Hormonal Treatment and other Options in men with locally Advanced Prostate Cancer

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Introduction
There is no universally accepted definition of locally advanced prostate cancer.

The term is loosely used to encompass a spectrum of disease profiles that show high-risk features.
High-risk patients

- A categorization that defines three risk groups (high, intermediate and low risk) according to established prognostic factors has been described by D’Amico et al.

- High-risk patients were defined as men with a greater than 50% (at 5 years) chance of failure after primary therapy, including any patient with AJCC stage T3a or above, pretreatment PSA levels higher than 20 ng/mL or a biopsy GS ≥ 8.

Locally advanced prostate cancer include any of the following:

- **Clinical stage** American Joint Committee on Cancer (AJCC) T3 (tumors extending to the periprostatic area or into seminal vesicles), T4 (larger tumors invading the external sphincter, bladder neck, rectum, levator ani muscles or fixed to the pelvic side wall) or N1 (regional pelvic lymph node involvement associated with any local T stage), without evidence of distant metastases M0.

- **Clinical stages T1 and T2 (‘localized’)** at diagnosis, where so-called ‘high-risk’ features indicate the likelihood of extraprostatic invasion or clinically undetectable metastatic disease.

- Clinically localized disease but are found to have pathological extraprostatic disease (pT3), positive surgical margins, lymph node involvement or high-grade disease after radical prostatectomy.
Management options for high-risk prostate cancer

- Watchful waiting
- Radical prostatectomy (RP)
- Radiotherapy (RT)
- Hormonal therapy
- Combination

2008 EAU Guidelines
Men with high-risk prostate cancer generally have a **significant risk of disease progression and cancer-related death** if left untreated.

Two specific challenges:
- **a need for local control**
- **a need to treat any microscopic metastases** likely to be present but undetectable until disease progression.

The optimal treatment approach will therefore often necessitate **multiple modalities**.
The best approach to locally advanced prostate cancer

- The uncertainties of clinical staging contribute to this controversy.
- An exact classification of these subgroups is only possible based on the histopathological specimen after surgical removal of the prostate. Therefore, pre-treatment clinical staging is uncertain.
- Patients with cT3 disease who actually harbour overstaged pT2pN0 prostate cancer may be cured by local therapy, whereas patients with occult lymph node metastases are unlikely to benefit meaningfully from such treatment.

- The exact *combinations*, *timing* and *intensity* of treatment continue to be strongly debated.

- *Management decisions* should be made after all treatments have been discussed and after the *balance of benefits and side effects* of each therapy modality has been considered by the patient with regard to his own individual circumstances.
Watchful waiting / Androgen deprivation therapy
Watchful waiting involves observation with late palliative treatment (usually hormone therapy) for men who develop symptoms of progressive disease.

Only limited data are available on conservative treatment of locally advanced prostate cancer.

In one study (Adolfsson et al.), disease-specific 10 year survival was 74% with a corresponding overall survival rate of 34%. Disease-specific survival was approximately 10% lower than in conservatively treated patients with clinically localized disease. However, compared with other treatments and in terms of survival deferred treatment may be an option for select patients with such tumors and a life expectancy of 10 years or less.

2008 EAU Guidelines (Watchful waiting)

- T3–T4: Option in asymptomatic patients with T3, biopsy Gleason score ≤ 7, and a life expectancy < 10 yr (grade C recommendation)

- N+, M0: Asymptomatic patients. Patient driven. May have a negative influence on survival (grade C recommendation)
Androgen deprivation therapy

- In the past patients with prostate cancer almost always had extensive disease at presentation. Since aggressive local treatment was high in complications and low in long-term control, most of these patients were treated with primary androgen ablation (AA).
- AA remained the primary mode of treatment for prostate cancer into the 1980s, although it was recognized to be noncurative.
2008 EAU Guidelines
(Hormonal therapy)

- T3–T4: Symptomatic patients, extensive T3–T4, high PSA level (> 25 ng/ml), unfit patients. Better than watchful waiting (grade A recommendation)

- N+, M0: Standard therapy (grade A recommendation)
Two main methods of achieving prostate cancer control using hormone therapy

- **The first** is to remove the supply of endogenous testosterone with **castration-based therapy**. This can be achieved with either bilateral surgical orchiectomy or a medical approach using luteinizing hormone-releasing hormone agonists (LHRHa). The side effects of LHRHa include **erectile dysfunction**, **loss of libido**, **hot flushes**, **osteopaenia/osteoporosis**, **weight gain** and **breast swelling**.

- **An alternative approach** is to reduce the effect of endogenous hormones with drugs that block androgen receptors (**antiandrogens**). Bicalutamide 150 mg helped maintain physical capacity and bone mineral density; however, **gynecomastia and mastalgia** are frequently associated toxicities.

- Both treatments have proven **effective** for locally advanced prostate cancer, and the **different side effect** profiles can allow clinicians and patients to choose the best approach to maintain **quality of life** for each patient.
There has been some debate as to whether there are advantages of immediate androgen deprivation therapy as opposed to an initial period of observation or watchful waiting.

Some early nonrandomized studies concluded that immediate orchietomy was not associated with a survival advantage compared with therapy delayed until metastatic progression.
Modest advantages of immediate androgen deprivation

- However, analysis of a randomized controlled trial involving 943 men not suitable for curative treatment by the Medical Research Council suggested benefits for immediate vs. delayed hormonal treatment.
  - The rates of distant progression were 26% for men treated with immediate castration-based therapy and 46% for men whose treatment was deferred.
  - This study showed an apparent advantage in treating patients immediately with androgen deprivation therapy in terms of distant progression, but mortality was significantly changed only in the subgroup with M0 (locally advanced) disease.

Modest advantages of immediate androgen deprivation

- In another study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) trial 30891 (Studer et al.), 985 men with newly diagnosed prostate cancer (T0-4, N0-2, M0) were randomly assigned to immediate vs. delayed orchietomy given at the time of symptomatic progression.

- The group that received immediate androgen deprivation showed a modest but statistically significant increase in overall survival, but no significant difference was seen in prostate cancer mortality or symptom-free survival.

J Clin Oncol 2006;24:1868–76.
Castration vs. Antiandrogen

- In two combined randomised trials of 480 patients with non-metastatic locally advanced prostate cancer (cT3–T4), bicalutamide monotherapy (150 mg daily) was compared with castration.

  - After a median follow-up of 6.3 years, mortality was 56%. There was no statistically significant difference between the 2 groups in overall survival (hazard ratio 1.05, upper 1-sided 95% confidence limit 1.31, p = 0.70) or time to progression (1.20, 1.45, p = 0.11). There were statistically significant benefits in the bicalutamide monotherapy group in the 2 quality of life parameters of sexual interest (p = 0.029) and physical capacity (p = 0.046).

  - Monotherapy with 150 mg. bicalutamide is an attractive alternative to castration in patients with locally advanced prostate cancer for whom immediate hormone therapy is indicated.

Early Prostate Cancer (EPC) study (7.4 years F/U)

- This trial was designed to evaluate the efficacy and tolerability of adding 150mg bicalutamide once daily to standard care (prostatectomy, radiotherapy or watchful waiting) in 8113 patients with localized or locally advanced nonmetastatic prostate cancer.
- The primary end points were objective progression-free survival (PFS) and overall survival.
- There was a trend towards increased survival for the subgroup with locally advanced disease treated with 150 mg bicalutamide, who would otherwise have undergone watchful waiting (HR 0.81; 95% CI 0.66–1.01; P = 0.06). A significant improvement in objective PFS in favor of 150 mg bicalutamide was also shown for this watchful-waiting group (HR 0.60; 95% CI 0.49–0.73; P < 0.0001).

Neoadjuvant hormonal therapy (NHT)
NHT prior to radical prostatectomy

- 2008 EAU Guidelines (radical prostatectomy)
  - T3–T4: Optional for selected patients with limited ≤ T3a, Gleason ≤ 8, PSA < 20 ng/ml, and a life expectancy > 10 yr (grade C recommendation)
  - N+, M0: No standard option (grade C recommendation)
A clinical benefit of neoadjuvant hormonal therapy prior to RP has not been proven.

For clinically locally advanced prostate cancer, however, only limited data with low statistical power are available. Neoadjuvant hormonal treatment may decrease tumor volume and the rate of detectable positive surgical margins.

No evidence, however, is available supporting a benefit concerning disease progression and overall survival.


NHT prior to definitive radiotherapy

- 2008 EAU Guidelines (Radiotherapy)
  - T3–T4: T3 with a life expectancy > 5–10 yr. Dose escalation > 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (grade A recommendation)
  - N+, M0: No standard option (grade C recommendation)
Radiotherapy alone have two fundamental problems in eradicating advanced cancer.

1. **Normal tissue toxicity** limits the total dose of radiation that can be delivered. Radiation kills cancer proportionally. Each incremental increase in dose kills a larger proportion of cancer cells and with dose limitations some cancers simply are too large to be cured by radiation alone.

2. Patients with locally advanced cancers are at significant risk for dissemination.

   This means that, despite improved local treatment, many men will ultimately progress to metastatic disease that can cause debilitating morbidity and increase the mortality.

It was postulated that adding AA to RT might improve results from the aspects of decreasing disseminated disease and improving local control.
The aims of NHT prior to radiotherapy

- to **reduce the tumor bulk** (average of 25%–30% cytoreduction of the prostate and potentially allow smaller fields of radiotherapy to be used while sparing the surrounding normal tissues) **and potentially** **treat microscopic metastases** together with the primary tumor.


- There have also been reports that there may be a **sensitizing effect** between hormone therapy and radiation treatment.

Historically advanced prostate cancer had been treated with androgen ablation. With the evolution of radiation therapy it was shown that some patients with advanced but non-metastatic disease could be cured or at least have progression delayed.

Subsequently a series of studies demonstrated that the combination of radiation and AA resulted in improved results over those of radiation therapy alone, although the failure rate was still high.
The RTOG 86–10 study (Pilepich et al.)

- investigated the addition of hormone therapy (goserelin & flutamide) for 2 months before and 2 months during RT compared with RT alone in 456 men with locally advanced prostate cancer.

- At a median follow-up of 6.7 years, the patients in the combined modality arm had a significantly improved 5-year cause-specific survival of 90% vs. 85%. A subgroup analysis showed that men with Gleason sum 6 tumors had an overall survival advantage at 5 years of 70% vs. 52%.

- The authors recommended neoadjuvant hormonal therapy as standard treatment in this subgroup in contrast to adjuvant hormonal treatment in patients with an unfavorable Gleason score of 7–10.

Adjuvant hormonal therapy
The clear message is that surgery alone cannot reliably cure patients with T3 disease, which requires the addition of adjuvant treatment with AA or radiation.

More recently the thinking has been changing and some surgical groups have greatly expanded their definition of patients who are candidates for surgery.

A group from the Mayo Clinic reported a large series of patients with clinical T3 prostate cancer representing a considerable clinical overstaging: 27% of patients had actually a pT2 tumor. The rate of positive lymph nodes was 27%. Biochemical control, disease-specific and overall survival were significantly less favorable in the cT3 group, compared with the cT2 group. The differences were, however, only small.

Adjuvant hormonal therapy after radical prostatectomy

- **Positive lymph nodes** indicate systemic disease & poor prognosis. **Positive lymph nodes** may be expected in cT3 disease in 8–48%.
  

- In the case of **lymph node metastases** after RP, but not in node-negative disease, adjuvant hormonal treatment **seems to improve survival**.

- One small but highly significant study by Messing *et al.* showed benefits for men with pathological lymph node involvement.
  
The ECOG 7887 trial (Messing et al.)

- compared adjuvant hormone ablation after radical prostatectomy and deferred hormonal therapy in patients with nodal metastases.

- A total of 98 patients with locally advanced prostate cancer (T1–2/N+disease) who had undergone pelvic lymphadenectomy were included in the study.

- These patients were randomized to receive adjuvant AA (n = 47) or to be followed until disease progression (n = 51) and then given hormonal therapy.

- At a median follow-up of 11.9 years, adjuvant AA increased the survival by 2.6 years compared with surgery alone in node-positive patients. The median survival in the adjuvant hormone ablation and deferred treatment groups was 13.9 & 11.3 years, respectively.
The use of ADT as adjuvant therapy after RP in patients with Stage pT3–T4N0 disease has been assessed in one prospective, randomized study.

This trial randomized 352 patients to surveillance or indefinite flutamide after RP.

At a median follow-up of 6 years, the hazard ratio for patients in the flutamide arm was 0.51 (95% confidence interval 0.32 to 0.81) for PFS and 1.04 (95% confidence interval 0.53 to 2.02) for overall survival.

The study was considered to have negative findings.
## Effect of adjuvant hormonal treatment after radical prostatectomy: overview over prospective randomised trials

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Adjuvant hormonal therapy after radiotherapy

- External beam radiotherapy alone provides unfavorable survival rates in locally advanced prostate cancer. Adjuvant hormonal treatment may improve outcome in this setting.

- Adjuvant androgen suppression immediately after radical radiotherapy has been shown to significantly increase overall survival and PFS and significantly reduce local progression, distant metastases and biochemical progression in several large, randomized studies.
## Effect of adjuvant hormonal treatment after EBRT: overview over prospective randomised trials

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The EORTC 22863 trial (Bolla et al.)

- evaluated the effectiveness of adjuvant therapy with 3.6 mg goserelin initiated at the onset of radiotherapy and continued for 3 years in patients with high-risk nonmetastatic prostate cancer.
- A total of 415 patients were randomized to receive either RT with immediate hormone treatment or RT alone with hormonal treatment for disease progression.
- Results reported after a median follow-up of 5.5 years showed a significant improvement in overall survival (78% vs. 62%) and disease-free survival (74% vs. 40%) in favor of immediate adjuvant treatment.

977 men were randomly chosen to receive either pelvic radiation plus 3.6mg goserelin (started during the last week of radiotherapy to be continued indefinitely every month) or radiotherapy alone with hormonal treatment commencing at relapse.

Results at a median follow-up of 7.6 years indicated that adjuvant goserelin significantly improved the absolute survival compared with radiation monotherapy (estimated 10-year survival rate 49% vs. 39%; P = 0.002).

The greatest benefits were seen in the subgroups with high Gleason grades (grades 8–10).

Early Prostate Cancer (EPC) study (7.4 years F/U)

- 150 mg bicalutamide adjuvant treatment to radiotherapy has resulted in **significantly improved overall survival compared with radiotherapy alone** (HR, 0.65; P = 0.03) for men with locally advanced prostate cancer at a median follow-up of 7.4 years.

- The prostate cancer mortality for this subgroup was **24%** for patients treated with radiotherapy alone compared with **16%** for men treated with combined modality therapy.

- This represents a significant overall survival benefit for **non-castration based hormonal therapy** given as adjuvant treatment to radiotherapy.

- These results give clinicians and patients a **choice** regarding which adjuvant hormone therapy to use **without** the concern of **reducing** treatment efficacy.

There are uncertainties regarding the optimal timing and duration of hormone therapy.

Timing has varied among different trials. Goserelin was added during the final week of RTOG 85–31 and during the first week of EORTC 22863.

There were also differences in the duration of adjuvant goserelin therapy in these studies.

The quality of life of the patient is an important factor when deciding on the duration of therapy, and any long-term side effects must also be considered.
The RTOG 92–02 study (Hanks et al.)

- investigated concurrent only vs. long-term (continued for 2 years) adjuvant AA.
- Although five-year survival was no different between the arms at 80% in those continuing AA vs. 78% in those who stopped, biochemical failure at 5 years was significantly worse in those who stopped AA (56% vs. 28%).
- In the exploratory subset analysis of patients with Gleason scores 8 to 10, LT adjuvant AD resulted in a survival advantage.

The secondary analysis of RTOG 85–31 (Souhami et al.)

- evaluated the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy.
- There were 189 analyzable patients. Patients were divided in groups based on the tertile of hormonal therapy duration (HTD) as follows: < or = 1 year, more than 1 year and < or = 5 years, and more than 5 years.
- The HTD more than 5 years group showed significantly associated with better overall survival and disease-free survival than other HTD groups.

Bolla et al. (2009)

- randomly assigned patients with locally advanced prostate cancer who had received EBRT plus 6 months of AA to two groups, one to receive no further treatment (short-term suppression) and the other to receive 2.5 years of further treatment with a LHRHa (long-term suppression).

- A total of 1113 men were registered, after a median follow-up of 6.4 years, the 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; P=0.65 for noninferiority).

- The combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiotherapy plus 3 years of androgen suppression in the treatment of locally advanced prostate cancer.

RADICALS
(Radiotherapy and Androgen Deprivation In Combination After Local Surgery)

- It has 2 randomisations, the first carried out within 3 months after radical prostatectomy, is defined as the hormone duration randomisation, with 3 randomisation arms: no hormones, 6 months, or 24 months. The second randomisation, carried out before the administration of radiotherapy, is defined as the radiotherapy timing randomisation, with 2 arms: immediate (or adjuvant) radiotherapy or early salvage radiotherapy (defined as a PSA > 0.1 ng/ml with 2 consecutive rises or 3 consecutive rises in PSA). Patients may enter one or both randomisations.

- RADICALS has a recruitment target of 2600 men for the radiotherapy timing randomisation arm and 3500 men for the hormone randomisation arm that also explores the duration of hormone therapy.

RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery)
Other options
Chemotherapy
Chemotherapy is the other option to try to improve radiation or radical prostatectomy results with increased locoregional and systemic control.

In cancers such as those in the head and neck area or lung combination therapy has been successful in improving results.
To assess the feasibility and tolerance of neoadjuvant and concomitant estramustine phosphate and vinblastine (EV) with high-dose 3D-CRT for patients with unfavorable-risk prostate cancer.

Neoadjuvant and concomitant EV with high-dose 3D-CRT is well tolerated in patients with unfavorable risk prostate cancer. Although the incidence of modest (grade 2) late GI and GU toxicities seem to be increased compared with 3D-CRT alone or in combination with AA therapy, no severe toxicities were encountered with this regimen.

In prostate cancer one of the first chemotherapy studies completed was a phase II study in 30 patients using 5-fluorouracil (at a dose of 200 mg/m2 daily was started on day 1 and continued 7 days weekly until the last day of radiation.) given concomitantly with 70.2 Gy radiation.

All patients had a least T3A disease. The response was modest with 83% of patients achieving a greater than 50% decrease in PSA and 43% attaining PSA less than 1 ng/ml.

Toxicity was acceptable. The modest response rate indicates that better chemotherapy that improves local and systemic failure is necessary to improve the results.

Mitoxantrone

- Until relatively recently, mitoxantrone has been considered the chemotherapy standard in the treatment of metastatic HRPC.
- Mitoxantrone plus prednisone reduces pain and improves the quality of life in men with advanced, HRPC, but it does not improve survival.

Docetaxel

- The **efficacy** of chemotherapy for high-risk, localized prostate cancer is not known; however, **docetaxel** chemotherapy **improves the survival** of patients with metastatic, castration-resistant prostate cancer when combined with either prednisone or estramustine.

- Since **docetaxel** has demonstrated significant **improvement in survival** in phase III trials when **compared to mitoxantrone**, **docetaxel** is now recognized as the **new standard**.


- **Maximally tolerated dose:**
  - 20 mg/m² weekly (Kumar *et al.* J Clin Oncol 2004;22:1909–15.)
  - 30 (or 40) mg/m² weekly, 70 (or 75) mg/m² every 3 week
TAX 327 study (Berthold et al.)

- Compared docetaxel administered every 3 weeks (D3), weekly docetaxel (D1), and mitoxantrone (M), each with prednisone (P), in 1,006 men with metastatic HRPC.
- Median survival time
  - D3P arm – 19.2 months (95% CI, 17.5 to 21.3 months),
  - D1P arm – 17.8 months (95% CI, 16.2 to 19.2 months),
  - MP arm – 16.3 months (95% CI, 14.3 to 17.9 months).
- More patients survived >/= 3 years in the D3P and D1P arms (18.6% and 16.6%, respectively) compared with the MP arm (13.5%).
- Survival of men with metastatic HRPC is significantly longer after treatment with D3P than with MP.

The SWOG 9916 study (Daniel et al.)

- randomized 674 evaluable patients with androgen-independent, metastatic prostate cancer.
- **Docetaxel and estramustine** every 21 days versus mitoxantrone and prednisone.
- An improved median overall survival was documented in patients receiving docetaxel and estramustine (17.5 months vs. 15.6 months, P=0.02 by the log-rank test).
- The improvement in median survival of nearly two months with docetaxel and estramustine, as compared with mitoxantrone and prednisone, provides support for this approach in men with metastatic, androgen-independent prostate cancer.

Neoadjuvant chemotherapy

- Ryan et al. reported neoadjuvant (two 8-week cycles) vinblastine and estramustine, followed by high dose (75.6 Gy) 3D–CRT with concomitant chemotherapy in patients at high risk.

- At a median follow-up of 5 years 35% of the patients remained biochemically free of recurrence.

- These long-term findings support the continued study of chemotherapy combined with RT as a potential alternative to prolonged AA.

Neoadjuvant docetaxel-based chemotherapy

Several groups have investigated the utility of neoadjuvant docetaxel-based chemotherapy in localized, high risk patients in an attempt to improve systemic control in this group of men.
Neoadjuvant docetaxel-based chemotherapy

- Neoadjuvant chemotherapy with docetaxel was investigated in high risk disease prior to RP in a small number of patients. Toxicity was mild to moderate, complete histopathological remissions did not occur.


- The rare high-grade neuroendocrine prostate carcinoma constitutes an exception. In this highly aggressive tumor entity chemotherapy may induce complete remissions in some cases, the prognosis is, nevertheless, dismal.

PHASE II TRIAL OF NEOADJUVANT DOCETAXEL BEFORE RADICAL PROSTATECTOMY FOR LOCALLY ADVANCED PROSTATE CANCER

ROBERT DREICER, CRISTINA MAGI-GALLUZZI, MING ZHOU, JASON ROTAHERMEL, ALWYN REUTHER, JAMES ULCHAKER, CRAIG ZIPPE, AMR FERGANY, AND ERIC A. KLEIN

ABSTRACT

Objectives. To perform a Phase II trial of docetaxel administered on a weekly schedule for 6 weeks before radical prostatectomy (RP) in patients with locally advanced prostate cancer.

Methods. Treatment consisted of six doses of docetaxel 40 mg/m² intravenously administered weekly for 6 weeks followed by RP. Eligibility criteria included clinical Stage T2b, prostate-specific antigen (PSA) level 15 ng/mL or greater or Gleason sum 8 or greater, and no evidence of metastatic disease. The primary endpoint was feasibility and drug-related and surgical-related toxicities. Secondary endpoints included pre-RP PSA level, local response, pathologic outcomes, and time to PSA failure.

Results. Twenty-nine patients were entered; 80% completed all 6 weeks of therapy and 97% underwent RP. The median PSA level was 12 ng/mL (range 2.5 to 43.3), the median Gleason sum was 8 (range 6 to 9), and all had Stage T2b or greater disease. A statistically significant reduction in the prechemotherapy versus postchemotherapy mean PSA level was observed (12.00 ± 1.86 ng/mL versus 8.42 ± 1.63 ng/mL, P <0.03), with 79% of patients experiencing some reduction and 24% a more than 50% reduction in PSA level in response to docetaxel alone. No unexpected toxicities and no intraoperative complications occurred. Pathologic analysis demonstrated residual carcinoma in all cases. Three patients (11%) had organ-confined disease, and 26 (93%) had achieved an undetectable PSA postoperatively. At a median follow-up of 23 months (range 1.5 to 36), 20 patients were disease free with no additional therapy.

Conclusions. This trial establishes the baseline effect of short-course high-dose docetaxel alone on locally advanced prostate cancer. Additional study of this paradigm with other agents alone and in combination with docetaxel seems warranted. UROLOGY 63: 1138–1142, 2004. © 2004 Elsevier Inc.
Multicenter phase II study of combined neoadjuvant docetaxel and hormone therapy before RP for patients with high risk localized PCa.

- All patients received **AA** (6.6 mg buserelin acetate every 8 weeks for 3 doses & antiandrogen for 4 weeks) with **docetaxel** (35 mg/m$^2$ weekly for 6 of 8 weeks for 3 doses).

- Of the 64 patients completing protocol therapy 2 had a **complete pathological response**.

- Pathological stage was T2 in 53% and T3 in 44% of patients. Four patients had N1 disease and positive surgical margins were identified in 27%.

- At a median follow up of **42.7 months** (range 25.6 to 65.6) 19 patients (30%) had disease relapse.

- Combined androgen deprivation and docetaxel before prostatectomy was **feasible**, and resulted in **encouraging recurrence-free survival**. While pathological down staging was observed, pathological complete response rates were rare.

*J Urol* 2008;180:565–70.
Neoadjuvant docetaxel/estramustine prior to RT or EBRT in high risk localized PCa: A phase II trial

- investigated safety, tolerability, and efficacy of neoadjuvant docetaxel/estramustine prior to radical prostatectomy or external beam radiotherapy in high risk localized prostate cancer.
- Of the 22 evaluable patients, 12 underwent RP and 10 underwent EBRT.
- Twenty–one of 22 patients achieved a PSA reduction > 25% (Specifically, 20 patients achieved a PSA decline of 50%, 1 patient achieved a PSA decline of 25% but 50%, and 1 was not assessable).
- There were no pathologic complete responses. With a median follow–up of 24 months, the 2–year progression–free survival was 45%.

Urol Oncol. Epub 2009 Dec 16.
Adjuvant chemotherapy

- The Hussain study (Kibel et al.) led to the recent completion of a nonrandomized Phase II trial using adjuvant docetaxel in patients at high risk for recurrence after radical prostatectomy.
  - At median follow-up of 29.2 months, 46 evaluated patients (60.5%) progressed.
  - Median PFS was 15.7 months (95% CI 12.8–25.1), with a predicted PFS of 10 months.
  - Grade III toxicity occurred in 20 (26%) of patients and included hyperglycemia, dyspnea, cardiac arrhythmias and pulmonary fibrosis. Grade IV hyperglycemia occurred in two patients and resolved. Finally, a gastrointestinal bleed resulted in the death of one patient and may have been related to the treatment.
  - This study demonstrates that docetaxel is a reasonable adjuvant therapy for high-risk prostate cancer following surgery, but has the potential for significant toxicity.

The SWOG 9921 study

- aims to investigate \textit{adjuvant} hormonal therapy compared with the combination of hormonal therapy with mitoxantrone and prednisone in high-risk patients after RP. This study has a primary endpoint of a 30% improvement in overall survival.

- The study enrolled approximately 950 pts but closed early owing to an increased risk of developing myelogenous leukemia in the pts receiving mitoxantrone.
The TAX 3501 study

- A phase III multi-centre trial comparing immediate with deferred treatment with a LHRHa, with or without docetaxel.
- Patients considered to be at high risk of relapse after prostatectomy for localized prostate cancer are selected on the basis of Kattan nomogram.
- The primary endpoint is PFS.
- Unfortunately, TAX 3501 closed prematurely owing to poor accrual.
A Veterans’ Administration Cooperative Group Trial

- will randomize patients with T3, G7–10, and N0 diseases after prostatectomy to 4 months of docetaxel and PD compared with surveillance alone.
- These trials have not yet reported and are awaited (2012) with much interest.
Other options
Future treatment modalities include molecular targeted therapies.

Prostate cancer has been an ideal model to study the multiple steps required in the metastatic cascade. These steps have been utilized in the development of metastasis inhibitors.

Because prostate cancer metastasizes preferentially to the bone, special attention will be given to agents that interfere with this pattern of metastasis.

Specifically, the efficacy of angiogenesis inhibitors, metalloproteinase inhibitors, inhibitors of prostate cancer cell–endothelial cell interactions, and bisphosphonates will be reported.
Bone-targeting agents

- Both osteoblasts and osteoclasts have been shown to play a central role in the interactions between the metastatic prostate cancer cells and bone.
- Other components in the bone, such as the endothelium and stroma, may also play important roles in this process.
- Clinical trials targeting osteoblasts use radiopharmaceuticals (strontium-89 and samarium-153), the endothelin A receptor inhibitor atrasentan, or the vitamin D analog calcitriol.
- Agents that target osteoclasts include bisphosphonates.
- Those that target endothelial cells include thalidomide and bevacizumab.
- Although these clinical trials for bone metastasis may provide effective treatments, novel concepts of how prostate cancer cells selectively metastasize to bone may advance our understanding and provide improved treatments for this difficult clinical problem.
Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer

- **Bisphosphonates** might modulate the development of symptomatic bone metastases (antimetastatic drug) in men with prostate cancer. The MRC PR051 and PR042 randomised controlled trials assessed the role of adjuvant sodium clodronate in men with metastatic (M1) and non-metastatic (M0) prostate cancer, respectively.

- An oral, first-generation bisphosphonate, sodium clodronate, improves overall survival in men with M1 prostate cancer who are starting hormone therapy (HR 0.77, 95% CI 0.60–0.98; p=0.032), but there is no evidence of an effect in men with M0 prostate cancer (HR 1.12, 0.89–1.42; p=0.94).

Immunomodulatory cytokine gene therapy

- Currently, numerous preclinical studies have reported immunomodulatory cytokine gene therapy, such as IL-2, IL-12, B7-1 (CD80), B7-2 (CD86) & granulocyte-macrophage colony-stimulating factor (GM-CSF).

- Several clinical studies have been approved that potentially will show that these immunomodulatory gene therapies may generate an effective local and systemic antitumor activity and that should provide options for patients with prostate cancer.
Several immunomodulatory agents capable of inducing passive immune activation by way of enhancing antigen recognition by T cells have been evaluated.

GM-CSF acts at multiple levels of hematopoietic cell differentiation and promotes the uptake of prostate cancer antigens by dendritic cells, leading to subsequent cross-priming of T cells that ultimately generate an appropriate immune response.

Thalidomide, an immunomodulatory agent with T-cell stimulatory and antiangiogenic activity through blockade of bFGF, VEGF and IL-6, has shown clinical activity in patients with CRPC.

Garcia et al.: Neoadjuvant GM-CSF and thalidomide was safe and feasible and did not affect the perioperative morbidity of RP. Although no pathologic complete responses were observed, significant posttreatment tumor T-cell and dendritic cell infiltration was noted.

Specific Immunotherapy

- **T cells and antibodies** are powerful components of the specific antitumor immune response. **CD8+ cytotoxic T lymphocytes (CTLs)** efficiently destroy tumor cells. **CD4+ T cells** improve the antigen-presenting capacity of **dendritic cells (DCs)** and support the stimulation of tumor-reactive CTLs.

- **Monoclonal antibodies** exhibit their antitumor effects via antibody-dependent cellular cytotoxicity and complement activation. Anti-human epidermal growth factor receptor-2 (HER2) MAb **trastuzumab**, anti-epidermal growth factor receptor (EGFR) MAbs **cetuximab** and **panitumumab**, and the anti-vascular endothelial growth factor (VEGF) MAb **bevacizumab**. **Monoclonal antibodies directed against surface antigens** were also used.
Specific Immunotherapy

- Much attention has been given to the identification of tumor antigens that represent attractive targets for specific immunotherapy.

- Several prostate cancer–related antigens were described and used in clinical trials. Such studies were based on the administration of peptides, proteins, or DNA. Furthermore, men with prostate cancer were vaccinated with peptide–, protein–, or RNA–loaded DCs, which display an extraordinary capacity to induce tumor–reactive T cells.
Phase I study with an autologous tumor cell vaccine for locally advanced or metastatic prostate cancer

- **Immunotherapy** is a novel approach to Pca treatment and may eventually become part of the anticancer armamentarium, along with surgery, radiotherapy and chemotherapy, especially in the setting of minimal residual disease.

- In theory, the tumor itself is the best antigenic source to induce an immune response (active specific immunotherapy), since it presents a unique range of antigens peculiar to the affected individual.

- Eleven ≥pT3 and/or N+ patients were vaccinated (intradermal). Toxicity was generally limited to the inoculation sites. **Delayed-type hypersensitivity reactions** (seems to induce cellular immune responses) ≥10 mm were observed in 2 patients and ≥5 mm in 6 patients. Two patients had a decrease in PSA levels after vaccine administration. There seems to be some influence of the vaccine in **PSA evolution** after RRP.

Conclusions

- **Watchful waiting**
  Option for select patients
  Life expectancy of 10 years or less

- **Androgen deprivation therapy**
  Standard therapy (N+)
  Early hormonal treatment: (When no local treatment is considered) modest survival benefit
Conclusions

- **NHT prior to radical prostatectomy**
  - Decrease tumor volume & the rate of positive surgical margins.
  - No benefit concerning disease progression & overall survival.

- **NHT prior to radiotherapy**
  - Reduce the tumor bulk, treat microscopic metastases & there may be a sensitizing effect.
  - A subgroup (Gleason sum ≤6 tumors) seems to have an overall survival advantage.
Conclusions

- Adjuvant hormonal therapy after RP
  Seems to improve survival in the case of lymph node metastases after RP.

- Adjuvant hormonal therapy after RT
  Has been shown to significantly increase progression-free survival and overall survival.
  Optimal timing and duration: in favor of immediate AA & longer duration.
Conclusions

- Other options
  - Chemotherapy
    Docetaxel-based chemotherapy is now recognized as the new standard.
    Further investigation: phase III trials, efficacy relative to AA, etc.
  - Antimetastatic drugs, Bone targeted treatment
  - Immunomodulatory cytokine gene therapy
  - Specific Immunotherapy: T cells and antibodies, Monoclonal antibodies, tumor antigens (vaccine)