Table 2. *Bladder compliance before and after drug and Oxo-M administration*

Oxo-M*	No. Rats	Mean ± SEM Bladder Compliance (ml/cm H_2O)		
		Control	After Oxo-M	After Oxo-M + Vehicle or Imidafenacin
+ Highest imidafenacin dose:				
Vehicle	8	0.0155 ± 0.0005	0.0171 ± 0.0008	0.0178 ± 0.0010
Imidafenacin (30 μg/kg)	8	0.0158 ± 0.0013	0.0165 ± 0.0012	0.0179 ± 0.0012
+ CAP:				
Vehicle	6	0.0115 ± 0.0008	0.0125 ± 0.0010	0.0121 ± 0.0009
CAP (10^{-5})	14	0.0143 ± 0.0007	0.0127 ± 0.0008	0.0139 ± 0.0009

*Dose 25 μM at 0.04 ml per minute for 8 minutes.

Therefore, we hypothesized that imidafenacin and 5-HMT would have an inhibitory effect on the SAA of Aδ and C fibers of the mechanosensitive primary bladder afferent nerves. However, our results revealed that neither imidafenacin nor 5-HMT inhibited the SAA of either type of afferent fiber. The great discrepancy between this and previous[5,6] studies may be attributable to the difference of agents or time points after drug administration. In the previous studies changes were assessed 30, 60, 90 and 120 minutes after drug administration but we analyzed changes 3 minutes after drug administration. We further investigated the change in SAA 20 minutes after administering the highest imidafenacin dose (30 μg/kg). The result clearly showed that imidafenacin did not change the SAA of either type of afferent fiber (fig. 2, *C*). Again this was inconsistent with previous findings in studies of oxybutynin and darifenacin.[5,6] Imidafenacin has higher affinity for the M1 and M3 receptor subtypes than for the M2 receptor subtype, darifenacin has higher affinity only for the M3 receptor subtype, and oxybutynin and 5-HMT have affinity for the M1 to M3 subtypes.[2,4] Therefore, mAChR subtype selectivity may not reasonably explain the discrepancy.

Mechanosensitive bladder afferents consist of various nerve types with different response properties to CAP, K^+ and menthol.[20–22] We previously noted that mechanosensitive bladder C-fiber afferents can be classified as CAP sensitive and insensitive with the latter more prevalent and activated by TRPV4 agonists and intravesical ATP instillation.[8,9] Imidafenacin and 5-HMT can inhibit detrusor overactivity through RTX sensitive C fibers in

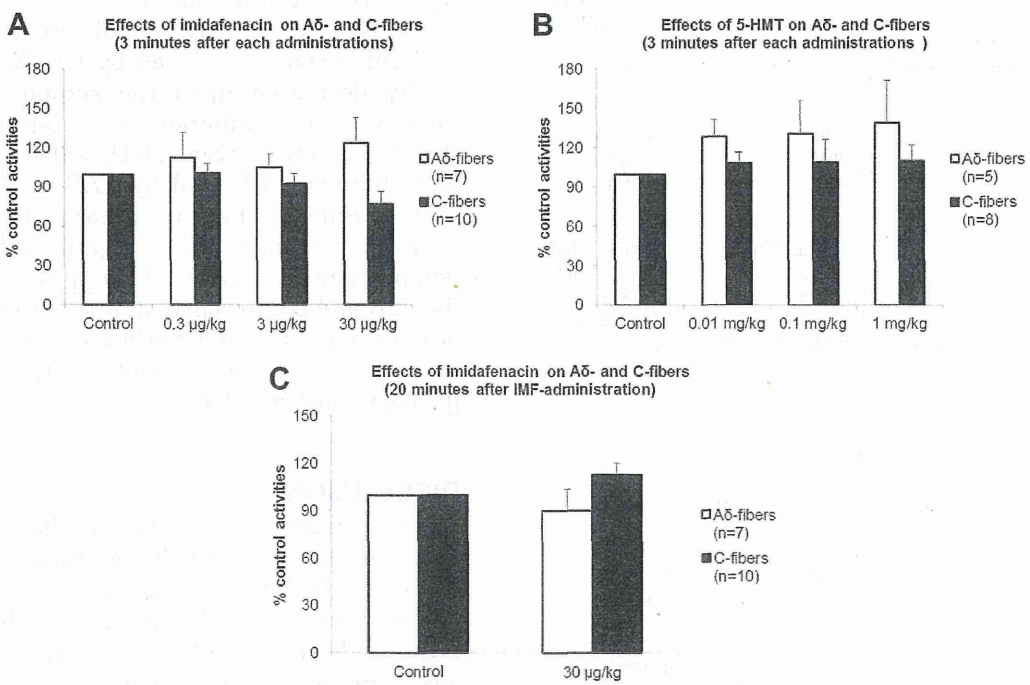

Figure 2. Mean ± SEM responses before and after cumulative intravenous drug administration shown as percent of control activity (*A* to *C*). *IMF,* imidafenacin. No significant difference between control and drug responses (1-way ANOVA and Dunnett test or paired Student t-test).

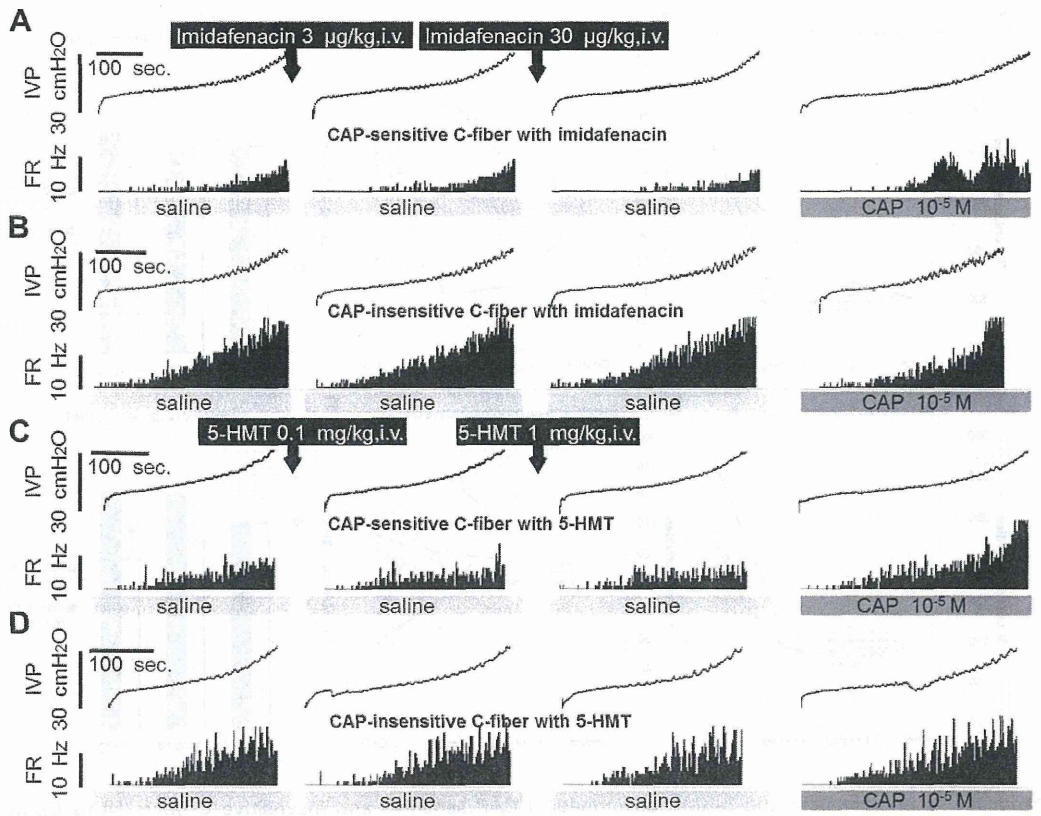

Figure 3. Representative traces show intravesical pressure (*IVP*) and firing rate (*FR*) of mechanosensitive afferent nerve activity by imidafenacin and 5-HMT in CAP sensitive and insensitive C fibers (*A* to *D*). *i.v.*, intravenously.

rats with cerebral infarction.[10,11] Therefore, we postulated that imidafenacin and 5-HMT may contribute to mechano-afferent transduction through CAP sensitive fibers. The results of this study clearly show that imidafenacin and 5-HMT significantly decreased the SAA of CAP sensitive C fibers but not of CAP insensitive C fibers. Thus, it is conceivable that the inhibitory action of imidafenacin and 5-HMT was masked when evaluating the overall C-fiber SAA because of the larger population of the CAP insensitive subgroup.

Selective inhibition on CAP sensitive fibers was observed only at the highest doses of imidafenacin and 5-HMT. To determine whether such high drug doses act on mAChRs or on other effectors located near the bladder lumen, the ie urothelium and/or suburothelial afferent nerves, we further studied intravesical instillation of the mAChR agonist Oxo-M.[14,17,23] As a result, the facilitatory responses of the C-fiber SAA to intravesical Oxo-M was suppressed by the same dose of intravenous imidafenacin. This strongly suggests that the doses of imidafenacin used acted on bladder mAChRs located near the bladder lumen. In terms of overall responses the C fibers that responded to intravesical Oxo-M were significantly activated by intravesical CAP, although some did not respond well to CAP. In contrast, Oxo-M insensitive C fibers did not respond to CAP. These results suggest that CAP sensitive C fibers are mostly responsive to activation of bladder mAChRs by intravesical Oxo-M.

Higher doses of imidafenacin and 5-HMT administered cumulatively significantly increased bladder compliance. However, the highest dose of imidafenacin induced no significant change in bladder compliance 20 minutes after single administration (table 1). This may have been due to the number of cystometry cycles rather than to the pharmacological effects of the agents. Our previous studies using a similar experimental protocol showed a tendency toward increased bladder compliance during repeat measurements even after saline administration, which supports this speculation.[8,24] A previous study using cystometrogram measurements in urethane anesthetized rats demonstrated that imidafenacin at a lower dose (3 μg/kg intravenously) increased bladder capacity without a change in micturition pressure or postvoid residual volume while a dose of 10 μg/kg intravenously decreased micturition pressure and

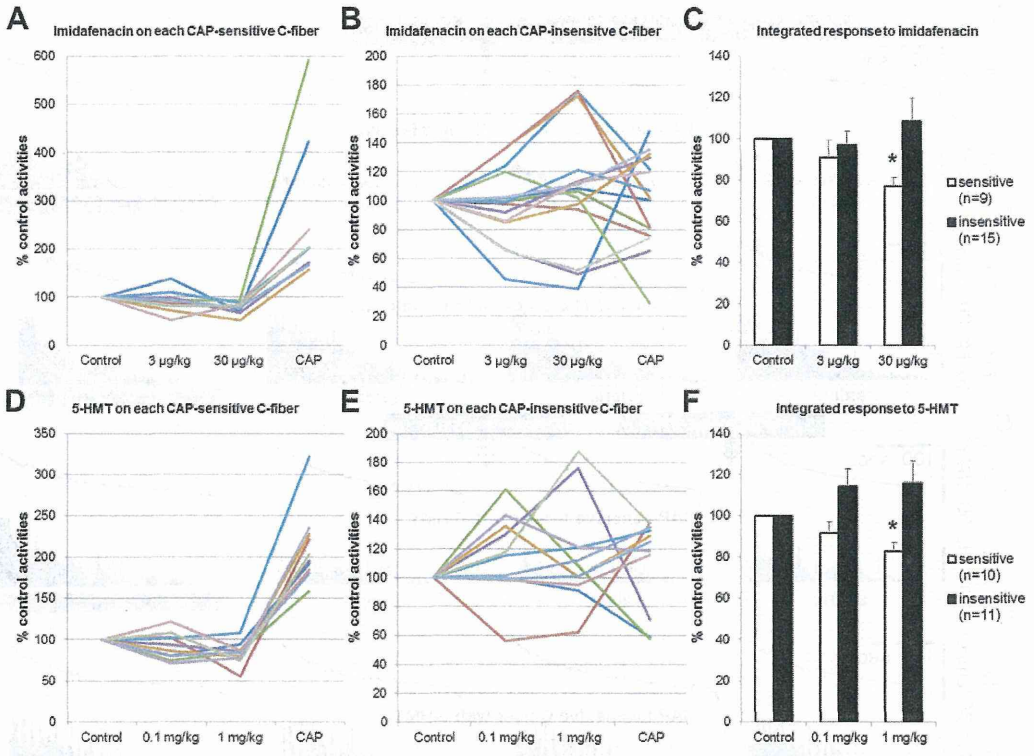

Figure 4. Responses to imidafenacin and 5-HMT on individual CAP sensitive and insensitive C fibers (*A* to *D*), and summarized imidafenacin and 5-HMT results (*C* and *F*). Values are shown as mean ± SEM percent of control activity. Asterisk indicates significantly different vs control (1-way ANOVA and repeated measures Dunnett test $p < 0.05$).

increased post-void residual volume.[15] In contrast, only a higher dose of imidafenacin (30 μg/kg intravenously) showed a significant inhibitory effect on CAP sensitive C-fiber afferent activity in the current study. The effective dose to increase bladder capacity in the previous study and the dose to

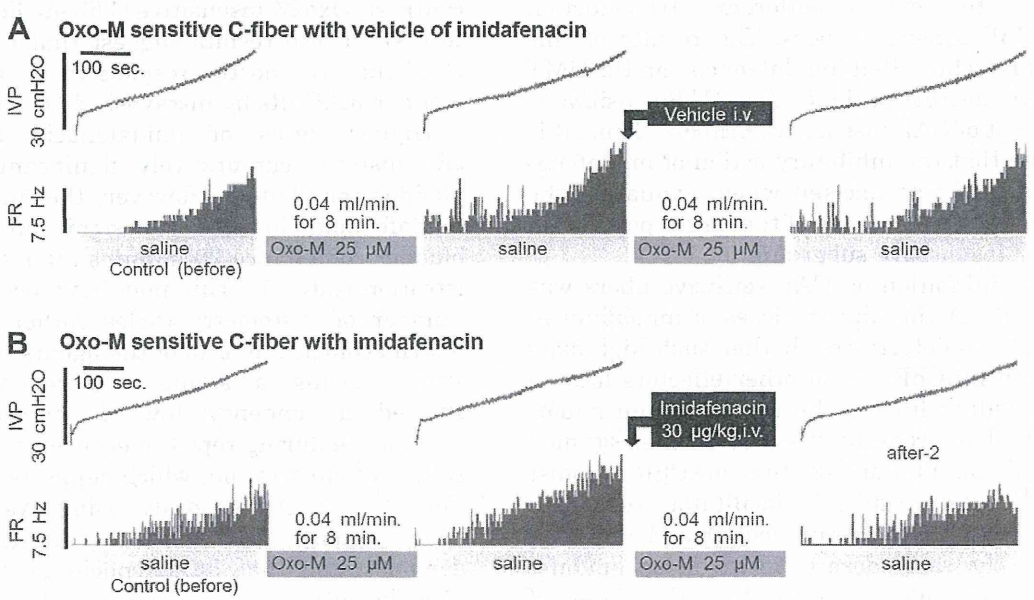

Figure 5. Representative traces show mechanosensitive afferent nerve activity intravesical pressure (*IVP*) and firing rate (*FR*) of Oxo-M sensitive C fibers after vehicle or imidafenacin (*A* and *B*). *i.v.*, intravenously.

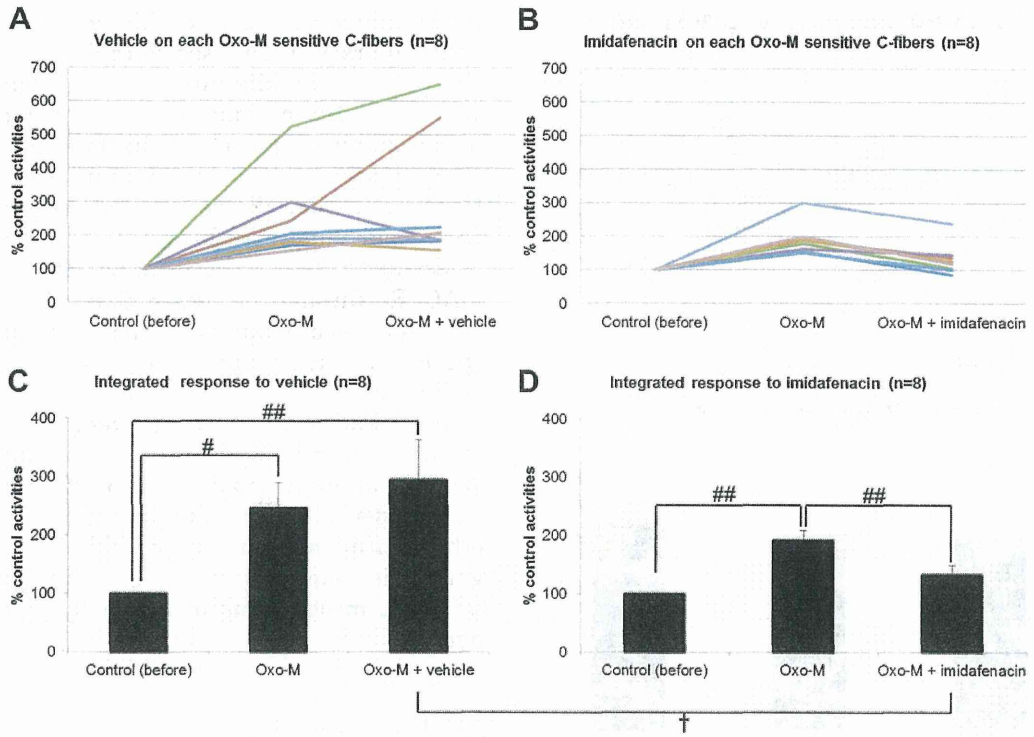

Figure 6. Oxo-M sensitive C fiber (*A* and *B*), and integrated Oxo-M sensitive C-fiber responses to vehicle and imidafenacin during whole filling phase after Oxo-M alone and in presence of vehicle (*C* and *D*) in 8 nerve fibers each. Values are shown as mean ± SEM percent of control activity. Single pound sign indicates significantly different (2-way ANOVA and Tukey test $p < 0.05$). Double pound signs indicate significantly different (2-way ANOVA and Tukey test $p < 0.01$). Dagger indicates significantly different (unpaired Student t test $p < 0.05$).

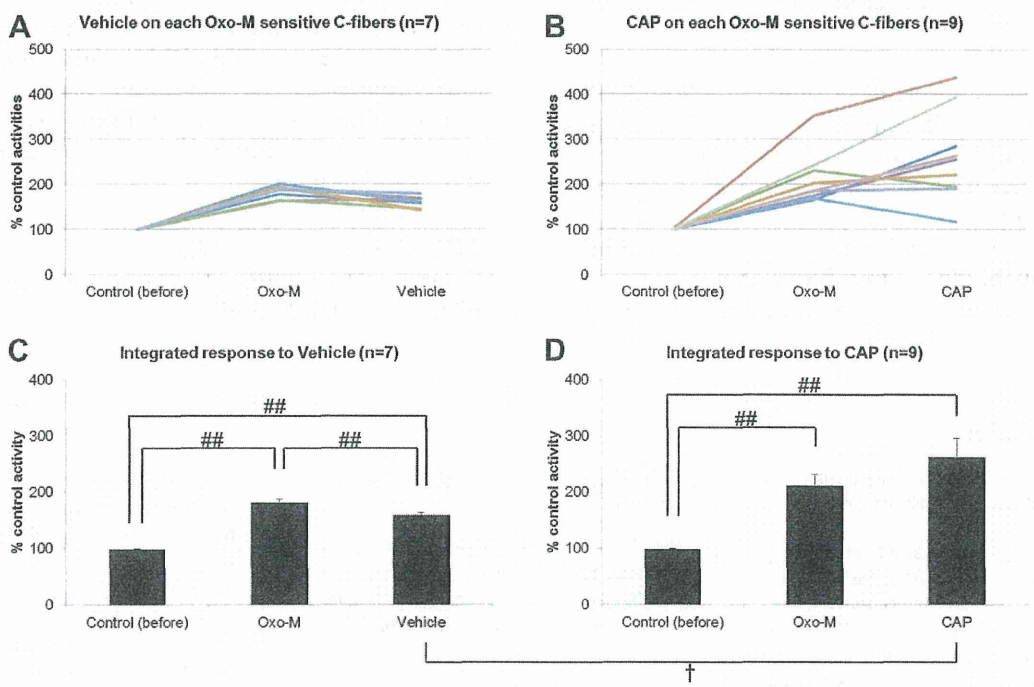

Figure 7. Responses to vehicle and CAP in individual Oxo-M sensitive C fibers (*A* and *B*) and integrated Oxo-M sensitive C-fiber responses during whole filling phase after Oxo-M and vehicle or CAP (*C* and *D*) in 7 or 9 nerve fibers each. Values are shown as mean ± SEM percent of control activity. Pound signs indicate significantly different (2-way ANOVA and Tukey test $p < 0.01$). Dagger indicates significantly different (unpaired Student t test $p < 0.05$).

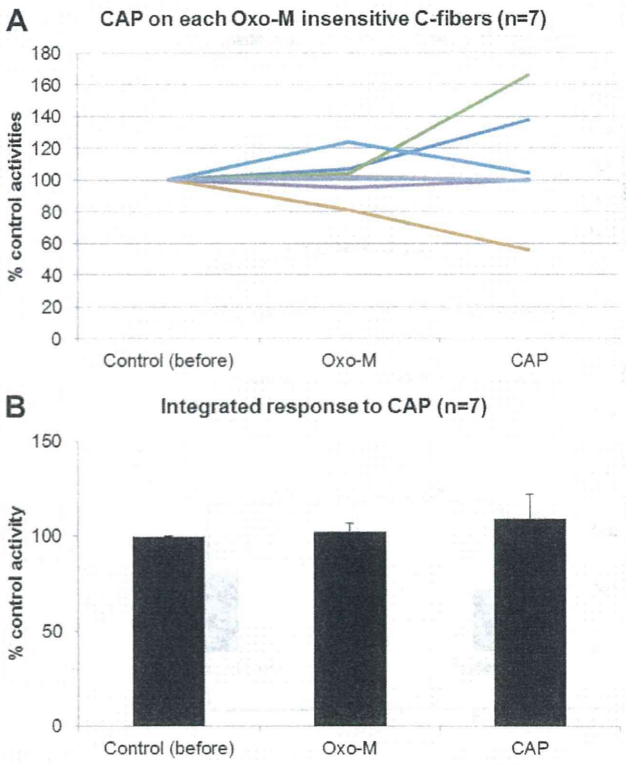

Figure 8. Responses of 7 individual Oxo-M insensitive and integrated Oxo-M insensitive C fibers each during whole filling phase after Oxo-M and CAP (*A* and *B*). Values are shown as mean ± SEM percent of control activity. No significant difference between groups (2-way ANOVA and Tukey test).

suppress mechanosensitive bladder afferent fibers in the current study appear discrepant, which may have been due to the different experimental setups, such as transection of the bilateral L6 roots in the current series.

In this study we did not investigate the effect of the drug on bladder capacity or micturition pressure. However, since single bolus administration of imidafenacin at the dose (30 μg/kg intravenously) that suppressed CAP sensitive C-fiber afferent activity did not significantly increase bladder compliance, imidafenacin may not act on the tonus of the detrusor smooth muscle at the dose that suppresses CAP sensitive C-fiber afferent activity. Taken together the current results indicate that imidafenacin can suppress the afferent activity of CAP sensitive C fibers selectively by inhibiting bladder mAChRs through an action other than decreasing detrusor smooth muscle tonus, at least under the special experimental conditions of the current study.

We acknowledge the controversy about the effect of antimuscarinic agents on mechanosensitive Aδ-fiber afferent activity.[5,6] The effects of atropine on bladder afferent function differ from those of other antimuscarinic agents.[12,25] Further investigation is required to explore the possibility of different mechanisms of action by antimuscarinic agents.

CONCLUSIONS

To our knowledge the current series demonstrates for the first time that imidafenacin and 5-HMT can selectively inhibit the mechanosensitive bladder afferent activity of CAP sensitive C fibers but not Aδ fibers or CAP insensitive C fibers. These effects are mediated by the antagonism of bladder muscarinic receptors in urethane anesthetized rats. The findings suggest a possible additional action of antimuscarinics, eg inhibitory action on bladder sensory function in pathophysiological conditions, as therapeutic agents for OAB or other bladder sensory disorders.

ACKNOWLEDGMENTS

Kyorin Pharmaceutical provided imidafenacin. Pfizer provided 5-HMT.

REFERENCES

1. Andersson KE: Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004; **3:** 46.

2. Kobayashi F, Yageta Y, Segawa M et al: Effects of imidafenacin (KRP-197/ONO-8025), a new anti-cholinergic agent, on muscarinic acetylcholine receptors. High affinities for M3 and M1 receptor subtypes and selectivity for urinary bladder over salivary gland. Arzneimittelforschung 2007; **57:** 92.

3. Yamada S, Seki M, Ogoda M et al: Selective binding of bladder muscarinic receptors in relation to the pharmacokinetics of a novel antimuscarinic agent, imidafenacin, to treat overactive bladder. J Pharmacol Exp Ther 2011; **336:** 365.

4. Ney P, Pandita RK, Newgreen DT et al: Pharmacological characterization of a novel investigational antimuscarinic drug, fesoterodine, in vitro and in vivo. BJU Int 2008; **101:** 1036.

5. Iijima K, De Wachter S and Wyndaele JJ: Effects of the M3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. Eur Urol 2007; **52:** 842.

6. De Laet K, De Wachter S and Wyndaele JJ: Systemic oxybutynin decreases afferent activity of the pelvic nerve of the rat: new insights into the working mechanism of antimuscarinics. Neurourol Urodyn 2006; **25:** 156.

7. Birder LA, Kanai AJ, de Groat WC et al: Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci U S A 2001; **98:** 13396.

8. Aizawa N, Igawa Y, Andersson KE et al: Effects of intravesical instillation of ATP on rat bladder primary afferent activity and its relationship with capsaicin-sensitivity. Neurourol Urodyn 2011; **30:** 163.

9. Aizawa N, Wyndaele JJ, Homma Y et al: Effects of TRPV4 cation channel activation on the primary bladder afferent activities of the rat. Neurourol Urodyn 2012; **31:** 148.

10. Yokoyama O, Tanaka I, Kusukawa N et al: Antimuscarinics suppress adenosine triphosphate and prostaglandin E2 release from urothelium with potential improvement in detrusor overactivity in rats with cerebral infarction. J Urol 2011; **185:** 2392.

11. Yokoyama O, Yusup A, Miwa Y et al: Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 2005; **174:** 2032.

12. Watanabe N, Akino H, Kurokawa T et al: Antidiuretic effect of antimuscarinic agents in rat model depends on C-fibre afferent nerves in the bladder. BJU Int 2013; **112:** 131.

13. Sengupta JN and Gebhart GF: Mechanosensitive properties of pelvic nerve afferent fibers innervating the urinary bladder of the rat. J Neurophysiol 1994; **72:** 2420.

14. Kullmann FA, Artim DE, Birder LA et al: Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. J Neurosci 2008; **28:** 1977.

15. Yamazaki T, Muraki Y and Anraku T: In vivo bladder selectivity of imidafenacin, a novel antimuscarinic agent, assessed by using an effectiveness index for bladder capacity in rats. Naunyn Schmiedebergs Arch Pharmacol 2011; **384:** 319.

16. Fullhase C, Soler R, Gratzke C et al: Urodynamic evaluation of fesoterodine metabolite, doxazosin and their combination in a rat model of partial urethral obstruction. BJU Int 2010; **106:** 287.

17. Yu Y and de Groat WC: Effects of stimulation of muscarinic receptors on bladder afferent nerves in the in vitro bladder-pelvic afferent nerve preparation of the rat. Brain Res 2010; **1361:** 43.

18. Andersson KE and Yoshida M: Antimuscarinics and the overactive detrusor—which is the main mechanism of action? Eur Urol 2003; **43:** 1.

19. Yoshida M, Miyamae K, Iwashita H et al: Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology 2004; **63:** 17.

20. Shea VK, Cai R, Crepps B et al: Sensory fibers of the pelvic nerve innervating the Rat's urinary bladder. J Neurophysiol 2000; **84:** 1924.

21. Jiang CH, Mazieres L and Lindstrom S: Cold- and menthol-sensitive C afferents of cat urinary bladder. J Physiol 2002; **543:** 211.

22. Jiang W and Morrison J: Sensitisation of pelvic nerve afferent neurones from the rat bladder. J Auton Nerv Syst 1996; **58:** 181.

23. Kullmann FA, Artim D, Beckel J et al: Heterogeneity of muscarinic receptor-mediated Ca2+ responses in cultured urothelial cells from rat. Am J Physiol Renal Physiol 2008; **294:** F971.

24. Aizawa N, Igawa Y, Nishizawa O et al: Effects of CL316,243, a beta 3-adrenoceptor agonist, and intravesical prostaglandin E2 on the primary bladder afferent activity of the rat. Neurourol Urodyn 2010; **29:** 771.

25. Daly DM, Chess-Williams R, Chapple C et al: The inhibitory role of acetylcholine and muscarinic receptors in bladder afferent activity. Eur Urol 2010; **58:** 22.

Cancer Science
Japanese Cancer Association JCA
Open Access

Robot-assisted versus other types of radical prostatectomy: Population-based safety and cost comparison in Japan, 2012–2013

Toru Sugihara,[1,2] Hideo Yasunaga,[3] Hiromasa Horiguchi,[4] Hiroki Matsui,[3] Tetsuya Fujimura,[2] Hiroaki Nishimatsu,[2] Hiroshi Fukuhara,[2] Haruki Kume,[2] Yu Changhong,[1] Michael W. Kattan,[1] Kiyohide Fushimi[5] and Yukio Homma[2]

[1]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA; [2]Department of Urology, The University of Tokyo, Tokyo; [3]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo; [4]Department of Clinical Data Management and Research, Clinical Research Center, National Hospital Organization Headquarters, Tokyo; [5]Department of Health Care Informatics, Tokyo Medical and Dental University, Tokyo, Japan

Key words

Laparoscopy, minimally invasive, prostatic neoplasm, robot technology, surgical procedures

Correspondence:

Toru Sugihara, Department of Quantitative Health Sciences, Cleveland Clinic Main Campus, JJN3-01, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
Tel: +1-216-444-8273; Fax: +1-216-445-7659;
E-mail: ezy04707@nifty.com

Funding Information

Saga Prefecture, Japan; Ministry of Health, Labor, and Welfare, Japan; Council for Science and Technology Policy, Japan.

Received April 9, 2014; Revised August 17, 2014; Accepted August 19, 2014

Cancer Sci (2014)

doi: 10.1111/cas.12523

In 2012, Japanese national insurance started covering robot-assisted surgery. We carried out a population-based comparison between robot-assisted and three other types of radical prostatectomy to evaluate the safety of robot-assisted prostatectomy during its initial year. We abstracted data for 7202 open, 2483 laparoscopic, 1181 minimal incision endoscopic, and 2126 robot-assisted radical prostatectomies for oncological stage T3 or less from the Diagnosis Procedure Combination database (April 2012–March 2013). Complication rate, transfusion rate, anesthesia time, postoperative length of stay, and cost were evaluated by pairwise one-to-one propensity-score matching and multivariable analyses with covariants of age, comorbidity, oncological stage, hospital volume, and hospital academic status. The proportion of robot-assisted radical prostatectomies dramatically increased from 8.6% to 24.1% during the first year. Compared with open, laparoscopic, and minimal incision endoscopic surgery, robot-assisted surgery was generally associated with a significantly lower complication rate (odds ratios, 0.25, 0.20, 0.33, respectively), autologous transfusion rate (0.04, 0.31, 0.10), homologous transfusion rate (0.16, 0.48, 0.14), lower cost excluding operation (differences, −5.1%, −1.8% [not significant], −10.8%) and shorter postoperative length of stay (–9.1%, +0.9% [not significant], –18.5%, respectively). However, robot-assisted surgery also resulted in a + 42.6% increase in anesthesia time and +52.4% increase in total cost compared with open surgery (all $P < 0.05$). Introduction of robotic surgery led to a dynamic change in prostate cancer surgery. Even in its initial year, robot-assisted radical prostatectomy was carried out with several favorable safety aspects compared to the conventional surgeries despite its having the longest anesthesia time and the highest cost.

Prostate cancer is a global public health issue, and radical prostatectomy has been widely recognized as a standard treatment for patients with localized disease.[1] The open approach was traditionally carried out. However, after the development of laparoscopic technology and the use of surgical robotic devices, minimally invasive approaches have steadily become more popular. The use of RARP, especially, has spread rapidly in the USA and Europe. Several RCTs, systematic reviews, and meta-analyses have described the superiority of RARP over LRP and ORP in terms of blood loss, complications, incontinence, and loss of sexual function.[2–8]

Compared to North America and European countries, the introduction of minimally invasive radical prostatectomy in Japan was rather different. National universal health care insurance officially began covering LRP in 2006 and MIE-RP (gasless single-port-access endoscopic surgery) in 2008. The restriction for RARP was not lifted until April 2012. Even though RARP was a latecomer to the surgical armamentarium in Japan, the number of robotic surgeries increased dramatically after its approval. Japan soon had the second largest number of surgical robots worldwide.[9] This abrupt prevalence of RARP usage caused some concern about the skillfulness of surgeons with this new technology. Although it was generally thought that the learning curve for robot-assisted surgery was shorter than that for other minimally invasive operations, there was a high incidence of complications reported in the initial cases.[10] Thus, an outcomes study involving a large number of institutions became necessary to verify the safety and feasibility of RARP compared with conventional prostatectomy approaches. The aim of the present study was to evaluate perioperative outcomes among four types of radical prostatectomy during the initial year of RARP application. For the study group, we relied on a Japanese population-based database.

Material and Methods

Data source for the study. The comparisons in the current study were carried out based on the DPC database, a Japanese

inpatient administrative claims database. In 2012, it had data of 6 852 195 hospitalizations from 1057 participating hospitals, representing approximately 50% of acute care hospitalizations throughout Japan.[11] This database holds clinical information on such areas as: (i) the main diagnoses, comorbidities at admission, and complications after admission; (ii) surgical procedures; (iii) discharge status; and (iv) use of medical resources. Diagnoses were coded according to the ICD-10. Because the data in the DPC database were thoroughly de-identified and the present study was designed as a secondary analysis of the administrative claims data, informed consent was not required. The institutional review board and ethics committee of The University of Tokyo (Tokyo, Japan) approved the study.

Data sampling and measured outcomes. Selected patients were those undergoing ORP, LRP, MIE-RP, or RARP (Japanese surgical codes K843, K843-2, K843-3, and K939-4, respectively) for the main diagnosis of malignant neoplasm of the prostate (ICD-10 code C61) from April 2012 to March 2013. Minimum incision endoscopic radical prostatectomy is a technique using a single, small incision that permits extraction of the specimen without gas insufflation, trocar ports, or injury to the peritoneum.[12]

Available baseline characteristics about the patient and hospital were age, comorbidities at admission, body mass index, smoking index (pack-year), oncological stage (according to the International Union Against Cancer),[13] hospital academic status (academic or non-academic), and hospital volume (annual caseload of radical prostatectomy at each hospital). Comorbidities were converted to a score of the CCI according to Quan *et al.*[14]

The outcomes assessed were perioperative complications (see Table S1), blood transfusion, anesthesia time, postoperative length of stay, and costs including and excluding the operation. The costs were calculated at the currency rate of ¥100 = $US1.

Statistical analysis. For univariable comparisons, the χ^2-test and Mann–Whitney *U*-test were adopted, as appropriate. The threshold for significance was $P < 0.05$.

To improve the quality of comparisons, multiple imputation and propensity-score matching was carried out as follows. First, because there were some missing values for the body mass index, smoking index, and oncological stage, we performed multiple imputation to replace each missing value with a set of substituted plausible values by creating five filling-in copies to reduce bias caused by incomplete data.[15,16] In the process of missing imputation, predictive mean matching and polytomous regressions were used appropriately. After imputation, patients with T4, N+, or M+ were removed because of their small numbers. Second, in each imputed copy, one-to-one propensity-score matching was performed pairwise three times (i.e., RARP *vs* ORP, RARP *vs* LRP, and RARP *vs* MIE-RP).[17] This matching methodology mimics randomized allocations to case and control groups, consequently reducing the bias that occurs because of the lack of randomization. A probability of allocation in the RARP group was estimated in each subject as a propensity score based on a logistic regression model incorporating potential confounders: age, CCI, body mass index, smoking index, oncological stage, hospital academic status, and hospital volume. The matching was executed using the nearest neighborhood approach with a caliper width equal to 0.2 of the standard deviation of the propensity score.[18] Third, after matching, multivariable linear or logistic regression analyses were carried out for each outcome with covariates—type of radical prostatectomy, age, CCI, body mass index, smoking index, oncological stage, hospital academic status, hospital volume—in each imputed copy. In these multivariable models, generalized estimating equations were applied to adjust for hospital clustering effects.[19] Finally, the results of the five imputed copies were combined into one model, from which the statistical inference was taken. The values of anesthesia time, postoperative length of stay, and costs were log-transformed in the linear regression models because of their skewed distributions. All statistical analyses were carried out using R version 3.0.2 software (R Foundation for Statistical Computing, Vienna, Austria) with RMS 4.0-0, Zelig 4.1-3, Mice 2.17, and MatchIt 2.4-21 packages.[15,20–24]

To confirm the trend change for radical prostatectomy, a frequency distribution in the caseloads for four types of radical prostatectomy was determined, and the trend was analyzed using the Cochran–Armitage trend test.

Results

During the study period, 7202 ORP (55.4%), 2483 LRP (19.1%), 1181 MIE-RP (9.1%), and 2126 RARP cases (16.4%)

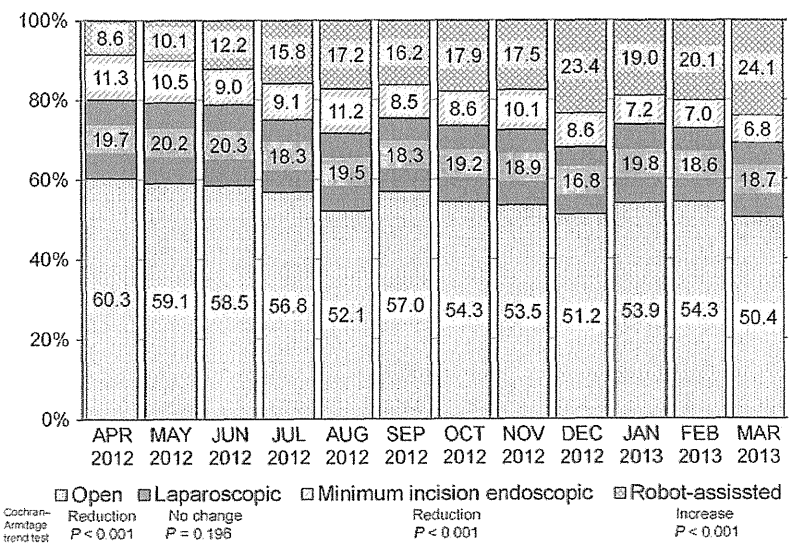

Fig. 1. Chronological trends for the four types of radical prostatectomy in Japan's Diagnosis Procedure Combination database between April 2012 and March 2013.

Table 1. Patient baseline characteristics among four types of radical prostatectomy registered in the Japanese Diagnosis Procedure Combination database between April 2012 and March 2013

Characteristic	Type of radical prostatectomy, *n* (%) or median (IQR)				*P*-value
	Open	Laparoscopic	MIE-RP	Robot-assisted	
Total	7202 (100.0)	2483 (100.0)	1181 (100.0)	2126 (100.0)	
No. of hospitals	552	90	68	45	
Age, years	68 (64–72)	68 (64–71)	67 (63–71)	67 (62–71)	<0.001
Charlson comorbidity index					
0	5405 (75.0)	1877 (75.6)	887 (75.1)	1908 (89.7)	<0.001
1	1167 (16.2)	409 (16.5)	196 (16.6)	166 (7.8)	
≥2	630 (8.7)	197 (7.9)	98 (8.3)	52 (2.4)	
Body mass index	23.7 (22.0–25.6)	23.8 (22.0–25.7)	23.7 (22.0–25.5)	23.7 (22.1–25.6)	0.497
Missing	48 (0.7)	15 (0.6)	39 (3.3)	13 (0.6)	
Smoking index, pack-year	0 (0–30)	5 (0–35)	8 (0–35)	0 (0–26)	<0.001
Missing	870 (12.1)	363 (14.6)	207 (17.5)	445 (20.9)	
Stage					
T1	1701 (23.6)	707 (28.5)	255 (21.6)	961 (45.2)	<0.001
T2	3941 (54.7)	1244 (50.1)	608 (51.5)	879 (41.3)	
T3	772 (10.7)	152 (6.1)	148 (12.5)	122 (5.7)	
T4, N+, or M+	161 (2.2)	32 (1.3)	25 (2.1)	14 (0.7)	
Missing	627 (8.7)	348 (14.0)	145 (12.3)	150 (7.1)	
Type of hospital					
Academic	1102 (15.3)	1267 (51.0)	335 (28.4)	1594 (75.0)	<0.001
Non-academic	6100 (84.7)	1216 (49.0)	846 (71.6)	532 (25.0)	
Hospital volume	25 (14–40)	61 (34–91)	34 (22–50)	96 (59–155)	<0.001
Perioperative outcome					
Autologous transfusion	5951 (82.6)	1038 (41.8)	835 (70.7)	260 (12.2)	<0.001
Homologous transfusion	523 (7.3)	56 (2.3)	68 (5.8)	15 (0.7)	<0.001
Overall complications	380 (5.3)	98 (3.9)	48 (4.1)	18 (0.8)	<0.001
Sepsis/DIC	15 (0.2)	4 (0.2)	1 (0.1)	2 (0.1)	0.600
Pulmonary embolism	14 (0.2)	2 (0.1)	1 (0.1)	1 (0.0)	0.288
Cardiac events	80 (1.1)	34 (1.4)	6 (0.5)	3 (0.1)	<0.001
Vascular complications	49 (0.7)	4 (0.2)	3 (0.3)	2 (0.1)	<0.001
Respiratory complications	35 (0.5)	16 (0.6)	3 (0.3)	4 (0.2)	0.085
Peritonitis or peritoneal abscess	16 (0.2)	7 (0.3)	2 (0.2)	0 (0.0)	0.139
Ileus	20 (0.3)	2 (0.1)	2 (0.2)	4 (0.2)	0.309
Genitourinary complications	63 (0.9)	26 (1.0)	9 (0.8)	1 (0.0)	<0.001
Disruption of operation wound	68 (0.9)	3 (0.1)	9 (0.8)	1 (0.0)	<0.001
Colorectal injury	34 (0.5)	7 (0.3)	6 (0.5)	0 (0.0)	0.010
Other intraoperative complications	23 (0.3)	4 (0.2)	9 (0.8)	0 (0.0)	<0.001
Others†	25 (0.3)	5 (0.2)	5 (0.4)	1 (0.0)	0.079
Anesthesia time, min‡	268 (223–323)	329 (270–386)	304 (252–356)	322 (279–382)	<0.001
Postoperative length of stay, days‡	14 (11–17)	11 (9–14)	13 (11–17)	11 (9–13)	<0.001
Total costs, $US‡§	10 946 (10 098–12 035)	14 160 (13 409–15 121)	12 911 (12 063–14 147)	15 676 (14 984–16 495)	<0.001
Costs excluding operation, $US‡§	4616 (3940–5526)	4208 (3527–4982)	4642 (3878–5855)	4434 (3758–5123)	<0.001

†The number of events was 10 or less. In-hospital mortality (n = 9, P = 0.22), pseudomembranous enterocolitis (n = 5, P = 0.10), stroke (n = 9, P = 0.87), pneumonia or flu (n = 10, P = 0.56), and acute renal failure (n = 5, P = 0.40). ‡Values were transformed into log-10 values for the modeling because of their skewed distributions. §$US1 = ¥100. DIC, disseminated intravascular coagulopathy; IQR, interquartile range; MIE-RP, minimal incision endoscopic radical prostatectomy.

were abstracted from 552, 90, 68, and 45 institutes in the DPC database. The number of cases accounted for approximately 60% of all radical prostatectomies carried out in Japan.[25] Figure 1 shows the chronological trend for the four types of radical prostatectomy between April 2012 and March 2013. The proportion of RARP increased by approximately 2.8 times during the 12 months (from 8.6% to 24.1%; Cochran–Armitage trend test, $P < 0.001$), whereas ORP and MIE-RP lost their share ($P < 0.001$). Table 1 presents the details of the patient baseline characteristics and the outcomes without background adjustment. In general, compared to the three conventional radical prostatectomies, RARP was carried out in patients with a slightly younger age, lower CCI, and earlier oncological stage at the institutions with high hospital volume and academic sta-

Table 2. Multivariate regression analyses for propensity-score-adjusted outcomes among robot-assisted radical prostatectomy (RARP) versus three other types of radical prostatectomy registered in the Japanese Diagnosis Procedure Combination database between April 2012 and March 2013

Parameter	RARP versus ORP		RARP versus LRP		RARP versus MIE-RP	
	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Average no. of pairs	989		1407		592	
No. of hospitals included	45 *vs* 163		45 *vs* 77		43 *vs* 57	
Logistic regression model (odds ratio)						
Overall complications	0.25 (0.15–0.41)	<0.001	0.20 (0.13–0.31)	<0.001	0.33 (0.18–0.64)	<0.001
Autologous transfusion	0.04 (0.03–0.05)	<0.001	0.31 (0.26–0.38)	<0.001	0.10 (0.07–0.14)	<0.001
Homologous transfusion	0.16 (0.08–0.32)	<0.001	0.48 (0.25–0.91)	0.025	0.14 (0.06–0.33)	<0.001
Linear regression model (difference in percentage)						
Anesthesia time, min†	+42.6% (39.0–46.2)	<0.001	+6.9% (5.0–8.8)	<0.001	+23.9% (20.4–27.4)	<0.001
Postoperative length of stay†	−9.1% (−12.0 to −6.2)	<0.001	+0.9% (−1.5 to 3.4)	0.459	−18.5% (−21.5 to −15.4)	<0.001
Total costs, $US†‡	+52.4% (49.5–55.4)	<0.001	+13.2% (11.9–14.6)	<0.001	+22.8% (19.7–26.1)	<0.001
Costs excluding operation, $US†‡	−5.1% (−7.3 to −2.9)	<0.001	−1.8% (−4.4 to 0.9)	0.195	−10.3% (−13.0 to −7.4)	<0.001

The effect of hospital clustering was regulated by generalized estimating equations. †Values were transformed into log-10 values for the modeling because of their skewed distributions. ‡$US1 = ¥100. CI, confidence interval; LRP, laparoscopic radical prostatectomy; MIE-RP, minimal incision endoscopic radical prostatectomy.

tus. Regarding outcomes, low incidences of transfusion and complications drew our attention. After the process of missing imputation and the subsequent one-to-one propensity-score matching process, 989, 1407, and 592 pairs (on average) were generated between RARP versus ORP, RARP versus LRP, and RARP versus MIE-RP Table S2. Average C-statistics of the propensity score for each matching were 0.933, 0.757, and 0.898, respectively. After the matching, the background variations were closely balanced (data not shown).

Table 2 shows the results of the multivariable regression analyses for the outcomes. Compared with ORP, LRP, and MIE-RP, RARP was generally associated with a significantly lower complication rate (odds ratios 0.25, 0.20, 0.33, respectively), autologous transfusion rate (0.04, 0.31, 0.10, respectively), and homologous transfusion rate (0.16, 0.48, 0.14, respectively) as well as lower cost excluding operation (differences, −5.1%, −1.8% [not significant], −10.8%,) and a shorter postoperative length of stay (−9.1%, +0.9% [not significant], −18.5%, respectively). However, RARP also showed a + 42.6% increase in anesthesia time and a + 52.4% increase in total cost compared with open surgery. The postoperative length of stay for the RARP group was comparable to that for the LRP group.

Discussion

This study is the first to compare perioperative outcomes between RARP and conventional radical prostatectomies in Japan at the national level. We knew that with 2012 being the first year of RARP approval by the Japanese national universal health care insurance the accumulation of experience with RARP would be limited. Despite that, by using a national database population for our analysis of perioperative outcomes, we showed that RARP was associated with substantially lower incidences of transfusion use and complications. We also found that the high total cost of RARP must be kept in mind.

Fewer than 20 hospitals in Japan had surgical robots at the end of 2011. It was reported, however, that the plan was to introduce more than 100 surgical robots by the end of 2013 throughout Japan.[9] According to our data, RARP, which in April 2012 had the smallest share among the four types of radical prostatectomy that we studied, steadily increased its caseload and became the second most popular approach after the first 12 months of its availability. In the face of this dynamic change, it is essential to evaluate the safety and feasibility of RARP compared with other conventional surgeries. The present study provided a comprehensive answer that RARP successfully produced satisfactory performance at least in terms of perioperative outcomes during its initial year in Japan. The most distinctive feature was the difference in transfusion use between ORP and RARP, where the odds ratios of autologous and homologous transfusion use during RARP were about 1/25th and 1/7th, respectively, of those during ORP. Claims of a less invasive nature of RARP over ORP have been described in several publications.[4–7] The results of the current study are noteworthy in that the favorable outcomes with RARP had been achieved at an early phase of the introduction of the technology. The shorter postoperative length of stay and lower cost excluding operation associated with RARP also supports the concept of less invasiveness and quicker recovery with RARP than with ORP or MIE-RP.

However, in terms of comparisons between RARP and LRP, several reviews and RCTs noted that the difference in perioperative outcomes between the two techniques was marginal. For example, three of four recent meta-analyses and both RCTs reported similar transfusion rates for RARP and LRP,[2–8] whereas our data indicated significantly lower rates of complications and transfusions with RARP compared with those with LRP. One reasonable explanation was that this was a population-based study that included not only highly skillful facilities but also a wide variety of hospitals, which might more directly reflect the outcomes in real-world clinical practice.

Regarding the anesthesia time, RARP had the longest duration among the four types of radical prostatectomy, even though existing publications mainly reported similar or shorter operation times for RARP than for LRP.[3,5,6,8] This difference is probably because many of our RARP surgeons were still only at the half-way point of their learning curve. Doumerc *et al.*[26] reported that experience with approximately 110 RARPs was required to achieve the proficiency of a 3-h operation time. However, we think that other favorable outcomes of RARP offset the negative feature of a long anesthesia time.