Combining hormonal therapy with local treatment in prostate cancer

Hormonal treatment remains a mainstay of systemic therapy for prostate cancer despite recent developments in chemotherapy and intensive research with targeted drugs and immunotherapy. Its efficacy in palliative management of advanced disease has prompted its use as an adjunct to local treatments in earlier disease stages, but results of trials in some settings remain inconclusive.

Over the last ten to fifteen years, hormonal therapy has emerged as an important component not only of the treatment of advanced disease but also in the definitive treatment of localised and locally advanced prostate cancer.

Hormonal therapy (HT) can be used before local treatment, as induction hormonotherapy, with the main aim of improving local control, or after local treatment, as adjuvant hormonotherapy, directed at improving progression-free survival and overall survival.

The rationale for induction HT is to improve the results of local treatment by tumour downstaging before surgery or radiotherapy, with the aim of increasing the probability of radical, margin-negative surgery and facilitating radiotherapy. It can also improve treatment results by reducing the number of clonogenic cells and increasing cell apoptosis, which improves the efficacy of radiotherapy.

European School of Oncology
e-grandround

The European School of Oncology now presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

In this issue, Elżbieta Senkus-Konefka, Department of Oncology and Radiotherapy, Medical University of Gdansk, looks at the evidence for adding hormonal therapy to local treatment in prostate cancer. Her presentation was summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.cancerworld.org/mediaservice

When hormonal therapy is given as adjuvant treatment, the aim is not so much to improve the result with local treatment – because that has already been achieved – but to decrease the risk of dissemination by destroying micrometastases, which would hopefully increase the chances of survival.

Does hormonotherapy increase overall survival?

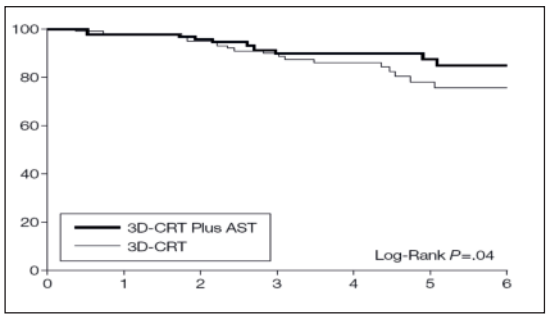
The main aim of any treatment for cancer is to improve overall survival. Does HT achieve improvement in overall survival?

HT before radical surgery

A number of trials have evaluated the use of HT before radical surgery and most have had similar results, showing a reduction in both the size and stage of the tumour. The majority of trials showed a reduction in the percentage of involved surgical margins, but, unfortunately, this did not translate into improvement in longer term endpoints such as progression-free survival or overall survival.

Only three trials have assessed the impact of this treatment approach on overall survival. A meta-analysis of these trials demonstrated that HT before surgery had no impact on overall survival.

THE HARVARD TRIAL



This small trial showed a significant increase in survival in patients given short-term HT in combination with radiotherapy

Source: D'Amico JAMA 2004

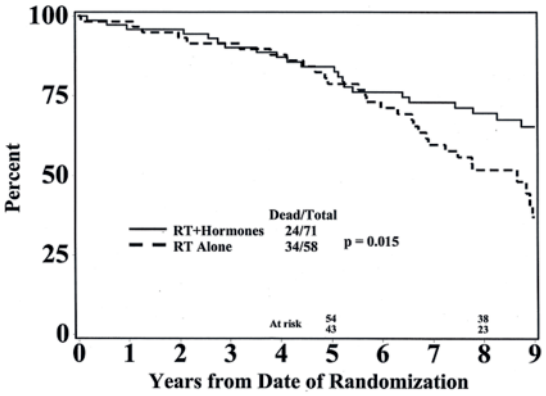
HT as an induction before radical radiotherapy

The first data on the use of HT as an induction before radical radiotherapy came from the RTOG 86-10 trial, which randomised patients with locally advanced disease to radical radiotherapy alone, or radiotherapy with HT (given for two months before radiotherapy and two months during radiotherapy).

Results showed no significant improvement in overall survival, although there was a tendency for the survival curves to diverge at five to six years following surgery.

The Harvard trial randomised patients with early, high-risk disease (PSA ≥10 ng/ml, Gleason score ≥7, or extracapsular extension) to treatment with radiotherapy alone, or radiotherapy given with six months HT (administered before and during radiotherapy and for two months after). Although this was a small trial, results showed a significant improvement in overall survival in patients treated with the combination of hormonal therapy and radiotherapy.

OVERALL SURVIVAL FOR GLEASON SCORE 2–6



Induction HT improved survival in the RTOG 86-10 patients with a low Gleason score

Source: MV Pilepich et al. *Int J Radiat Oncol Biol Phys* 50:1243–1252

Does induction hormonotherapy prolong overall survival in some patients?

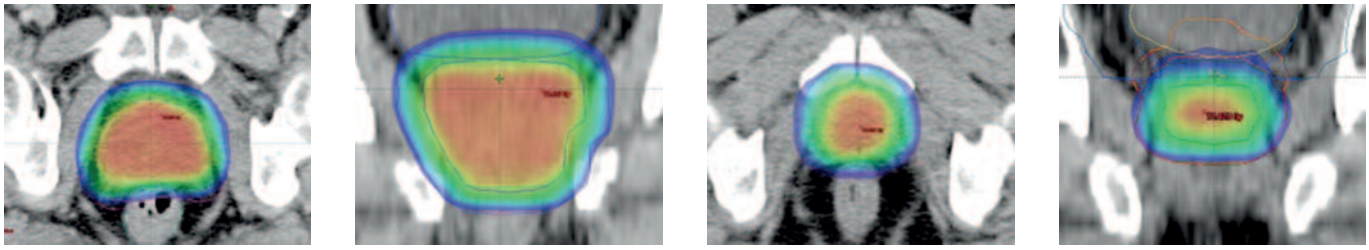
Although HT does not seem to improve survival in all patients, it may achieve this in certain subgroups. A subgroup analysis of patients in the RTOG 86-10 trial found a significant improvement in survival in patients who had low-grade disease (Gleason score 2–6) who were treated with combination therapy.

This seems surprising, because in most trials greatest benefit has been seen in higher risk patients because of higher baseline risk (assuming similar relative improvements from treatment in all subgroups). The reason for the benefit in lowest risk patients may be that in low-grade tumours with low risk of dissemination, the effect of local treatment is proportionally greater in the face of low competing risk from distant disease. Short-term induction HT seems to have minimal impact on micrometastases, with its main effect being to improve the results of local treatment. The largest benefit from this modality is therefore derived by patients in whom local cure has the greatest impact on long-term results.

Other benefits of hormonotherapy

The RTOG 86-10 study showed significant improvement in local control, a significant decrease in the number of prostate cancer deaths and improvement in cancer-specific survival in patients treated with hormonal therapy.

DOWNSIZING WITH INDUCTION HORMONOTHERAPY



Mean prostate volume before hormonotherapy = 53 cm³ **Mean prostate volume after hormonotherapy = 35 cm³**

The smaller the prostate, the less radiation damage to normal tissue. On average, HT reduces the prostate volume by 33%

Source: R Kucway et al. *J Urol* 167:2443–2447

These benefits were also seen in the Trans-Tasman ROG 96.01, which was a three-arm trial in patients with locally advanced prostate cancer who were randomly allocated to radiotherapy alone, radiotherapy preceded by three months of HT, or radiotherapy preceded by six months of HT. Results showed significant improvement in local control in both groups treated with HT compared to those given radiotherapy alone. There was also a significant decrease in distant metastases in patients treated with a six-month course of HT, together with a significant reduction in prostate cancer deaths.

How does induction HT combined with radiotherapy achieve its benefits?

The first benefit of HT is purely geometric, in that it induces shrinkage of the prostate. If the prostate is smaller, this reduces the amount of noncancerous tissue that is inadvertently irradiated and so reduces damage to the normal tissue.

HT also affects tissue biology, with animal studies showing that it improves the efficacy of radiotherapy. One study showed that the dose of radiation required to achieve 50% tumour sterilisation in laboratory animals was over 80 Gy when used alone, compared to only 40 Gy with neoadjuvant androgen suppression. This meant that the same effect was achieved with approximately half the dose of radiation. This benefit is particularly apparent when HT is given before local treatment, while it is less when HT is given after local treatment as adjuvant androgen suppression.

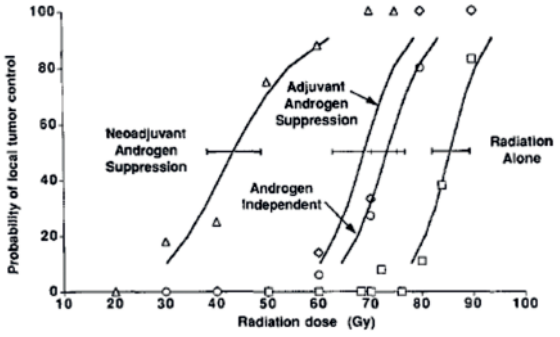
Effects of adjuvant hormonotherapy after radical prostatectomy

What do we know about the effect of HT after radical prostatectomy? The first data came from early VACURG studies conducted in the 1960s and 1970s, which demonstrated that the addition of HT reduced survival. This negative finding resulted in the use of HT in this setting being abandoned for many years.

The next data came from the ECOG 7887 study in the late 1990s. Patients who were node-positive after radical prostatectomy were randomly allocated to observation or HT. Despite the small trial size, results showed a very significant improvement in overall survival with HT.

This trial is considered very important from a biological point of view, although there are very few patients in this group in clinical practice, because patients with positive lymph nodes are

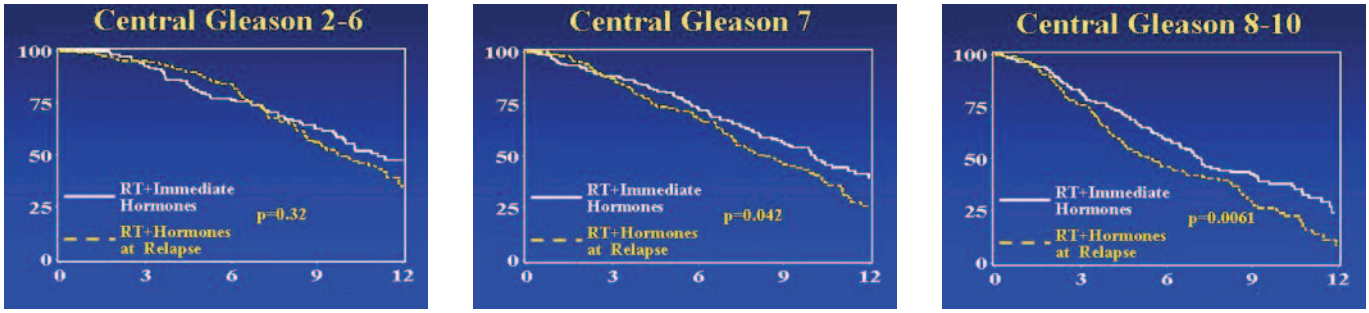
BIOLOGICAL EFFECT OF INDUCTION HORMONOTHERAPY



Results of animal studies show that neoadjuvant HT, in particular, may increase the efficacy of radiotherapy

Source: AL Zeitman et al. *Int J Radiat Oncol Biol Phys* 38:1067–1070

RADIOTHERAPY PLUS HORMONOTHERAPY – RTOG 85-31



Only patients with higher grade tumours were found to gain survival benefit from adding hormonotherapy

Source: MV Pilepich et al. ASCO 2003

currently not routinely treated with radical prostatectomy.

Another trial assessing the role of HT in conjunction with surgery, which randomised patients with locally advanced prostate cancer without nodal involvement to flutamide or to observation following prostatectomy, showed some improvement in recurrence-free survival, but no effect on overall survival. However, there was marked toxicity with flutamide, with 42% of patients discontinuing treatment mostly because of unacceptable side-effects.

More data are available on the use of HT as an adjuvant to radical radiotherapy. The EORTC 22863 study randomised patients to radiotherapy alone or to radiotherapy with HT (gosereline), given for three years during and after radiotherapy. Results demonstrated significant improvement in disease-free survival and overall survival in favour of patients treated with a combination of HT and radiotherapy.

The RTOG 85-31 trial included patients with nodal involvement or locally advanced disease who were randomly allocated to radiotherapy alone or radiotherapy with HT, started during the last week of radiation therapy and given until disease recurrence. There was a significant improvement in terms of locoregional control and risk of distant metastases with combination therapy. Results also showed a significant improvement in disease-free survival. Initial results showed no increase in overall survival, but the last update, published in 2005, demonstrated also a significant improvement in overall survival. Subgroup analysis revealed the greatest benefit in patients with highest grade tumours (8–10). A significant improvement was also observed in those with Gleason score 7 tumours, but there was no improvement observed in patients with low-grade tumours. A further subgroup analysis showed significant improvement in overall survival in patients with nodal involvement.

Adjuvant hormonotherapy in early prostate cancer

Most randomised trials have been conducted in patients with locally advanced disease, but what do we know about early prostate cancer? The largest data set comes from the Early Prostate Cancer Trial, which included 8,113 patients, making it the largest trial of HT in prostate cancer. Patients received standard management before being randomised to either observation or anti-androgen therapy with bicalutamide (150 mg). The standard management was surgery, radiation therapy or watchful waiting, depending on the physician's choice and local treatment policy. Most patients were treated with surgery in the American arm of the trial, while those in the Scandinavian part underwent mostly watchful waiting, whereas most patients managed with radiation therapy were in the 'rest of the world' trial.

The rationale of the trial was to assess the effect of HT when used in conjunction with standard management rather than sophisticated treatments, so that results would be applicable to everyday practice. It also looked at the use of anti-androgens, because of their lower risk of side-effects in terms of maintenance of sexual interest, physical ability and bone mineral density. These agents offer a more acceptable option for younger patients wishing to maintain sexual and physical activity.

The majority of the patients (3,799 patients) had early prostate cancer and were treated with local treatment modalities, 1,727 patients with early prostate cancer underwent watchful waiting, 2,025 patients had locally advanced prostate cancer and were managed by local treatment modalities, and 657 patients with locally advanced prostate cancer received no active local management.

Results showed some improvement in progression-free survival with anti-androgen therapy and no effect on overall survival in the patients as a whole. There was no effect of anti-androgen therapy on progression-free survival in the subgroup of patients with early prostate cancer. Anti-androgen therapy had no effect on overall survival in patients treated with local modalities, with a trend towards reduced overall survival in patients undergoing observation, indicating that this treatment may be detrimental for this group of patients.

Patients with locally advanced disease who were treated with both radical prostatectomy and definitive radiotherapy showed significant improvement in progression-free survival. Anti-androgen therapy had no effect on overall survival in patients undergoing prostatectomy, but significant improvement was seen in patients having radical radiotherapy. There was also a strong trend towards improved overall survival in the observation group.

Does treatment duration matter?

One possible explanation for the different results seen in particular trials is the difference in the duration of hormonal therapy. The general impression is that longer treatment achieves a better outcome. This question was asked by the EORTC 22961 trial. It followed up a previous trial showing significant benefit with HT for three years. However, such a treatment is costly and potentially toxic, so the trial compared short-duration hormonal therapy (six months) with 'standard' (longer) duration (three years). The noninferiority trial included patients with nodal involvement or locally advanced disease, who were treated with a combination of radical radiotherapy to the pelvis with six months of maximum androgen blockade before being randomly allocated to a further 30 months of HT or observation. Results demonstrated a significant difference in favour of longer treatment.

Does patient selection matter?

Patient selection may be another possible explanation for the conflicting results seen in different trials. Higher risk patients, including Gleason 8–10 patients in the RTOG 85-31 and RTOG 92-02 trials, and locally advanced cancer patients in the EPC trial, benefited the most. The only exception is the RTOG 86-10 trial, in which the lower risk patients showed the most benefit; however, the difference here may be explained by different aims and 'targets' of induction and adjuvant treatment.

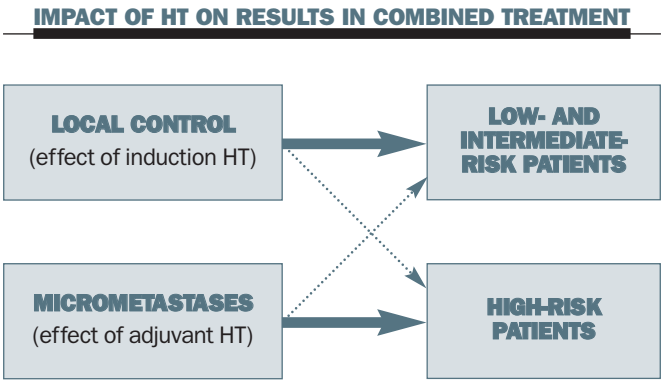
The optimal timing of hormonal therapy depends essentially on the stage of disease and risk category. There are two main targets for hormonotherapy. One is local control, which is achieved mainly with induction HT. The other is micrometastases, targeted with adjuvant HT. Local control is most important in low-risk patients, thus the effect of induction HT may be greater in this group. The impact of local control on overall results is less marked in high-risk patients, because of their higher risk of distant metastases, which makes adjuvant HT more important in this group.

Potential problems with hormonotherapy

Unfortunately, like everything in life, HT has some pitfalls, mainly in its side-effects. Prostate cancer has a relatively good prognosis, particularly in early disease – the stage at which most patients are now diagnosed. It is also a slowly progressing disease, so, in the elderly population affected, many may not live long enough to have problems from their prostate cancer. We have to weigh the good prognosis and slow development of early prostate cancer with the effects of treatment on morbidity and quality of life.

HT may cause an increase in body fat due to decreased insulin sensitivity, prolongation of the QT interval, a decrease in bone mineral density and other complications. The risk of osteoporosis in prostate cancer patients treated with androgen ablation increases with the duration of HT, from about 35% in the untreated population to more than 80% in patients treated with HT for 10 years.

The databases of the Surveillance, Epidemiology, and End Results (SEER) registry – an American cancer registry covering about 14% of the US population – and Medicare – a US health insurance provider covering more than 90% of people over 65 – were analysed for the incidence of various comorbidities in relation to HT in 73,196 prostate ▶▶



Patients benefit from HT in different ways depending on their level of risk

Hein Van Poppel (HVP), Department of Urology, Catholic University Hospital, Leuven, Belgium, hosted a question and answer session with Elżbieta Senkus-Konefka (ESK)

Question: *When should adjuvant HT start – should it be used immediately or deferred until recurrence?*

ESK: Data from randomised studies in locally advanced disease show that there is overall survival benefit in using HT early, during and after radiation therapy. In this patient subgroup, with proven benefit in randomised trials, I would start HT early.

Question: *In which patients, and before which treatment – radical prostatectomy or radiotherapy – would you consider neo-adjuvant HT?*

ESK: There are currently no data supporting the use of HT before surgery. For patients referred for radiotherapy, the current recommendation is to use HT in locally advanced disease. I would also use HT in high-risk disease (Gleason 8–10 or PSA >20µg/l) and, consider short-term HT in average risk disease with Gleason 7 or PSA >10µg/l. The other indication for HT before radiation therapy is a very-large-sized prostate, because of geometric reasons.

HVP: So, neo-adjuvant therapy is indicated for higher risk patients or in patients with very large prostates.

Question: *A patient underwent a radical prostatectomy and he proved to have a Gleason score of 9, grade 5+4. The margins were positive, but his PSA after surgery was less than 0.02 µg/l. Would you give adjuvant therapy now or only after PSA elevation?*

ESK: I would definitely refer this patient for radiation therapy because of his positive surgical margins. I know some urologists do not agree in giving radiation therapy to all patients, but there are quite good data from three randomised trials confirming the benefit of early adjuvant radiation therapy in comparison to salvage radiation therapy. In respect of systemic treatment, there are no good data on the benefit of adjuvant HT in postsurgical cases, apart from in patients with positive lymph nodes (the ECOG trial). I would rather opt for putting a patient into a randomised study in this case.

Question: *For the same patient, with a Gleason of 9 but negative surgical margins and a PSA that is undetectable after radical prostatectomy, would you consider giving radiotherapy because of his poor Gleason score?*

ESK: There are no good data regarding the impact of radiotherapy on local recurrence rates in this population. This patient has a high competing risk of dissemination, so I would probably not go for adjuvant radiation therapy in this patient.

Question: *You have addressed the problem of increased cardiovascular morbidity and mortality, even with shorter HT. Can we do anything to reduce this? Do we need to screen patients for cardiovascular morbidity before treatment? What would you propose to avoid this complication?*

ESK: There is no clear recommendation for screening patients. I think taking a good history is usually satisfactory. If we know that this patient has diabetes, coronary disease, hypertension or other complications, we would perform additional tests, but if a patient has no significant medical history, I think it would be enough to take the information from the patient.

Question: *If you say that increased morbidity and mortality has been well demonstrated with LHRH agonists, or maybe with the antagonists which are upcoming, would you avoid these treatments in patients with comorbidities and use pure anti-androgen therapy with non-steroidal anti-androgens such as flutamide or bicalutamide?*

ESK: Data from the Harvard trial show that the benefit of HT was limited to patients with a low comorbidity score, with no benefit in patients with high comorbidity. There are more and more data emerging to show that hormones are beneficial, but only in patients who do not have high rates of comorbidity. This is a very important factor in deciding which patients should get HT and which should not.

Question: *Do you think that there will be a place for anti-androgens instead of medical castration in patients with this morbidity, because if they have comorbidity, LHRH agonists will have a detrimental effect and you will not see the benefit of HT, but if you give them an anti-androgen then maybe the benefit will be more obvious?*

ESK: The only data on the anti-androgens are from the Early Prostate Cancer Trial and a flutamide trial. The flutamide trial demonstrated the treatment is not feasible because of toxicity. Bicalutamide is less toxic, but data are not very encouraging. There is some effect in locally advanced disease, but I think the efficacy of this treatment is not well proven and it needs confirmation in further trials. There were no survival benefits demonstrated, apart from in subgroup analysis.

Question: *A patient had a prostatectomy in 1996. After a PSA relapse in 1998, he was started on hormones, being given bicalutamide for five years on continuous treatment and five years on* ▶▶

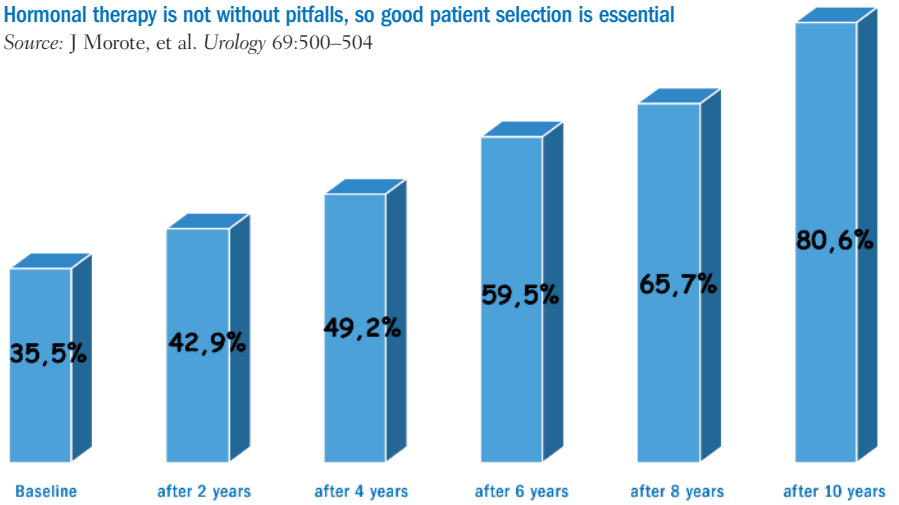
cancer patients over 65 years. Around one-third of patients (36.3%) were treated with an LHRH analogue, and 6.9% of patients with orchidectomy.

The risk of diabetes, coronary disease, myocardial infarction and sudden cardiac death were all increased in patients treated with LHRH analogues. This effect was less prominent in patients treated with orchidectomy, most probably because of the small number analysed.

It can be expected that the risk of complications is related to the duration of hormonal treatment. However, a subanalysis for patients who underwent HT for only one to four months showed a significant increase in the risk of diabetes and coronary disease, indicating increased risk even with treatment of short duration. This was a retrospective analysis, but data from the prospective Harvard trial also showed a significant increase of fatal myocardial infarction in patients who underwent hormonal treatment for only six months.

OSTEOPOROSIS FOLLOWING ANDROGEN ABLATION

Hormonal therapy is not without pitfalls, so good patient selection is essential
Source: J Morote, et al. *Urology* 69:500–504



Summing up

The efficacy of hormonotherapy in combination with local treatment has been investigated in various clinical settings in a number of prospective randomised trials. The combination of hormonal treatment and radiotherapy is most beneficial for locally advanced prostate cancer and has become a standard of care for this stage of disease.

Concomitant use of these two treatment modalities seems to be particularly effective, whereas hormonal therapy preceding radiotherapy is recommended in patients with large prostate volume, to improve dosimetric parameters.

Long-term hormonal therapy following radiotherapy has been demonstrated to improve overall survival in patients with locally advanced disease.

In early prostate cancer, the value of postoperative hormonal treatment is unclear and it should not be used outside controlled clinical trials. There are also no indications for routine use of preoperative hormonal therapy. Current research on hormonal therapy is focusing not only on improving its anti-cancer efficacy, but also on decreasing treatment toxicity and improving patients' quality of life.

intermittent HT. For how long is adjuvant HT effective and how long is he going to respond to intermittent HT?
Answer: The data we have on the time between biochemical recurrence and metastatic disease in untreated patients indicates an average of eight years. There is not much data in treated patients, especially with intermittent HT. This is really an emerging treatment that it is hoped will be effective for longer than continuous HT. Hopefully, the patient's condition will be controlled for a number more years, but there is no definite answer to this question.
Question: *Considering toxicity – if you had a patient who had radiotherapy and is on HT, but he suffers a lot from side-effects, we know that six months is not statistically equal to three years, but what do you do in practice? Do you discuss this with the patient and maybe stop at six months?*
ESK: Our aim is to improve the quantity and quality of life, and we have to find a balance that benefits the patient. If a person is very uncomfortable with hormones, we need to make the patient aware of the risks and possible benefits, explaining that the benefit is not that large. We would discuss this with the patient, and, very often, we would stop HT because of its toxicity.
HVP: We need to be reasonable, and if patients do very badly with all the side-effects of the hormones we should stop at six months, because it is just statistics that indicate that three years [of HT] is better than six months.