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Cancer-Free or Overall Survival Rate Following Radical Prostatectomy is not Influenced by Perioperative Pain Management

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Abstract

Objective: There is controversial data regarding influence of anesthetic techniques on the outcome of patients undergoing cancer surgery. In particular, whether patients benefit from the application of regional techniques is elaborately discussed. Therefore we enrolled a retrospective analysis to determine the influence of different anesthetic techniques in patients who underwent radical prostatectomy due to prostate cancer.

Methods: After ethics approval, we viewed our medical record archive for patients that received radical prostatectomy between 1995 and 2005 and included 300 patients. They were divided according to their postoperative pain regime (systemic opioids vs. epidural analgesia). Recurrence-free survival was defined as the primary endpoint and overall survival as the secondary endpoint. The study period covered at least the first five post-operative years.

Results: We documented no difference in recurrence-free or overall survival comparing the two analgesic regimes. However, we observed that higher body-mass-indexes (BMI) significantly correlated with a worse outcome (recurrence-free survival p=0.037, overall survival p=0.02). Other factors influencing the outcome were the Gleason score (5-6 vs. 10 p=0.016; 7 vs. 10 p=0.08) and surgical margins free of cancer (p=0.04).

Conclusion: In this study, different anesthetic techniques did not influence recurrence-free or overall survival rate. Interestingly, we could identify BMI as a risk factor with potential impact on the outcome of patients undergoing radical prostatectomy. Adequately powered prospective randomized trials are required to decide on the effect of regional anesthesia in patients who underwent radical prostatectomy.

Keywords: Pain management; Epidural analgesia; PCA; Prostatectomy; Retrospective

Introduction

According to the World Health Organization (WHO), cancer is the second leading cause of death in higher-income countries [1]. Because of this, there is continuous research to optimize cancer treatment. However, even though surgical control of the primary cancer may be achieved, patients die from systemic spreading of the disease. Contributing factors for metastases are the release of malignant cells during operation [2,3], pre-existing micrometastases before the operation and a perioperative depression of the immune system as a consequence of the surgical stress response [4-7]. Being a vital part of the immune system, natural killer cells (NK cells) seem to play the main role in controlling malignant cells [8].

As several anesthesia-related factors, e.g. opioids and inhalational agents [9,10] have a negative impact on the activity of NK cells, the combination of general and regional anesthesia appears to be a swift way to reduce the perioperative demand for systemic and inhalational agents. Additionally, sufficient regional anesthesia attenuates the surgical stress response through modulation of the sympathetic nervous system [11,12]. Already several investigators have tried to determine these effects, but while data for breast cancer [13] and melanoma [14] showed a positive effect of regional anesthesia on the long-term survival, in patients with prostate cancer controversial results were obtained [15,16]. In their retrospective analysis of patients undergoing open radical prostatectomy, Biki and co-workers documented a significant decrease in biochemical cancer recurrence (defined as an increase in prostate-specific antigen, PSA) after 36 months in those men who had an epidural anesthesia in addition to general anesthesia compared to general anesthesia alone [15]. In a similar approach, Wuethrich retrospectively analysed patients undergoing open radical prostatectomy [16]. In contrast to the study by Biki, after 10 years no differences in biochemical cancer recurrence were detected.

Given this background with conflicting data, we tried to contribute with our survey to the growing body of evidence that anesthetic management may influence cancer recurrence in patients with radical prostatectomy due to prostate cancer.

Methods

After approval of the ethics committee, we checked our archives for patients who underwent radical retropubic prostatectomy between 01.01.1995 and 31.05.2005. Criteria for inclusion were: completely documented, standardized postoperative pain management either by intravenous patient-controlled analgesia with piritramide (i.v. pca; bolus: 1.5 mg, blocking period: 10 min, 4 h maximum: 30 mg) or by continuous epidural analgesia (EA; bupivacaine 0.06% with fentanyl 2 µg ml^{-1}). All patients had the same anesthesiological treatment based on these institutional standard operation procedures. While obtaining written informed consent, the patients' postoperative pain regime–EA or systemic opioids-was defined.

We excluded patients who underwent additional chemo-, radio-

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or hormone-therapy, who had inadequate epidural analgesia or those with incomplete documentation (e. g. lack of documentation of pain scale, analgesics given, etc.).

In the morning prior to the operation, the patients received oral premedication with oxazepam (5-10 mg). General anesthesia was induced by intravenous administration of fentanyl followed by thiopental, propofol or etomidate. Neuromuscular relaxation was achieved by atracurium, suxamethoniumchlorid or rocuronium and followed by endotracheal intubation. Anesthesia was maintained with a N_2O/O_2-mixture (FiO_2 0.3-0.5) and isoflurane. If necessary, bolus injections of fentanyl or relaxant were administered repeatedly. After the year 2000, isoflurane was replaced by sevoflurane and N_2O was left out. After 2004, sufentanil was used instead of fentanyl.

In the Post-Anesthesia Care Unit (PACU), intravenous pain control was achieved by piritramide bolus injection. Sufficient pain control was defined by rest pain not exceeding 3 on a numeric rating scale ranging from zero to ten. Thereafter, i.v. PCA was started.

In EA patients, a lumbar epidural catheter (L2-4) was placed prior to the induction of general anesthesia (loss of resistance method, intrathecal position was ruled out by the administration of 3-4 ml of lidocaine 1% with added epinephrine 1:200 000). This was followed by balanced general anesthesia as described above. Approximately 30-45 min prior to emergence from anesthesia, 15 ml of bupivacaine 0.25% was injected through the epidural catheter. Once the surgery had been completed, general anesthesia was terminated and patients were extubated in the presence of adequate spontaneous ventilation and sufficient reflex activity. After arrival at the PACU, an epidural infusion of bupivacaine/fentanyl was started. The primary infusion rate was calculated according to the patient's body length and ranged between 12 and 20 ml per minute (maximum dose 0.4 mg kg h^{-1} bupivacaine and 50 µg h^{-1} fentanyl). In the presence of inadequate analgesia (rest pain >3 on a numeric rating scale ranging from zero to ten), metamizole was infused intravenously (5000 mg/24 h) as a rescue protocol. Furthermore pain was treated with bolus injection of 5-10 ml of lidocain 1% followed by 5 ml bupivacain 0.25 % and a stepwise increase of the infusion rate of 2-4 ml/h. In the case of persistent inadequate analgesia (defined as unchanged pain after 30 min), epidural analgesia was discontinued and converted to systemic opioid analgesia as described above. Such patients were excluded from the survey.

Statistics

Statistic analysis was performed using SPSS (SPSS Version 18, SPSS GmbH Software, Chicago, Illinois). Recurrence-free survival was defined as the primary endpoint and overall survival as the secondary endpoint. The influence of anesthesia and ASA-classification on overall survival and recurrence-free survival was tested with log-rank tests. For identification of prognostic-relevant factors we conducted a Cox-regression. After that we tried to identify relevant variables in the Cox-regression with a forward stepwise selection model. To secure the detected variables we applied a backward stepwise selection model for control.

Results

By checking the database of our pain service, we identified 982 patients for this retrospective study, whereof 345 had an i.v. PCA and 637 an EA for postoperative pain treatment. We had to exclude 682 patients because of incomplete documentation, loss to follow-up or insufficient EA with subsequent change in pain management. The groups were unequally distributed with 108 patients (36%) in the i.v. PCA group and 192 patients (64%) in the EA group (Figure 1). There were no significant differences in the demographic distributions of age, ASA or body mass index (BMI) between the groups (Table 1). Clinical presentation and histopathology also did not differ between the groups (Table 2).

Recurrence-free survival

Biochemical recurrence–the primary endpoint in recurrence-free survival–was defined as postoperative increase in PSA >0.1 ng ml^{-1} and clinical recurrence–the secondary endpoint–was defined as detection of metastases. Recurrence-free survival was accordingly defined as the time between operation and death without any sign of recurrence. There was no difference between the treatment groups (Table 3 and Figure 2). Additionally, ASA-state, age and Gleason score had no influence on the recurrence-free survival time (Table 4). However, we documented a significant influence of the surgical margin (p=0.04) and the BMI (p=0.037).

Patients without cancer-free surgical margins had a significantly higher risk for cancer recurrence than patients with R0 resection (cancer-free surgical margin). With a hazard ratio of 1.59, these patients had a 58.6% higher risk for PSA increase or growth of metastases compared to patients with margins free of cancer. Also, patients with BMI values exceeding 25 had an increased risk of cancer recurrence. Each BMI unit above 25 was attended by a 7.3% higher risk of this fatal event.

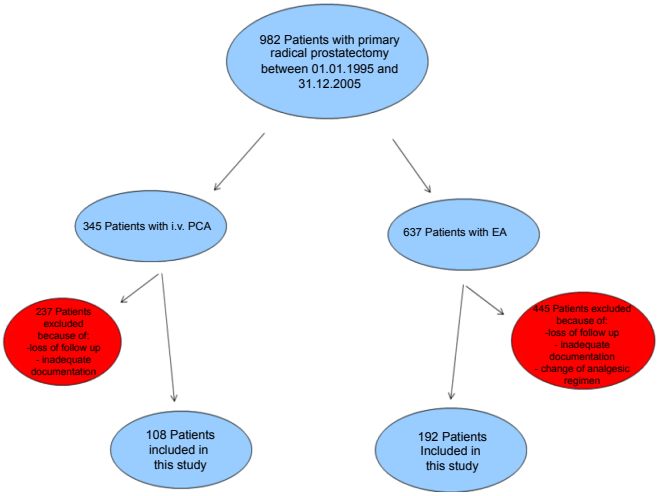

Figure 1: CONSORT flow diagram.

	i.v. PCA	*EA*
Patients treated	108 (36.0%)	192 (64.0%)
Age [years]		
average/median	73.1/74.0	74.2/74.0
standard deviation	6.8	6.4
minimum	54.0	54.0
maximum	88.0	88.0
BMI [kg m^{-2}]		
normal weight (18.5-25)	42 (39.6%)	75 (39.0%)
overweight (25.1-30)	47 (44.3%)	100 (52.1%)
obese (>30)	17(16.1%)	17 (8.9%)
ASA		
- 1 (healthy)	7 (6.5%)	21 (11.0%)
- 2 (mild systemic disease)	60 (55.5%)	107 (56.0%)
- 3 and 4 (severe systemic disease with constant threat to life)	41 (38.0%)	63 (33.0%)

Table 1: Demographic distribution.

		i.v. PCA	*EA*
PSA preoperative [ng/ml]			
	average/median	4.0/9.2	13.3/8.5
	standard deviation	18.9	19.7
	minimum/maximum	0.0/160.0	0.0/168.0
Gleason score			
	2-4	4 (4.5%)	5 (3.5%)
	5-6	23 (25.8%)	43 (30.3%)
	7	42 (47.2%)	61 (43.0%)
	8-10	20 (22.5%)	33 (23.2%)
prostate weight [g]			
	average/median	37.4/30.0	37.5/30.0
	standard deviation	22.5	27.8
	minimum/maximum	7.0/150.0	0.0/300
TNM classification			
Nx	yes	8 (7.5%)	21 (11.2%)
	no	98 (92.5%)	166 (88.8%)
N0	yes	93 (87.7%)	158 (84.5%)
	no	13 (12.3%)	29 (15.5%)
N1	yes	5 (4.7%)	8 (4.3%)
	no	101 (95.3%)	179 (95.7)
M0	yes	105 (100.0%)	180 (98.4%)
	no		3 (1.6%)
M1	yes		2 (1.1%)
	no	105 (100.0%)	181 (98.9%)
R0	yes	82 (78.1%)	143 (79.0%)
	no	23 (21.9%)	38 (21.0%)
R1	yes	23 (21.9%)	38 (21.0%)
	No	82 (78.1%)	143 (79.0%)

Table 2: Clinical symptoms and histopathology.

		i.v. PCA	EA
biochemical recurrence (PSA >0.1ng/ml)			
	yes	45 (42.9%)	79 (42.5%)
	no	60 (57.1%)	107 (57.5%)
metastases			
	yes	5 (4.7%)	14 (7.7%)
	no	101 (95.3%)	169 (92.3%)
death			
	yes	14 (13.6%)	30 (16.6%)
	no	89 (86.4%)	151 (83.4%)

Table 3: Clinical outcome.

	i.v. PCA	*EA*
ASA		
- 1 (healthy)	7 (6.4%)	21 (11.0%)
- 2 (mild systemic disease)	60 (55.6%)	107 (56.0%)
- 3 and 4 (severe systemic disease with constant threat to life)	41 (38.0%)	63 (33.0%)
age [years]		
50-59	5 (3.8%)	4 (2.1%)
60-69	24 (18.2%)	35 (18.2%)
70-79	58 (43.9%)	108 (56.3%)
80-89	45 (34.1%)	45 (23.4%)
Gleason-Score		
2-4	4 (4.6%)	5 (3.5%)
5-6	23 (25.8%)	43 (30.3%)
7	42 (47.2%)	61 (43.0%)
8-10	20 (22.4%)	33 (23.2%)
tumour-free surgical margin	82 (36.4%)	143 (63.6%)
pain management	108 (36.0%)	192 (64.0%)
bmi [kg m^{-2}]		
normal weight (18.5–25)	42 (39.6%)	75 (39.0%)
overweight (25.1–30)	47 (44.3%)	100 (52.1%)
obese (>30)	17 (16.1%)	17 (8.9%)

Table 4: Factors potentially influencing the recurrence-free survival.

Overall survival

There was no difference in the median survival time between the treatment groups. Other factors without influence on overall survival were cancer-free surgical margin and age of patient (Table 5). The ASA state showed a non-significant tendency to influence overall survival (p=0.055, Table 5). In contrast, Gleason score and BMI had a significant impact on the overall survival (Table 5). A preoperative Gleason score of 5-6 reduced the risk for death by 72.4% (p=0.016) compared to a Gleason score of 10. With a Gleason score of 7 the risk for dying was still reduced by 69.6% (p=0.008). Patients with a BMI>30 had a significantly higher risk of dying than patients with BMI between 18.5 and 25 (p=0.002).

Discussion

Cancer-related deaths are still increasing and factors affecting the outcome of patients with malignancies are of growing interest. Thus, the perioperative anesthetic management in cancer surgery came into scientific focus and brought promising results [13-19]. Compared to previous investigations, in our retrospective survey different anesthetic

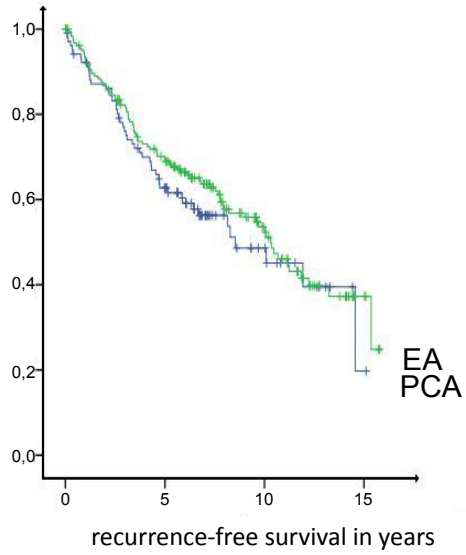

Figure 2: Correlation between recurrence-free survival and pain treatment (Cumulative survival).

	i.v. PCA	*EA*
ASA		
- 1 (healthy)	7 (6.5%)	21 (11.0%)
- 2 (mild systemic disease)	60 (55.6%)	107 (56.0%)
- 3 and 4 (severe systemic disease with constant threat to life)	41 (37.9%)	63 (33.0%)
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Table 5: Factors potentially influencing overall-survival.

management did not result in different cancer-related outcomes. However, we identified other factors with influence on our patients' outcomes. Patients with surgical margins free of cancer had a better recurrence-free survival but similar overall survival in comparison to those with residual cancer. Interestingly, patients with higher BMI had a lower recurrence-free survival and lower overall survival.

The main results of our study are concordant with the findings of Wuethrich and co-workers who likewise compared cancer-patients after prostatectomy with regard to the anesthetic management [16]. In total 261 patients with either EA or i.v. PCA were analysed retrospectively. Covering a study period of 10 years, no difference in overall survival or recurrence-free survival was documented. In contrast to these findings are the results of Biki and co-workers. In a similar design they analysed 225 patients that had either EA or i.v. PCA with morphine for postoperative pain management after radical prostatectomy. Their follow-up lasted 3 years and they documented a significant difference in recurrence-free survival time (EA 93%; PCA 78% $p<0.01$).

Several factors may have contributed to these different results, e.g. different time-spans were regarded. After 3 years of surveillance, our data also suggests a beneficial impact of EA regarding recurrence-free survival. However, this difference equalized after some more years. Along with this, the data of Wuethrich and co-workers displayed the same beneficial EA effect after 3 years, whereas after 4 years recurrence-free survival rates changed to become better in the i.v. PCA group.

Another methodological problem impedes the comparison of the three studies, as different systemic opioids were administered. We used piritramide, and Biki and Wuethrich used morphine. It is well known that different opioids have different impacts on the integrity of the immune system [20]. Furthermore, there was no detailed information concerning non-opioid analgesics, even though their application is mentioned. Unfortunately the same is true for our patient collective, because of missing data regarding the co-analgesics. There was a standard regimen consisting of paracetamol as a co-analgesic, but it was at the discretion of the treating physician to use other non-opoids in addition to or as replacement of paracetamol. Potential beneficial effects of non-opioid analgesics are currently under discussion and seem granted for diclofenac and paracetamol [21,22]. So even if theoretically the non-opioids should be equally distributed in both study groups, a potential effect of either strategy could be enhanced or blunted by them. Further limitations are associated with the studies' retrospective and therefore neither randomized nor controlled design. This makes the studies more vulnerable to confounders. So, on one hand, a long study period enables reliable outcome data to be obtained, but on the other hand-even if surgical technique does not change significantly over the observed years-it seems certain that different surgeons with different experiences and skills will conduct the operations. Concerning anesthetic management, the transition from thiopental to propofol, from isoflurane to sevoflurane and abandoning nitrous oxide may itself have influenced the outcome of our patients [23-25]. The use of etomidate, which is known to inhibit the function of the adrenal cortex [26], could have influenced the outcome just as well, but was equally used in both groups. Therefore it should not have influenced the result of our study. Yet, despite the above named flaws, retrospective surveys still serve to generate a hypothesis and not to approve or refuse one. Adequately designed randomized controlled trials (RCTs) are underway to address this topic [27]. So even if we did not confirm the results of Biki, it seems too early to neglect the idea that anesthetic management has an impact on cancer development.

Several of our findings were in concordance with other investigators. Like Biki, we documented a longer overall survival rate in patients with lower Gleason scores [28-30] and affirmed the importance of cancer-free surgical margins regarding recurrence-free survival time [31,32]. Interestingly, cancer-free surgical margins had no influence on the overall survival rate [32]. Furthermore we could confirm the results of a meta-analysis that found a higher recurrence rate for different malignancies in obese patients [33]. If this association is related to more than just difficult surgical conditions or belongs to pro-cancer effects of fatty tissue itself was not in the focus of our survey, but clearly contrasts earlier stated adipo-protective effects [34,35].

Conclusion

In this retrospective study, different postoperative pain management (EA vs. i.v. PCA) after radical prostatectomy did not influence patient outcome in regard to cancer–free or overall survival. These findings are contrary to other published data. However, due to methodological limitations, a final assessment cannot be made. Only adequately designed RCTs enable us to answer the question of whether regional anesthesia has a beneficial influence on the outcome of patients after prostatectomy.

Till then, the proven effects of EA–reduced opioid and inhalational agent requirements–may be considered in the anesthetic management of these patients.

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This work contains parts of the medical thesis work of MP.

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