

# Review and Case Report: Active Surveillance Therapy with Citrus-Peel Extracts' Efficacy Against Prostate Cancer

Shinji Kageyama<sup>1\*</sup>, Shinsuke Hayami<sup>2</sup>, Seiji Ohmura<sup>3</sup>, Michiko Suzawa<sup>4</sup> and Shizuo Yamada<sup>5</sup>

<sup>1</sup>Kageyama Urology Clinic, Japan

<sup>2</sup>Department of Urology, Fujieda City General Hospital, Japan

<sup>3</sup>Ohmura Clinic, Japan

<sup>4</sup>Miyauchi Citrus Laboratories, Japan

<sup>5</sup>Center of Pharma-Food Research, Shizuoka University, Japan

\*Corresponding author: Shinji Kageyama, Kageyama Urology Clinic, 420-0838 9-5, Aioi-cho, Shizuoka-shi, Shizuoka, Japan



## ARTICLE INFO

**Received:** 📅 March 19, 2022

**Published:** 📅 March 28, 2022

**Citation:** Shinji Kageyama, Shinsuke Hayami, Seiji Ohmura, Michiko Suzawa, Shizuo Yamada. Review and Case Report: Active Surveillance Therapy with Citrus-Peel Extracts' Efficacy Against Prostate Cancer. Biomed J Sci & Tech Res 42(5)-2022. BJSTR. MS.ID.006827.

**Keywords:** Active Surveillance; Complementary or Alternative Medicine (Cam); Gold Lotion; Nobiletin; Polymethoxyflavones

## ABSTRACT

Active surveillance therapy (AS), patients feel uneasiness about not taking any conventional medications. Sixty one years old man was diagnosed with prostate cancer at the clinical stage of T2aNoMo with Gleason 3+4 and PSA of 6.4 ng/mL. This patient chose AS. Nine years later, his PSA value gradually increased to over 10 ng/mL. Although the PSA level was rising, MRI examination did not indicate obvious abnormal lesions. The patient heard about Gold Lotion (GL) by word of mouth and was willing to try it out on him. After drinking GL, MRI showed no abnormal results. He received another biopsy, and collected specimens showed G3+4. He continued with AS with GL and his PSA value remained less than 11 ng/mL for about 4 years. In some limited cases, the addition of GL drinking to AS can be considered as an effective method to eliminate patients' anxiety (145 wards).

**Abbreviations:** CAM: Complementary and Alternative Medicine; NIH: National Institute of Health; PMFs: Polymethoxyflavones; AS : Active Surveillance Therapy ; GL :Gold Lotion

## Introduction

Prostate cancer is the most common cancer for men in Japan. It usually grows very slowly. Most men who develop prostate cancer are older than 65 years and do not die from the disease since prostate cancer usually grows very slowly [1]. The withdrawal rate from active surveillance therapy to a second (traditional) therapy is said to be 14 – 41% [2]. During active surveillance therapy, patients feel uneasiness for not taking any traditional medications. Some of them thus turn to noninvasive therapy such as complementary and alternative medicine (CAM) [3].

## Case Report

This is a case of a 76-year-old male. Because his PSA value rose to 6.4 ng/mL at the age of 61, he was recommended a prostatic biopsy by other doctors. According to the pathological examination, two out of six specimens indicated G3+4. CT and bone scintigraphy revealed his stage was T2aNoMo. This patient chose active surveillance therapy. Obvious changes were not observed for about nine years; however, in 2014 his PSA value gradually increased to over 10 ng/mL. Then he started drinking citrus-peel extract known

as GL among researchers (Gold Lotion produced by Miyauchi Citrus Research Center, Ltd., Takasaki, Japan) as a CAM therapy. We recommended another biopsy to him to be assured of no prostate cancer progression. The patient under active surveillance was a little anxious about receiving no traditional medical treatment, so that careful follow-up of PSA levels was required. Although the PSA level was rising, MRI examination did not indicate obvious abnormal lesions. The patient heard about GL by word of mouth and was willing to try it out on him. One-year drinking of GL

showed no abnormal results in MRI, except for prostatic adenoma (Figure 1). His PSA increased to 11.2 ng/mL. He decided to have another biopsy. Collected specimens showed no sign of progression in Gleason score but a small number of cancer cells (one out of six specimens with G3+4) in September 2015. He decided to continue active surveillance therapy with GL. As of November 2017, his PSA value remained less than 11 ng/mL for about 4 years despite small interruption periods of GL drinking (Figures 2A & 2B).

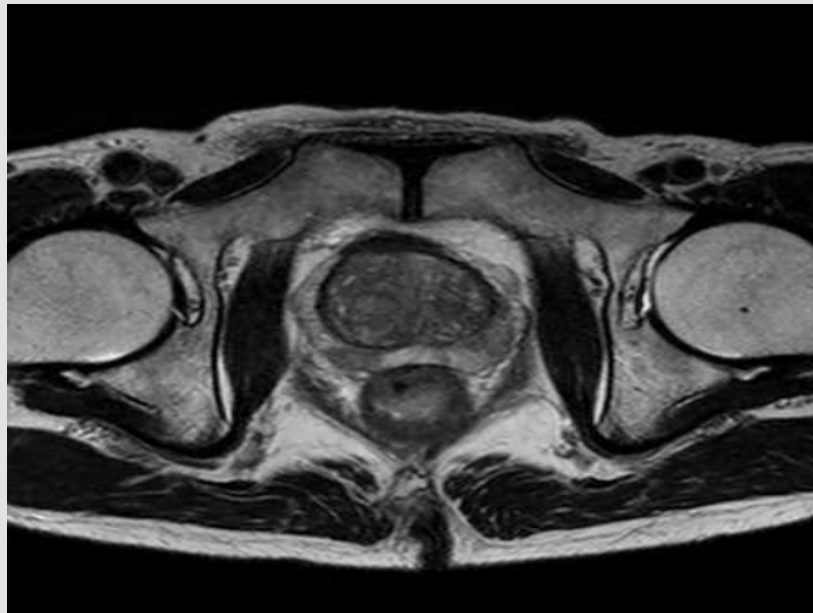


Figure 1: MRI showed large prostate adenoma; however, the margin is smooth with no lymph node swelling.

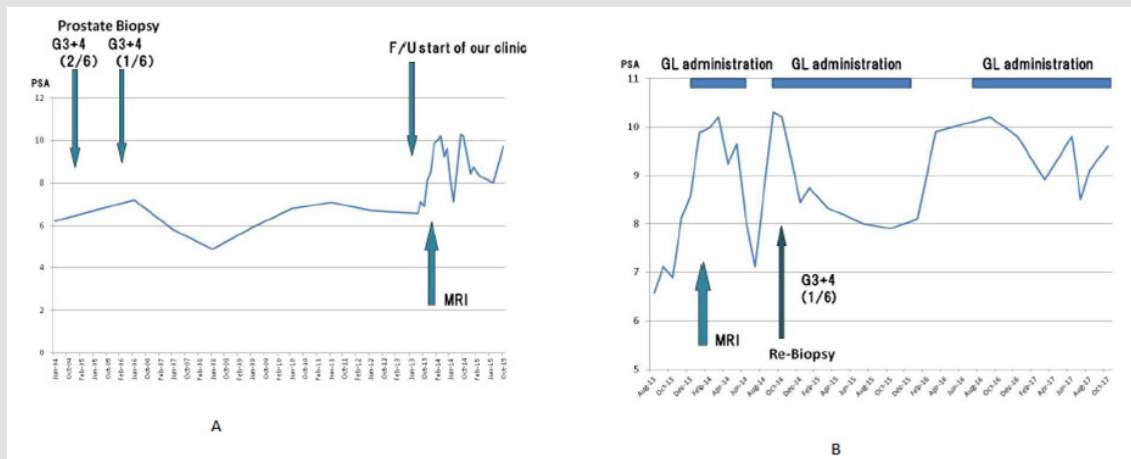


Figure 2: Clinical course of this patient

- A. From the initial diagnosis from 2006 to 2014,
- B. After GL drinking period from 2014 to 2019.

## Discussion and Conclusion

Complementary and alternative medicine (CAM) is a form of treatment used in addition to or instead of standard therapy. Standard treatments go through a long and careful research process to prove they are safe and effective, but less is known about most types of CAM. In the treatment of advanced-stage cancer, CAM is carried out as palliative therapy, about which the National Institute of Health (NIH) provides precise information on their website: calcium, green tea [4], lycopene, pomegranate, selenium and vitamin E, soy, and modified citrus pectin. Selenium and vitamin E are probably two of the most popular dietary supplements being considered for their use in the reduction of prostate cancer risk. Thirty-six percent of cancer patients in Hawaii used CAM [5]. GL, containing citrus pectin, also contains a high amount of nobiletin which is effective against prostate cancer cells, according to an *in vivo* nude mouse study [6]. Furthermore, GL contains other

polymethoxyflavones (PMFs), exerting beneficial effects through antigrowth, antiangiogenesis, and cell cycle arrest commands or mediate signals to live or die by apoptosis.

Treatment with GL by both intraperitoneal (i.p.) injection and oral administration dramatically reduced both weights (57%-100% inhibition) and volumes (78%-94% inhibition) of the tumors without any observed toxicity. These inhibitory effects were accompanied by mechanistic down-regulation of the protein levels of inflammatory enzymes (inducible nitric oxide synthase, iNOS and cyclooxygenase-2, COX-2), metastasis (matrix metalloproteinase-2, MMP-2 and MMP-9), angiogenesis (vascular endothelial growth factor, VEGF), and proliferative molecules, as well as by the induction of apoptosis in prostate tumors [7]. Recent research showed flavonoid has a useful compound to prevent proliferation and migration of prostate cancer cells through PI3K/Akt/NFκB signaling [8]. Among other GL cases, some patients showed favorable clinical results (Figure 3).

**Summary of using Gold Lotion™**

decade	age	Drinking duration (year)	Volume /day (CC)	Initial PSA	Nadir PSA	Combained other treatments
2004	80	1	10	278	1	LH-RH
2005	67	2	15	24.4	13.3	none
2008	66	7	10	0.3	0.02	none
2012	70	2	10~30	0.2	0.05	After Prostatectomy
2013	69	1.5	30	16.1	10.5	none
2017	70	2	20	9.2	3.1	None (From personal communication)
2019 (our case)	71	4	20	10.1	6.6	none

(Adding our case to Miyauchi citrus laboratory data)

**Figure 3:** List of patients who used GL and clinical and results (supported by Miyauchi citrus laboratories).

During active surveillance therapy, particularly for the patient who often tends to develop anxiety [9], CAM was a useful method to get rid of his anxiety. Although it is unknown whether the rise in PSA when starting to drink GL was due to cancer progression, there was no deterioration in his urination condition nor an increase in the amount of residual urine that indicates the progression of cancer [10]. The rise in PSA may be assumed to be an indication of progression. However, after the start of GL oral administration,

his serum free testosterone level stayed normal; therefore, the effect on the endocrine system seems low. Hence, it is my opinion that subsequent treatments shall not be negatively influenced by the use of GL. In conclusion, in some limited cases, the addition of GL to Active Surveillance therapy can be considered as an effective method to eliminate patients' anxiety, and some anticancer effects can be expected.

## COI Disclosure

None.

## References

1. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics. CA Cancer J Clin 64(1): 9-29.
2. Cooperberg MR, Carroll PR, Klotz L (2011) Active surveillance for prostate cancer: progress and promise. J Clin Oncol 29(27): 3669-3679.
3. Philippou Y, Hadjipavliou M, Khan S, Rane A (2013) Complementary and alternative medicine (CAM) in prostate and bladder cancer. BJU int 112(8): 1073-1079.
4. Brausi M, Rizzi F, Bettuzzi S (2008) Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. Eur Urol 54(2): 472-473.
5. Gotay CC (1999) Use of complementary and alternative medicine in Hawaii cancer patients. Hawaii Med J 58(3): 49-51.
6. Guazzi P, Suzawa M, Di Cerbo A (2017) Effectiveness of a formulated product (Gold Lotion) in improving the quality of life (QoL) of oncological cats: preliminary results. J Vet Med Allied Sci 1: 1-4.
7. Li S, Pan M H, Wang Z, Lambros T, Ho C T (2008) Biological activity, metabolism and separation of polymethoxyflavonoids from citrus peels. Tree and Forestry and biotechnology 2: 36-51.
8. Erdogan S, Doganlar O, Doganlar ZB, Serttas R, Trukebul K, et al. (2016) The flavonoid apigenin reduces prostate cancer CD44(+) stem cell survival and migration through PI3/Akt/NF-kB signaling. Life Sci 162: 77-86.
9. Kageyama S, Hayami S, Ohmura S et al. (2022) A se report: Active surveillance therapy with Citrus-peel extracts' efficacy against prostate cancer. Case Rep Reiv (in press).
10. Johansson E, Bill Axelson A, Holmberg L, Erik Onelöv, Jan-Erik Johansson (2009) Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the randomized Scandinavian Prostate Cancer Group Study Number4 (SPCG-4) clinical trial. Eur Urol 55(2): 422-430.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.42.006827

Shinji Kageyama. Biomed J Sci & Tech Res



This work is licensed under Creative Commons Attribution 4.0 License

Submission Link: <https://biomedres.us/submit-manuscript.php>



### Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

<https://biomedres.us/>