Complementary Therapies for Hormone Refractory Prostate Cancer

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There is an ever-increasing demand for complementary therapies by patients with prostate cancer. Often, patients' expectations of such treatments are too high. In particular, complementary treatment cannot replace the potentially curative methods such as radical prostatectomy and radiation therapy. During the early stages of the disease, when cancer growth is still confined to the prostate, complementary treatments are primarily intended to enhance recognized standard therapy practices. During the hormone refractory stage of the disease, however, complementary treatment has gained significance due to its low toxicity.

Prostate Cancer – Where do we Stand Today?

Prostate cancer is today the most frequent malignant tumour in men – more frequent than lung cancer. In the UK, 32,000 new cases are registered each year. In about 50% of these cases it can be expected that the disease progresses to an incurable stage and that in ten percent to 20% of the cases metastases can already be verified at the time of primary diagnosis.[1] More than 10,000 men die each year from prostate cancer in the UK, the disease representing around 13% of the approximately 77,000 male deaths from cancer in this country. The prevalence of the disease is, however, much higher, since only a small number of prostate cancer cases is ever diagnosed due to slow growth and late appearance of the tumour. The increase in incidence can mainly be considered the result of improved screening procedure by means of prostate specific antigen (PSA). Since mainly older men are affected by prostate cancer, and the age structure of most West European industrial societies continues to move towards longer life expectancy, the number of new cases of the most frequent type of cancer in men will also continue to increase. This trend is alarming; as we presently cannot offer any treatment for this disease which we know for sure will lead to cure, prolong life expectancy, or at least do the patient more good than evil. Demands will be made by increasingly better informed and critical patients on urologists, radiologists and oncologists to provide competent and objective information on the advantages and disadvantages of the therapeutic options available. This also includes complementary therapies, as more and more patients today are looking for less traumatic and less toxic treatment.[2-6]

Present day potentially curative therapies, such as radical prostatectomy and radiation treatment, only make sense as long as the cancer is confined to the prostate and metastases have not developed. Unfortunately, these treatment methods lead in a high percentage of cases to unacceptable and permanent side-effects, e.g. erectile impotency in 60%-100%, rectal disorders in 15%-40% and urinary incontinence in 10%-30% of patients.[7-11] Furthermore, with regard to 'cure', the results of treatment by these invasive methods are still unsatisfactory; recurrence rates of between 20%- 50% are reported.[12-17] The curative effect of local treatment methods, such as radical operation and radiation therapy, are largely dependent on correct patient selection. Current customary diagnostic procedures, however, often underestimate the extent of the disease, so that patients receiving surgery or radiation treatment are in reality no longer candidates for these methods of treatment, because their prostate cancer has spread from the organ and has already formed micrometastases.

There is presently still no cure for metastatic prostate cancer,[18,19] and the testosterone ablating therapies such as orchidectomy or the administration of LHRH agonists and anti-androgens frequently only achieve short-term tumour control (months to a few years). Long-term results are unsatisfactory and most prostate cancer patients become hormone refractory. At this stage there is often fast progression of the disease and metastases develop. Various lines of initial treatment, such as newer combinations of chemotherapy, use of radioisotopes (e.g. samarium-153), blocking of growth factors by monoclonal antibodies, immune therapies (e.g. dendritic cell vaccines), angiogenesis blocking strategies, re-differentiation of cancer cells by means of retinoids and vitamin D analogues and finally gene therapy, are presently undergoing clinical trials for this particular situation, but up to now none of these measures has brought patients significant advantages.

Complementary Treatment Methods

Due especially to the unpleasant and often permanent side-effects and the high rate of treatment failure, many patients with prostate cancer seek alternative or complementary treatment methods. Their expectations are often unrealistic, as many complementary treatment methods are advocated without proof of efficacy regarding inhibition of cancer growth or prolongation of life. During the early stages of the disease (cancerous growth limited to the prostate) complementary therapies are primarily intended to enhance recognized standard practices. For patients with metastases and the

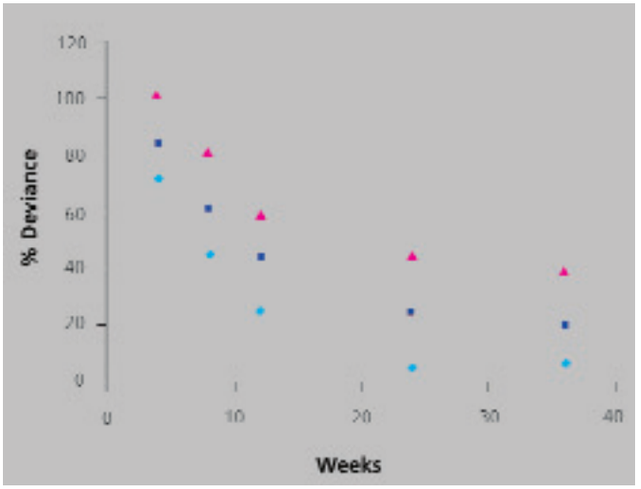

Fig.1: *PSA course of 194 hormone refractory prostate cancer patients under treatment with Prostasol, Curcumin complex, Biobran and IMUPROS™. Mean values (+/- standard errors) of the percent changes in comparison with initial readings (100%) are shown*

development of a hormone refractory stage, the situation is somewhat different. An increasing number of patients are requesting solely complementary treatment to avoid the frequently toxic effects of chemotherapy. The following treatment consisting of a combination of phytotherapy, immune therapy and antioxidative/orthomolecular therapy has proven for us to be exceptionally effective:

Phytotherapy with Prostasol and Curcumin complex

Prostasol is available in the UK, on the European market and in the US as a food supplement. It consists of various sitosterols (*camptosterol, stimgasterol, brassicasterol*), Quercetin (*phytooestrogen, flavonoid*), *Pygeum africanum* (pygeum), *Serenoa repens* (saw palmetto), *Panax pseudoginseng* (ginseng), *Zingiber officinale* (ginger), *Urtica diotica* (stinging nettle), *Scutellaria* (scull cap) and *Ganoderma lucidum* (filamentous fungi). Laboratory tests on *Prostasol* in two independent laboratories in Switzerland detected neither synthetic ingredients, such as oestrogens, anti-inflammatory drugs, glucocorticoids or narcotics, nor any heavy metal pollutants or pesticides.[20] Following oral intake of 900 to 2800 mg of *Prostasol* there is a > 50% drop within a few months in the PSA reading in approximately 70% of hormone refractory prostate cancer patients (see Fig. 1 and 3). This sort of decrease is often associated with a decline in metastatic pain and a general improvement in quality of life.[21] In about one third of the patients there is a decrease in tumour mass in the primary tumour and/or the metastases (see Figs. 4a,b-5a,b). Blood count, coagulation parameters, serum electrolytes, serum enzymes (SGPT, SGOT, alkaline phosphatase, gamma GT), as well as bilirubin, creatine and uric acid levels remain unchanged during the intake of *Prostasol*. There are few side-effects on the whole and these consist of increased sensitivity of the breast nipples during the first two months of intake in about 40% of the patients, bloating in about ten percent and short-term diarrhoea in about five percent of the cases. Superficial leg vein thrombosis is reported in less than one percent of patients,[22] although a causal connection here is unclear, since the disease itself increases the risk of thrombosis.

Experimental research has proven that most constituents of *Prostasol* can block cancer growth and are capable of inducing apoptosis in prostate cancer cells. Phytosterols such as camptosterol and beta-sitosterol, which occur in large quantities in vegetables and fruit, do in fact have strong antioxidative effects and increase the apoptosis rate in human prostate cancer cells (LNCaP) fourfold.[23] In animal experiments, these phytosterols prevented both growth and metastases of transplanted human prostate cancer cells.[24] An immune stimulating effect in humans by phytosterols has been verified with an increase in T and NK cells in peripheral blood following intake during four weeks.[25] Recently, Chan *et al*[26] showed that extracts of scutellaria contain the flavonoid baicalin which at lowest concentrations already causes 50% apoptosis in DU145 prostate cancer cells. Stinging nettle extracts are known to suppress the growth of prostate cancer cells. Lichius *et al*[27] were able to determine that the polysaccharide fraction of a 20% methanol extraction of stinging nettle root blocked the growth of prostate carcinoma cells from lymph gland metastases by 50%. Other components of *Prostasol* are known to possess anti-tumour properties. For example, ganoderma is described as developing its anti-tumour effect by releasing cytokines such as TNF-alpha and INF-gamma.[28] Knowles, *et al*[29] have reported that already 100 micromoles of quercetin lead to a complete growth inhibition in hormone resistant prostate cancer cells (PC-3 cell culture). Surh[30] made known that the phenols 6-ginerol and 6-paradol that are present in ginger have a distinct anti-tumour effect. Liu, *et al*[31] have proved that saponin and ginsenosid (Rg-3), extracted from ginseng, bring about a significant decline in prostate cancer cells associated with a reduction in PSA and androgen-receptor expression. Furthermore, ginseng extracts also caused classical apoptosis by inhibition of bcl-2 gene activity, and also significantly reduced the metastatic potential of prostate cancer cells. Iguchi and co-workers also described a similarly strong apoptic effect of *Serenoa repens* extract, which at least in part is based on the cytotoxic properties of myristoleic acid.[32]

Curcumin complex consists of a standardized quantity of curcumin, bioperin and resveratrol. Curcumin is an extract of the turmeric root and known as a tyrosin kinase inhibitor with documented efficacy against cancer cells in general[33,34] and against prostate cancer cells *in-vitro* and *in-vivo* in particular.[35-39] By suppressing the cell 'survival' factors NF-kappaB and the so-called *Akt* factor (signal protein kinase) and by influencing growth factors, curcumin can apparently intervene in the cell cycle of prostate cancer cells and thus lead to inhibition of cell division and apoptosis. Bioperin, a black pepper extract, is a known inhibitor of glucoronidase in the gastrointestinal tract and in the liver. This substance improves the absorption of curcumin and its bioavailability in humans by over 2,000% without producing side-effects.[40] Resveratrol is found in grapes and is a phytoalexin with pronounced antioxidative and cancer inhibiting properties. Even at micromolar concentrations, it

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inhibits growth and induces apoptosis in hormone sensitive as well as hormone refractory prostate cancer cells.[41-43] In particular, a combination of resveratrol and beta-sitosterol (main component of *Prostasol*) triggers distinct inhibition of cancer growth, possibly by inducing apoptosis, directly blocking cell division and affecting prostaglandin synthesis.[44]

Antioxidative/Orthomolecular Therapy with IMUPROS

IMUPROS™ is available in Europe and the UK as a food supplement. It contains an antioxidative combination of vitamins and trace elements, as well as a proprietary mixture of genistein, lycopene and epigallocatechin gallate. The manufacturer claims that the single active ingredients are from natural sources only. A special manufacturing process (time-release coatings) ensures that the single active ingredients do not interact within the capsule. The single ingredients are released at varying times into the gastrointestinal tract, allowing undisturbed reabsorbtion into the blood and improving bioavailability. Selenium and vitamin E are two important components of this combination of agents. Selenium activates the phase 2 enzyme glutathione peroxidase in the cell and thus boosts the elimination of free oxygen radicals.[45] The recently published results of the *Nutritional Prevention of Cancer (NPC) Trial* in the US have shown a distinct reduction in the frequency of prostate cancer by selenium substitution with 0.2 mg per day.[46] Similar effects were shown in earlier studies where selenium substitution versus placebo reduced the risk of prostate cancer by approximately 60%.[47-49] The preventive effect of vitamin E was investigated in the Alpha tocopherol, Beta-carotene Cancer Prevention Study. Here, among almost 30,000 men at the age of 50-69 years, a daily intake of 50 mg of alpha tocopherol reduced prostate cancer incidence by 32% and prostate-related mortality by 41%.[50] These results, however, were from patients with low initial plasma selenium values who were smokers. Whether men with normal selenium levels who are non-smokers would benefit from selenium and vitamin E substitution remains unclear.[51] The worldwide largest prostate cancer prevention study 'SELECT',[52] which started in August 2001 in the US, should now resolve this doubt and reveal whether selenium and vitamin E guard against prostate cancer. A total of 32,400 men are to take part in this double-blind, randomized and placebo controlled study over a period of 12 years. Epigallocatechin gallate (EGCG), a polyphenol in green tea (*Camellia sinensis*), has stronger antioxidative properties than vitamin E and C. Experimental investigations have shown that EGCG can modulate the androgen effect,[53] intervene at various points in the prostate cancer cell cycle,[54,55] and induce apoptosis both in androgen-sensitive and androgen-refractory prostate cancer cell cultures.[56] Furthermore, ECGC retards the angiogenesis by decreasing interleucin-8 and VE-cadherin production and acts anti-metastatically in animal models with transplanted prostate cancer.[57,58] Lycopene, a carotenoid with particularly strong antioxidative effects has become very popular in recent years in the prevention of prostate cancer. Dosage-related suppression of growth by lycopene in prostate cancer cell cultures has been verified.[59] A diet rich in lycopene reduces DNA damage caused by oxidative stress and decreases PSA values by approximately 17% in patients with prostate cancer.[60] *IMUPROS*™ has no side-effects and is well tolerated.

As an added advantage it allows a drastic reduction in the daily amount of tablets or capsules otherwise required if the above mentioned active ingredients are designed as preventive or supportive therapy for prostate cancer. Whilst previously patients had to take approximately 20-30 tablets or capsules of the active ingredients daily, three to six tablets of *IMUPROS*™ per day already provide a comparable dosage of active ingredient for complementary therapy.

Arabinoxylan, the immunostimulant in Biobran, causes a significant rise in the number and activity of T and B cells, as well as natural killer cells (NK cells). This has been proved in both animal experiments[66,67] and prostate cancer patients (see Fig. 2). Furthermore, Biobran increases macrophage activity, leading to a consecutive increase in TNF alpha and IL 6.[68]

Immunotherapy with Biobran and Mistletoe Extract

The stimulation of specific immune system functions is a sensible treatment strategy with prostate cancer. Experimental studies in active and passive immunotherapy, especially the use of so-called dendritic cell vaccines, have not only confirmed the basic theoretical approach,[61-63] but have also led to clinical results.[64-65] The aim of immunological therapies is to improve the immune response of cytotoxic T cells to prostate cancer. Arabinoxylan, the immunostimulant in Biobran, causes a significant rise in the number and activity of T and B cells, as well as natural killer cells (NK cells). This has been proved in both animal experiments[66,67] and prostate cancer patients (see Fig. 2). Furthermore, Biobran increases macrophage activity, leading to a consecutive increase in TNF alpha and IL 6.[68] Therefore, through the increased activity by arabinoxylan in both the humeral and cellular immune systems, an improved immune response is achieved.

We use Biobran on patients with hormone refractory prostate cancer in a dosage of 15-30 mg/kg/day, not only in combination with the above described phytotherapy, but also together with chemotherapy or radiation treatment in the hope of improving immune defence mechanisms and decreasing therapy-related side-effects. At present, however, no placebo-controlled studies exist on the efficacy of Biobran in prostate carcinoma.

The administration of mistletoe extract is today the most frequent complementary measure in oncological practice. At present, both standardized mistletoe extract and lectin preparations are in use. Mistletoe therapy causes unspecific stimulation of the immune system by activation of macrophages, neutrophile

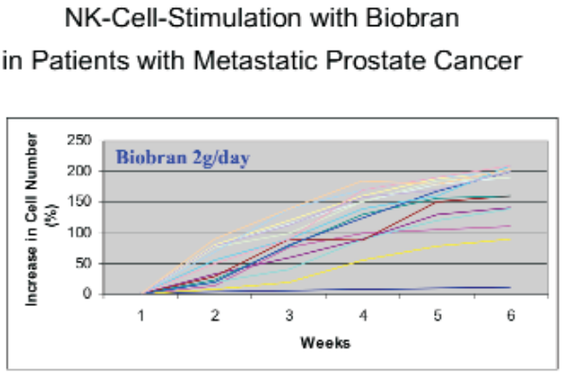

Fig. 2: *NK cell stimulation in 14 patients with hormone refractory prostate cancer taking 15-20 mg/kg/day of Biobran over a period of six weeks.*

The Special Case

This 70-year-old patient became ill in autumn 2000. His symptoms were a therapy-resistant cough. Lung x-rays showed multiple round lesions. Biopsy revealed PSA productive cells. Large core needle biopsy of the prostate confirmed the diagnosis of metastatic prostate carcinoma. Initially, the patient refused any treatment due to the very advanced stage. However, when his PSA increased to almost 1000 ng/ml and in the meantime bone metastases were revealed, the patient decided to proceed with the above described phytotherapy in combination with the antioxidative and immune supportive therapy. During this process his PSA values dropped to <0.1 ng/ml within 10 months and even now, 4 years after commencing therapy, have remained constant. Figure 3 shows the course of PSA values of the patient from September 2001 to August 2002 (further presentation from August 2002 to date was foregone since readings up to February 2005 remained constant at <0.1 ng/ml).

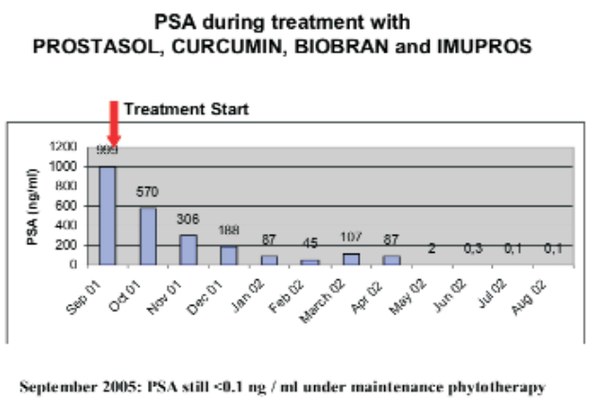

Fig. 3: *Course of PSA values of a patient with metastatic prostate carcinoma under treatment with Prostasol, Curumin complex, Biobran and* IMUPROS™. *During the period of decline in the PSA there was also almost complete resolution of the lung metastases. Figure 4a and b show the lung x-rays before and one year after complementary treatment. Today no round lesions are discernable.*

granulocytes and NK cells, as well as the release of TNF-alpha, GM-CSF and various interleukins. In addition, mistletoe lectins have a certain cytotoxic effect by inhibiting ribosomal protein synthesis (similar to ricin and abrin). Finally, mistletoe lectins increase the release of beta-endorphins, which possibly could account for the improvement in wellbeing (increased appetite, better sleep, less pain, improved performance) experienced under mistletoe therapy.[69-70] Although mistletoe alone cannot decrease the PSA value with either androgen sensitive or androgen refractory prostate cancer, it can be presumed that both the immune defense functions and the quality of life for patients with prostate cancer can be enhanced as has been proven for colorectal carcinomas[71] and gliomas.[72] More recent studies confer new values on lectin standardized mistletoe therapy in the area of evidence based medicine. A retrolective cohort study on 689 patients with breast cancer was able to establish a significant reduction in tumour and therapy-related disorders (e.g. nausea and vomiting, weakness, loss of appetite), as well as a trend towards prolongation of the recurrence-free survival time.[73]

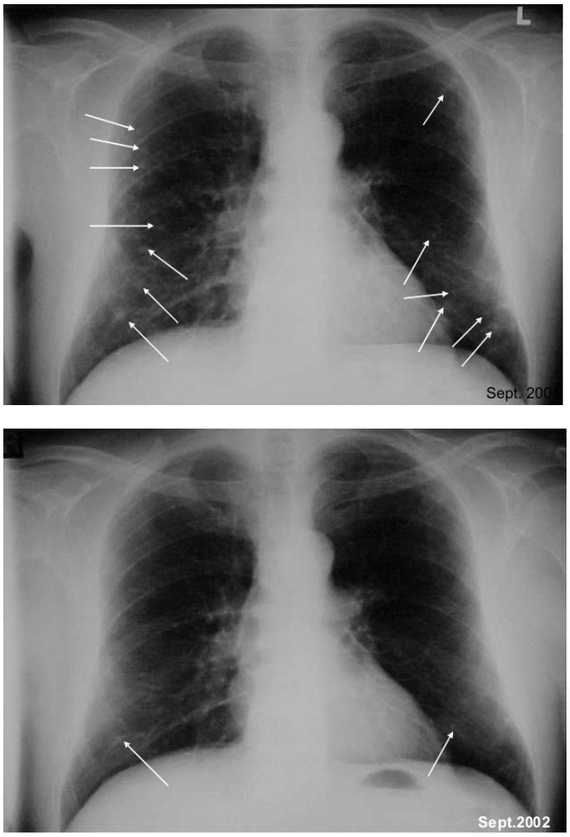

Fig. 4a: *Thorax – X-ray of the same patient before complementary treatment with* Prostasol, Curumin *complex,* Biobran *and* IMUPROS™. ***Fig. 4b:*** *One year after complementary treatment with* Prostasol, Curumin complex, Biobran *and* IMUPROS™. *During the course of treatment signs of bone metastases in the technetium scan also disappeared. Figure 5a and b show the bone scintigram of the patient before and after one-year treatment. Today no signs of bone metastases are evident.*

Dietary Measures

It is estimated that about 35%- 40% of all cancers are partly caused by poor or insufficient nutrition.[74] Nutritional consultation and education, therefore, seems a sensible measure within the framework of primary and secondary prevention of cancer in general, as well as in the specific example of complementary therapy for prostate cancer. Too high a calorie intake per day, and the obesity often associated with it, will not only increase the risk of prostate cancer, but also increase the death rate of this disease.[75-77] Restricting calorie intake in animal experiments can prevent the development of cancer and arrest its growth.[78] Asian men have a much lower incidence of prostate cancer than men living in western cultures.[79] Vegetarians also seem to suffer less from prostate cancer.[80] Both Asians and vegetarians consume less fat but a greater share of plant foods, which as a preventive measure and during treatment for prostate cancer can certainly be regarded as a desirable dietary directive. The role of fat intake in prostate cancer genesis remains controversial.[81,82] In particular, saturated fats in meat, milk and cheese are however linked with an increased risk of prostate cancer.[83,84] An increase in the testosterone level of the blood following fat intake,[85] and the direct influence on the activity of nuclear receptors in the prostate cell do in all probability play a role in this process. Arachidonic acid,

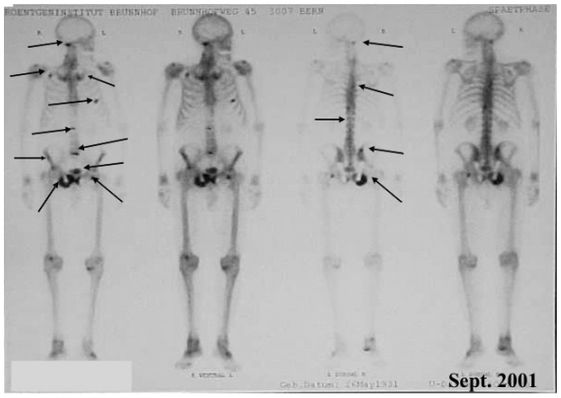

Fig. 5a: *Bone scintigram of the same patient before complementary treatment*

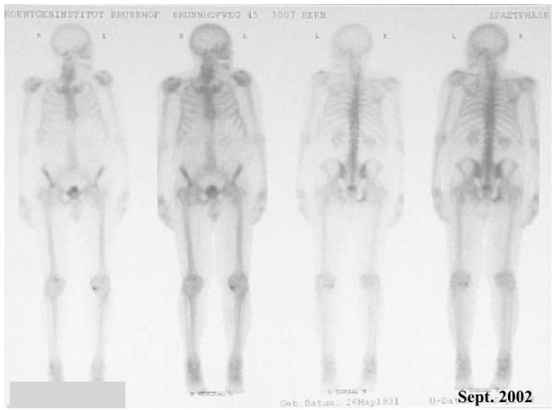

Fig. 5b: Bone scintigram of the same patient one year after complementary treatment with Prostasol, Curumin complex, Biobran *and* IMUPROS™

linolenic acid and alpha-linolenic acid are those polysaturated fats occurring in margarine and salad oils which are considered possible risk factors for the development of prostate cancer. In particular arachidonic acid, an omega-6 fatty acid, presents a potential risk due to its possible conversion into 5-HETE and 12-HETE, as these biologically active fats stimulate both the growth and survival of prostate cancer cells and also increase the invasive capability of these cells and angiogenesis in the tumour region.[86] A change of diet from meat, milk and cheese to a mainly vegetarian diet can reduce the blood level of arachidonic acid by 80%-90% within a period of two to three months. Restricting the consumption of dairy products and the ensuing decrease in the daily intake of calcium also helps reduce the risk of prostate cancer.[87] Apart from an appropriate decrease in excessive calorie intake and a reduction in the proportion of animal fats in the diet, the abundant intake of fresh fruit and vegetables plays a role in the prevention and treatment of prostate cancer. Although on the whole, evidence of the protective effect of fruit and vegetables is weak, a recent multicentric study on over 1,600 patients showed that in particular, peas, beans, lentils and soya beans, together with yellow and orange-coloured vegetables, will provide a protective effect with regard to prostate cancer.[88] Is it possible to derive and recommend a workable 'prostate diet' from what has just been discussed? We think so, and recommend to our patients a reduction in their total calorie intake and in animal fats in their diet. Furthermore, we also recommend restricting the intake of dairy products and at the same time increasing their intake of fresh fruit and vegetables.

Critical Evaluation

The complementary therapeutic measures for patients with hormone refractory prostate cancer presented here are the subject of controversial discussion in urological and oncological circles, primarily because definite evidence of the clinical efficacy of many of the preparations and treatment methods mentioned here is not yet available. Phytotherapy with *Prostasol* and Curcumin complex, the antioxidative and dietary measures and the immune support programme described cannot replace recognized standard therapies for prostate cancer, in particular for patients in the initial stages of the disease. However, since at present, no effective standard therapy for the hormone refractory stage of prostate cancer exists, and previous clinical experience with these complementary measures has led to a biochemical and clinical response in two-thirds of the patients, we consider the implementation of the complementary measures described here for this patient group to be fully justifiable. The systematic investigation in controlled clinical studies of the effect of these therapeutic measures with regard to quality of life and prolongation of life is a highly desirable objective.

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