

# Lycopene for Advanced Hormone Refractory Prostate Cancer: A Prospective, Open Phase II Pilot Study

Carla Schwenke,\* Burkhard Ubrig, Petra Thürmann, Christian Eggersmann and Stephan Roth

From the Departments of Urology and Paediatric Urology and Philipp-Klee-Institute for Clinical Pharmacology (PT), Witten/Herdecke University, Witten and Helios-Hospital of Wuppertal, Wuppertal, Germany

## Abbreviations and Acronyms

EORTC = European Organisation for Research and Treatment of Cancer

HRPC = hormone refractory prostate cancer

PSA = prostate specific antigen

Submitted for publication July 21, 2008.

Study received Witten/Herdecke University ethics committee approval.

Supported by the Bergisch Urologische Gesellschaft e. V. and Helios Kliniken GmbH, Berlin.

\* Correspondence: Klinik für Urologie, Klinikum Bremen Mitte, Lehrklinik der Universität Göttingen, St. Jürgen Str. 1, 28203 Bremen, Germany (telephone: +494214975431; FAX: +494214973315; e-mail: carla.schwenke@klinikum-bremen-mitte.de).

For another article on a related topic see page 1393.

**Purpose:** We investigated the influence of lycopene on the clinical and laboratory course in men with hormone refractory prostate cancer. To our knowledge this study represents the first time that subjective assessments of the course of therapy have been recorded.

**Material and Methods:** We performed a prospective, open phase II pilot study, in which patients with progressive hormone refractory prostate cancer were included. Lycopene supplementation (15 mg) was given daily for 6 months. Followup laboratory tests and clinical examinations were done monthly. Changes to analgesic use and quality of life (European Organisation for Research and Treatment of Cancer QLQ-C30) were measured. The study end point was a significant change in serum prostate specific antigen, clinical progression or the end of the 6-month observation period.

**Results:** A total of 18 patients 64 to 85 years old (median age 73) were enrolled in the study during a 20-month period, of whom 17 could be analyzed. Five of the 17 patients (29%) withdrew from the study prematurely, including 4 of 5 because of prostate specific antigen progression and/or tumor associated complications, and 1 due to an allergic reaction to lycopene. Median prostate specific antigen doubled in 6 months from 42.7 ng/ml (range 13.8 to 521.6) in 17 patients to 96.4 ng/ml (range 13.5 to 1,240) in 12. Stable prostate specific antigen was observed in 5 of 17 patients (29%). None of the patients had a greater than 50% decrease in prostate specific antigen. Patients experienced a slight deterioration in mean health status at the end of the study compared to the outset. However, two-thirds of the patients experienced an improved or unchanged situation regardless of the clinical and biochemical course.

**Conclusions:** No clinically relevant benefits were shown for patients with advanced stages of the disease.

**Key Words:** prostate, prostatic neoplasms, lycopene, quality of life, prostate-specific antigen

HORMONE refractory prostate cancer is an advanced disease for which there is no standard treatment. Life expectancy in men at this tumor stage is approximately 18 months.<sup>1</sup>

Dietary supplements have recently gained interest as potential therapeutic agents because of their wide availability

and low cost, and the low incidence of adverse effects. Lycopene, which is the red pigment in tomatoes, has in particular been believed to have potential effects on prostate cancer progression. A recently published case report described an 18-month clinical remission of HRPC with the administration of lycopene (10

mg per day) combined with  $3 \times 300$  mg saw palmetto extract per day.<sup>2</sup> An earlier large-scale prospective epidemiological study in around 48,000 healthy men indicated that there is an association between men who regularly consume foods containing tomatoes and a lower risk of prostate cancer.<sup>3</sup>

Nonetheless, hardly any systematic prospective study has assessed the clinical efficacy of lycopene for HRPC during a sufficiently long time period. Thus, we performed a prospective, open, phase II pilot trial to evaluate the clinical effects of lycopene supplementation in a group of patients with advanced stages of prostate cancer.

## METHODS

Patients received 1 capsule of lycopene (Puritans Pride, Oakdale, New York) with 15 mg active ingredient daily for 6 months. At the preliminary stages we had the lycopene content of the preparation tested at a laboratory elsewhere in a representative test series.<sup>4</sup> Patient compliance was 99.8%, as evaluated by monthly pill count. Patients were recruited into the study during 20 months.

Study end points were an increase or decrease in serum PSA, clinical progression or reaching the end of the 6-month observation period. In this study the criterion for a response to HRPC was a greater than 50% decrease in serum PSA. PSA was considered stable when there was a variance of  $\pm 25\%$  compared to baseline in accordance with the criteria of EORTC and the 1985 National Prostatic Cancer Project.<sup>5</sup> A greater than 25% increase in PSA was considered progressive disease.

Patients with progressive HRPC were included in the study. All patients had histologically confirmed prostate cancer, which was treated with hormone ablation using luteinizing hormone-releasing hormone analogues or bilateral orchiectomy. Study inclusion criteria mandated that patients had progressive HRPC with an increase in PSA on 3 successive tests or with clinically verifiable prostate cancer progression.<sup>6</sup> Patients were excluded from study when they were on concomitant secondary therapy that affects PSA, including palliative transurethral prostate resection, localized radiotherapy or chemotherapy, or they were receiving lycopene, multivitamins and minerals as well as other plant preparations.

Followup assessments were done at monthly intervals. At these visits serum PSA, blood count, coagulation parameters, alkaline phosphatase, electrolytes, creatinine, lactate dehydrogenase, cholesterol, transaminases, serum lycopene and lycopene metabolites were measured. Furthermore, a medical history was obtained and physical examination was performed.

Quality of life was measured using EORTC QLQ C-30<sup>3</sup> at study entry and withdrawal. Use of this quality of life instrument included the functional scale with the 5 domains of physical, role, emotional, cognitive and social functioning, the symptom scale with the 9 domains of fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact, and global health status. A 10-point change in individual quality of life scores was considered clinically relevant.

This represents a slight to moderate change for better or worse, as validated to be clinically meaningful in prior study.<sup>7</sup>

Clinical status was assessed at the beginning and the end of the study. In addition to physical examination, analgesic use, sonography of the urogenital tract, urine flow and bone scintigraphy were recorded. Testosterone was also determined at the beginning of the study so that castrate levels could be monitored.

Serum lycopene was analyzed elsewhere.<sup>4</sup> Data were analyzed descriptively using Microsoft® Excel® from Microsoft Office, version x.0. Data are shown as the mean  $\pm$  SD, median and range.

The study was approved by the Witten/Herdecke University ethics committee. Informed written consent was obtained from all patients before study enrollment.

## RESULTS

### Patients

A total of 18 patients between 64 and 84 years old (median age 73) were enrolled in the study. Median time from initial diagnosis to study enrollment was 4.5 years (range 2 to 20). All patients had increasing PSA despite castrate testosterone levels. Table 1 lists patient data.

Of the 18 patients 17 could be analyzed. One patient who withdrew from the study after receiving lycopene for 4 weeks was not included in the analysis. Five of the 17 patients (29%) withdrew from the study before the 6-month end point because of PSA progression and/or complications. Three of these 5 patients had PSA progression, including 2 in whom another therapy was initiated and 1 with clinically relevant macrohematuria, which required surgical intervention. Another patient also had clinically relevant macrohematuria due to prostate cancer. He underwent laparotomy for perforated sigmoid diverticulitis and died postoperatively. The remaining patient withdrew from the study due to allergic exanthema. Complications, such as macrohematuria, diverticulitis and death in 1 patient, were not considered adverse effects of lycopene, but rather consequences of advanced prostate cancer or a fateful course of events.

**Table 1.** Patient specifics and previous therapy

|                                                                                                                                            |       |              |
|--------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------|
| No. pts                                                                                                                                    | 17    |              |
| Mean age (range)                                                                                                                           | 74    | (64–85)      |
| Mean illness history (yrs)                                                                                                                 | 5     | (2–20)       |
| Mean ng/ml baseline PSA (range)                                                                                                            | 42.68 | (13.8–521.6) |
| No. previous therapy (%):                                                                                                                  |       |              |
| Radical prostatectomy                                                                                                                      | 4     | (23.5)       |
| High dose radiotherapy                                                                                                                     | 5     | (29.4)       |
| Testosterone withdrawal                                                                                                                    | 17    | (100)        |
| Bone radiotherapy                                                                                                                          | 2     | (11.8)       |
| Other (antiandrogen withdrawal, secondary hormone therapy, chemotherapy, mistletoe, lectinol, palliative transurethral prostate resection) | 16    | (94.1)       |

**Table 2.** PSA slope while on lycopene supplementation for 6 months

| Pt No. | PSA Slope |        |        |        |        |       |        |
|--------|-----------|--------|--------|--------|--------|-------|--------|
|        | 0 Mos     | 1 Mo   | 2 Mos  | 3 Mos  | 4 Mos  | 5 Mos | 6 Mos  |
| 1      | 34.17     | 49.67  | 53.51  | 55.14  | 91.91  | 95.06 | 102.08 |
| 2      | 47.23     | 60.64  | 75.61  | 71.13  | 91.33  | 99.16 | 95.47  |
| 3      | 13.8      | 14.12  | 17.58  | 15.25  | 16.25  | 14.8  | 16.97  |
| 4      | 114.34    | 103.98 | 116.68 | 148.03 | 188.7  | 254.4 | 266.27 |
| 5      | 361.41    | 373.16 | 359.4  |        |        |       |        |
| 6      | 521.6     | 580.6  | 434.62 |        |        |       |        |
| 7      | 151.04    | 146.63 | 172.3  | 170.07 | 187.21 | 210.9 | 147.92 |
| 8      | 42.68     | 44.93  | 47.17  | 49.98  | 48.57  | 53.69 | 60.56  |
| 9      | 118.96    | 124.74 | 213.05 | 251.52 | 295.4  | 419.4 | 1240   |
| 10     | 27.17     | 25.29  | 37.83  | 47.87  | 51.93  | 78.69 | 100.93 |
| 11     | 17.58     | 25.16  | 37.3   | 57.93  | 77.4   |       |        |
| 12     | 13.93     | 15.45  | 11.21  | 10.16  | 10.74  | 13    | 13.54  |
| 13     | 35.7      | 48.33  | 50.91  | 44.95  | 53.22  | 54.55 | 52.34  |
| 14     | 23.37     | 28.82  | 29.88  | 36.57  | 50.77  |       |        |
| 15     | 58.56     | 106.71 | 154.2  | 291    |        |       |        |
| 16     | 50.21     | 50.29  | 76.04  | 76.15  | 83.71  | 74.08 | 97.39  |
| 17     | 14.37     | 17.77  | 17.92  | 20.04  | 24.86  | N.N.  | 22.19  |

### Clinical Course

The median lycopene level was 0.22  $\mu\text{mol/l}$  (range 0.07 to 1.27) at baseline. Lycopene increased adequately within 4 weeks with a mean 0.41  $\mu\text{mol/l}$  increase from baseline to a median of 0.63  $\mu\text{mol/l}$ .

According to the clinical parameters of urinary obstruction and post-void residual urine the condition in 4 of the 17 patients worsened slightly. None of these patients required placement of a new urinary drainage system, such as a Double-J® catheter, nephrostomy or transurethral/suprapubic bladder catheter. However, there were also no cases of clinically relevant remission.

### Adverse Effects

Two patients experienced gastrointestinal complaints with upper abdominal pain and flatulence. These symptoms were directly connected to ingesting lycopene. These complaints were resolved by having the patients ingest the capsules with meals. There was 1 case of allergic exanthema, which was probably an adverse effect caused by lycopene. One patient described worsened hot flashes. In 1 case there was an initial diagnosis of hypertension during the study. Overall the preparation used in the study was well tolerated.

### PSA Progression

At study entry median serum PSA in the 17 patients was 42.7 ng/ml (range 13.8 to 521.6). By the end of the study PSA had almost doubled to 96.43 ng/ml (range 13.5 to 1,240) in 12 patients. Table 2 shows the course of PSA values during 6 months in each patient. We observed stable PSA during the study in 5 of the 17 patients (29%), that is in patients 3, 7, 12, 13 and 17. In 3 patients PSA stabilization was already observed during month 1 after treatment initiation. In the 2 remaining patients PSA increased during treatment month 1 but remained stable thereafter for 5 months. This observation is in agreement with the fact that steady state levels of lycopene are achieved after 4 to 5 weeks of treatment and treatment effects may be delayed.<sup>8</sup>

No patient had a PSA decrease of more than 50%. Figure 1 shows the results on a logarithmic scale.

### Quality of Life

EORTC QLQ C-30<sup>3</sup> was completed properly by 14 patients at the beginning and the end of the study

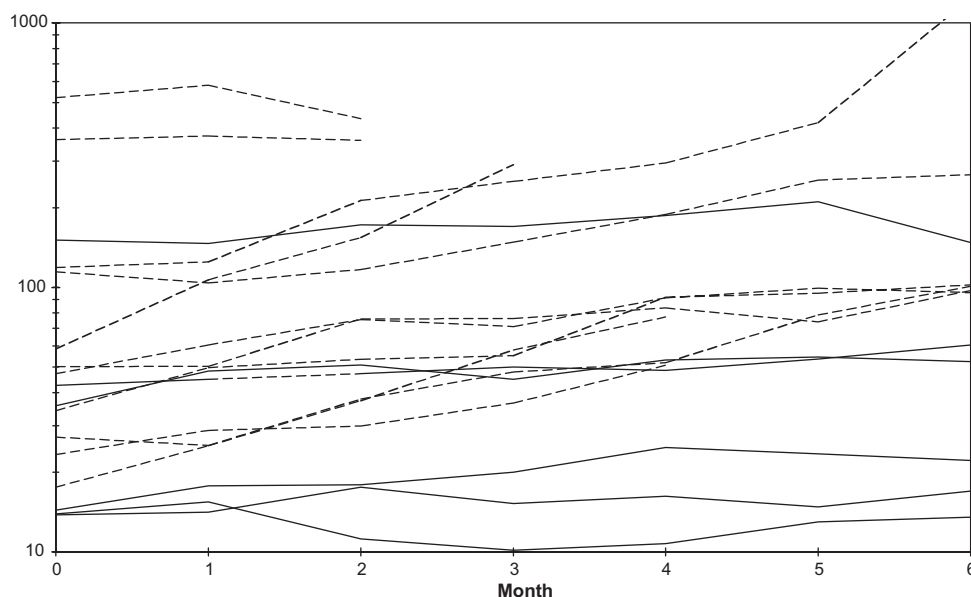
**Figure 1.** PSA progression. Continuous line indicates stable PSA in 5 of 17 patients (29%)

**Table 3.** Change in quality of life score in 14 patients at study entry vs withdrawal using EORTC QLQ C-30<sup>3</sup>

|             | No. Score (%) <sup>*</sup> |          |               |
|-------------|----------------------------|----------|---------------|
|             | Functional                 | Symptoms | Global Health |
| Improvement | 4 (28.6)                   | 1 (7.1)  | 2 (14.3)      |
| No change   | 6 (42.9)                   | 8 (57.1) | 7 (50)        |
| Worsening   | 4 (28.6)                   | 5 (35.7) | 5 (35.7)      |

\* Significance was considered at 10 points.

(table 3). The mean change in health status was  $-11.4 \pm 22.13$  points, indicating clinically relevant deterioration. The symptom score increased by  $3.29 \pm 10.65$  points with a high score representing a high level of symptomatology and problems. The functional score decreased by  $-2.07 \pm 14.87$  points, showing no clinically relevant changes (fig. 2).

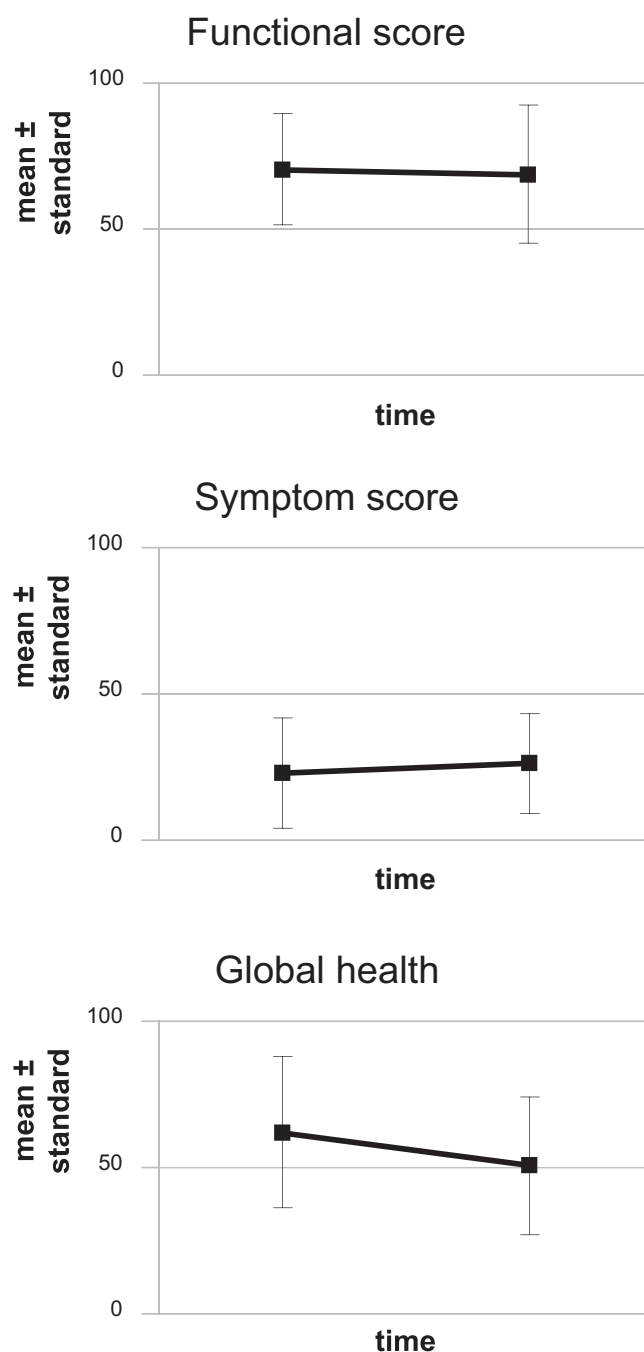
## DISCUSSION

Treatment with lycopene was well tolerated with few adverse effects. Although stable PSA was observed in 5 patients (29%), no patient achieved relevant laboratory or clinical tumor remission. Since a life prolonging effect can only be anticipated for a decrease in PSA of more than 50%,<sup>9–12</sup> it may be assumed that none of these patients experienced a life prolonging effect.

With respect to lycopene dosing the increase in plasma lycopene by  $0.41 \mu\text{mol/l}$  was comparable to the increase in plasma levels observed in previous studies in healthy volunteers.<sup>8</sup> Therefore, the lack of a therapeutic effect cannot be explained by insufficient patient compliance.

Although many anticarcinogenic and even tumor treating effects have been associated with lycopene in previous epidemiological, animal experimental and preclinical studies, there are only 2 reports in the literature in which supplementation with lycopene in patients with HRPC resulted in biochemical and clinical tumor remission during several months.<sup>2,13</sup> A dose escalating, phase I-II study in 36 men with biochemical relapse after radical prostatectomy<sup>14</sup> built on the series by Matlaga et al, who described what is to our knowledge the only case of tumor remission under supplementation with lycopene and saw palmetto extract for HRPC.<sup>2</sup> The 6-man cohorts were each supplemented with 15, 30, 45, 60, 90 and 120 mg lycopene daily for 1 year. None of the men had a PSA decrease of greater than 50% and 37% of them showed progression, defined as a PSA increase of greater than 50%. The study was unable to detect a therapeutically beneficial effect for lycopene for less advanced prostate cancer (median PSA 4.4 ng/ml at study entry) and it could not verify any efficacy for lycopene.

The research group of Ansari and Gupta from India provided 10 mg per day lycopene supplementation to 20 men with HRPC for 3 months.<sup>13</sup> They noted a complete response (PSA decrease to less than 4 ng/ml) in 1 patient (5%), a partial response (greater than 50% PSA decrease) in 6 and stable disease in 10 (50%). Only 3 patients (15%) had progression. These remarkable results could not be replicated in our study in 18 patients with HRPC or in the study by Clark et al in 36 men with biochemical relapse.<sup>14</sup> Ethnic differences or different dietary

**Figure 2.** Mean change in quality of life from baseline

practices may possibly account for the different outcomes in the Indian vs the German and American study populations.

The few other clinical studies available show a tumor suppressive effect.<sup>15,16</sup> In a randomized, phase II study in 26 men Kucuk et al compared tumor volume in the prostate after radical prostatectomy, various biomarkers and the preoperative slope of serum PSA.<sup>15</sup> They concluded that lycopene can reduce prostate cancer growth in terms of tumor size. The question of whether lycopene substitution for 13 to 30 days with 55% to 77% patient compliance (as described in the study) is effective must be critically assessed. As in our study, Clark et al found adequate plasma lycopene after 4 weeks and plasma lycopene did not plateau until after 3 months.<sup>14</sup> In the study by Ansari and Gupta 54 men with metastatic prostate cancer before hormone ablative therapy were assigned to an orchiectomy or to an orchiectomy plus lycopene group and examined at a 2-year followup visit to assess the duration of the PSA decrease.<sup>16</sup> The investigators found that the orchiectomy plus lycopene group achieved more rapid and longer lasting PSA regression. However, Ansari and Gupta did not have a convincing study design, such as cross-matching 2 significant patient groups, which could validly predict PSA progression during androgen deprivation therapy. Miller et al observed that the PSA slope after castration can vary greatly among individuals.<sup>17</sup> Also, patients with rapid PSA decreases and PSA nadirs less than 4 ng/ml have a markedly longer PSA plateau phase than patients who have a high PSA nadir. Therefore, one may expect that the effect of hormone deprivation would last longer in the group with the more rapid PSA decrease and lower PSA nadir regardless of lycopene supplementation.

An interesting aspect of the PSA slopes measured in our study is the PSA plateau noted in 5 patients who were treated with lycopene. After PSA relapse while on androgen deprivation therapy only exponential PSA slopes have been reported.<sup>17,18</sup> To our knowledge a plateau phase has never been described as part of the natural course of HRPC. Since all of our patients by definition were experiencing biochemical progression, the PSA plateau appears to have been a consequence of lycopene supplementa-

tion. Nonetheless, there is no way that our study could be used to draw valid conclusions about the significance of this effect because there is no possibility of comparing this with the PSA increase without lycopene supplementation. Schröder et al also observed a significant delay in the PSA increase in their randomized, double-blind, placebo controlled study in 49 patients on a soy based dietary supplement that included lycopene.<sup>19</sup> They used a crossover study design to determine that each study group had a delayed increase in PSA when being given the supplement but not when being given the placebo.

In addition to the objective parameters, to our knowledge our study represents the first time that the effect of this therapy has been subjectively assessed. Analysis of the EORTC questionnaire QLQ C-30<sup>3</sup> showed that patients experienced stable functional well-being and no change regarding symptoms at the end of the study. There was a slight deterioration in general health status, as one may expect considering the objective progression of the disease.

Apart from the mean changes it should be noted that two-thirds of the patients experienced an improved or unchanged situation independently of the clinical course and PSA progression. The degree to which frequent contact and medical care during the study or actual therapy in the sense of a placebo effect was responsible for this outcome remains open.

## CONCLUSIONS

Systematic lycopene supplementation for HRPC did not yield a PSA decrease of greater than 50% and, thus, there was no life prolonging effect in any patient. Five of the 17 patients showed plateau-like PSA stabilization. A range of effects has been attributed to lycopene that makes this active ingredient an interesting potential therapeutic agent. However, no clinically relevant benefit was found in patients with advanced stages of disease.

## ACKNOWLEDGMENTS

Hedwig Wennmachers and Heinrich Heimlich assisted with supplement transfer, and Dr. Wolfgang Schalch, DMS, Basel, Switzerland, provided advice and measured plasma lycopene.

## REFERENCES

1. Sternberg CN: Systemic treatment and new developments in advanced prostate cancer. *Eur J Cancer* 2001; **37**: 147.
2. Matlaga BR, Hall MC, Stindt D and Torti FM: Response of hormone-refractory prostate cancer to lycopene. *J Urol* 2001; **166**: 613.
3. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA and Willett WC: Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* 1995; **87**: 1767.
4. Aebischer CP, Schierle J and Schüep W: Simultaneous determination of retinol, tocopherols, carotene, lycopene, and xanthophylls in plasma by means of reversed-phase high-performance liquid chromatography. *Meth Enzymol* 1999; **299**: 348.
5. Newling DW: Criteria for response to treatment of metastatic prostatic cancer. *Prog Clin Biol Res* 1985; **185A**: 205.

6. American Society for Radiology and Oncology Consensus Statement: Guidelines for PSA following radiation therapy. *Int J Radiat Biol* 1997; **37**: 1035.
7. Osoba D, Rodrigues G, Myles J, Zee B and Pater J: Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139–44.
8. Cohn W, Thürmann P, Tenter U, Aebischer C, Schierle J and Schalch W: Comparative multiple dose plasma kinetics of lycopene administered in tomato juice, tomato soup or lycopene tablets. *Eur J Nutr* 2004; **43**: 304–312.
9. Smith DC, Dunn RL, Strawderman MS and Pienta KJ: Change in serum prostate-specific antigen as a marker of response to cytotoxic therapy for hormone-refractory prostate cancer. *J Clin Oncol* 1998; **16**: 1835.
10. Bubley GJ, Carducci M, Dawson N, Daliani D, Eisenberger M, Figg WD et al: Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999; **11**: 3461.
11. Scher HI, Kelly WM, Zhang ZF, Ouyang P, Sun M, Schwartz M et al: Post-therapy serum prostate-specific antigen level and survival in patients with androgen-independent prostate cancer. *J Natl Cancer Inst* 1999; **91**: 244.
12. Small EJ, McMillan A, Meyer M, Chen L, Slichenmyer WJ, Lenehan PF et al: Serum prostate-specific antigen decline as a marker of clinical outcome in hormone-refractory prostate cancer patients: association with progression-free survival, pain end points, and survival. *J Clin Oncol* 2001; **19**: 1304.
13. Ansari MS and Gupta NP: Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer. *Urol Oncol* 2004; **22**: 415.
14. Clark PE, Hall MC, Borden LS Jr, Miller AA, Hu JJ, Lee WR et al: Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. *Urology* 2006; **67**: 1257.
15. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F et al: Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol* 2001; **10**: 861.
16. Ansari MS and Gupta NP: A comparison of lycopene and orchiectomy vs orchiectomy alone in the management of advanced prostate cancer. *BJU Int* 2003; **92**: 375.
17. Miller JL, Ahmann FR, Drach GW, Emerson SS and Bottaccini MR: The clinical usefulness of serum prostate specific antigen after hormonal therapy of metastatic prostate cancer. *J Urol* 1992; **147**: 956.
18. Isaacs JT and Coffey DS: Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. *Cancer Res* 1981; **41**: 5070.
19. Schröder FH, Roobol MJ, Boeve ER, de Mutsert R, Zijlgeest-van Leeuwen SD, Kersten I et al: Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. *Eur Urol* 2005; **48**: 922.