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Treatment of Advanced Prostate Carcinoma in Kyrgyzstan

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Abstract

Background and Aims: Human prostate cancer is a heterogeneous combination of androgen-dependent and androgen-independent cells, and then potential strategies for eradication of cell mixture have been focused on androgen ablation and radiation or cytotoxic drugs. This study explored the efficacy of two treatment protocols.

Methods: A retrospective review was performed on a total 302 patients with distant metastases between 1986 and 1995 in Kyrgyzstan. This study includes 146 patients with systemically recurrent prostate cancer (group 1) and 156 patients with primary metastasized carcinoma (group 2). In each group the patients were treated by chemo-hormonal therapy or only by hormonal therapy. In Group 1 patients were treated with hormone deprivation alone by fosfestrol (n=68) and a combination of polychemotherapy and fosfestrol (n=78). In Group 2 only hormonal treatment had 62 (39.7 %) and a combined chemo-hormonal therapy had 94 (60.3%) patients. The patients were also grouped by the load of metastases, in low (< 5 metastases), intermediate (> 5 metastases confined to one organ or skeleton) and high (multiorgan metastasis).

Results: A statistically significant prolonged survival in patients treated with chemo-hormonal therapy compared to the patients treated with hormonal therapy alone in both groups. In group 1 and 2 the median survival in the chemo-hormonal group was 24.5 and 25 months ($p < 0.0001$) versus 8 and 10.5 months in hormone group ($p < 0.0001$), respectively. Metastases distention did not change the significant disease specific survival advantage of the combined chemo-hormonal treatment in both groups.

Conclusions: Chemo-hormonal therapy in recurrent metastasized and primary metastasized prostatic cancers significantly have prolonged overall and disease specific survival in comparison to hormonal therapy alone. Combined chemo-hormonal treatment should be started early in metastasized cancer, before the outgrow of hormone refractory tumor cell clones.

Keywords: Prostatic Neoplasm, Metastatic, Relapse, Chemotherapy

Introduction

The most common cancer in men is prostate cancer and, after lung cancer, the second most common cause of death. While the lifetime risk for a person of being diagnosed with prostate cancer is 12.3%, the lifetime risk of dying for prostate cancer is no more than 3.8%, and in this respect it is evidently special from most other cancers (1). As prostate cancer frequently grows very gradually (1), metastatic prostate cancer is a rising health problem and is the

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second cause of cancer mortality in male gender (2).

The incidence rate of prostatic cancer is significantly different among countries, and it is higher in the Western countries than Asia. Probably the low incidence of prostatic cancer in Asia may be due to genetic, dietary or environmental factors and their lifestyles (3).

Unfortunately incidence of prostatic cancer has been rose in Russia, Kazakhstan, and Armenia, more aggressive than to other localizations (4).

From the other point of view, the Republic of Kyrgyzstan is a country with a multiethnic population of both European and Asian origin (5). Conversely, although it is an Asian country with low incidence of prostate carcinoma, but as a former member of the Soviet Union, the Russian population is still high and subsequently prostatic cancer may be frequent.

Prostate cancer is a heterogeneous disease at first happens as an androgen-dependent tumor, and most patients have a good response to androgen–ablation treatment but, the disease often occurs again as an androgen–independent tumor, which no responds to the ablation therapy (6).

This natural history of prostate cancer, complicates treatment protocols and makes difficult the planning and explanation of clinical trials (1). Fortunately, so many therapies have been designed in the management of prostatic cancer includes: alternative hormonal therapies, chemotherapy, radioisotopes, and investigational agents or combination of them. Palliative care and quality of life have been one of the most important options in treatment of them (2, 7).

We present a retrospective survival analysis of patients treated for recurrent and primary metastatic prostate cancer and demonstrate that combined hormone deprivation and chemotherapy improve overall and disease specific survival compared with hormonal therapy alone.

Materials and Methods

Participants:

Between 1986 and 1995, 302 male patients with metastatic prostate cancer referred to our center for management. Treatment protocol has been approved by the Hospital Ethics Committee and before registration in the study all patients accepted informed consent. All patients with primary or recurrent metastatic prostate carcinoma were included. Metastasis was confirmed by bone scan, bone and lung x-rays, abdominal and pelvic sonography and/or CT scan. The patients divided initially into two groups including: 146 patients with systemically recurrent prostate cancer (group 1) and 156 patients were treated for primary metastasized carcinoma (group 2). After primary treatment all the patients were routinely followed by digital rectal examination (DRE), transrectal ultrasound (TRUS), ultrasonic scanning of lymph nodes and organs, bone scans, monthly PSA evaluation during the first year and 4 times a year after that. X-rays were made every six months. This enabled early detection and treatment of cancer recurrence.

Then we classified the entire population by the metastasis load into low (<5 metastases), intermediate (>5 metastases confined to one organ or bones) and high (multiorgan metastasis).

Metastasis-free survival was documented for all patients at the interval between the end of the primary treatment and the first detection of distant metastases.

In this study, locally advanced prostate carcinoma means stages T2b-4N0-2M0 (8, 9).

Setting:

1-Radiation therapy: Radiation treatment was performed with a Co-60 at 'Rokus-M' apparatus using large field irradiation for primary tumor (60-65 Gy)

and regional lymph nodes (40-45 Gy). Patients were given a whole dose of 60-65 Gy in fractions of 1.8 to 2 Gy/day.

2-Hormonal therapy: Hormonal therapy consisted of surgical castration or estrogen treatment. Estrogen therapy started with 60 to 80 mg i.m./day for 20 to 30 days. Patients received 6 cycles with 3-week intervals between each cycle. In cases of tumor growth, hormone treatment was continued with fosfestrol 600 mg daily for 20 days. Patients with cardiovascular disease were treated with antiandrogens (flutamide 750 mg/d or cyproteron acetate 10 mg/day). No patient received LHRH agonists.

3-Chemotherapy comprised three agents: Cyclophosphamide 600 mg /m2, adriamycin 50 mg/m2, and 5-fluorouracil 500 mg/m2 intravenously at 1 and 8 days with a 3-week interval. In general 6 or more cycles were administered. Additional estrogen therapy consisted of fosfestrol 600 mg/day i.v. for 20 days, afterwards per os (0.3 g/day) in weekly cycles with 3-week intervals or with sinestrol 60-80mg/day (from 1 to 2 months). There was a one-month interval during the estrogen therapy with a total of 4 to 6 cycles of estrogen. The course was repeated following an interval of 3 months.

In patients suffering from cardiovascular disease or renal failure, chemotherapy consisted of cyclophosphamide 600mg/m2 and fluorouracil 500mg/m2 at the first and eighth day every 3 weeks.

Treatment schedule:

1- Primary treatment in group 1 consisted of local radiation therapy, hormonal therapy, combined radio-hormonal therapy, combined chemo-hormonal therapy and combined radio-chemo-hormonal therapy. All failures with distant metastases were then treated either with hormone deprivation alone, usually with fosfestrol or a combination of polychemotherapy and fosfestrol.

2- Patients in group 2 (metastatic) were treated whether with a combination of chemotherapy and hormone deprivation, or hormone deprivation as sole treatment. Chemo-hormonal therapy was recommended if they were considered strong enough to withstand the possible side effects of polychemotherapy.

Statistics:

Statistical analysis was made by the Kaplan-Maier method and a log rank test for the analysis of differences in survival due to different treatment modalities. Significance level was set at $p < 0.05$.

Results

Mean patient age in group 1 was 66.6 years (median 66 years), in group 2 was 65 years (median 65 years).

Metastasis:

G1: At recurrence, 111 (76.0%) patients presented with bone metastases, 5 (3.4%) with distant lymph node metastasis, 4 (2.7%) with bone and lymph node metastases, 10 (6.8%) with bone and liver metastases, 12 (8.2%) with bone and lung metastases.

G2: Among the patients with systemic disease at first presentation (group 2), 112 (71.8%) had bone metastasis, 5 (3.2%) distant lymph node metastasis, 3 (1.9%) liver metastasis, 4 (2.7%) lung metastasis, and 32 (20.5%) metastasis combinations.

Treatment:

G1: All patients of group 1 were given primary treatment for clinically localized or locally advanced prostate cancer that consisted of local radiation therapy, hormonal therapy, combined radio-hormonal therapy, combined chemo-hormonal therapy and combined radio-chemo-hormonal therapy in 31 (21.2%), 46 (31.5%), 35 (24.0%), 17 (11.6%), and 17 (11.6%), respectively.

Overall median metastasis-free survival, independent of the treatment option, was 12 months (mean 19 months). The diverging survival rates depended on the type of primary treatment.

Table 1. Metastasis free survival after different forms of primary treatment

Method of treatment	Patient number	Median metastasis free survival(month)
RT+CHT+HT	15	37
RT+HT	33	14
RT	29	11
CHT+HT	16	12.5
HT	43	9.5

RT, Radiation therapy; **CHT**, Chemotherapy; **HT**, Hormonal therapy

As shown in Table 1, the combination of local regional external beam radiotherapy, hormone deprivation and polychemotherapy provided the best results with a median metastasis-free survival of 37 months followed by combined radiotherapy and hormone treatment, chemo-hormonal therapy, radiotherapy and single hormonal deprivation with estrogen. An overall survival after failure from primary treatment has been summarized in Figure 1-3

G2: A total of 94 (60.3%) patients were treated with a combination of chemotherapy and hormone deprivation, 62 (39.7%) were given hormone deprivation as sole treatment.

A total of 68 (46.6%) patients were treated with hormonal therapy alone (estrogen, castration), and 78 (53.4%) with chemo-hormonal therapy. Overall and disease specific survival were documented.

All failures with distant metastases were then treated either with hormone deprivation alone, usually with fosfestrol (n=68) or a combination of polychemotherapy and fosfestrol (n=78). Median survival after the start of treatment was 15.5 months (mean 21.5 months) for the whole group no matter whether treatment was estrogen alone or in combination.

Median disease specific survival was 15.8 (mean 21.7) months. However, if stratified by treatment, a

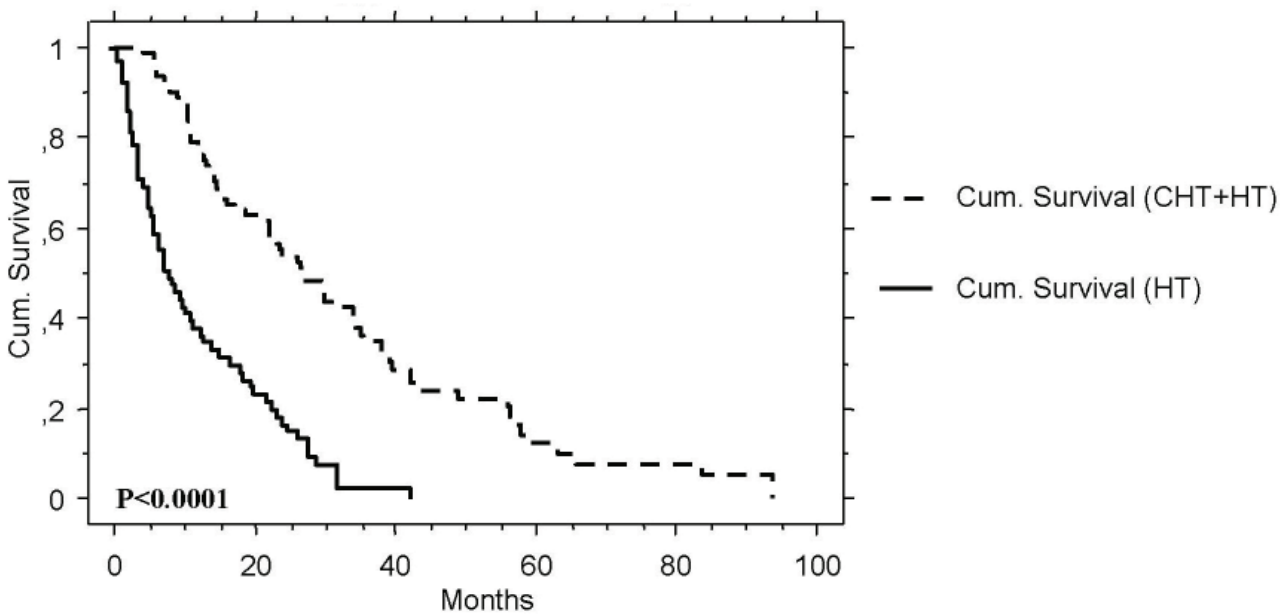

Figure 1. Kaplan-Maier plot of overall survival after failure from primary treatment. Correlation to secondary treatment. CHT, chemotherapy; HT, Hormonal therapy.

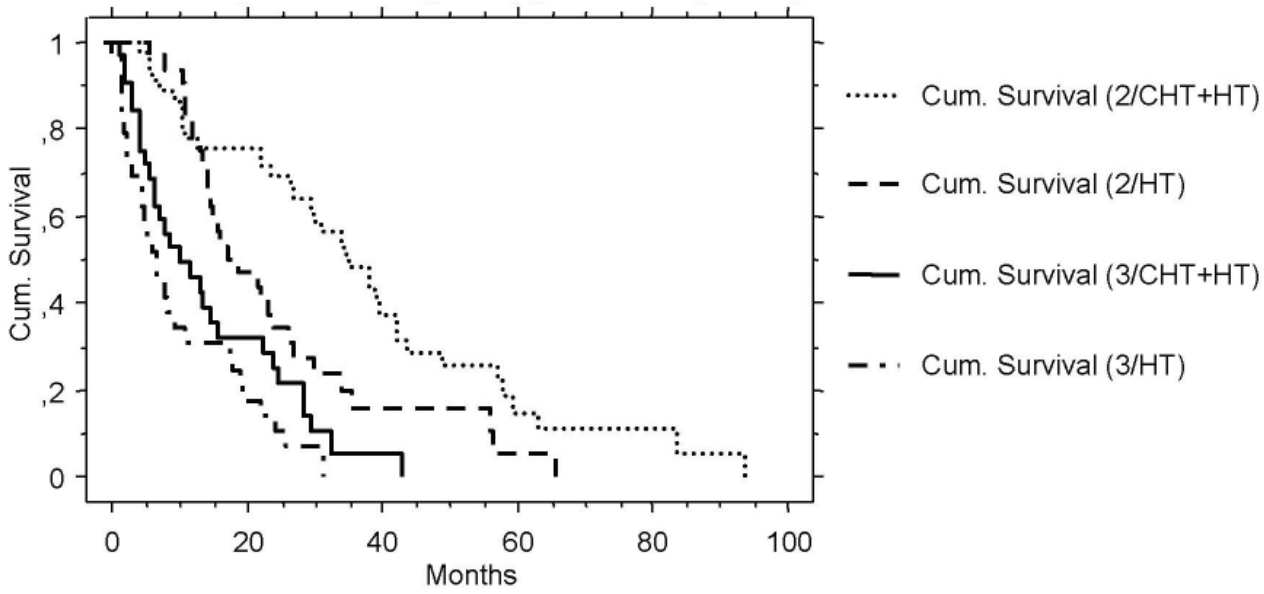

Figure 2. Kaplan-Maier plot of overall survival after failure from primary treatment. Correlation to secondary treatment stratified by WHO-tumor grade (grade 2 and 3). CHT, chemotherapy; HT, Hormonal therapy.

statistically significant prolonged survival was found in the patients treated with chemo- and hormonal therapy compared to the group of patients given hormonal therapy alone (figures 1 and 4). The median survival in the chemo-hormonal group was 24.5 months compared to 8 months in the hormone group ($p < 0.0001$). This difference was not influenced by the tumor grade, since patients with identical grading showed clearly different survival, depending on the treatment strategy (Figures 2 and 5). As it could also not be ruled out that patients with very high tumor load were preferentially treated with sole hormone

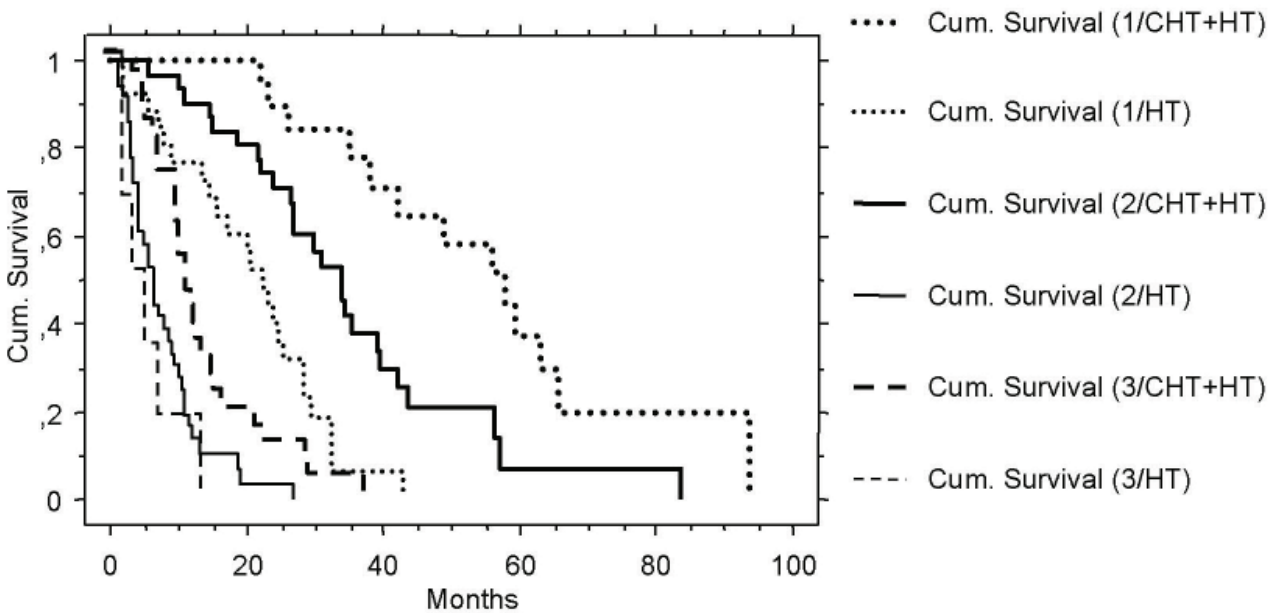

Figure 3. Kaplan-Maier plot of overall survival after failure from primary treatment. Correlation to secondary treatment stratified by metastasis load (MTS 1: <5 metastases, MTS 2: >5 metastases confined to one organ or bones; MTS 3: multiorgan metastasis). CHT, chemotherapy; HT, Hormonal therapy

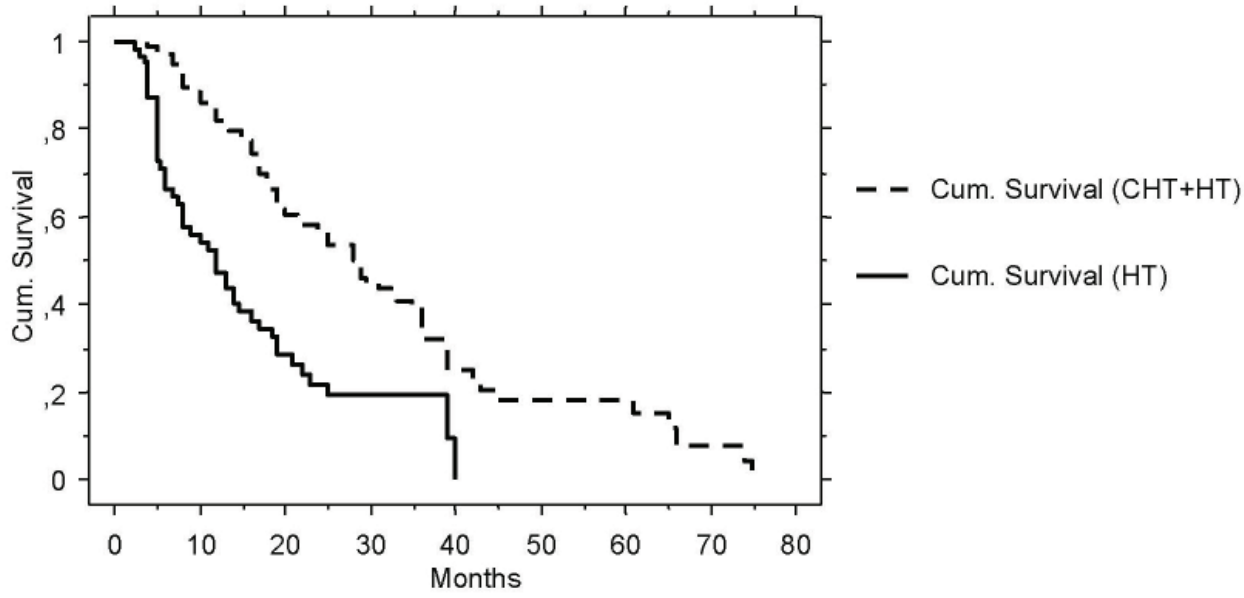

Figure 4. Overall survival of patients with primary metastasized tumors. Relation to treatment modality. CHT, chemotherapy; HT, Hormonal therapy

deprivation. The extent of metastases did not change the significant disease specific survival advantage of the combined chemo-hormonal treatment (figures 3 and 6).

Patients that presented with metastatic disease at the beginning survived slightly longer with prostate cancer than men with metastases after tumor recurrence. This fact is attributed to the selection of more aggressive cancer cells by the primary treatment, independent of radiation or surgical treatment (median overall survival in group 2 was 17.5 months). The same significant survival advantage was demonstrated by the combination treatment, including chemotherapy compared to estrogen treatment alone in patients

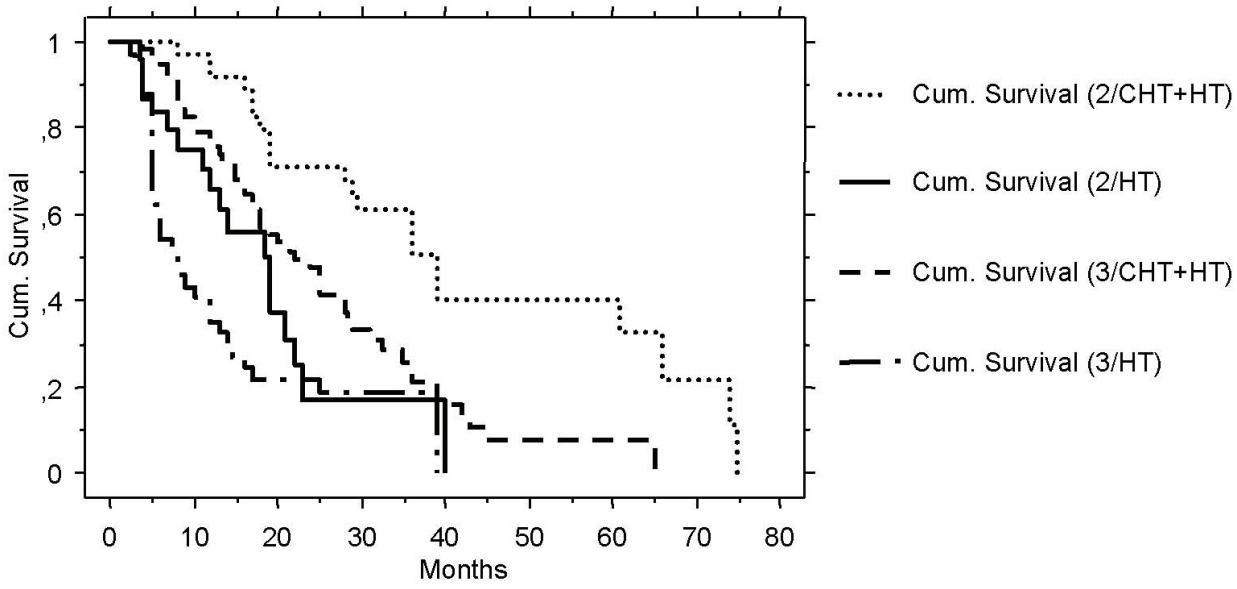

Figure 5. Overall survival of patients with primary metastasized tumors. Relation to treatment modality, stratified by WHO-tumor grade (Grade 2 and 3). CHT, chemotherapy; HT, Hormonal therapy

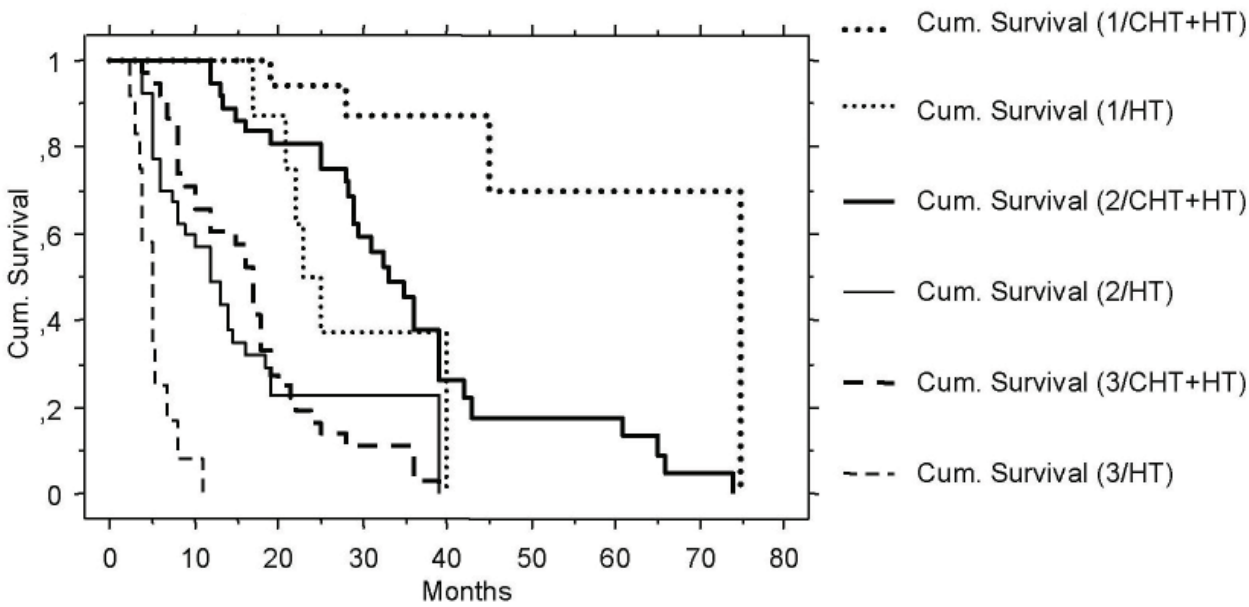

Figure 6. Overall survival of patients with primary metastasized tumors. Relation to treatment modality, stratified by metastasis load (MTS 1: <5 metastases, MTS 2: >5 metastases confined to one organ or bones; MTS 3: multiorgan metastasis). CHT, chemotherapy; HT, Hormonal therapy

with primary distant metastases (Figure 4). The median overall survival in the chemo-hormonal group was 25 months, compared to 10.5 months in patients treated with hormone ablation alone ($p < 0.0001$). This divergence prevailed after stratification for tumor grade or metastasis load (Figures 5 and 6).

Discussion

Prostate carcinomas are heterogeneous and composed of androgen-dependent and independent cells (2, 10). On castration, androgen-dependent tumor cells undergo apoptosis and die off, resulting in tumor regression.

However, androgen-independent cell growth occurs simultaneously leading to tumor recurrence. Thus, selective androgen ablation promotes androgen-independent cell growth that ultimately comprises the tumor mass. This scenario has been demonstrated in several experimental in vitro and in vivo systems including the Dunning rat prostate carcinoma model and the human prostate carcinoma cell line LNCaP (11). In the androgen-dependent Shionogi carcinoma model, the effects of androgen ablation on stem cell composition have provided further insight. Recurrent tumors after initial androgen ablation were enriched with androgen-independent stem cells by a factor of 500, suggesting that initial antihormonal treatment promotes the growth of androgen-independent clones (12). These androgen-independent cells, however, might be sensitive to chemotherapy, propagating combined treatment of androgen withdrawal and chemotherapy, which should be started early, when the number of independent cells is low.

We demonstrated that different non-surgical treatment options for localized or locally advanced prostate cancer have a different impact on metastasis-free survival in these patients. The combinations with chemotherapy always gave better results than monotherapy either as radiation or hormone deprivation. We also showed that chemo-hormonal therapy significantly prolonged overall and disease specific survival compared to hormonal therapy alone in recurrent metastasized and primary metastasize cancers.

Hormonal deprivation is currently the standard treatment for metastasized prostate carcinoma, either recurrent or primary. Response duration to

androgen ablation in metastasized tumors is finite, lasting for a median of 12 to 16 months and disease specific survival around 24 months (13, 14). In our group of primary metastasized cancers the overall disease specific survival was 17.5 months and for patients with sole androgen ablation it was only 12 months. There may be several reasons for this low survival rate: hormone ablation was achieved with diethylstilbestrol and fosfestrol, a treatment, that is no longer common. Moreover, other than bilateral orchiectomy, it is the only affordable modality in Kyrgyzstan. LHRH agonists and antiandrogens are too expensive and cannot be used regularly.

Complete androgen ablation is also not performed for the same reason. However, it has been shown that estrogens and luteinizing hormone-releasing hormones are equally as effective as orchiectomy (15, 16) and that all three alternatives reliably produce castration testosterone levels. Socioeconomic or ethnical reasons can also account for this low survival rate. The male population is almost unaware of prostate cancer and constant access to early tumor detection is scarce. PSA testing can only be afforded by few with the result that most patients regularly present with complicated, extensive high volume metastasized disease, which may also limit the effectiveness of any therapy. This could explain the fact that the median survival among patients treated with combined hormone and chemotherapy is as low as the published survival rates for hormonal deprivation alone.

The effectiveness of chemotherapy in prostate carcinoma has been a long debated subject as several studies with different drugs and combinations in hormone refractory cancer produced disappointing results. In 1985 Eisenberger et al reviewed 17 randomized clinical trials on 1,464 patients and found an objective response rate (complete and partial response) of 4.5% (17). In 1992 Yagoda and Petrylak reviewed 26 trials with chemotherapy conducted between 1987 and 1991 and reported an overall response of 8.7% (18). However, the outcome is changing with the advent of new drugs and new combinations of already existing drugs, even in hormone refractory cancer, impressive results have been achieved with objective response and subjective response rates of up to 70%, including the disappearance of measurable disease, significant relief in bone pain and PSA reduction of more than 50% in 60 to 70% of patients (19, 20). From these results it may be concluded that it is recommendable to commence chemotherapy before the onset of hormone refractory disease.

Between 1986 and 1990, we conducted a prospective randomized study in 111 patients with locally advanced prostate carcinoma (stages T2b-4N0-2M0) (8, 9). Patients were treated in 5 6 different groups (estrogen therapy alone, radiotherapy alone, chemo- and estrogen therapy, radio- and estrogen therapy, and radio- chemo- and estrogen therapy). In this study, we found that the median progression free survival after combined chemo-and hormonal therapy was three times longer than after sole hormone ablation with estrogens (39.4 months vs. 12.9 months). These results encouraged us to apply chemotherapy together with hormone deprivation in metastatic recurrent and primary metastatic carcinomas. Up to now, there is only scarce literature on this issue with contrary results: Janknegt et al compared orchiectomy alone or in combination with estramustinphosphate in randomized trial (21). They did not find a significant difference in time to progression in both arms. Similar results were reported from the South West Oncology Group (SWOG) showing a higher initial response for combined treatment with hormone ablation and combination therapy with cyclophosphamide and doxorubicin, which was not reflected in improved survival data (7). However, this study has been criticized, because the dose intensity of chemotherapy was too low. De Reijke et al treated 189 patients with metastasized cancer and poor prognostic factors either with orchiectomy or

orchiectomy and mitomycin C (22).

No significant differences were found for time to overall, objective and subjective progression between the two treatment arms, but a trend in favor of orchiectomy alone was observed for overall survival, which may partly be explained by the significant toxicity of mitomycin C leading to discontinuation in 31% of the patients with hematological toxicity and 7% with renal deterioration. The 8% of the patients in the combined treatment arm died of toxicity and infection. Application of a less toxic chemotherapy regimen might have resulted in more favorable outcome for the combined treatment group. On the other hand, there are studies in the favor of combined treatment regimens from Japan and Europe (23, 24). Recently, follow up data of a randomize trial of total androgen blockade (TAB, accomplished by bilateral orchiectomy plus flutamide) versus TAB plus 18 weeks of epirubicin (2 mg/m^2/wk) has been reported by Pummer et al (24). This study of 145 patients demonstrated statistically significant improvement in time to progression (from 12 to 18 months) and a strong trend in overall survival (from 22 to 30 months) favoring the combination treatment. A quality-of-life examination showed favorable results for those with prolonged disease free interval, despite the acute effects of weekly chemotherapy.

Conclusions

We are aware about the possible biases of retrospective studies as ours: We did not prospectively control for performance score and can therefore not rule out an unbalanced distribution of comorbidity status. However, the only medical exclusions for chemotherapy were cardiovascular disease and chronic renal failure, which occurred in about 25 % of the patients. All other patients treated with hormone ablation alone, refused chemotherapy due to personal reasons that were not related to medical restrictions. On the other hand we stratified the patients in three groups according to the extent of metastasis, which by itself influences survival and correlates with patient performance. Even, after stratification we still saw a significant difference in overall survival in favor of combined treatment.

In conclusion, we found that chemo-hormonal therapy significantly prolonged overall and disease specific survival over hormonal therapy alone in recurrent metastasized and primary metastasized cancers. Although, these data are retrospective and may be biased due to socioeconomic constrictions of a third world country, we believe, that they can serve as a proof of principle that combined chemo-hormonal treatment should be started early in metastasized cancer, before the outgrow of hormone refractory tumor cell clones and also give further support to the introduction of randomized trials of combined treatment in metastasized hormone responsive prostate carcinoma.

Conflict of Interest

None declared.

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