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Potential Influence of the Anesthetic Technique Used during Open Radical Prostatectomy on Prostate Cancer-related Outcome

A Retrospective Study

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ABSTRACT

Background: Recently published studies suggest that the anesthetic technique used during oncologic surgery affects cancer recurrence. To evaluate the effect of anesthetic technique on disease progression and long-term survival, we compared patients receiving general anesthesia plus intraoperative and postoperative thoracic epidural analgesia with patients receiving general anesthesia alone undergoing open retropubic radical prostatectomy with extended pelvic lymph node dissection.

Methods: Two sequential series were studied. Patients receiving general anesthesia combined with epidural analgesia (January 1994–June 1997, n = 103) were retrospectively compared with a group given general anesthesia combined with ketorolac-morphine analgesia (July 1997–December 2000, n = 158). Biochemical recurrence-free survival, clinical progression-free survival, cancer-specific survival, and overall survival were assessed using the Kaplan–Meier technique and compared using a multivariate Cox-proportional-hazards regression model and an alternative model with inverse probability weights to adjust for propensity score.

Results: Using propensity score adjustment with inverse probability weights, general anesthesia combined with epidural analgesia resulted in improved clinical progression-free survival (hazard ratio, 0.45; 95% confidence interval, 0.27–0.75, $P = 0.002$). No significant differences in the two groups were found for biochemical recurrence-free survival, cancer-specific survival, or overall survival. Higher preoperative serum values for prostate-specific antigen, specimen Gleason score of at least 7, non–organ-confined tumor stage, and positive lymph node status were independent predictors of biochemical recurrence-free survival.

Conclusions: General anesthesia with epidural analgesia was associated with a reduced risk of clinical cancer progression. However, no significant difference was found between general anesthesia plus postoperative ketorolac-morphine analgesia and general anesthesia plus intraoperative and postoperative thoracic epidural analgesia in biochemical recurrence-free survival, cancer-specific survival, or overall survival.

What We Already Know about This Topic

- Whether intraoperative anesthetic management affects cancer progression after cancer surgery is unclear

What This Article Tells Us That Is New

- In a nonrandomized, retrospective review of more than 250 patients having retropubic prostatic resection for cancer, there was no difference in biochemical recurrence-free survival, overall survival, or cancer-specific survival in a comparison of general anesthesia and general anesthesia plus epidural anesthesia/analgesia, although the risk of clinical cancer progression was reduced with the latter combined technique

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RECENTLY published studies suggest that the anesthetic technique performed during oncologic surgery affects disease recurrence.[1,2] Among the possible reasons for this effect are the influence of the anesthetic technique itself or the effect of the specific anesthetic drug on host and tumor cell biology. Combined regional and general anesthesia has been reported to decrease the recurrence rate after surgery for breast cancer (paravertebral block)[2] and prostate cancer (thoracic epidural analgesia),[1] but no data have been

published on the effects of various types of anesthesia on cancer-specific and overall survival.

Open radical retropubic prostatectomy is one of several options to treat significant prostate cancer.[3–5] Outcome after open radical retropubic prostatectomy is dependent on tumor stage, Gleason score, lymph node stage, margin status, and possibly the extent of pelvic lymph node dissection.[6–11] The goal of this study was to determine whether the type of anesthesia performed during a standardized open radical retropubic prostatectomy for prostate cancer affects disease progression and/or survival.

Materials and Methods

This study was approved by the Ethics Committee of the University Hospital Bern, Berne, Switzerland (Kantonale Ethik Kommission Bern). Our institution has performed the same standardized open radical retropubic prostatectomy with extended pelvic lymph node dissection for the last 20 yr, and all patients are followed prospectively.[6,12–17] The data on all 307 patients (median age, 64 yr; interquartile range, 57–67 yr) who underwent open radical retropubic prostatectomy with pelvic lymph node dissection for clinically localized prostate cancer between January 1994 and December 2000 were reviewed concerning the type of anesthesia performed. Until June 1997, all patients received general anesthesia combined with intraoperative and postoperative thoracic epidural analgesia (TEA). Thereafter, until December 2000, general anesthesia with IV ketorolac and morphine for postoperative analgesia was provided. The anesthetic technique was changed in 1997 because of vasodilation as a result of sympathicolysis induced by TEA; the intention was to reduce intraoperative blood loss and to introduce ketorolac to the postoperative analgesic concept.

For purposes of this study, the patients were divided into two groups: "general anesthesia/TEA," patients who underwent combined general anesthesia with intraoperative and postoperative TEA (n = 103, series 1, January 1994–June 1997), and "general anesthesia/IV analgesia," patients given general anesthesia alone with postoperative IV ketorolac and morphine for analgesia (n = 158, series 2, July 1997–December 2000) Patients (n = 45) who needed opioids postoperatively because of insufficient TEA or for whom ketorolac was contraindicated were excluded from the study; one further patient was lost to follow-up and excluded.

All 261 patients underwent the same balanced general anesthesia, including induction with thiopental (2–3 mg/kg), fentanyl (2 μg/kg), rocuronium (0.1 mg/kg), or atracurium (0.5 mg/kg). Anesthesia was maintained with nitrous oxide and isoflurane.

For TEA, the catheter was placed at thoracic level T10–T11 or T11–T12 and activated intraoperatively with 0.25% bupivacaine at a rate of 8–10 ml/h. Patients given TEA received no cyclooxygenase inhibitors intraoperatively. For postoperative epidural analgesia, a standard solution containing 0.1% bupivacaine combined with 2 μg/ml epinephrine and 2 μg/ml fentanyl was administered at a rate of 8–15 ml/h for at least 48 h after surgery. In addition, 1,000 mg paracetamol was given intravenously every 6 h.

For patients with general anesthesia/IV analgesia, 1–2 μg/kg boluses of fentanyl were given intraoperatively at the discretion of the anesthesiologist. The standard postoperative analgesia in these patients consisted of 30 mg ketorolac intravenously every 8 h and 1,000 mg paracetamol intravenously every 6 h over 48 h. Morphine 2 mg intravenously was given at the patient's request to supplement analgesia. The first dose of ketorolac was administrated at the time of fascial closure.

Baseline data evaluated were age, American Society of Anesthesiologists (ASA) physical status classification, duration of anesthesia, blood loss, transfusion, total intraoperative dose of fentanyl, preoperative prostate-specific antigen levels (PSA), specimen Gleason score, tumor (pT) stage, and nodal (pN) stage (TNM classification of malignant tumors of the International Union Against Cancer 1997). Specimen Gleason scores were categorized into three groups: Gleason score under 7, Gleason score equal to 7, and Gleason score above 7. Tumors were classified as organ-confined (pT1 to pT2c) and non–organ-confined (pT3a to pT4).

Statistics

The two anesthetic groups were compared on potential baseline confounders using chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables (table 1). Biochemical recurrence (BCR) was defined as a PSA value more than 0.2 ng/ml. Clinical progression was defined as radiologic evidence of local recurrence or distant metastatic disease. BCR-free survival was calculated from operation to BCR or death, clinical progression-free survival from operation to clinical progression or death, cancer-specific survival from operation to death due to tumor, and overall survival from operation to death of any cause. For patients who had not experienced the event of interest, the respective event time was censored at the time of the last urologic follow-up. For cancer-specific survival it could also be censored at death not caused by tumor. The four endpoints were estimated using the Kaplan–Meier method.

Because patients were not randomly allocated to the two anesthetic groups, the propensity score was applied to reduce the potential bias and to make the two groups more comparable.[18] A logistic regression of anesthetic technique on all baseline variables (table 1) was fit; the propensity score was defined as the probability of receiving general anesthesia/TEA. The resulting c-index was 0.943, indicating excellent discrimination.[19] The distributions of propensity scores in the two groups were so different that it was unfeasible to use the matching or the stratification method to balance between groups with respect to the propensity score.

The joint effects of anesthetic technique and potential baseline confounders on BCR-free survival, clinical progression-free survival, cancer-specific survival, and overall survival were therefore analyzed using multivariate Cox proportional hazard regression models including the propensity score as a covariate. Confounders considered were age, ASA physical status, preoperative PSA

Table 1. Demographic, Oncologic, and Operative Characteristics of Patients Undergoing Radical Prostatectomy with Extended Pelvic Lymph Node Dissection

	General Anesthesia with Intravenous Ketorolac-Morphine Analgesia (n = 158)	General Anesthesia with Epidural Analgesia (n = 103)	*P* Value
Age (yr)	64 [59–68]	63 [57–67]	0.29*
ASA physical status			
I	35 (22)	10 (10)	0.01†
II	106 (67)	74 (72)	—
III	17 (11)	19 (18)	—
Preoperative PSA (ng/ml)	11.0 [7.0–17.1]	12.3 [7.5–21.9]	0.14*
Organ-confined disease (pT1-2abc)	87 (55)	50 (49)	0.30†
Non–organ-confined disease (pT3a–4)	71 (45)	53 (51)	—
Positive lymph nodes (pN+)	35 (22)	30 (29)	0.20†
Specimen Gleason score (<7)	99 (62)	65 (63)	0.86†
Specimen Gleason score (=7)	34 (22)	24 (23)	—
Specimen Gleason score (>7)	25 (16)	14 (14)	—
Duration of anesthesia (min)	230 [195–265]	210 [180–240]	0.09*
Blood loss (ml)	1,200 [900–1700]	1,500 [1,000–2000]	0.06*
Transfusion (yes/no)	16 (10)	22 (21)	0.01†
Intraoperative Fentanyl (mg)	0.70 [0.55–0.80]‡	0.30 [0.20–0.50]§	< 0.0001*

Data reported as number (%) and median [first-third quartile].

* *P* values obtained from Wilcoxon rank sum test. † *P*-values obtained from chi-square test. ‡ Two missing values. § One missing value. ASA = American Society of Anesthesiologists; pN = nodal stage; PSA = prostate-specific antigen; pT = tumor stage.

levels, duration of anesthesia, blood loss, specimen Gleason score (less than 7, equal to 7, and more than 7), organ-confined or non–organ-confined disease, positive lymph nodes (pN+), and transfusion. To achieve model parsimony and stability, the backward selection procedure was applied with the drop-out criterion *P* more than 0.1 but the propensity score and anesthetic technique were forced to stay in the model. To have a better graphical presentation of the endpoints with adjustment for a continuous covariate, an alternative analysis was performed to adjust for propensity score with inverse probability weights.[20]

The significance level for all parameters was 0.05. Because this study is exploratory, no correction for multiple testing was applied. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC.).

Results

There was no statistically significant difference between the two anesthetic groups with regard to baseline parameters with the exception of ASA physical status ($P = 0.01$), dose of fentanyl received intraoperatively ($P < 0.0001$), and transfusion ($P = 0.01$) (table 1). The median follow-up time was 8.5 yr in the general anesthesia/IV analgesia group and 11.9 yr in the general anesthesia/TEA group ($P < 0.0001$).

BCR-free Survival

The unadjusted estimate of BCR-free survival rate was 54% [95% confidence interval, 46–61%] and 50% [40–59%] at 5 yr and 31% [19–43%] and 30% [22–39%] at 10 yr in the general anesthesia/IV analgesia group and the general anesthesia/TEA group, respectively.

Specimen Gleason scores of 7 and more than 7 compared with Gleason scores less than 7 (hazard ratio [HR] 2.09, $P = 0.0001$ and HR 3.39, $P < 0.0001$), non–organ-confined disease (HR 1.93, $P = 0.0001$), preoperative PSA levels (HR 1.02, $P < 0.0001$), and blood transfusion (HR 1.45, $P = 0.08$) were negative predictors (table 2). The effect of anesthetic technique was not significant in the Cox model (HR 0.82, $P = 0.42$) or in the adjusted analysis with inverse probability weights (HR 1.14, $P = 0.40$, fig. 1).

Clinical Progression-free Survival

In the general anesthesia/IV analgesia group and the general anesthesia/TEA groups, the unadjusted estimates of clinical progression-free survival rate were 77% [95% confidence interval, 69–83%] and 76% [67–83%], respectively, at 5 yr and 64% [55–72%] and 62% [52–71%], respectively, at 10 yr.

Specimen Gleason scores equal to 7 and more than 7 compared with Gleason scores less than 7 (HR 1.69, $P = 0.07$ and HR 3.87, $P < 0.0001$), age (HR .05, $P = 0.01$) and positive lymph nodes (HR 4.07, $P < 0.0001$) were negative predictors (table 2). The beneficial effect of the general anesthesia/TEA was significant in the Cox model (HR 0.40, $P = 0.009$) and in the adjusted analysis with inverse probability weights (HR 0.45, $P = 0.002$, fig. 2).

Cancer-specific Survival

In the general anesthesia/IV analgesia and the general anesthesia/TEA groups, the unadjusted estimates of cancer-specific survival rate were 95% [95% confidence interval, 90–97%] and 92% [84–96%], respectively, at 5 yr and 87% [78–92%] and 86% [78–92%], respectively, at 10 yr.

Specimen Gleason scores equal to 7 and more than 7 (HR 5.29, $P = 0.02$ and HR 16.60, $P < 0.0001$), non–organ-confined disease (HR 2.92, $P = 0.07$), and positive lymph

Table 2. Biochemical Recurrence (BCR)-free Survival, Clinical Progression-free Survival, Cancer-specific Survival, and Overall Survival in a Multivariate Cox Regression Model Including the Propensity Score and in an Analysis Adjusted for Propensity Score with Inverse Probability Weights

	Multivariate Cox Model		Adjusted Analysis with Inverse Probability Weights	
	Hazard Ratio (95% CI) for BCR Recurrence or Death	*P* Value	Hazard Ratio (95% CI) for BCR Recurrence or Death	*P* Value
General Anesthesia with TEA *vs.* General Anesthesia with IV Analgesia	0.82 (0.50–1.34)	0.421	1.14 (0.84–1.54)	0.399
Preoperative PSA (ng/ml)	1.02 (1.01–1.03)	< 0.0001	—	—
pT Stage (Non–organ-confined *vs.* Organ-confined)	1.93 (1.38–2.68)	0.0001	—	—
Transfusion (yes *vs.* no)	1.45 (0.95–2.20)	0.084	—	—
Specimen Gleason score	—	—	—	—
7 *vs.* <7	2.09 (1.44–3.05)	0.0001	—	—
>7 *vs.* <7	3.39 (2.22–5.19)	< 0.0001	—	—
Propensity Score	1.41 (0.72–2.76)	0.311	—	—
Clinical Progression-free Survival	Hazard Ratio (95% CI) for Progression or Death	*P* Value	Hazard Ratio (95% CI) for Progression or Death	*P* Value
General Anesthesia with TEA *vs.* General Anesthesia with IV Analgesia	0.40 (0.20–0.79)	0.009	0.45 (0.27–0.75)	0.002
Age (yr)	1.05 (1.01–1.09)	0.010	—	—
pN Stage (Positive *vs.* Negative)	4.07 (2.51–6.59)	< 0.0001	—	—
Specimen Gleason score	—	—	—	—
7 *vs.* <7	1.69 (0.96–2.96)	0.068	—	—
>7 *vs.* <7	3.87 (2.19–6.81)	< 0.0001	—	—
Propensity Score	4.14 (1.70–10.13)	0.002	—	—
Cancer-specific Survival	Hazard Ratio (95% CI) for Cancer-specific Death	*P* Value	Hazard Ratio (95% CI) for Cancer-specific Death	*P* Value
General Anesthesia with TEA *vs.* General Anesthesia with IV Analgesia	0.95 (0.36–2.47)	0.947	0.45 (0.18–1.13)	0.089
pT Stage (Non–organ-confined *vs.* Organ-confined)	2.92 (0.93–9.16)	0.066	—	—
pN Stage (Positive *vs.* Negative)	2.51 (0.97–6.46)	0.058	—	—
Specimen Gleason score	—	—	—	—
7 *vs.* <7	5.29 (1.32–21.21)	0.019	—	—
>7 *vs.* <7	16.59 (4.30–63.99)	< 0.0001	—	—
Propensity Score	2.02 (0.61–6.72)	0.251	—	—
Overall Survival	Hazard Ratio (95% CI) for Any Death	*P* Value	Hazard Ratio (95% CI) for Any Death	*P* Value
General Anesthesia with TEA *vs.* General Anesthesia with IV Analgesia	1.01 (0.44–2.32)	0.975	0.61 (0.29–1.28)	0.190
pN Stage (Positive *vs.* Negative)	2.48 (1.31–4.67)	0.005	—	—
Specimen Gleason score	—	—	—	—
7 *vs.* <7	2.05 (0.95–4.43)	0.066	—	—
>7 *vs.* <7	4.54 (2.15–9.56)	< 0.0001	—	—
Propensity Score	1.76 (0.63–4.93)	0.281	—	—

CI = confidence interval; IV = intravenous; pN = nodal stage; PSA = prostate specific antigen; pT = tumor stage; TEA = thoracic epidural analgesia.

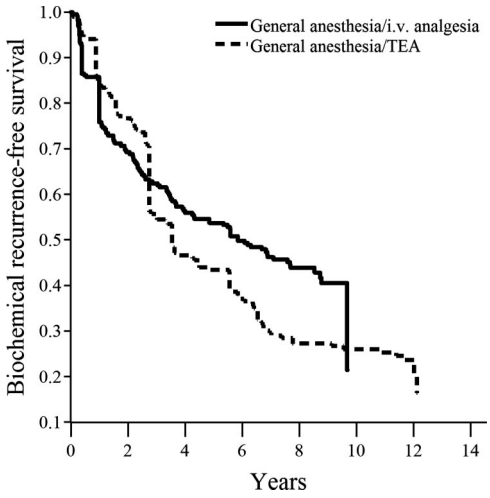

Fig. 1. Biochemical recurrence-free survival curves adjusted for propensity score with inverse probability weights in 158 patients given general anesthesia with ketorolac-morphine analgesia (general anesthesia/intravenous [i.v.] analgesia) and in 103 patients given combined general anesthesia and thoracic epidural analgesia (general anesthesia/thoracic epidural analgesia [TEA]) ($P = 0.399$).

nodes (HR 2.51, $P = 0.06$) were negative predictors (table 2). The effect of anesthetic technique was not significant in the Cox model (HR 0.95, $P = 0.91$) or in the adjusted analysis with inverse probability weights (HR 0.45, $P = 0.089$, fig. 3).

Overall Survival

In the general anesthesia/IV analgesia group and the general anesthesia/TEA groups, the unadjusted estimates of overall survival rate were 93% [95% confidence interval, 88–96%] and 86% [78–92%], respectively, at 5 yr and 79% [70–86%] and 77% [68–84%], respectively, at 10 yr.

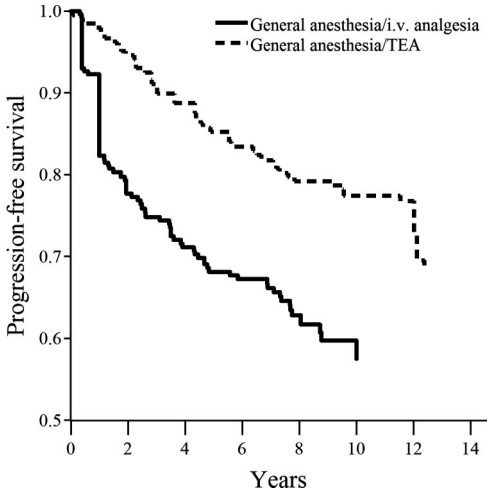

Fig. 2. Clinical progression-free survival curves adjusted for propensity score with inverse probability weights in 158 patients given general anesthesia with ketorolac-morphine analgesia (general anesthesia/intravenous [i.v.] analgesia) and in 103 patients given combined general anesthesia and thoracic epidural analgesia (general anesthesia/thoracic epidural analgesia [TEA]) ($P = 0.002$).

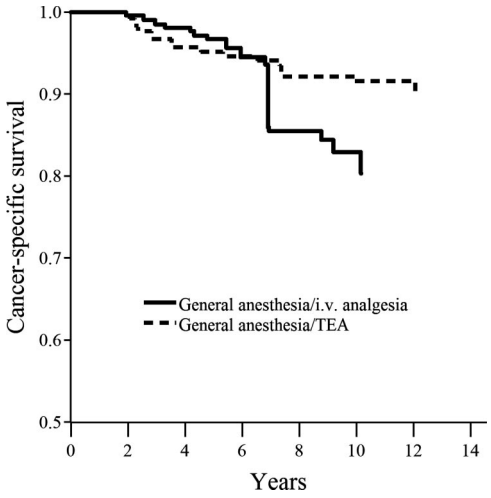

Fig. 3. Cancer-specific survival curves adjusted for propensity score with inverse probability weights in 158 patients given general anesthesia with ketorolac-morphine analgesia (general anesthesia/intravenous [i.v.] analgesia) and in 103 patients given combined general anesthesia and thoracic epidural analgesia (general anesthesia/thoracic epidural analgesia [TEA]) ($P = 0.089$).

High specimen Gleason score equal to 7 and more than 7 (HR 2.05, $P = 0.07$ and HR 4.54, $P < 0.0001$) and positive lymph nodes (HR 2.48, $P = 0.005$) were negative predictors (table 2). The type of anesthesia was not a significant predictor of overall survival in the Cox model (HR 1.01, $P = 0.97$) or in the adjusted analysis with inverse probability weights (HR 0.61, $P = 0.19$, fig. 4).

Discussion

Two studies have shown that combined regional and general anesthesia may be associated with a reduced risk of cancer

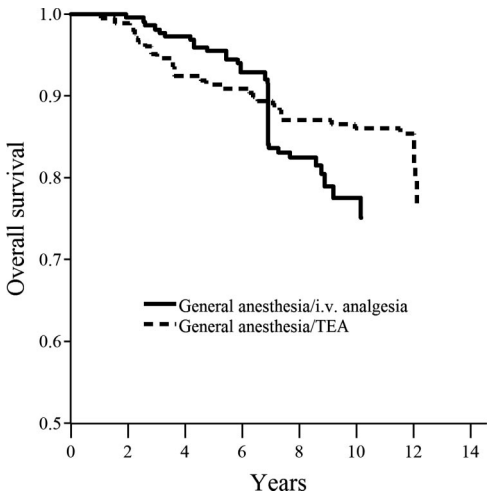

Fig. 4. Overall survival curves adjusted for propensity score with inverse probability weights in 158 patients given general anesthesia with ketorolac-morphine analgesia (general anesthesia/intravenous [i.v.] analgesia) and in 103 patients given combined general anesthesia and thoracic epidural analgesia (general anesthesia/thoracic epidural analgesia [TEA]) ($p = 0.19$).

recurrence in prostate[1] and breast cancer.[2] Furthermore, three large prospective multicenter randomized studies on gynecologic tumors have been initiated to test the hypothesis that local or distal recurrence is reduced in patients undergoing paravertebral blockade (ClinicalTrials.gov identifier NCT00418457) or epidural analgesia (NCT00531349 and NTC00295945), reflecting the growing interest in this topic.

The factors supporting a positive effect of regional anesthesia/analgesia are the lower suppression of the host's adapted and innate immune responses, the reduced release of stress factors, and decreased need for volatile anesthetics and IV opioids.[21,22] Excess prostaglandin release and endogenous cortisol contribute to postoperative immune suppression.[23] Regional anesthesia/analgesia attenuates the release of endogenous opioids, reduces the need for anesthetic gases, and lowers the dosage of morphine.[24] A consequently less compromised immune response would be expected with a better inhibition of tumor growth and spread. Reducing surgical stress response by regional analgesia, however, does not lead to inhibition of neoangiogenesis in breast cancer.[25] On the other hand, nonsteroidal antiinflammatory substances inhibit the synthesis of prostaglandins and have therefore been suggested as potential chemopreventive agents. Cyclooxygenase 2 is induced in response to tumor promoters and prostaglandin synthesis is increased in prostate cancer in humans.[26]

In our study, after adjusting for the propensity score, we found a significant difference in clinical progression-free survival between the two groups, suggesting that the general anesthesia/TEA technique was more beneficial. In the present study, in which the number of patients is comparable with that in the study by Biki *et al.*,[1] we found no difference between the two groups in BCR-free survival. More importantly, we could not find a significant difference between the two groups in cancer-specific or overall survival outcome variables, which were not evaluated by Biki *et al.*[1] The lack of significance might be due to small sample size and nonproportional hazards.

In multivariate analyses, BCR-free survival was associated with higher preoperative PSA values, pT stage, transfusion, and specimen Gleason scores. This is in line with the literature showing that BCR after open radical retropubic prostatectomy with pelvic lymph node dissection is associated with multiple factors, including pretreatment PSA levels, specimen Gleason score, pathologic stage, lymph node status, and surgical margin status.[8,27,28] The cumulative cancer-specific survival and overall survival found in this study are comparable with that reported after open radical retropubic prostatectomy for clinically localized prostate cancer.[5,29] Because approximately 50% had non–organ-confined prostate cancer and as such were at high risk for disease progression, an anesthesia-dependent difference in outcome should be discernible. In cohorts composed of only low-risk patients, by contrast, detection of an anesthesia/analgesia-dependent influence on disease-specific survival may be more difficult.

We could not confirm the effect on BCR-free survival observed by Biki *et al.*[1]; however, we did find a difference in recurrence-free survival, which was not reported in their study. This may be the result of the dissimilar effect of the different drugs applied. Opioids have been shown to have an adverse effect on the immune system by impairing cellular and humoral immune functions.[30–32] Another effect of opioids is the promotion of angiogenesis-dependent tumor growth through the μ receptors present on endothelial cells, which has been observed in a human breast cancer xenograft model.[33] There is also evidence that morphine induces neoangiogenesis in animals.[31] For intraoperatively administrated fentanyl, the immune suppression is thought to be dose-dependent.[30] Although more fentanyl was administrated to our patients who did not receive epidural analgesia, we could not demonstrate a negative effect of the fentanyl dosage on survival in the univariate and multivariate analyses. Ketorolac, by contrast, may reduce cancer progression based on the overexpression of the cyclooxygenase 2 enzyme in prostate cancer cells compared with normal or benign hypertrophied cells.[26] Cyclooxygenase 2 inhibitors induce apoptosis in prostate cancer cell lines.[34,35]

The present retrospective study has limitations: it was not randomized, and a selection bias cannot be definitively ruled out, even with the propensity score analysis. Two consecutive series of patients were studied and the change in anesthetic technique was applied to all subsequent patients. Surgical and anesthetic procedures are also well standardized in our institution, so that the patients in each group underwent comparable surgery and anesthesia. The potential difference between anesthetic groups might be diluted because of some imbalanced baseline characteristics. The nearly nonoverlapping distributions of propensity scores of the two anesthetic groups imply that the group status might be confounded by other factors. Hence, we cannot rule out the possibility that the observed between-group differences might be due at least in part to the difference in the confounding factors. The most possible confounder is intraoperatively administrated fentanyl. The assumption of proportion hazard was not satisfied in many analyses; hence, Cox regression is not the most powerful approach to detect difference. This is clearly a retrospective study, and we cannot rule out the possibility that we did not have enough statistical power to detect potential differences between the two anesthetic groups.

Conclusions

In this retrospective study, a positive effect of epidural analgesia on clinical progression-free survival was observed, confirming the previously reported effect on cancer-related outcome. In addition, no significant difference was found in BCR-free, cancer-specific, or overall survival between general anesthesia combined with TEA and general anesthesia alone plus postoperative morphine-ketorolac analgesia in patients undergoing open radical retropubic prostatectomy with extended pelvic lymph node dissection. Prospective, randomized, controlled clinical trials are warranted to reliably assess this important clinical question.

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