.15 |
| Pathologic Gleason grade | | | |
| $\leq 6$ | 294 (44%) | 95 (36%) | 0.003 |
| 7 | 342 (51%) | 144 (55%) | |
| $\geq 8$ | 29 (4%) | 25 (9%) | |
| Extracapsular extension | 149 (22%) | 83 (31%) | 0.004 |
| Lymph node involvement | 24 (4%) | 17 (6%) | 0.058 |
| Seminal vesicle invasion | 33 (5%) | 20 (8%) | 0.12 |
| Positive surgical margin | 77 (12%) | 30 (11%) | 1 |
| Blood transfusion | 318 (48%) | 144 (55%) | 0.064 |

*$P$ values from a Chi square test or rank sum test

All reported values are frequency (percent) or median [interquartile range]

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

BCR. The results are reported in adherence with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17]

## Results

Of the 929 patients, 264 had spinal anesthesia and 665 had general anesthesia. Patient characteristics by anesthesia type are found in Table 1. Patients receiving spinal anesthesia had higher Gleason grades and higher rates of ECE compared with those who received general anesthesia. The medians of surgical time between both groups are similar, and the general anesthesia group has a larger skew in the direction of longer surgical time.

Overall, 97 patients experienced BCR. Among patients who did not have a recurrence, the median follow-up time was 4.6 yr. After adjusting for preoperative serum PSA, pathologic tumour characteristics, and postoperative factors (including blood transfusion status), patients who received spinal anesthesia had slightly higher observed rates of BCR compared with those who received general anesthesia (hazard ratio = 1.10; 95% confidence interval (CI) 0.7 to 1.74; $P = 0.7$); however, this difference in BCR rate is not statistically significant (Table 2). In addition, Cox proportional hazards regression evaluating the surgeon's experience did not suggest a learning curve during the study period ($P = 0.3$).

**Table 2** Adjusted risk of biochemical recurrence after radical prostatectomy

| | Hazard Ratio | 95% Confidence Interval | $P$ value |
|---|---|---|---|
| Anesthesia type | | | |
| General | Ref | Ref | Ref |
| Spinal | 1.10 | 0.7 to 1.74 | 0.7 |
| Preoperative PSA* | NA | NA | <0.0001 |
| Pathologic Gleason grade | | | |
| $\leq 6$ | Ref | Ref | Ref |
| 7 | 3.62 | 1.72 to 7.64 | 0.001 |
| $\geq 8$ | 8.12 | 3.40 to 19.36 | <0.0001 |
| Seminal vesicle invasion | 2.27 | 1.37 to 3.76 | <0.002 |
| Lymph node involvement | 1.60 | 0.91 to 2.80 | 0.10 |
| Extracapsular extension | 2.69 | 1.63 to 4.42 | <0.0001 |
| Blood transfusion | 0.99 | 0.66 to 1.49 | 1 |

PSA = prostate-specific antigen; Ref = reference value

*Entered into the model using restricted cubic splines with knots at the tertiles

We performed a sensitivity analysis to determine the effect of the duration of surgery on our results. We included surgical time into the regression model, and the results and the conclusions were unchanged. In addition, we evaluated the effect of body mass index on the association between anesthesia technique and BCR. We included body mass index into the regression model, and the results were unchanged.

## Discussion

We did not find patients receiving general anesthesia at an increased risk of prostate cancer recurrence when compared with those receiving spinal anesthesia. The factors that independently predicted BCR were preoperative PSA, pathologic Gleason grade, ECE, and SVI. It is of interest that our current study contrasts with earlier observations of prostate cancer in which spinal anesthesia reduced clinical tumour progression and disease recurrence. In our view, the conclusions of these prior observational studies should be interpreted with caution because of limitations in case mix, selection bias, surgeon

experience, and in some cases, small sample size. Furthermore, the interpretation of retrospective cohort trials should not suggest a causal relationship because of unmeasured confounders impacting the association between factors.

The hypothesis that spinal anesthesia for oncologic surgery might be associated with decreased disease recurrence has been supported by retrospective observational studies. The studies evaluating anesthesia technique and prostate cancer recurrence after RP are contradictory. Nevertheless, a secondary analysis of 99 patients who underwent RP and had previously participated in a randomized controlled trial evaluating non-oncological outcomes, including pain control, blood loss, and the need for perioperative blood transfusion, found no difference in disease recurrence and cancer-specific survival between various anesthesia techniques (hazard ratio 1.33; 95% CI 0.64 to 2.77).[13] Despite the randomization of patients to anesthesia technique in this study, the small sample size limited the ability to detect differences in oncological outcomes. Two studies in patients with prostate cancer reported improved oncologic outcomes among those who received epidural anesthesia compared with those who received general anesthesia.[10,14] In one of these studies, Biki *et al*. retrospectively evaluated 225 patients and found that patients who received epidural with general anesthesia followed by postoperative epidural local analgesia had a 57% lower risk of BCR after RP when compared with general with opioid anesthesia followed by opioid analgesia (hazard ratio = 0.43).[10] First, the use of general anesthesia in both arms confounds the effect of epidural analgesia alone on BCR. Second, comparing data from a national database of 3,837 patients who underwent RP showed the estimated risk of BCR associated with a known adverse prognostic factor such as LNI was 42% (hazard ratio = 0.58).[18] Therefore, the 57% lower risk associated with epidural anesthesia is most likely due to confounding factors. In the second study, Wuethrich *et al.* evaluated 261 patients and showed that general anesthesia combined with epidural analgesia increased the time to clinical progression after adjusting for differences using the propensity score; however, no significant differences were observed for cancer-specific and overall survival.[14] In contrast, two studies failed to show any association between anesthesia technique and outcomes specific to prostate cancer.[11,13] These disparate outcomes are likely due to unmeasured confounders and heterogeneity in surgical technique as evidenced by the increase in the rate of positive surgical margins in each study. In order to inform clinical practice, more research is needed to elucidate the role of anesthesia technique in surgical outcomes, particularly independent of surgeon factors and tumour pathology in a large patient cohort.

In contrast, we retrospectively studied anesthesia data in prospectively collected oncologic data from a large consecutive series of patients treated by a single experienced surgeon to identify the association of anesthesia technique on prostate cancer recurrence. Importantly, we examined data of patients with prostate cancer who were treated with RP before, during, or after a period in which spinal anesthesia was used based on the preferences of the surgeon (P.T.S.). After this period, general anesthesia became the preferred technique for RP as part of an institutional initiative to standardize RP clinical pathways. In our view, this quasi-experimental analysis of time trend and transition in standard of care reduces the confounding by indication.

A potential confounding variable is differences in outcome attributed to opioid use between the groups. Studies have reported suppression in cell-mediated and humoral immunity associated with opioids.[19] Experiments in animal models have shown a reduced burden of metastatic tumours associated with enhanced activity of natural killer cells by non-opioid analgesics.[20] We acknowledge that patients in the spinal anesthesia group received minimal doses of fentanyl in comparison with the general anesthesia group, which potentially could favour better outcomes in the spinal anesthesia group. All prostate cancer patients treated by RP in this study were enrolled in standardized clinical postoperative pathways. Although we did not present data on opioid requirements, consistent with our clinical experience, once the spinal anesthetic wore off, patients required a similar range of opioid analgesia postoperatively, thereby reducing the effect of this potentially confounding variable on the recurrence of tumours. Furthermore, a randomized study of spinal anesthesia compared with general anesthesia in men treated with RP failed to show a difference in pain on postoperative day one.[21] Therefore, it is unlikely that one group would have been exposed to significantly more opioids postoperatively to impact cancer outcomes.

The difficulty in measuring differences in disease recurrence by comparing anesthesia technique is related to the latent natural history of prostate cancer.[22] Biochemical recurrence, defined as elevation of PSA after RP, is a commonly accepted surrogate marker for metastatic progression and disease-specific survival. Nevertheless, BCR is not synonymous with the detection of clinically significant prostate cancer. The median interval between BCR and metastasis is eight years, and the median interval between metastasis and death is five years.[23,24] Therefore, prospective studies would require lengthy follow-up to yield informative data regarding prostate cancer deaths. Importantly, a prospective evaluation lacking randomization of treatment groups based on anesthesia technique still does not equate to causation.

Our study has several limitations and considerations. First, the influence of selection bias in a large observational retrospective study cannot be dismissed. Nevertheless, the study design mitigates factors related to selection bias by adjusting for factors associated with BCR and comparing patient outcomes before an institutional shift in anesthesia care for RP with outcomes of patients treated after this period. Second, we did not characterize the effect of specific perioperative anesthetic agents that have been shown to interfere with immune mechanisms.[11] Third, the reported results do not address other important clinical endpoints, including survival. Nevertheless, BCR is a highly predictive intermediate endpoint for survival and increases the probability for disease-related interventions, including hormone therapy and radiation treatment, associated with adverse events. The strengths of our study include the large cohort of patients treated by a single experienced surgeon and critical evaluation of anesthetic technique in a model adjusting for known tumour characteristics and postoperative risk factors associated with BCR. In addition, surgical technique, clinical management, and patient selection criteria are consistent throughout the study period; therefore, the results of this multivariable analysis evaluating anesthetic technique on outcomes in the period 1999-2008 are strengthened using this period analysis approach.

This study emphasizes real-world difficulties in conducting prospective trials to evaluate the impact of spinal anesthesia on cancer-specific outcomes. Currently, there are three ongoing prospective randomized controlled trials regarding the effect of spinal anesthesia on the recurrence of colorectal, lung, and breast cancers (ClinicalTrials.gov identifiers NCT00418457, NCT011 79308, and NCT00684229). A fourth trial in endometrial cancer (ClinicalTrials.gov NCT00531349) was abandoned because of a lack of accrual, which exemplifies the practical difficulty in enrolling a large cohort for these investigations. In order to show the survival advantage in a future randomized trial – assuming five-year follow-up and a study design powered to find a 10% reduction in risk – more than 25,000 subjects would be required. Moreover, analysis of disease-specific outcomes would necessitate ten to 15 years of follow-up. Therefore, prospective trials in prostate cancer of sufficient power and duration are unlikely.

In the absence of prospective trials evaluating the preventative effect of spinal anesthesia on cancer recurrence, the estimates of improved cancer survival attributed to anesthetic technique based on retrospective studies should be interpreted cautiously. We did not find evidence to suggest an oncologic benefit of spinal anesthesia despite a large cohort of patients with prostate cancer adjusted for case mix and controlling for surgeon experience.

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**Conflicts of interest** None declared.

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