

Current Progress and Controversies in Prostate Cancer Management

De-Xin Dong, Zhi-Gang Ji

Department of Urology, Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, Beijing 100730, China

Abstract

Objective: The optimal management strategy for prostate cancer (PCa) remains controversial. We performed a systemic review of current progress and controversies regarding the diagnosis and treatment of PCa.

Data Sources: We searched PubMed for recently published articles up to July 2017 using the following key words: “prostate cancer,” “progress,” “controversy,” “immunotherapy,” and “prevention.”

Study Selection: Articles were obtained and reviewed to provide a systematic review of the current progress and controversies regarding PCa management.

Results: The value of serum prostate-specific antigen (PSA) screening remains controversial, but PSA screening is recommended to facilitate the early diagnosis of PCa in high-risk groups. Prostate biopsy via the transrectal or perineal approach has both advantages and disadvantages. There was a significant correlation between testosterone levels and PCa prognosis. The current research is focused on the mechanisms responsible for PCa. Active surveillance has been proposed as a management strategy for low-risk, localized PCa, but there is an urgent need for further clinical studies to establish the criteria for recommending this approach. The main complications of radical resection for PCa are urinary incontinence and erectile dysfunction, though three-dimensional laparoscopic and robot-assisted laparoscopic techniques have obvious advantages over radical surgery. Radiotherapy is also a therapeutic option for PCa, while immunotherapies may alter the prostate tumor microenvironment. Ongoing studies aim to provide guidance on effective sequential and combination strategies. Prevention remains an important strategy for reducing PCa morbidity and mortality.

Conclusions: The diagnosis, treatment, and prevention of PCa are complex issues, worthy of intensive study. Further studies are needed to improve the management of PCa.

Key words: Active Surveillance; Advance; Immunotherapy; Prevention; Prostate Cancer

INTRODUCTION

Prostate cancer (PCa) is the most common malignant male tumor in Europe and the United States and has the second-highest mortality rate among male malignant carcinomas.^[1] However, the optimal management strategy for PCa remains controversial. We therefore reviewed the advances and controversies regarding PCa management.

SERUM PROSTATE-SPECIFIC ANTIGEN SCREENING

Digital rectal examination (DRE) represented the best screening method for PCa in China before the 1990s; however, DRE can only locate tumors in the back peripheral zone of the prostate gland, and therefore only detects advanced PCa. The introduction of serum prostate-specific antigen (PSA) tests for PCa screening has greatly increased

the detection rate. PSA-related variables include free PSA, free/T ratio, PSA density, and PSA velocity. The combination of PSA screening and DRE is currently recognized as the optimal screening method for the detection of early PCa.

In 2008, the U.S. Preventive Services Task Force (USPSTF) evaluated randomized controlled trials of the benefits of PCa screening, cohort and cross-sectional studies of the psychological harm of false-positive PSA test results, and

Address for correspondence: Prof. Zhi-Gang Ji,
Department of Urology, Chinese Academy of Medical Sciences,
Peking Union Medical College Hospital, Beijing 100730, China
E-Mail: jzg1129@medmail.com.cn

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2017 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 17-04-2017 **Edited by:** Yi Cui

How to cite this article: Dong DX, Ji ZG. Current Progress and Controversies in Prostate Cancer Management. Chin Med J 2017;130:2991-5.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.220317

evidence for the natural history of PSA-detected PCa to address previously identified gaps in the evidence from the 2002 USPSTF recommendations. The USPSTF concluded that there was currently insufficient evidence to assess the balance of the benefits and harms of screening for PCa in men younger than 75 years and recommended that screening should not be performed in men aged 75 years or older (Grade D recommendation).^[2] The American Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial analyzed PSA screening results for 76,693 men aged 55–74 years over 6 years and combined with DRE results for 4 years. They found that the rate of PCa diagnosis was higher in the routine serum PSA screening group compared with the control group (relative risk [RR] = 1.22, 95% confidence interval [CI]: 1.16–1.29), though there was no significant difference in mortality between the two groups (RR = 1.13, 95% CI: 0.75–1.70).^[3] In contrast, the European Randomized Study of Screening for PCa found that PSA screening reduced the mortality rate of PCa after a long-term follow-up of 13 years.^[4]

Based on the existing literature, statistical data, and cases, the value of PSA screening in different regions and populations thus remains controversial. Serum PSA screening is recommended for the early detection and timely treatment of PCa in high-risk populations, including elderly men with lower urinary tract symptoms, patients with a family history of PCa, and elderly men in areas with a high incidence of PCa.

DIFFERENT APPROACHES FOR PROSTATE BIOPSY

Prostate biopsy is the most reliable method for diagnosing PCa. Prostate biopsy can be carried out via a rectal or perineal approach, of which the rectal approach is the most common method. However, both approaches are associated with specific advantages and disadvantages.

The advantages of biopsy via the perineal approach include greater accuracy due to the use of a template and a relatively high positivity rate. Furthermore, the puncture point does not pass through the mucous membrane of the rectum, thus reducing the risks of sepsis and rectal abscess formation. The perineal approach is also associated with fewer complications because the puncture point is parallel to the urethra, and the incidence of hematuria is therefore low. In our single institution, we carried out transrectal ultrasound-guided transperineal saturation biopsy in 1139 men who had PSA levels >4.0 ng/ml, positive rectal examination, or abnormal prostate ultrasound, computed tomography, or magnetic resonance imaging (MRI) results. The incidence of PCa was 38.1%, with no serious complications such as infection or rectal abscess formation.^[5,6]

Prostate biopsy supported by transperineal image fusion has recently been developed as a new method to improve the accuracy of PCa detection. Transperineal prostate biopsy supported by MRI/transrectal ultrasound image fusion using the Ginsburg protocol yielded high detection rates for cancers

with Gleason score 7–10. However, because the negative predictive value for excluding Gleason score 7–10 cancers was very high, prostate biopsies may not be needed in all men with elevated PSA values and nonsuspicious multiparametric MRI.^[7]

SERUM TESTOSTERONE IN THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

The risk of PCa has been a major concern of testosterone therapy (TTh). However, Morgentaler^[8] found no firm evidence to suggest that higher endogenous testosterone levels or TTh itself were associated with an increased risk of PCa or high-grade PCa. Furthermore, a prospective longitudinal study involving 3886 men with PCa and 6448 age-matched controls showed no relationship between serum androgens and PCa risk.^[9] In the REDUCE trial, 3255 men underwent prostate biopsy at years 2 and 4, revealing no association between PCa risk and serum testosterone or dihydrotestosterone.^[10] In a meta-analysis of 22 randomized controlled trials involving 2351 men, those who received TTh were at no greater risk of developing PCa compared with men who received placebo.^[11]

In contrast, subsequent studies showed that low testosterone levels were associated with higher Gleason score, greater stage at radical PCa surgery, increased seminal vesicle involvement, higher biochemical recurrence rates, and reduced survival.^[12] Low testosterone levels were thus associated with a poorer PCa prognosis. Prostate tumors in patients with low testosterone levels showed higher pathological grades and greater malignancy. Batz reported 164 cases of PCa, including 18 high-grade and 146 low-grade cases with serum total testosterone and free testosterone levels of $307 \pm 24 \mu\text{g/L}$ and $1.14 \pm 0.09 \mu\text{g/L}$, respectively, in high-grade PCa, and $452 \pm 12 \mu\text{g/L}$ and $1.51 \pm 0.04 \mu\text{g/L}$, respectively, in low-grade PCa, with a significant difference between the two groups.^[13] Furthermore, low free testosterone levels were an independent predictor of progression in a cohort of men undergoing active surveillance.^[14]

MECHANISMS OF PROSTATE CANCER

PCa initiation, progression, and treatment are influenced by androgens. Prostate tumors are highly sensitive to androgens and regress after medical or surgical castration. Numerous studies have tried to establish a link between elevated androgen levels and an increased risk of PCa. A meta-analysis of previously published studies of hormonal predictors of PCa concluded that men with total testosterone levels in the highest quartile were 2.34 times more likely to develop PCa.^[15]

Genetic polymorphisms are a current research hotspot in relation to PCa, and approximately 10% of PCa cases are believed to have a heritable component. Genes may predispose to PCa by modulating the response of the host to certain environmental factors, or by interacting with other genes. Molecular epidemiologic studies have identified

several specific genetic polymorphisms, including in the 5 α -reductase type 2 gene, androgen-responsive genes, and related microRNAs.^[16,17]

ACTIVE SURVEILLANCE FOR EARLY PROSTATE CANCER

Active surveillance has been proposed as a management strategy for low-risk, localized PCa, and contemporary data suggest that active surveillance has been increasingly used worldwide. Although the protocols of published surveillance cohorts have differed, the reported rates of metastatic disease and PCa-specific mortality are very low in the intermediate term (5–10 years). Active surveillance could be individualized based on the level of risk, and in light of the individual's personal preferences. There is currently an urgent need for further clinical studies to establish the indications and criteria for active surveillance and the optimal schedule.^[18-20]

Active surveillance requires clear and uniform inclusion criteria. Different medical centers currently use different inclusion criteria, such as Epstein criteria, Memorial Sloan-Kettering Cancer Center criteria, University of California San Francisco standard, and the University of Toronto active surveillance protocol. Broad standards may reduce the safety of monitoring, while too-strict standards will reduce the number of enrolled patients.^[21,22]

Repeat biopsy is important for patients undergoing active surveillance to detect the evidence of pathological progress. Although the biopsy cycles reported in different studies vary, it should be emphasized that frequently repeated biopsies may have adverse psychological effects, as well as increasing the financial burden to the patient and the risk of infection; unnecessary biopsy should thus be avoided as far as possible. The development of molecular biomarkers may facilitate the accurate identification of PCa progression in the future.^[22]

COMPLICATIONS OF RADICAL PROSTATECTOMY

The main complications of radical prostatectomy are urinary incontinence and erectile dysfunction. However, technological progress has led to rapid developments in three-dimensional laparoscopy and robot-assisted laparoscopy. Robot-assisted laparoscopic radical prostatectomy is associated with the advantages of less bleeding and blood transfusion, and better recovery of urinary incontinence and erectile function compared with open surgery, as well as the disadvantages of longer operation time and greater expense.^[23-25]

Since Walsh^[26] proposed the concept of the nerve vascular bundle in radical prostatectomy, more surgeons have paid attention to the preservation of this structure, leading to a dramatic reduction in the incidence of postoperative erectile dysfunction. The recovery of erectile function is associated with age; after surgery including preservation of the unilateral and bilateral neurovascular bundles, respectively, erectile function recovered in 90% and 91% of patients aged <50 years, 58% and 82% of patients aged 50–69 years

old, and 20% of patients recovered in aged >70 years after preservation of the neurovascular bundles.^[26] Protection of the nerve vascular bundle can also reduce the incidence of postoperative urinary incontinence, with the incidence of urinary incontinence after radical prostatectomy being proportional to the patient's age.^[27] Bladder neck-sparing dissection allows for the early return of urinary continence following radical prostatectomy, without compromising cancer control.^[28]

RADIOOTHERAPY FOR PROSTATE CANCER

Radiotherapy is a treatment option for PCa. Radiotherapy has demonstrated radical effects in men with localized (T₁₋₂N₀M₀) PCa and has been shown to be an effective adjunct in patients with high-risk and recurrent PCa.

Radiotherapy for PCa mainly involves external radiation therapy and brachytherapy. External radiation therapy includes conventional external beam radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated external-beam radiotherapy, image-guided radiation therapy, and stereotactic body radiotherapy. External radiation therapy is suitable for T1a-T4a PCa, while the indications for brachytherapy include local, locally advanced, and locally recurrent PCa. Brachytherapy is also a promising and minimally invasive treatment for elderly patients with PCa who are unable to tolerate radical prostatectomy.^[29] With the development of three-dimensional conformal radiotherapy, intensity-modulated external-beam radiotherapy, and image-guided radiation therapy, radiotherapy can greatly improve the survival and local control rates of PCa, as well as reducing the complications associated with radiotherapy.^[30]

The choice between radical surgery and radiotherapy for patients with localized PCa has been hotly debated among urologists and radiation oncologists. However, theoretical guidance is based on limited evidence from retrospective studies and clinical experience, and large-scale randomized controlled clinical studies are currently lacking. The decision regarding radical surgery or radiotherapy in patients with localized PCa thus presently depends largely on the doctor, the patient's physical condition, and the expected quality of life.^[31]

IMMUNOTHERAPY FOR PROSTATE CANCER

Therapeutic cancer vaccines and immunomodulating agents have demonstrated activity in the treatment of PCa. Immunotherapies may alter the prostate tumor microenvironment, and PCa patients with good prognostic factors, such as minimal disease burden, appear to achieve the optimal benefit from immunotherapy. Ongoing studies are currently aimed at providing guidance on effective sequential and combination strategies.^[32]

Sipuleucel-T was approved by the Food and Drug Administration in 2010 for the treatment of minimally symptomatic metastatic castration-resistant PCa, based on the results of the double-blind placebo-controlled phase III

IMPACT trial, in which 512 patients were randomly assigned to receive sipuleucel-T every 2 weeks for a total of three doses, or placebo. Median overall survival was increased by 4.1 months in patients receiving sipuleucel-T.^[33] The preliminary results of ongoing trials evaluating vaccines in combination with immune checkpoint inhibitors have been promising and suggest that vaccine therapies may be more clinically effective when given earlier in the course of PCa.^[34] Combining these vaccine platforms with antiandrogens, cytoreductive treatment, radiation, or other immunotherapies may enhance their efficacy.^[35]

PROSTATE CANCER PREVENTION

Prevention is an important strategy for reducing PCa morbidity and mortality. Cancer prevention is defined as primary (prevention of incident disease), secondary (identification and treatment of preclinical disease), or tertiary (prevention of progression or recurrence).

Primary prevention of PCa has focused on chemoprevention, vitamin supplements (selenium, Vitamin E, and Vitamin C), and 5 α -reductase inhibitors (finasteride and dutasteride). While vitamin supplements have consistently proven ineffective, two randomized trials demonstrated the efficacy of 5 α -reductase inhibitors in reducing the risk of incident PCa. Secondary prevention involves PSA screening for the early diagnosis of preclinical, but potentially lethal cancers. Early detection of early-stage tumors prevents progression to locally advanced disease and metastases. Tertiary prevention of PCa has focused on chemotherapy to prevent the progression or recurrence of clinical disease, including use of the 5 α -reductase inhibitor dutasteride and dietary supplements (i.e., macronutrients).^[36]

CONCLUSIONS

The incidence and mortality of PCa are increasing year by year. The diagnosis, treatment, and prevention of PCa are complex issues, worthy of intensive study. However, there remains a large gap between China and advanced countries in terms of basic research and combined management of PCa, and further studies are needed to improve the management of PCa.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yanqun N, Zhangqun Y, Guang S. Chinese Guideline on Diagnosis and Treatment of Urinary Disease. Beijing: People's Publishing House; 2011. p. 49-79.
2. Moyer VA, U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;157:120-34. doi: 10.7326/0003-4819-157-2-201207170-00459.
3. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D,

Church TR, *et al.* Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: Mortality results after 13 years of follow-up. *J Natl Cancer Inst* 2012;104:125-32. doi: 10.1093/jnci/djr500.

4. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, *et al.* Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014;384:2027-35. doi: 10.1016/S0140-6736(14)60525-0.
5. Yan W, Li H, Zhou Y, Huang Z, Rong S, Xia M, *et al.* Prostate carcinoma spatial distribution patterns in Chinese men investigated with systematic transperineal ultrasound guided 11-region biopsy. *Urol Oncol* 2009;27:520-4. doi: 10.1016/j.urolonc.2008.05.002.
6. Li H, Yan W, Zhou Y, Ji Z, Chen J. Transperineal ultrasound-guided saturation biopsies using 11-region template of prostate: Report of 303 cases. *Urology* 2007;70:1157-61. doi: 10.1016/j.urology.2007.07.072.
7. Hansen N, Patrino G, Wadhwa K, Gaziev G, Miano R, Barrett T, *et al.* Magnetic resonance and ultrasound image fusion supported transperineal prostate biopsy using the Ginsburg protocol: Technique, learning points, and biopsy results. *Eur Urol* 2016;70:332-40. doi: 10.1016/j.eururo.2016.02.064.
8. Morgentaler A. Controversies and advances with testosterone therapy: A 40-year perspective. *Urology* 2016;89:27-32. doi: 10.1016/j.urology.2015.11.034.
9. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: A collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008;100:170-83. doi: 10.1093/jnci/djm323.
10. Muller RL, Gerber L, Moreira DM, Andriole G, Castro-Santamaria R, Freedland SJ. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. *Eur Urol* 2012;62:757-64. doi: 10.1016/j.eururo.2012.05.025.
11. Cui Y, Zong H, Yan H, Zhang Y. The effect of testosterone replacement therapy on prostate cancer: A systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2014;17:132-43. doi: 10.1038/pcan.2013.60.
12. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: From physiology to clinical implications. *Eur Urol* 2014;65:115-23. doi: 10.1016/j.eururo.2013.08.015.
13. San Francisco IF, Rojas PA, DeWolf WC, Morgentaler A. Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance. *BJU Int* 2014;114:229-35. doi: 10.1111/bju.12682.
14. Isom-Batz G, Bianco FJ Jr., Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *J Urol* 2005;173:1935-7. doi: 10.1097/01.ju.0000158040.33531.e7.
15. Shaneyfelt T, Husein R, Bublely G, Mantzoros CS. Hormonal predictors of prostate cancer: A meta-analysis. *J Clin Oncol* 2000;18:847-53. doi: 10.1159/000102906.
16. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000;21:427-33.
17. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, *et al.* MicroRNA expression profiles classify human cancers. *Nature* 2005;435:834-8.
18. Tosoian JJ, Carter HB, Lepor A, Loeb S. Active surveillance for prostate cancer: Current evidence and contemporary state of practice. *Nat Rev Urol* 2016;13:205-15. doi: 10.1038/nrurol.2016.45.
19. Chung MS, Lee SH. Current status of active surveillance in prostate cancer. *Investig Clin Urol* 2016;57:14-20. doi: 10.4111/icu.2016.57.1.14.
20. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J, *et al.* Active surveillance in men with localized prostate cancer: A systematic review. *Ann Intern Med* 2012;156:582-90. doi: 10.7326/0003-4819-156-8-201204170-00397.
21. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, *et al.* Active surveillance program for prostate cancer: An update of the

- Johns Hopkins experience. *J Clin Oncol* 2011;29:2185-90. doi: 10.1200/JCO.2010.32.8112.
22. Tosoian JJ, JohnBull E, Trock BJ, Landis P, Epstein JI, Partin AW, *et al.* Pathological outcomes in men with low risk and very low risk prostate cancer: Implications on the practice of active surveillance. *J Urol* 2013;190:1218-22. doi: 10.1016/j.juro.2013.04.071.
 23. Kinoshita H, Nakagawa K, Usui Y, Iwamura M, Ito A, Miyajima A, *et al.* High-definition resolution three-dimensional imaging systems in laparoscopic radical prostatectomy: Randomized comparative study with high-definition resolution two-dimensional systems. *Surg Endosc* 2015;29:2203-9. doi: 10.1007/s00464-014-3925-8.
 24. Leow JJ, Chang SL, Meyer CP, Wang Y, Hanske J, Sammon JD, *et al.* Robot-assisted versus open radical prostatectomy: A Contemporary analysis of an all-payer discharge database. *Eur Urol* 2016;70:837-45. doi: 10.1016/j.eururo.2016.01.044.
 25. Patel VR, Coelho RF, Chauhan S, Orvieto MA, Palmer KJ, Rocco B, *et al.* Continence, potency and oncological outcomes after robotic-assisted radical prostatectomy: Early trifecta results of a high-volume surgeon. *BJU Int* 2010;106:696-702. doi: 10.1111/j.1464-410X.2010.09541.x.
 26. Walsh PC. Radical prostatectomy, preservation of sexual function, cancer control. The controversy. *Urol Clin North Am* 1987;14:663-73.
 27. MA-AUA, Mid-Atlantic section of the American Urological Association, 66th annual meeting, Cambridge, Maryland, USA, September 25-28, 2008. Abstracts. *Can J Urol* 2008;15:4200-18.
 28. Gu X, Araki M, Wong C. Continence outcomes after bladder neck preservation during robot-assisted laparoscopic prostatectomy (RALP). *Minim Invasive Ther Allied Technol* 2015;24:364-71. doi: 10.3109/13645706.2015.1027711.
 29. Yamada Y, Kollmeier MA, Pei X, Kan CC, Cohen GN, Donat SM, *et al.* A phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. *Brachytherapy* 2014;13:111-6. doi: 10.1016/j.brachy.2013.11.005.
 30. Latorzeff I, Mazurier J, Boutry C, Dudouet P, Richaud P, de Crevoisier R. Benefit of intensity modulated and image-guided radiotherapy in prostate cancer. *Cancer Radiother* 2010;14:479-87. doi: 10.1016/j.canrad.2010.06.013.
 31. Welz S, Nyazi M, Belka C, Ganswindt U. Surgery vs. Radiotherapy in localized prostate cancer. Which is best? *Radiat Oncol* 2008;3:23. doi: 10.1186/1748-717X-3-23.
 32. Cordes LM, Gulley JL, Madan RA. The evolving role of immunotherapy in prostate cancer. *Curr Opin Oncol* 2016;28:232-40. doi: 10.1097/CCO.0000000000000281.
 33. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, *et al.* Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-22. doi: 10.1056/NEJMoa1001294.
 34. Strauss J, Madan RA. Therapeutic vaccines for prostate cancer: Recent advances and future directions. *Expert Rev Vaccines* 2016;15:907-14. doi: 10.1586/14760584.2016.1155988.
 35. Wong KK, Li WA, Mooney DJ, Dranoff G. Advances in therapeutic cancer vaccines. *Adv Immunol* 2016;130:191-249. doi: 10.1016/bs.ai.2015.12.001.
 36. Hamilton Z, Parsons JK. Prostate cancer prevention: Concepts and clinical trials. *Curr Urol Rep* 2016;17:35. doi: 10.1007/s11934-016-0587-1.