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Opioids and premature biochemical recurrence of prostate cancer: a randomised prospective clinical trial

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Abstract

Background: Prostate cancer is one of the most prevalent neoplasms in male patients, and surgery is the main treatment. Opioids can have immune modulating effects, but their relation to cancer recurrence is unclear. We evaluated whether opioids used during prostatectomy can affect biochemical recurrence-free survival.

Methods: We randomised 146 patients with prostate cancer scheduled for prostatectomy into opioid-free anaesthesia or opioid-based anaesthesia groups. Baseline characteristics, perioperative data, and level of prostate-specific antigen every 6 months for 2 yr after surgery were recorded. Prostate-specific antigen >0.2 ng ml^{-1} was considered biochemical recurrence. A survival analysis compared time with biochemical recurrence between the groups, and a Cox regression was modelled to evaluate which variables affect biochemical recurrence-free survival.

Results: We observed 31 biochemical recurrence events: 17 in the opioid-free anaesthesia group and 14 in the opioid-based anaesthesia group. Biochemical recurrence-free survival was not statistically different between groups (P=0.54). Cox regression revealed that biochemical recurrence-free survival was shorter in cases of obesity (hazard ratio [HR] 1.63, confidence interval [CI] 0.16–3.10; p=0.03), high D'Amico risk (HR 1.58, CI 0.35–2.81; P=0.012), laparoscopic surgery (HR 1.6, CI 0.38–2.84; P=0.01), stage 3 tumour pathology (HR 1.60, CI 0.20–299) and N1 status (HR 1.34, CI 0.28–2.41), and positive surgical margins (HR 1.37, CI 0.50–2.24; P=0.002). The anaesthesia technique did not affect time to biochemical recurrence (HR −1.03, CI −2.65–0.49; P=0.18).

Conclusions: Intraoperative opioid use did not modify biochemical recurrence rates and biochemical recurrence-free survival in patients with intermediate and high D'Amico risk prostate cancer undergoing radical prostatectomy.

Clinical trial registration: NCT03212456.

Keywords: biochemical recurrence; cancer recurrence; multimodal analgesia; opioid; opioid-free anaesthesia; prostatectomy; prostate cancer

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Editor's key points

- Opioid use has been implicated in cancer recurrence.
- A small prospective randomised trial evaluated whether opioids used during prostatectomy affect biochemical recurrence-free survival in prostate cancer.
- Intraoperative opioid use did not modify biochemical recurrence rates and biochemical recurrence-free survival in patients with intermediate and high D'Amico risk prostate cancer after radical prostatectomy.
- Future studies with larger sample sizes and longer follow-up periods are required to determine whether opioids can change oncological outcomes.

Prostate cancer is among the most prevalent cancers in men,[1] and surgery is the main treatment. Outcomes after radical retropubic prostatectomy depend on tumour evolution that can be defined by D'Amico classification risk,[2] lymph node stage, and the margins of the resected tumour.[3] Events in the perioperative period, such as surgical manipulation of the tumour, blood transfusion, pain, and severe hypothermia, may also affect the oncological outcome.[4] The consequences of these events include development of a complex inflammatory response; depression of the immune system; and activation of the hypothalamus–pituitary–adrenal axis.[5,6] In this context, the decisions by the anaesthesiologist in the intraoperative period may play an important role in cancer outcome.

Opioids have the potential to cause significant harm despite their benefits. As a result, strategies such as multimodal opioid-sparing and opioid-free techniques have been developed. Since opioids are the standard treatment for severe pain, anaesthesia was often based on the use of opioids. However, there is a trend to limit opioid use in the perioperative period because of their many adverse effects, including nausea and vomiting, hyperalgesia, postoperative opioid abuse, and deaths.[7] As a result there has been growing use of multimodal analgesia, the use of multiple analgesic agents simultaneously to suppress nociceptive signalling during both general and regional anaesthesia, aiming to reduce or avoid use of opioids.[8–10]

Opioids also have immune modulating effects when used in oncological patients.[11] Their effects on cancer recurrence remain controversial. Biochemical recurrence in patients with prostate cancer has been shown to be reduced in patients who received epidural anaesthesia *vs* opioid-based anaesthesia (OBA).[12] Similar studies have been published, most of them retrospective with several confounding variables, lack of a standard definition of recurrence-free survival, different tumour types, and different techniques of anaesthesia.[13–16] The aim of this study was to determine, from evaluation of data for biochemical recurrence and postoperative discharge from hospital, whether the use of opioids during radical retropubic prostatectomy for prostate cancer affects progression of disease.

Methods

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) and carried out at the Instituto do Câncer do Estado de São Paulo (ICESP). It was registered with ClinicalTrials.gov (NCT03212456). The primary outcome was to evaluate whether the use of opioid-free anaesthesia (OFA) is associated with reduction in biochemical recurrence compared with OBA; the secondary outcomes were postoperative pain, need for rescue analgesia, patient satisfaction, adverse events, and postoperative neutrophil-to-lymphocyte ratio (NLR) between the two groups.

Trial design and participants

This was a prospective, randomised, blinded clinical trial. Patients were considered eligible if they were aged 40–80 yr, diagnosed with localised prostate cancer with moderate or high risk of biochemical recurrence according to D'Amico criteria, and scheduled for open or laparoscopic prostatectomy. Exclusion criteria were patients who did not agree to sign the informed consent, coagulopathy, or contraindications for transversus abdominis plane (TAP) block, atrioventricular block or a concomitant procedure during prostate surgery. Patients were assessed on the day before surgery by one of the members of the research team, who evaluated eligibility and obtained the written informed consent.

Randomisation and blinding

The research team used an internet-based system (www.random.org, accessed on 10 January 2017). Patients were randomly assigned in a 1:1 ratio to either an OFA or OBA group. Patients, anaesthetists, and surgeons remained blinded to the assignment group during the whole perioperative period. The researchers who assessed postoperative prostate-specific antigen (PSA) were aware of the randomisation of patients; this information was obtained by medical records for each subject.

Procedures and outcomes

Anaesthesia induction was standardised in both groups with propofol (1.5–2.5 mg kg^{-1}), dextroketamine (0.1 mg kg^{-1}), lidocaine (1.0 mg kg^{-1}), and cisatracurium (0.15 mg kg^{-1}). The OFA group received a TAP block with ropivacaine 0.375%, 20 ml on each side; the OBA group received a TAP block with saline 20 ml on each side, and fentanyl 3–5 μg kg^{-1}.

Anaesthesia was maintained in both groups with propofol by target-controlled infusion (Marsh model, target 2–3 ng ml^{-1}), dextroketamine (0.1 mg kg^{-1} h^{-1}), lidocaine (1.0 mg kg^{-1} h^{-1}), and dexmedetomidine (0.2–0.7 μg kg^{-1} h^{-1}). Subjects received additional doses of fentanyl, as required.

Data collected in the intraoperative period included: age, ASA physical status, weight, height, BMI, Gleason score, D'Amico classification, preoperative NLR, blood loss, blood transfusion, total intraoperative dose of fentanyl, and surgery technique (open or laparoscopic). The following were assessed in the postoperative period: numeric pain scale; need for rescue analgesia; adverse events, such as nausea and vomiting, hypotension, and somnolence; patient satisfaction with anaesthetic technique ranging from 0 (worst) to 10 (best perception); and time (in min) to discharge from the PACU. The following data were also recorded: postoperative NLR, length of hospital stay, histological type of prostate cancer, surgical margins, pathological stages (tumour and lymph nodes), International Society of Urological Pathology classification, and PSA level every 6 months after surgery to evaluate biochemical recurrence and biochemical recurrence-free periods. A PSA >0.2 ng ml^{-1} was considered to be biochemical recurrence.

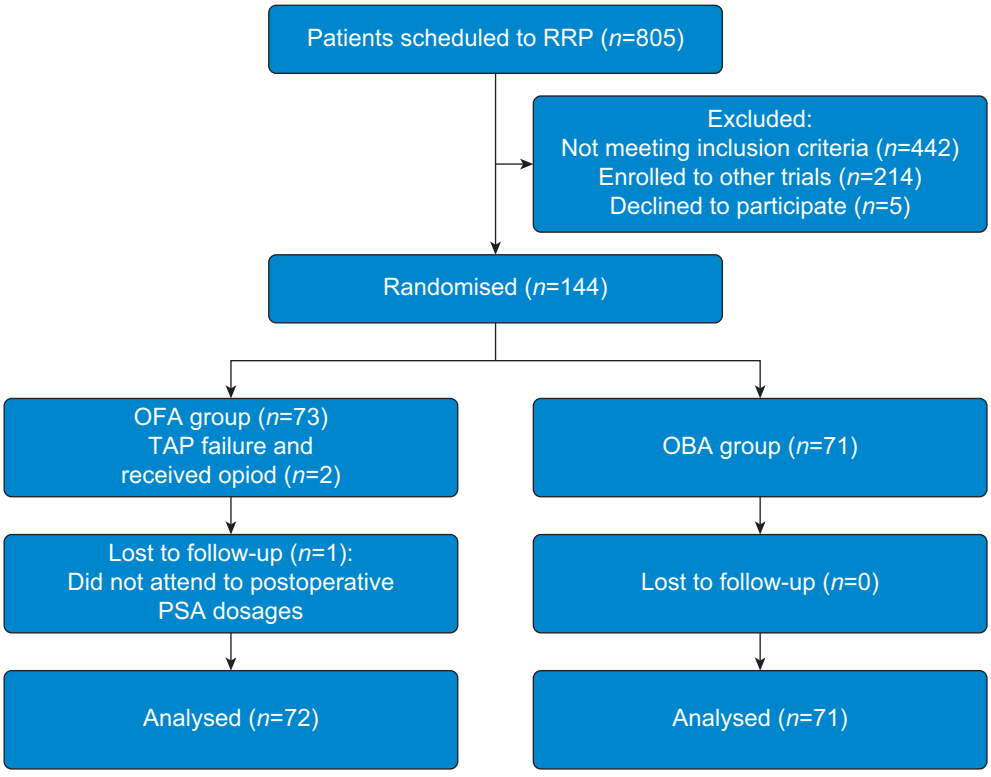

Fig 1. Flowchart of the study. OBA, opioid-based anaesthesia; OFA, opioid-free anaesthesia; PSA, prostate-specific antigen; RRP, radical retropubic prostatectomy; TAP, transversus abdominis plane.

Statistical analyses

Sample sizes were calculated considering a biochemical recurrence incidence of about 35%[17] and a reduction in biochemical recurrence incidence of 20%, with 95% confidence level, 80% power, and 5% dropout rate. We estimated that a total of 146 subjects would be required to detect a difference between groups at a significance level of 5% (two-sided).[18]

Sample distributions were evaluated using the Shappiro–Wilk test to evaluate data normality. The OFA and OBA groups were compared on baseline data using the χ^2 test for categorical data and the Wilcoxon rank sum test for continuous variables with non-normal distribution. Categorical data are presented by absolute (*n*) and relative (%) frequencies, and continuous variables as medians and interquartile ranges (25th–75th).

To analyse the difference between the groups in biochemical recurrence incidence and survival free of biochemical recurrence, the intention-to-treat principle was adopted. For subjects who had not experienced biochemical recurrence, time was ended at the day of the last urologic follow-up. For subjects who experienced biochemical recurrence, time was ended at the day of the positive PSA.

Survival analysis to compare biochemical recurrence-free periods between groups was performed using the Kaplan–Meier method and the confidence interval (CI) was obtained by logit transformation. A log-rank test was made to evaluate whether the curves of the two groups were similar or not. To assess which variables affected the time until biochemical recurrence, a Cox proportional hazards regression model was adjusted, considering anaesthetic group, age, BMI, preoperative NLR, bleeding, need for blood transfusion, surgical technique, pain, need for morphine rescue in the PACU, and total use of opioids in the perioperative period.

A significance level of $P<0.05$ was adopted for all tests. All statistical analyses were conducted in R software (R Development Core Team, 2016, version 4.0.2) using RStudio (version

Table 1 Baseline subject characteristics. NLR, neutrophil-to-lymphocyte ratio.

	Opioid-free anaesthesia	Opioid-based anaesthesia
Age (yr)	67 (63–73)	67 (63–71)
BMI, *n* (%)		
Normal	25 (34.2)	19 (25.3)
Overweight	29 (39.7)	39 (54.9)
Obesity	19 (26)	14 (19.7)
ASA physical status, *n* (%)		
2	64 (87.6)	64 (90.1)
3	9 (12.4)	7 (9.9)
D'Amico risk classification, *n* (%)		
Intermediate	44 (60.2)	49 (69)
High	29 (39.8)	22 (31)
Prostate volume (g)	40 (27–59)	46 (35–69.5)
Preoperative NLR	2.37 (1.85–2.82)	1.81 (1.45–2.69)
Total	**73**	**71**

Table 2 Perioperative data. ISUP, International Society of Urological Pathology.

	Opioid-free anaesthesia	Opioid-based anaesthesia	P-value
Blood loss (ml)	600 (400–1000)	600 (300–1000.75)	0.91
Blood transfusion, *n* (%)			0.72
No	68 (93.1)	64 (90.1)	
Yes	5 (6.9)	7 (9.9)	
Surgical technique, *n* (%)			0.89
Conventional	44 (60.2)	41 57.8)	
Laparoscopic	29 (39.8)	30 (42.2)	
Lymphadenectomy, *n* (%)			0.61
Obturatory	35 (47.9)	38 (53.5)	
Extended	38 (52.1)	33 (46.5)	
Pain in PACU, *n* (%)			0.03
No pain/light pain	50 (68.5)	60 (84.5)	
Moderate/severe	23 (31.5)	11 (15.5)	
Analgesia rescue with morphine, *n* (%)			0.09
No	51 (69.8)	59 (83)	
Yes	22 (30.2)	12 (17)	
PACU adverse events, *n* (%)			1.0
No	68 (93.1)	66 (92.9)	
Yes	5 (6.9)	5 (7.1)	
Satisfaction score	10 (9–10)	10 (9–10)	0.98
PACU discharge (min)	120 (95–155)	139.5 (99.25–182.5)	0.19
Hospital length of stay (days)	2 (1–3)	2 (1–3)	0.49
Postoperative NLR	6.57 (4.51–10.95)	6.96 (4.18–11.73)	0.80
Surgical margins, *n* (%)			0.66
Negative	49 (67)	51 (72)	
Positive	24 (33)	20 (28)	
Histological type, *n* (%)			0.11
Usual acinar adenocarcinoma	72 (98.6)	66 (92.9)	
Mixed acinar/ductal adenocarcinoma	1 (1.4)	5 (7.1)	
Pathology stage, tumour, *n* (%)			1.0
T2	40 (55)	38 (53.5)	
T3	33 (45)	33 (46.5)	
Pathology stage, lymph node, *n* (%)			0.56
N0	63 (87.5)	57 (83)	
N1	9 (12.5)	12 (17)	
ISUP classification, *n* (%)			0.52
1	3 (4)	4 (6)	
2	29 (40)	34 (48.5)	
3	25 (34)	15 (21)	
4	3 (4)	4 (6)	
5	13 (18)	13 (18.5)	
Biochemical recurrence, *n* (%)			0.71
No	55 (76.4)	57 (80.3)	
Yes	17 (23.6)	14 (19.7)	
Postoperative follow-up (days)	366 (170–677)	352 (176.5–682)	0.87
Total	**73**	**71**	

1.3.31073; R Foundation for Statistical Computing, Vienna, Austria).

Results

From January, 2017 to February, 2020, 144 subjects were enrolled, and 73 were randomised to the OFA group and 71 to the OBA group. Three were lost to follow-up, one in the OFA group and two in the OBA group. The study flowchart is shown in Figure 1. Patient characteristics (Table 1) and perioperative data (Table 2) were balanced between groups.

By August, 2020, 31 biochemical recurrence events were observed (22% of sample size): 17 in the OFA group and 14 in the OBA group (P=0.71). The follow-up period was also similar between groups (median of 366 days in the OFA group and 352 in the OBA group, P=0.65). Survival analyses are shown in Figure 2. There was no difference in biochemical recurrence-free survival between the two groups, and this was confirmed by the log-rank test (P=0.54).

The results for the adjusted Cox regression model are shown in Table 3. The survival analysis detected no difference in biochemical recurrence-free time between groups (hazard ratio [HR] −1.03, CI −2.65 to 0.49; P=0.18). Variables in the model that significantly reduced biochemical recurrence-free time were high-risk D'Amico classification (HR 1.58, CI 0.35–2.81; P=0.012), laparoscopic surgery (HR 1.6, CI 0.38–2.84; P=0.01), obesity (HR 1.63, CI 0.16–3.10; P=0.03), pathological stage T3 (HR 1.60, CI 0.20–299), pathological stage N1 (HR 1.34, CI 0.28–2.41), and positive surgical margins (HR 1.37, CI 0.50–2.24; P=0.002). The conditional survival curves for the variables that changed biochemical recurrence-free time are shown in Figure 3.

The median dose of fentanyl used in the OBA group was 4.3 μg kg^{-1}. Two subjects in the OFA group required fentanyl during RRP (radical retropubic prostatectomy), probably

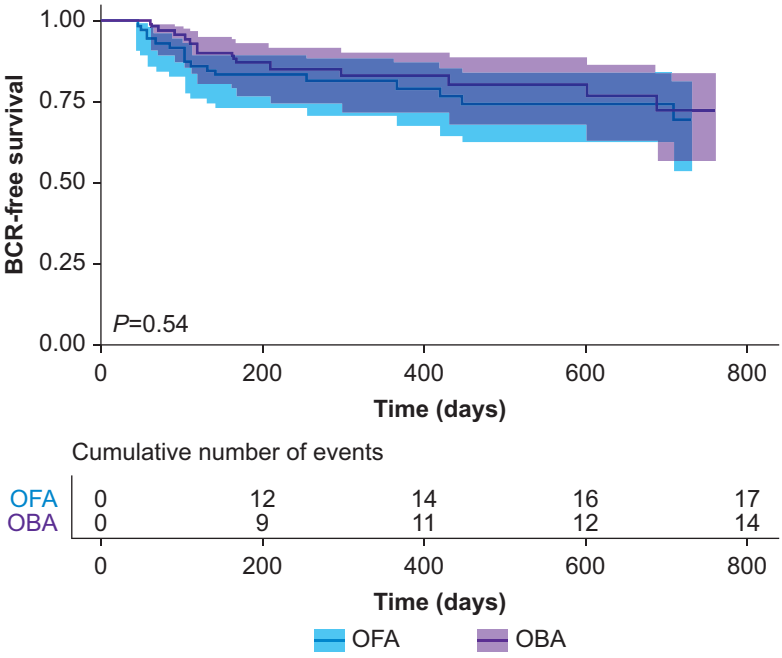

Fig 2. Kaplan–Meier curve for biochemical recurrence-free survival in the OFA and OBA groups. BCR, biochemical recurrence; OBA, opioid-based anaesthesia; OFA, opioid-free anaesthesia.

because of TAP block failure. Subjects in the OFA group had a higher frequency of moderate/severe pain (31% OFA *vs* 15% OBA; P=0.03), but there was no difference in the need for rescue analgesia with morphine in the PACU between groups (P=0.09). There was no difference in adverse events in the PACU between groups (P=1.0). Satisfaction rate was also similar in both groups (both had a median score of 10, P=0.98).

Preoperative NLR showed no association with biochemical recurrence (median 2.17 on biochemical recurrence *vs* 2.01 biochemical recurrence, P=0.84); and postoperative NLR median rates were not significantly different between the two groups (OFA median 6.57, inter-quartile range 4.51–10.95 *vs* OBA median 6.96, inter-quartile range 4.18–11.73, P=0.8).

OFA did not change the time to discharge from the PACU (OFA 120 min *vs* OBA 139.5 min, P=0.19), nor the length of hospital stay (median of 2 days in both groups, P=0.49).

Discussion

After initial treatment for localised prostate cancer, biochemical recurrence is the first signal for local recurrence or metastasis.[19] In our sample, a 21.5% rate of biochemical recurrence was found (11.8% of occurrences were in the OFA group and 9.7% in the OBA group). These values are consistent with biochemical recurrence rates previously reported.[17]

Our results did not show differences in the biochemical recurrence rates and the biochemical recurrence-free survival rates between the two groups, indicating that the intraoperative opioid (fentanyl) did not increase the biochemical recurrence rate, and also did not change the biochemical recurrence-free period for our follow-up (Fig. 2).

Our trial was designed to avoid as many confounding variables as possible, so that the survival analyses could be focused on opioid use. Thus, anaesthetic induction and maintenance were similar between the two groups: both had a multimodal analgesia strategy with drugs that have anti-inflammatory characteristics, preserve the immune system, and reduce the need for opioids in the perioperative period.[20–24] The groups differed only in the analgesia plan: use of TAP block in the OFA group and use of opioids in the OBA group.

Previous reports report that the mean time for biochemical recurrence, considering all D'Amico risk grades, is 3.1 yr.[25] In a review performed by the American Urology Academy when standardising the definition of biochemical recurrence, it was suggested that biochemical recurrence should be diagnosed when PSA is >0.2 ng ml^{-1} at 6–13 weeks after radical retropubic prostatectomy.[26]

The median period of follow-up was 366 days in the OFA group and 352 days in the OBA group, in line with the recommendations. Therefore, the similarity of survival curves in both groups could be a matter of time. Nevertheless, only patients with intermediate or high risk for recurrence were selected, aiming for a higher rate of biochemical recurrence in a shorter period.

A question suggested by our results is the effect of opioids on prostate cancer cells. Zylla and colleagues[27] found a positive correlation between mu opioid receptor expression and worse oncological outcomes, whereas Kampa and colleagues[28] found that opioids might decrease the proliferation of prostate cancer cell lines. Most available evidence evaluating how opioids affect biochemical recurrence of prostate cancer is derived from retrospective analyses with contradictory results.

Analysing the Cox proportional regression to identify which variables could modify biochemical recurrence-free survival, we found that the OFA group did not have longer

Table 3 Cox proportional hazards regression for time to biochemical recurrence. CI, confidence interval; ISUP, International Society of Urological Pathology; LP, laparoscopic prostatectomy; NLR, neutrophil-to-lymphocyte ratio; OBA, opioid-based anaesthesia; OFA, opioid-free anaesthesia; RRP, radical retropubic prostatectomy; Surg. tec., Surgical technique.

	Hazard ratio	Standard error	P-value	CI (2.5–97.5)
OFA group	Ref.			
OBA group	−1.0383	0.7782	0.18	−2.65–0.49
Age	−0.0527	0.0398	0.19	−0.13–0.02
NLR	0.3142	0.2041	0.12	−0.08–0.71
Blood loss	−0.0005	0.0004	0.17	−0.001–0.0002
Blood transfusion—No	Ref.			
Blood transfusion—Yes	−0.1982	0.9766	0.84	−2.11–1.71
BMI—normal	Ref.			
BMI—overweight	0.4419	0.6119	0.47	−0.76–1.64
BMI—obesity	1.6321	0.7517	0.03	0.16–3.10
Intermediate D'Amico	Ref.			
High D'Amico	1.583	0.6288	0.012	0.35–2.81
Surg. tec.—RRP	Ref.			
Surg. tec.—LP	1.6164	0.6278	0.01	0.38–2.84
Pain—no pain/mild	Ref.			
Pain—moderate/intense	−2.0314	1.9995	0.31	−5.95–1.88
Morphine in PACU—No	Ref.			
Morphine in PACU—Yes	1.7454	2.0499	0.39	−2.27–5.76
Perioperative opioid—No	Ref.			
Perioperative opioid—Yes	0.6945	0.8893	0.44	−1.07–2.45
Pathological stage—T2	Ref.			
Pathological stage—T3	1.6001	0.713	0.025	0.20–2.99
Pathological stage—N0	Ref.			
Pathological stage—N1	1.3454	0.5443	0.013	0.28–2.41
Surgical margins—negative	Ref.			
Surgical margins—positive	1.37	0.4435	0.002	0.50–2.24
ISUP—1	Ref.			
ISUP—2	−2.863	1.3132	0.029	−5.44 to −0.29
ISUP—3	−2.1838	1.3441	0.1	−4.82–0.45
ISUP—4	−3.0739	1.7912	0.086	−6.58–0.44
ISUP—5	−2.1679	1.3979	0.12	−4.91–0.57

survival than the OBA group. High risk D'Amico criteria, obesity, laparoscopic surgery, pathological stage T3, pathological stage N1, and positive surgical margins were associated with reduced biochemical recurrence-free survival. Of those results, obesity,[29] high D'Amico risk, pathological stages T3 and N1, and positive surgical margins are in accord with previous findings. As open surgery generates a greater inflammatory response and activation of the neuroendocrine system than laparoscopy,[4] it was expected that open prostatectomy would result in worse biochemical recurrence-free survival. Instead, our results found that laparoscopic surgery was associated with shorter biochemical recurrence-free survival. Previous trials that measured postoperative outcomes in open and laparoscopic prostatectomy concluded that laparoscopy was associated with better urinary and erectile function, lower bleeding, and shorter hospital stay. However, there was no difference in surgical margins and oncological outcomes between open and laparoscopic prostatectomy.[30,31]

In anaesthetic practice, opioids are the standard drugs for maintaining sympathetic control intraoperatively, and treating moderate to severe pain postoperatively. But with the rise of multimodal analgesia this trend has changed. In this context, a TAP block could assist a multimodal analgesia strategy.

To assess analgesic efficacy, we compared numeric pain scale and the need for rescue analgesia with morphine in the PACU. The results showed a greater incidence of moderate to severe pain in the OFA group (23 OFA *vs* 11 OBA; $P=0.03$), but with no difference in morphine need ($P=0.09$). The greater pain in the OFA group is probably related to failures in the TAP block. In addition to the variability in distribution of local anaesthetic, this block is guided by ultrasonography, and therefore efficacy depends on the performance of the anaesthesiologist. The lack of visceral analgesia when using this block may have also played a role in occurrence of pain in the OFA group, as previous reports have shown good analgesia when OFA is associated with regional anaesthesia.[32]

We found no difference between groups in time to PACU discharge or length of hospital stay. These results may be explained by the multimodal analgesia techniques that both groups received, resulting in a reduced fentanyl dose in the OBA group (median of 4.3 $\mu g\,kg^{-1}$). For both groups, the median length of hospital stay was 2 days, significantly lower than the mean hospitalisation period described for radical retropubic prostatectomy (8 days).[33]

Because NLR has been considered a simple and affordable estimation of the inflammatory response that can be associated with a worse oncological outcome,[34–36] we also evaluated the association of preoperative NLR with biochemical recurrence, and compared postoperative NLR between groups. For our sample, preoperative NLR had no association with biochemical recurrence, and postoperative NLR was not different between groups.

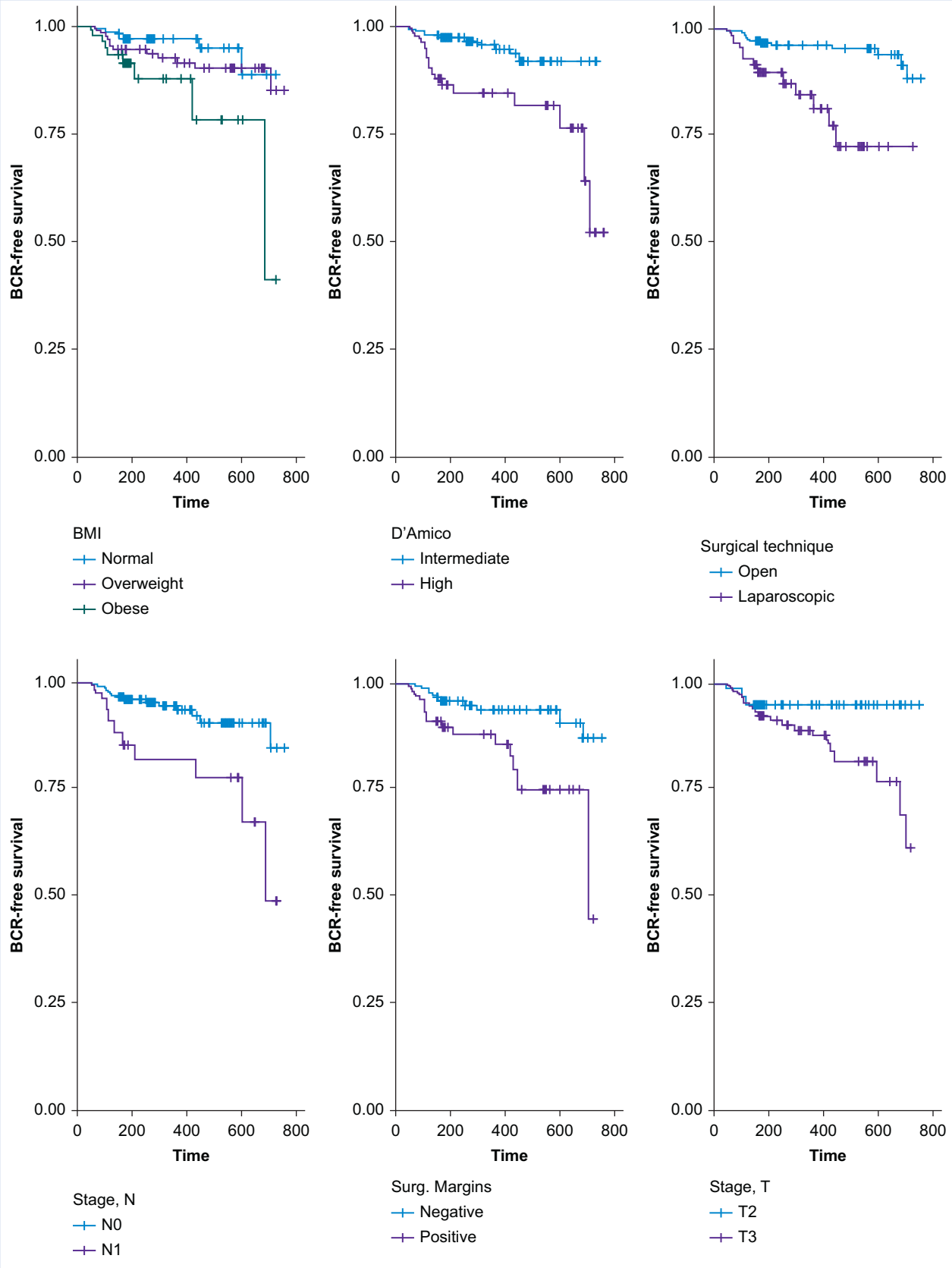

Fig 3. Conditional survival curves for biochemical recurrence with BMI, D'Amico risk classification, surgical technique, tumour stages, and surgical margins. BCR, biochemical recurrence.

Cancer progression is highly complex, modulated by many factors. Anaesthetic practice can improve oncological outcomes by reducing inflammation, enhancing immune function, and preventing pain. The mu opioid receptor is present in several cell types that participate in carcinogenesis and may affect oncogenic outcome,[37,38] such as lymphocytes and neoplastic cells, but whether opioids affect cancer progression is still unknown. Our trial attempted to answer to this question. Limitations include follow-up period and sample size, but it provides results that contribute to further clarification of the role of opioids in cancer progression. Future randomised studies with larger sample sizes and longer follow-up periods are required to determine whether opioids can change oncological outcomes.

We conclude that opioids do not modify biochemical recurrence rates and biochemical recurrence-free survival in patients with intermediate and high D'Amico risk after prostatectomy. Opioids did not increase postoperative NLR compared with OFA. The OFA group had more pain than the OBA group, probably because of TAP block failure, but this was not associated with a higher need for rescue analgesia. Patient satisfaction with anaesthesia technique and adverse events was also similar between groups.

Authors' contributions

Conception and design of the study, patient recruitment, data collection: FPR, CMS
Statistical analysis: FPR, MDC, CMS
Writing of the draft: FPR, JOCAJ, MJCC, MDC, CMS
Final approval of the version to be submitted: JOCAJ, MJCC, MDC, WCN, RFC, CMS
Critical revision: WCN, RFC

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Declarations of interest

The authors declare that they have no conflicts of interest.

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