



The Use of High-Intensity Focused Ultrasound (HIFU) Plus 150mg Bicalutamide as First Line Salvage Therapy for Local Recurrent Prostate Cancer

Jian-zhou Cao^{1,2}, Rui Su^{2,3,4}, Jin-feng Pan^{1,2}, Ze-jun Yan^{3,4*} and Qi Ma^{2,3,4,5*}

¹ Medical School, Ningbo University, Ningbo, China, ² Comprehensive Urogenital Cancer Center, Ningbo First Hospital, The Affiliated Hospital of Ningbo University, Ningbo, China, ³ Department of Urology, Ningbo First Hospital, The Affiliated Hospital of Ningbo University, Ningbo, China, ⁴ Ningbo Clinical Research Center for Urological Disease, Ningbo, China, ⁵ Translational Research Laboratory for Urology, The Key Laboratory of Ningbo City, Ningbo First Hospital, The Affiliated Hospital of Ningbo University, Ningbo, China

OPEN ACCESS

Edited by:

Fabio Grizzi,
Humanitas Research Hospital, Italy

Reviewed by:

Preston C. Sprenkle,
Yale University, United States
Benyi Li,
University of Kansas Medical Center,
United States

*Correspondence:

Ze-jun Yan
35485787@qq.com
Qi Ma
qi.ma@nbdyyy.com

Specialty section:

This article was submitted to
Genitourinary Oncology,
a section of the journal
Frontiers in Oncology

Received: 04 May 2021

Accepted: 29 October 2021

Published: 18 November 2021

Citation:

Cao J-z, Su R, Pan J-f, Yan Z-j
and Ma Q (2021) The Use of
High-Intensity Focused Ultrasound
(HIFU) Plus 150mg Bicalutamide
as First Line Salvage Therapy for
Local Recurrent Prostate Cancer.
Front. Oncol. 11:705025.
doi: 10.3389/fonc.2021.705025

Patients with localized prostate cancer (PCa) are often treated with radical prostatectomy (RP). However, more than 30% of such patients have high risk of recurrence. Salvage radiotherapy (SRT), androgen deprivation therapy (ADT) and combination of radiotherapy and ADT are the standard care for recurrent PCa. Recently, high intensity focused ultrasound (HIFU) has gradually applied in the treatment of recurrent PCa. Here, we proposed a hypothesis that combined HIFU and bicalutamide 150mg as first line salvage therapy to treat patients with local recurrent PCa with visible lesions due to the following advantages: (1) HIFU is effective in reducing local tumor load, and bicalutamide 150mg is a feasible and safety option to combine with HIFU. (2) Compared with radiotherapy, HIFU plus 150mg bicalutamide is minimal invasiveness with fewer adverse effects and better quality of life(QOL); (3) Radiotherapy can be preserved as the second-line salvage method in the cases who are failure to HIFU and 150mg bicalutamide combination. More clinical trials are warranted to confirm this hypothesis in treatment with recurrent PCa.

Keywords: high intensity focused ultrasound (HIFU), anti-androgen therapy, bicalutamide, hypothesis, local recurrent prostate cancer

INTRODUCTION/BACKGROUND

Patients with localized prostate cancer (PCa) are often treated with radical prostatectomy (RP), however, more than 30% of such patients have high risk of recurrence after prostatectomy (1–3). Currently, there are several treatment options for patients with recurrent PCa after radical prostatectomy (RP), such as salvage radiotherapy (SRT), androgen deprivation therapy (ADT), and combined radiotherapy with ADT (4–7). A double-blind, placebo-controlled trial (RTOG 9601) has confirmed that the addition of 24 months daily 150mg bicalutamide combined with salvage radiation therapy resulted in significantly higher rates of long-term overall survival (OS) and lower incidences of metastatic PCa and death from PCa than radiation therapy plus placebo in recurrent

PCa (8). Therefore, the National Comprehensive Cancer Network (NCCN) published the guideline in 2019 that recommended level 1 evidence supporting 150 mg of bicalutamide daily with radiotherapy combined for two years to treat recurrent PCa (9). However, these therapies also have some adverse effects that may influence the patient's quality of life (QOL), such as radiation enteritis and cystitis, rectal bleeding, rectal or anal stenosis, and sexual dysfunction. To further avoid these side effects without reducing patient survival benefits, we postulate that high intensity focused ultrasound (HIFU) combined with Bicalutamide 150mg may be another safe and effective treatment option for local recurrent PCa in carefully selected patients with: (1) Visible lesions on imaging; (2) Patients who cannot tolerate the side effects of radiotherapy or refuse to receive radiotherapy.

APPLICATION OF HIFU IN TREATMENT OF PCa

When HIFU is used for the treatment of PCa, it needs to place a high-power probe in the rectum or urethra to generate acoustic energy focused on the tissue target, which non-specifically ablates tissue through hyperthermia and mechanical effect (10–12). The thermal effects are achieved by heating local tissues to 60°C or higher (usually 1–3mm² area), resulting in near-instantaneous coagulative necrosis and cell death (13). The mechanical effects include cavitation, microstreaming, and radiation forces (11). The mechanical effect would cause cell membrane disruption and then form the cavity, leading the tissue ablation (10).

Under the guideline of the European Association of Urology (EAU), HIFU is described as an investigational treatment modality for PCa treatment (14). Madersbachers has reported 29 cases of PCa who received radical surgery after HIFU treatment, and the pathology showed that HIFU effectively ablated the tumor tissue, which demonstrated that HIFU has a good effect in reducing tumor load (15). Since then, clinicians have tried HIFU for localized PCa and the application of HIFU in early-stage PCa has been successfully written into the guidelines. Whether HIFU plays a role in recurrent PCa after radical prostatectomy and radiation has also been investigated. In the early years, a study reported 4 cases of recurrent PCa after RP were treated with HIFU as first line salvage treatment. These patients were suspected to be local recurrence in the region of the vesicourethral anastomosis with no biopsy, and no bone metastasis or regional lymph node swelling were found before HIFU. At 24-month of follow-up, 2/4 patients were biochemical recurrence-free (defined as an increase in PSA level > 0.2 ng/ml). No major complications were noted (16). Later, Asimakopoulos et al. presented a larger series of salvage HIFU after RP. All included patients were TRUS-evidenced local recurrence with no distant metastasis. During the follow-up, 17/19 patients (89.5%) were classified as success (Success was defined as PSA nadir ≤ 0.1 ng/ml obtained within 3 months from HIFU) (17). In the study of Palermo et al., 22 patients with peri-anastomotic recurrence

proved by TRUS were included and received HIFU as first line salvage therapy after radical prostatectomy. None of them showed distant metastasis by bone scan and total body CT scan. 45.5% patients showed a nadir PSA ≤ 0.4 ng/ml three months after HIFU and continue to be considered as a success at a median follow-up of 48 months (18).

In conclusion, though lack of high-quality studies currently, HIFU is a promising method to achieve local tumor control and may be a useful salvage treatment option in recurrent PCa.

DIFFERENT SIDE EFFECTS BETWEEN HIFU AND RADIOTHERAPY AS SALVAGE THERAPY FOR RECURRENT PCa

A small number of studies have shown that HIFU as first-line salvage therapy after RP has obtained satisfactory results and tolerable side effects. In Asimakopoulos's study, no case of urethrorectal fistula or anastomotic stricture was observed. Two cases of acute urinary retention were resolved with prolonged urethral catheterization. Four cases of stress urinary incontinence were observed; 2 (mild incontinence) were resolved after pelvic floor exercises within 6 months, while 2 cases of severe incontinence required surgical minimally invasive treatment¹⁷. Palermo et al. reported 22% stress urinary incontinence occurred after HIFU treatment. Two sevenths of the patients complained about erectile dysfunction after HIFU treatment. They did not observe cases of urethrorectal fistula or persistent lower urinary tract symptoms (18).

Compared with salvage HIFU, SRT has different complications in patients with recurrent PCa after RP. The side effects of radiotherapy for PCa mainly include gastrointestinal (GI) toxicity, genitourinary (GU) toxicity, Erectile dysfunction (ED) and myelosuppression (19). Lisanne et al. reported long-term treatment toxicity and urinary incontinence rate after radical prostatectomy using SRT. 244 patients were included. Median follow-up after SRT was 50 months. After SRT, *de novo* urinary incontinence complaints (grade ≥ 1) occurred in 6.1% and 17.6% of patients in the acute and late phase. Acute grade ≥ 2 GU and GI toxicity was 19.2% and 17.6%. Late grade ≥ 2 toxicity for GU was 29.9% and for GI was 21.3%, respectively (20). Pirus et al. performed a randomized phase III trial assessing acute toxicity and QOL after SRT. Acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6% patients with 64 Gy and in 16.6% and 1.7% patients with 70 Gy. Acute grade 2 and 3 GI toxicity was observed in 16.0% and 0.6% patients with 64 Gy, and in 15.4% and 2.3% patients with 70 Gy (21). Myelosuppression occurs less frequently during radiotherapy for PCa and is characterized by leukopenia, neutropenia, anemia, and/or thrombocytopenia (22). ED is also a major complication after radiotherapy, with an incidence of about 28% (23).

Thus, salvage HIFU and salvage radiotherapy have different side effects as local therapy in recurrent PCa. However, it should be noticed that SRT is the mainstream in current studies, and salvage HIFU need more time to accumulate acute and long-term safety data.

SRT IS STILL EFFECTIVE AND TOLERABLE FOR PATIENTS WHO ARE FAILURE AFTER FIRST LINE HIFU TREATMENT

A study by Filippo et al. intended to evaluate tolerance and acute toxicity in patients who failed to HIFU and salvaged by second line SRT. Acute grade 1 and grade 2 GU toxicities were recorded in 7/15 and 4/15 patients respectively; Acute grade 1 and grade 2 bowel toxicities in 4/15 and 1/15 patients; Acute grade 1 and grade 2 rectal toxicities in 3/15 and 2/15 respectively. No grade 3 or greater acute or late toxicities occurred (24). In another study to treat patients with SRT after HIFU failure, Fernando et al. found that GI toxicity was low. Acute GU toxicity grade \leq II rate was 45.8%. With only a few patients presenting grade III (8.3%) and grade IV (4.2%) toxicity. Late grade \geq III GU toxicity was registered in 16.7% of patients. The 3-year disease-free survival rate was 77.8% (25). Julien et al. also evaluated the tolerance and oncologic control with salvage radiotherapy (SRT) after HIFU failure. For the 83 patients treated with exclusive radiation therapy, PFS was 72.5% at 5 year. GI toxicity was low; GU toxicity grade \leq 2 was 34.5%, grade 3 (4.7%), grade 4 (1.2%), and grade 5 (1.2%). The incidence of severe ED was 14% pre-HIFU, and 51.9% and 82.3% pre-and post-SRT, respectively (26).

These studies suggested that SRT still provides satisfactory oncologic control and with little (or mild) additional toxicity even after HIFU failure.

THE VALUE OF BICALUTAMIDE 150MG IN THE TREATMENT OF LOCALIZED PCa

Bicalutamide is a competitive androgen receptor antagonist that inactivates androgen-regulated prostate cell growth and function, leading to cell apoptosis and inhibition of PCa growth. With an average follow-up of 7.2 years, William et al. found that bicalutamide 150mg plus curative radiation had significantly clinical benefits in terms of OS, PFS and PSA-PFS compared with radiotherapy alone with locally advanced PCa (27). See et al. demonstrated bicalutamide 150 mg significantly reduced the risk of PSA progression, irrespective of whether patients had received radical prostatectomy or radiotherapy as standard care (28). After a median follow-up of 9.7 years, Iversen et al. analyzed the Early Prostate Cancer (EPC) program. This program recruited 8113 patients, among them 4052 patients (49.9%) were randomized to bicalutamide 150 mg and 4061 patients (50.1%) to placebo, in addition to standard care of RT, RP or watchful waiting (W W). At the time of data cut-off, 3032 patients (37.4%) met the criteria for objective disease progression; among them 1483 patients (36.6%) in the bicalutamide and 1549 patients (38.1%) in the placebo group. In the WW group, the median PFS was 6.6 years for patients randomized to receive bicalutamide 150mg compared with 3.7 years for those who randomized to placebo. In addition, bicalutamide reduced the risk of death by 30% in patients with locally advanced disease received RT compared with placebo (29).

VIABILITY OF HIGH INTENSITY FOCUSED ULTRASOUND PLUS BICALUTAMIDE 150MG THERAPY

By virtue of the good effect of HIFU in reducing local tumor load and the good adjuvant effect of 150mg bicalutamide after local treatment, we postulate that HIFU plus bicalutamide 150mg may be a new feasible option for the treatment of recurrent PCa by the following reasons: (1) HIFU is effective in reducing local tumor load, and bicalutamide 150mg is a feasible and safety option to combine with HIFU; (2) HIFU plus 150mg bicalutamide may be a minimal invasive therapy with fewer adverse effects and better QOL; (3) Radiotherapy can be preserved as the second-line salvage method in the cases who are failure to HIFU and bicalutamide combination.

In addition, HIFU has been used as combination therapy to further increase drug delivery efficiency. This is accomplished by increasing blood flow into the heated tumor tissue while also dilating the tumor vessels, further expanding the fenestrae and allowing for greater extravasation (30). Though currently there are no data showed HIFU has synergistic effects with bicalutamide in clinical studies, Bakarev et al. reported that HIFU combined with maximum androgen blocking (flutamide with goserelin) was associated with a significant decrease in numerical density of microvessels in zones of prostate tumor in patients with relapsed PCa (31). In another study, Hahn et al. reported there was no direct correlation between androgen response and heat response, however, it is interesting to see differential response of castration-sensitive and insensitive tumors. Androgen independent PC3 cells were more resistant to high temperatures than androgen dependent VCaP cells. Pre-treatment of VCaP cells with testosterone leads to a more PC3-like kinetic of the heat response (32). As the connection between HIFU and androgen signal pathway is still unclear, more clinical and mechanism related studies could be performed to investigate whether HIFU has synergistic effects with bicalutamide.

MORE CONSIDERATIONS

The new generation of hormone therapeutic drugs mainly include abiraterone, an androgen synthesis inhibitor, and AR receptor antagonist such as enzalutamide, apalutamide and darolutamide. Several clinical trials have established these drugs' value in both metastatic hormone sensitive prostate cancer(mHSPC) and metastatic castration resistant prostate cancer(mCRPC) (33–35). In non-metastatic castration resistant prostate cancer(nmCRPC), AR receptor antagonists also have shown longer OS and PFS in clinical trials (36). In ENZAMET study, ADT combined with enzalutamide was compared with ADT combined with bicalutamide and other first generation of anti-androgen drugs in the treatment of mHSPC directly, and enzalutamide showed significant advantages over bicalutamide and other first generation of anti-androgen receptor drugs (37). However, evidence that supports new hormone therapy agents over bicalutamide in the treatment of local hormone sensitive

prostate cancer is lacking (38). Furthermore, currently, most new generation of hormone therapy drugs are combined with ADT during their clinical applications, and only 150mg bicalutamide monotherapy has demonstrated its efficacy in clinical studies (8, 28, 29). More clinical trials should be performed to confirm whether these new hormone therapy drugs with or without ADT are superior over 150mg bicalutamide in local recurrent PCa.

CONCLUSION

The hypothesis that HIFU plus 150mg bicalutamide as a safe and effective treatment option for local recurrent PCa in carefully selected patients is promising. The treatment goal is to achieve effective control of local recurrence and avoid distant metastasis, prolong the OS rate and improve QOL. Furthermore, radiotherapy, can be preserved as the second line salvage method in the cases who are failure to HIFU and 150mg bicalutamide combination. We believe that HIFU plus 150mg bicalutamide therapy is theoretically feasible, and further clinical trials are warranted.

REFERENCES

- Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. *JAMA* (2015) 314:80-2. doi: 10.1001/jama.2015.6036
- Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical Prostatectomy Versus Observation for Localized Prostate Cancer. *N Engl J Med* (2012) 367:203-13. doi: 10.1056/NEJMoa1113162
- Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The Impact of Anatomical Radical Retropubic Prostatectomy on Cancer Control: The 30-Year Anniversary. *J Urol* (2012) 188:2219-24. doi: 10.1016/j.juro.2012.08.028
- Isharwal S, Stephenson AJ. Post-Prostatectomy Radiation Therapy for Locally Recurrent Prostate Cancer. *Expert Rev Anticancer Ther* (2017) 17:1003-12. doi: 10.1080/14737140.2017.1378575
- Patel AR, Stephenson AJ. Radiation Therapy for Prostate Cancer After Prostatectomy: Adjuvant or Salvage? *Nat Rev Urol* (2011) 8:385-92. doi: 10.1038/nrurol.2011.80
- McCormick BZ, Mahmoud AM, Williams SB, Davis JW. Biochemical Recurrence After Radical Prostatectomy: Current Status of its Use as a Treatment Endpoint and Early Management Strategies. *Indian J Urol IJU J Urol Soc India* (2019) 35:6-17. doi: 10.4103/iju.IJU_355_18
- Carrie C, Hasbini A, de Laroche G, Richaud P, Guerif S, Latorzeff I, et al. Salvage Radiotherapy With or Without Short-Term Hormone Therapy for Rising Prostate-Specific Antigen Concentration After Radical Prostatectomy (GETUG-AFU 16): A Randomised, Multicentre, Open-Label Phase 3 Trial. *Lancet Oncol* (2016) 17:747-56. doi: 10.1016/s1470-2045(16)00111-x
- Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation With or Without Antiandrogen Therapy in Recurrent Prostate Cancer. *N Engl J Med* (2017) 376:417-28. doi: 10.1056/NEJMoa1607529
- Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw JNCCN* (2019) 17:479-505. doi: 10.6004/jnccn.2019.0023
- Murat FJ, Poissonnier L, Pasticier G, Gelet A. High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer. *Cancer Control J Moffitt Cancer Center* (2007) 14:244-9. doi: 10.1177/107327480701400307
- Rove KO, Sullivan KF, Crawford ED. High-Intensity Focused Ultrasound: Ready for Primetime. *Urol Clinics North Am* (2010) 37:27-35. doi: 10.1016/j.ucl.2009.11.010

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was supported by Zhejiang Natural Science Fund (Grant No.LY20H050002 to QM), Ningbo Social Development Fund (Grant No.202002N3192 to QM), and the Fund of Ningbo Clinical Research Center for Urological Disease (2019A21001).

- Lodeizen O, de Bruin M, Egger S, Crouzet S, Ghai S, Varkarakis I, et al. Ablation Energies for Focal Treatment of Prostate Cancer. *World J Urol* (2019) 37:409-18. doi: 10.1007/s00345-018-2364-x
- Dewhurst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic Principles of Thermal Dosimetry and Thermal Thresholds for Tissue Damage From Hyperthermia. *Int J Hyperthermia Off J Eur Soc Hyperthermic Oncol North Am Hyperthermia Group* (2003) 19:267-94. doi: 10.1080/0265673031000119006
- Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment With Curative Intent-Update 2013. *Eur Urol* (2014) 65:124-37. doi: 10.1016/j.eururo.2013.09.046
- Madersbacher S, Pedevilla M, Vingers L, Susani M, Marberger M. Effect of High-Intensity Focused Ultrasound on Human Prostate Cancer In Vivo. *Cancer Res* (1995) 55:3346-51.
- Hayashi M, Shinmei S, Asano K. Transrectal High-Intensity Focused Ultrasound for Treatment for Patients With Biochemical Failure After Radical Prostatectomy. *Int J Urol Off J Japanese Urol Assoc* (2007) 14:1048-50. doi: 10.1111/j.1442-2042.2007.01880.x
- Asimakopoulos AD, Miano R, Virgili G, Vespasiani G, Finazzi Agrò E. HIFU as Salvage First-Line Treatment for Palpable, TRUS-Evidenced, Biopsy-Proven Locally Recurrent Prostate Cancer After Radical Prostatectomy: A Pilot Study. *Urol Oncol* (2012) 30:577-83. doi: 10.1016/j.urolonc.2010.08.019
- Palermo G, Totaro A, Sacco E, Foschi N, Gulino G, Racioppi M, et al. High Intensity Focused Ultrasound as First Line Salvage Therapy in Prostate Cancer Local Relapse After Radical Prostatectomy: 4-Year Follow-Up Outcomes. *Minerva Urologica e Nefrologica = Ital J Urol Nephrol* (2017) 69:93-100. doi: 10.23736/s0393-2249.16.02696-5
- Linney H, Barrett S. Stereotactic Body Radiation Therapy for Patients With Early-Stage Prostate Cancer. *Anticancer Res* (2018) 38:1231-40. doi: 10.21873/anticancer.12344
- van Dessel LF, Reuvers SHM, Bangma CH, Aluwini S. Salvage Radiotherapy After Radical Prostatectomy: Long-Term Results of Urinary Incontinence, Toxicity and Treatment Outcomes. *Clin Trans Radiat Oncol* (2018) 11:26-32. doi: 10.1016/j.ctro.2018.05.001
- Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al. Acute Toxicity and Quality of Life After Dose-Intensified Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: First Results of the Randomized Trial SAKK 09/10. *J Clin Oncol Off J Am Soc Clin Oncol* (2015) 33:4158-66. doi: 10.1200/jco.2015.63.3529

22. Luo HC, Fu ZC, Cheng HH, Lei Y, Liao SG, Feng J, et al. Prostate Cancer Treated With Reduced-Volume Intensity-Modulated Radiation Therapy: Report on the 5-Year Outcome of a Prospective Series. *Medicine* (2017) 96:e9450. doi: 10.1097/md.00000000000009450
 23. Pan HY, Jiang J, Hoffman KE, Tang C, Choi SL, Nguyen QN, et al. Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36:1823–30. doi: 10.1200/jco.2017.75.5371
 24. Alongi F, Liardo RL, Iftode C, Lopci E, Villa E, Comito T, et al. 11C Choline PET Guided Salvage Radiotherapy With Volumetric Modulation Arc Therapy and Hypofractionation for Recurrent Prostate Cancer After HIFU Failure: Preliminary Results of Tolerability and Acute Toxicity. *Technol Cancer Res Treat* (2014) 13:395–401. doi: 10.7785/ctrtexpress.2013.600268
 25. Munoz F, Guarneri A, Botticella A, Gabriele P, Moretto F, Panaia R, et al. Salvage External Beam Radiotherapy for Recurrent Prostate Adenocarcinoma After High-Intensity Focused Ultrasound as Primary Treatment. *Urologia Internationalis* (2013) 90:288–93. doi: 10.1159/000345631
 26. Riviere J, Bernhard JC, Robert G, Wallerand H, Deti E, Maurice-Tison S, et al. Salvage Radiotherapy After High-Intensity Focussed Ultrasound for Recurrent Localised Prostate Cancer. *Eur Urol* (2010) 58:567–73. doi: 10.1016/j.eururo.2010.06.003
 27. See WA, Tyrrell CJ. The Addition of Bicalutamide 150 Mg to Radiotherapy Significantly Improves Overall Survival in Men With Locally Advanced Prostate Cancer. *J Cancer Res Clin Oncol* (2006) 132(Suppl 1):S7–16. doi: 10.1007/s00432-006-0132-6
 28. See W, Iversen P, Wirth M, McLeod D, Garside L, Morris T. Immediate Treatment With Bicalutamide 150mg as Adjuvant Therapy Significantly Reduces the Risk of PSA Progression in Early Prostate Cancer. *Eur Urol* (2003) 44:512–7. doi: 10.1016/s0302-2838(03)00366-x
 29. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP. Antiandrogen Monotherapy in Patients With Localized or Locally Advanced Prostate Cancer: Final Results From the Bicalutamide Early Prostate Cancer Programme at a Median Follow-Up of 9.7 Years. *BJU Int* (2010) 105:1074–81. doi: 10.1111/j.1464-410X.2010.09319.x
 30. Frazier N, Payne A, de Bever J, Dillon C, Panda A, Subrahmanyam N, et al. High Intensity Focused Ultrasound Hyperthermia for Enhanced Macromolecular Delivery. *J Controlled Release Off J Controlled Release Soc* (2016) 241:186–93. doi: 10.1016/j.jconrel.2016.09.030
 31. Bakarev MA, Levin VP, Kachesov IV, Abdullaev NA, Neimark AI. Status of the Microcirculatory Network as a Factor of Prognosis and Evaluation of Therapeutic Efficiency in Prostate Cancer Treated by High-Intensity Focused Ultrasound in Combination With Androgen Deprivation. *Bull Exp Biol Med* (2018) 165:682–7. doi: 10.1007/s10517-018-4241-4
 32. Hahn O, Heining FM, Janzen J, Becker JCR, Bertlich M, Thelen P, et al. Modulating the Heat Sensitivity of Prostate Cancer Cell Lines In Vitro: A New Impact for Focal Therapies. *Biomedicines* (2020) 8:585. doi: 10.3390/biomedicines8120585
 33. Swami U, McFarland TR, Nussenzveig R, Agarwal N. Advanced Prostate Cancer: Treatment Advances and Future Directions. *Trends Cancer* (2020) 6:702–15. doi: 10.1016/j.trecan.2020.04.010
 34. Cattrini C, Castro E, Lozano R, Zanardi E, Rubagotti A, Boccardo F, et al. Current Treatment Options for Metastatic Hormone-Sensitive Prostate Cancer. *Cancers (Basel)* (2019) 12:1355. doi: 10.3390/cancers11091355
 35. Chi K, Hotte SJ, Joshua AM, North S, Wyatt AW, Collins LL, et al. Treatment of mCRPC in the AR-Axis-Targeted Therapy-Resistant State. *Ann Oncol* (2015) 26:2044–56. doi: 10.1093/annonc/mdv267
 36. Mulati Y, Fan Y, Yu W, Zhang Q, He Z. Novel Androgen Receptor Inhibitors in Non-Metastatic, Castration-Resistant Prostate Cancer: A Systematic Review and Network Meta-Analysis. *Front Oncol* (2021) 11:733202. doi: 10.3389/fonc.2021.733202
 37. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide With Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med* (2019) 381:121–31. doi: 10.1056/NEJMoa1903835
 38. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated With Hormone Therapy. *N Engl J Med* (2017) 377:338–51. doi: 10.1056/NEJMoa1702900
- Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
- Copyright © 2021 Cao, Su, Pan, Yan and Ma. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.