REVIEW ARTICLE

Hormonal Therapy in the Elderly Prostate Cancer Patient

Jesco Pfitzenmaier, Jens E. Altwein

SUMMARY

Background: Prostatic cancer (PCa) is the most common cancer in men in Germany. The goal of this review is to define the indication for hormonal treatment in patients over age 70.

Methods: A selective search of the literature up to 2008 for the terms „prostate cancer“, „androgen suppression and deprivation“, „hormone therapy“, „LHRH analogs“, „antiandrogens“, „active surveillance“, and „watchful waiting“ was performed in the Medline and Cochrane databases. The guidelines of the American Society of Clinical Oncology (ASCO, 2007) and the European Society of Urology (EAU, 2008) were also taken into account.

Results: Hormonal therapy is not indicated for patients with organ-confined, well-differentiated or moderately differentiated tumors who are otherwise in good health. It is beneficial in the treatment of locally advanced cancer with an unfavorable Gleason score. For patients with organ-confined cancers who are in poor general condition, hormonal therapy is deferred until symptoms arise. The guidelines recommend hormonal therapy in case of PSA elevations greater than 1.5 ng/mL after attempted curative treatment. Symptomatic metastases require immediate hormonal therapy. Intermittent androgen deprivation is an attractive alternative.

Conclusions: In patients over age 70, an attempt at curative treatment is only reasonable if the life expectancy exceeds 10 years. Hormonal therapy is the treatment of choice for patients with undifferentiated, locally advanced prostate cancer, recurrences as defined by PSA elevation, and symptomatic metastases.

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Key words: prostate cancer, geriatric medicine, hormonal therapy, PSA testing, surveillance

Prostatic carcinoma (prostate cancer, PCa) is currently diagnosed in a local stage in 91% of patients. When the tumor is in this stage, treatment with curative intent is indicated as long as the patient's life expectancy is 10 years or more. In a population-based study involving 6183 men, it was found that 40% of men over 70 for whom radical prostatectomy was chosen did not, in fact, have a life expectancy justifying this form of treatment. Of the patients who underwent local radiotherapy instead, 70% died within 10 years (1).

Hormonal therapy is an option in this age group. This form of treatment takes advantage of the androgen dependency of prostate cancer. Androgens stimulate the growth, function, and proliferation of prostate cells. Testosterone is essential for the proliferation of prostatic carcinoma cells. The testes are the source of this androgen; 5% to 10% (androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate) is derived from the adrenal gland. Testosterone secretion is regulated by the hypothalamic-pituitary axis: luteinizing hormone releasing hormone (LHRH) stimulates testosterone secretion by way of LH, and testosterone, in turn, is reduced through the catalytic action of the enzyme 5-alpha reductase to 5-alpha dihydrotestosterone, which is ten times as potent and which then binds to the prostate-cell androgen receptor. When prostate cells are deprived of androgen stimulation, programmed cell death ensues. This is the mechanism underlying the effectiveness of androgen-withdrawal hormonal therapy of prostate cancer as well as that of bilateral orchiectomy.

Current alternatives to the latter two treatments include LHRH analogs, antiandrogens, and 5-alpha reductase inhibitors. Two types of treatment are of major relevance to patients over age 70 because of their diminished life expectancy:

- delayed hormonal therapy and
- immediate hormonal therapy.

In this article, we will present the essential features and indications of each of these types of treatment. This review is based on a search in PubMed (the Medline database) and in the Cochrane database for articles published up to 2008, as well as on the published guidelines of the European Association of Urology (EAU) (2008), the American Society for Clinical Oncology (ASCO) (2007), and the American Urological Association (AUA) (2007).

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Epidemiological data from Germany

More than 58 000 men are given the diagnosis of prostate cancer in Germany each year (2). This figure corresponds to 25.4% of the new cancer diagnoses in men; prostate cancer is thus the most common form of cancer in men. The mean age at diagnosis is 69 years. The annual incidence is 720 per 100 000 per year in the 70-to-74-year-old age group and peaks at approximately 750 per 100 000 per year in men aged 75 to 79. The relative 5-year survival rate of patients with prostate cancer is currently 87% (2). These epidemiological figures reveal the importance of an appropriate choice of initial therapy.

Hormonal therapy or "watchful waiting" in men over age 70

The expression "watchful waiting" has come into common use to designate delayed hormonal therapy of patients with prostate cancer. Palliative hormonal therapy is started only if the patient develops tumor symptoms such as bone pain or renal failure secondary to ureteric obstruction. Watchful waiting is not the same thing as active surveillance, a management strategy in which no treatment is given as long as the carcinoma seems to be relatively inactive (as implied by a PSA less than 15 ng/mL, a Gleason score of 6 or less, and tumor stage T1c–2a) and the patient's life expectancy is 15 years or more (3). The Gleason score is the most commonly used grading system for prostate cancer; it is used, for example, in the European guideline of 2008. The two most common histological patterns seen in the biopsy specimen (from 1 = near normal to 5 = undifferentiated carcinoma) are added together to yield a Gleason score from 2 to 10.

The Gleason score was the dependent variable in the uncontrolled Connecticut observational study, in which only 7% of patients with a Gleason score of 4 or below died of tumor-related causes. The figure rose to 45% with a Gleason score of 7 and to 66% with a Gleason score of 8 or above. Age did not influence the tumor-specific lethality, but nearly half of the patients required hormonal treatment because of progression. Extensive comorbidity, as quantified with the Charlson comorbidity index (*table 1*), raised the overall but not the tumor-specific lethality (evidence level IIa) (*tables 1 and 2*) (4, 5).

The Gleason score was also the most important tumor-associated prognostic factor for primary hormonal therapy in a prospective, uncontrolled study involving 227 patients (mean age 72.8 years), 80% of whom had a tumor-specific survival of 8 years or more. Patients whose Gleason score was 8 had a significantly shorter survival. The most important patient-associated factor for overall survival was comorbidity (*table 1*). Patients with a Charlson score of 0 or 1 survived twice as long as those with a Charlson score of 2 (evidence level IIb) (6).

A further important variable is the tumor stage. If hormonal therapy is initiated only after the onset of tumor-related symptoms in a patient with a locally advanced or asymptomatic metastatic prostate cancer, the rate of tumor-related complications (*table 3*), carcinoma-specific lethality, and overall lethality are significantly higher.

TABLE 1

Weighting of the 19 disease states that contribute to the Charlson score (5)

Weight	Comorbidity
1	Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer, mild hepatopathy, type II diabetes mellitus
2	Hemiplegia, moderately severe renal failure, severe diabetes, any kind of tumor, leukemia, lymphoma
3	Moderately severe hepatopathy
6	Metastatic tumor, AIDS

The classification 0, 1, or 2+ is commonly used. The Charlson score is the sum of the scores for the individual disease states (e.g., connective tissue disease and mild hepatopathy, Charlson score = 2)

TABLE 2

Evidence levels

Evidence level	Type of evidence
Ia	Meta-analysis of randomized studies
Ib	At least one randomized study
IIa	One well-designed, controlled study without randomization
IIb	At least one well-designed, quasi-experimental study
III	Well-designed, nonexperimental study
IV	Expert opinion

Evidence levels: United States Department of Health and Human Services, 1972

This was revealed by the phase III study of the Medical Research Council: The number of patients who died of tumor related causes was 203 among those who were given immediate hormonal therapy, as opposed to 257 among those who were given delayed hormonal therapy (evidence level Ib) (7). It follows that patients with asymptomatic and advanced prostate cancer should be given hormonal therapy without delay.

The suitability of patients over age 70 for hormonal therapy

It is agreed by all that hormonal therapy is indicated for an increasing percentage of patients with increasing age, but the only entirely uncontroversial indication for it is symptomatic, metastatic prostate cancer (4). Irritative and obstructive urinary symptoms can also be treated hormonally (8).

The patient's chronological age is less important than his biological age and life expectancy. In one study, the tumor-specific survival rates of patients with local prostate cancer were no different at age 60 and at age 80 if the patients were given hormonal treatment only in case of progression of their prostate cancer. In this age group, it was the Gleason score—a tumor-associated,

TABLE 3

Overall number of complications in the Phase III Study of the Medical Research Council (7)

	Immediate hormonal therapy (N = 469)	Delayed hormonal therapy (N = 465)
Pathological fracture	11	21
Spinal cord compression*	9	23
Ureteric obstruction*	33	55
Extraskelatal metastases*	37	55

*statistically significant

TABLE 4

10-year survival rate for men over age 70 with locally confined prostate cancer (T_{1,2}) under conservative management (typically, androgen deprivation; excerpted from [11])

PSA ng/mL	Charlson score 0–1		Charlson score ≥ 2	
	Gleason score 7	Gleason score 8–10	Gleason score 7	Gleason score 8–10
0–9.9	59% (50–68)	51% (40–64)	24% (15–38)	16% (8–32)
10–19.9	41% (31–54)	32% (22–48)	9% (4–21)	5% (1–16)
≥ 20	35% (26–47)	26% (17–40)	6% (2–15)	3% (1–10)

In parentheses: 95% confidence interval

rather than patient-associated, factor—that shortened metastasis-free 10-year survival: The figure for highly differentiated prostate cancer was 81%, while that for poorly differentiated prostate cancer was 26% (9).

The case studies mentioned above yielded survival figures based on the patients' chronological age. One may suspect, however, that the treating physicians were also influenced by their patients' comorbidities when choosing the therapy to be given to each. In a population-based study in the Netherlands, only 8% of the patients under age 69 had two or more comorbidities, as compared to 27% of patients aged 80 (10).

Among patients aged 70 to 74 with a long life expectancy, cancer-specific lethality increases with increasing Gleason scores (11). That is, a tumor-associated factor (the Gleason score) is more important than patient-associated factors (comorbidity/the Charlson score), even in patients in their eighth decade with a long life expectancy. If one combines tumor-associated and patient-associated (Charlson score) factors before hormonal therapy is initiated, the current survival tables of Tewari et al. (11) can be used to assess the usefulness of hormonal therapy (evidence level III) (table 4).

Immediate versus delayed hormonal therapy Androgen withdrawal

The ASCO guideline includes a meta-analysis of the six randomized studies that address the question of the timing of androgen withdrawal (LHRH analogs,

orchiectomy). The tumor-specific lethality was 17% lower when the treatment was initiated immediately, but the overall survival of these prostate cancer patients was no different in the immediate and delayed treatment groups (evidence level 1a) (12). The patients in the immediate treatment group were, however, more likely to be free of pain 7.8 years later (66.5% versus 57.8%) and suffered less commonly from renal failure due to ureteric obstruction (4.7% versus 11.4%) or from pathological fractures (0.6% versus 3.7%). About one-quarter of the patients died before hormonal therapy had to be initiated (evidence level 1b) (13).

When patients are primarily treated with prostatectomy with curative intent and later suffer a PSA recurrence, the EAU guideline of 2008 recommends androgen withdrawal or androgen blockade, e.g., with bicalutamide (150 mg/day). Local radiotherapy is given secondary priority and is recommended only if the PSA value is below 1.5 ng/mL. For PSA recurrences after radiotherapy for prostate cancer, androgen withdrawal should be considered only when systemic progression is suspected (EAU guideline 2008). Androgen withdrawal is necessary if distant metastases have been definitively documented.

Antiandrogenic monotherapy

Monotherapy with an antiandrogen in stage T_{3,4} (any N) or in stages T_{1–4} (N+) can be of benefit to patients over age 70 as well, instead of the injection of an LHRH analog (14). The side effects of immediate androgen withdrawal are an argument against its use in multimorbid patients over age 70. Antiandrogenic hormonal therapy has fewer side effects, and secondary androgen withdrawal is still effective (table 5).

The effectiveness of the antiandrogen bicalutamide was tested in the SPCG6 study in comparison to watchful waiting: Patients with locally confined (T_{1,2} N_{0–x} M₀) or locally advanced (T_{3,4} N₀₊ M₀) prostate cancer were treated either with bicalutamide 150 mg/day or with placebo in this phase III trial. After a median follow-up interval of 7.1 years, bicalutamide reduced the rate of progression among patients with locally advanced disease by 53% (relative risk reduction) (median progression-free survival time 8.8 versus 7.1 years). Bicalutamide reduced lethality by 35% (105/255, or 41.2%, with bicalutamide versus 131/250, or 52.4%, with placebo) (evidence level 1b) (14). The side effects of bicalutamide included breast pain (63%), gynecomastia (58%), and, less commonly, impotence.

Continuous versus intermittent hormonal therapy

The disadvantages of continuous androgen withdrawal are its side effects and its cost. In patients over age 70 with asymptomatic prostate cancer, the side effects are very bothersome (table 5). Numerous phase II trials (15–17) have shown that, the longer patients are treated with intermittent androgen withdrawal, the shorter the intervals between treatments become.

The PSA nadir after the initiation of androgen withdrawal is prognostically significant for progression

and survival time. A PSA nadir below 0.2 ng/mL is prognostically favorable (18). The interim evaluation of the phase III trial of the South European Urological Group, presented by Calais da Silva et al. at the 2006 ASCO meeting (abstract 4513), revealed no difference between continuous and intermittent hormonal therapy with respect to progression. The patients' quality of life was better with intermittent treatment, e.g., hot flashes were considerably rarer. In the single randomized phase III trial that has been completed to date involving the treatment of patients with locally advanced or metastatic prostate cancer with goserelin and bicalutamide, the progression-free interval was found to be longer with intermittent than with continuous therapy. These results were presented by Miller et al. at the 2007 ASCO meeting (abstract 5015). The side effects were the same in both arms of the trial.

Patients receiving intermittent androgen deprivation should always be treated until the PSA and testosterone have reached their lowest levels; as a rule, this takes at least seven months. The intervals between treatments become shorter with each cycle: ten months in the first cycle, versus three months in the eighth (19).

Types of hormonal therapy and their side effects

When a patient over age 70 and his physician together decide to initiate hormonal therapy, the standard mode of treatment is the administration of an LHRH analog. The simultaneous administration of the antiandrogens bicalutamide or flutamide (= maximal androgen blockade, MAB) was found in a meta-analysis of 27 prospective phase III trials to reduce overall lethality by about 2.9% (72.4% with MAB versus 75.3% without MAB, in a study population of 6500 patients) (evidence level 1a) (12, 20). It follows that patients should be informed in detail about the possible side effects before MAB is initiated.

Vasomotor symptoms

About 80% of men aged 70 or older complain of vasomotor symptoms (hot flashes) after androgen withdrawal through the use of LHRH analogs or castration. In about 40%, this is still the case after 8 years of treatment. Hot flashes can be treated symptomatically with clonidine, zypoterone acetate, or medroxyprogesterone acetate (21).

Depressive mood disturbance

A depressive mood disturbance is one of the regularly occurring side effects of hormonal therapy, with a frequency of about 6% (22). The diagnosis of a malignant tumor and the side effects of androgen withdrawal tend to worsen it. Depression resolves once hormonal therapy is terminated, even if no antidepressants are given (23).

Cognitive impairment

Cognitive impairment due to gonadal androgen deprivation is a problem whose seriousness has been underestimated. Reduced perceptual and cognitive abilities are

TABLE 5

Complications of hormonal therapy for prostate cancer

	Castration (orchiectomy, LHRH analogs)	Antiandrogenic monotherapy
Hot flashes	+++	(+)
Cardiovascular*	+ / +++	
Insulin resistance*	+	
Obesity	++	+
Depression	+	
Loss of libido	+++	(+)
Cognitive impairment	++	(+)
Muscle weakness	++	
Osteoporosis	+++	
Gynecomastia	+	+++
Breast pain	+	+++

+, mild; ++, moderate; +++, severe; *, only LHRH analogs; LHRH = gonadotropin releasing hormone;

The rate of termination of treatment is 10% for castration/androgen withdrawal and 21% for antiandrogenic monotherapy (12)

already a problem in men over 65 with falling testosterone levels (24). Cognitive function is impaired by androgen withdrawal in roughly every second patient with prostate cancer. The problem is further worsened by additional or continued pharmacological androgen withdrawal (evidence level Ib) (25). Estrogens may improve the cognitive deficit, as was shown in a case-control study of 18 patients receiving hormonal therapy compared to 17 normal control subjects (e1).

Diminution of muscular strength

A man's muscular strength is reduced by 12% to 66% as the result of androgen deprivation. Moreover, muscle mass declines by 20% to 30% by age 70 (e2). Because androgen deprivation reduces the amount of protein synthesis and the non-lipid body mass, obesity results. Thus, elderly patients should actively work against the loss of muscle by directed strength-training exercises (evidence level IV).

Osteoporosis

In general, bone density declines with increasing age. The administration of an LHRH analog increases the five-year risk of fracture from 12.6% to 19.4% (e3). In a comparative study, it was shown that bone density decreased by 2.5% under treatment with the LHRH analog leuporelin but increased by 2.5% under treatment with the antiandrogen bicalutamide (150 mg) (e4). Loss of initiative and loss of libido, as well as hot flashes, were also less severe in the bicalutamide group. Strength training and the administration of bisphosphonates after androgen withdrawal increase bone mass significantly in comparison to a control group.

Gynecomastia

Gynecomastia develops in as many as 25% of patients undergoing androgen withdrawal and in every second patient treated with bicalutamide or flutamide. Breast pain occurs at a similar frequency. Nonetheless, patients only rarely want to cease treatment for this reason. These problems can be prevented by prophylactic irradiation of the breast glands with 12–15 Gy before the initiation of treatment, or else by the administration of tamoxifen (20 mg/day) (evidence level III) (table 5) (e5).

Cardiovascular complications

Cardiovascular complications were known to develop as a result of the estrogenic treatment of advanced prostate cancer, which is no longer practiced; they have not been seen as a result of the injection of LHRH agonists. A current study involving 73 000 men with local/regional prostate cancer revealed risk elevations for coronary heart disease (hazard ratio [HR] 1.16), myocardial infarction (HR 1.14), and sudden cardiac death (HR 1.16). The authors conclude that long-term treatment with LHRH analogs raises the prostate cancer-independent risk of death more than short-term treatment does. Diabetics with prostate cancer have a 1.44 times greater risk of developing insulin-resistant diabetes. Surgical castration is also associated with a greater risk of developing diabetes mellitus, but its cardiovascular effect is neutral, unlike that of treatment with LHRH analogs (evidence level III) (e6).

Conclusion

Local treatment with curative intent is reasonable for a patient over age 70 only if his life expectancy exceeds 10 years. For all other patients, the particular tumor- and patient-associated factors that are present in the individual case and the side effects that can be expected to occur provide the basis for a decision whether to treat with androgen withdrawal or antiandrogenic hormonal therapy. Primary hormonal therapy is not indicated for patients in good general condition with locally confined prostate cancer, a favorable Gleason score (6 or below), and a PSA value under 15 ng/mL. Radiotherapy can be used as an alternative for patients who have a long life expectancy (greater than 10 years) and a strong desire for treatment. For locally advanced prostate cancer (T_{3,4}) with an unfavorable Gleason score (a score of 7 composed of 4+3, rather than 3+4, or a score of 8 or above), hormonal therapy is an appropriate means of delaying the development of tumor-related symptoms. Long-term observation, so-called watchful waiting, is reasonable for patients in poor general condition with local/regional prostate cancer. Hormonal therapy should only be considered when symptoms are present. In patients with asymptomatic metastases, immediate hormonal therapy is associated with a lower progression rate than initiating treatment only when symptoms arise. For symptomatic metastases, hormonal therapy is indicated. PSA recurrences after radical prostatectomy should be treated primarily with hormonal therapy; radiotherapy is reasonable in cases of local recurrence

Key messages

- Primary hormone therapy is not indicated for patients with prostate cancer who are over age 70, have a PSA less than 15 and a Gleason score of 6 or below, and are in good general condition.
- Hormone therapy is beneficial in the treatment of locally advanced prostate cancer with an unfavorable Gleason score.
- Patients with locally confined prostate cancer who are in poor general condition should be observed for further progression.
- Hormone therapy is indicated in the presence of symptomatic bone metastases.
- Hormone therapy is supported by published guidelines in cases of PSA recurrences greater than 1.5 ng/mL after treatment that is intended to be curative.

with a PSA level below 1.5 ng/mL. For PSA recurrences after primary radiotherapy, hormonal therapy is an option when there is systemic involvement.

Conflict of interest statement

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