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## Radical Prostatectomy in High Risk Prostate Cancer

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### 1. Introduction

Prostate cancer is the leading cancer diagnosis in men, and the second cause, after lung cancer, of cancer death in men in the U.S. Worldwide is the fourth most common cancer in men with variable incidence and mortality rates, based on geographic regions (1). In Europe is the most common solid tumor, with an incidence of 214 cases per 1000 men, outnumbering the lung and colorectal cancers, and is the second most common cause of cancer death in men.

In recent years, the incidence of prostate cancer is increasing in most countries due to the improvement and widespread use of PSA, aging and probably a real increase in incidence. In men after 40 years there is a progressively incidence increase, with a peak at age 80. The countries with the highest mortality rate for prostate cancer are: Switzerland, Scandinavia and the USA-adjusted death rates by age group between 15-20/100.000 inhabitants. By contrast, the Asian countries with Japan and China leading the way, have the lowest mortality rate (less than 5 per 100,000 population) (1).

The geographic incidence variations of prostate Cancer are multiple and complex, but there are genetic and environmental factors, which seem to be more involved in its genesis. African Americans are those who have higher rates of prostate ca. As mentioned above, China and Japan have lower rates in the incidence of prostate ca and USA one of the highest in the world, well, it is noteworthy that Asian Americans have lower incidence rate of prostate cancer than white Americans, the indicating that the genetic factor is crucial in the development of the disease.

The overall increase in the incidence of prostate cancer worldwide in recent decades, is justified with the development of PSA screening protocols of prostate Cancer. The diagnosis of prostate cancer is based on the determination of serum PSA. The risk of prostate cancer is depending on Serum PSA (2):

PSA 0-2 ng / ml: 15-25%.

PSA 2-4 ng / ml: 17-32%

PSA 4-10 ng / ml: 17-32%

PSA > 10 ng / ml: 43-65%.

There is still much controversy among health professionals about what is the best protocol for the screening of prostate cancer. The long awaited results of two prospective, randomised trials were published in 2009. The Prostate, Lung, Colorectal, and Ovarian

(PLCO) Cancer Screening Trial randomly assigned 76,693 men at 10 US centres to receive either annual screening with PSA and DRE or standard care as the control. After 7 years' follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22) (3). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13). The data at 10 years were 67% complete and consistent with these overall findings. The PLCO project team concluded that prostate cancer related mortality was very low and not significantly different between the two study groups. The European Randomized Study of Screening for Prostate Cancer (ERSPC) included a total of 162,243 men from seven countries aged between 55 and 69 years. The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screened group and 4.8% in the control group (4). The rate ratio for death from prostate cancer was 0.80 in the screened group compared with the control group. The absolute risk difference was 0.71 deaths per 1,000 men. This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from prostate cancer by 20%, but was associated with a high risk of over-diagnosis.

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40-52% versus 86% in the ERSPC. Thus, the PLCO trial will probably never be able to answer whether or not screening can influence prostate cancer mortality. In the ERSCP trial, the real benefit will only be evident after 10-15 years of follow-up, especially because the 41% reduction of metastasis in the screening arm will have an impact.

Recent sub-analysis, with longer follow up have shown a potential benefit of screening, lowering the number of men needed to screen, and the number of patients needed to treat to save one life.

Two key items remain open and empirical:

- at what age should early detection start
- what is the interval for PSA and DRE.

A baseline PSA determination at age 40 years has been suggested upon which the subsequent screening interval may then be based (5) (GR: B). A screening interval of 8 years might be enough in men with initial PSA levels < 1 ng/mL (6). Further PSA testing is not necessary in men older than 75 years and a baseline PSA < 3 ng/mL because of their very low risk of dying from prostate cancer (7).

D'Amico in 1998 proposed a classification according to risk group for prostate cancer based on T stage, PSA value and Gleason. This has allowed to simplify the classification of patients with prostate cancer as well as trying to unify its treatment. (Table 1)

The widespread use of PSA testing has led to a significant migration in stage and grade of prostate cancer, with > 90% of men in the current era diagnosed with clinically localised disease (8). Despite the trends towards lower-risk prostate cancer, 20-35% of patients with newly diagnosed prostate cancer are still classified as high risk, based on either PSA > 20 ng/mL, Gleason score > 8, or an advanced clinical stage (9). Patients classified with high-

risk prostate cancer are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from prostate cancer. Nevertheless, not all high-risk patients have a uniformly poor prognosis after RP (10). There is no consensus regarding the optimal treatment of men with high-risk prostate cancer. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence.

Low risk	Intermediate risk	High risk
T1-T2a & PSA<10 y Gleason ≤6	T2b or PSA 10-20 or Glesason 7	T2c-T3-T4 or PSA > 20 or Gleason ≥8

Table 1. D'Amico classification of patients according to risk group

As expected, survival and success of the treatment applied in prostate cancer is closely linked to the stadium and the risk presented by the patient. In this chapter we will focus on Prostate Cancer at high risk as well as the different therapeutic options, focusing on the radical prostatectomy as an effective treatment of the disease.

2. Defining high risk prostate cancer

The factors that best define the high risk prostate cancer are those described by D'Amico (11) approved by the American Urological Association in 2007 are:

Gleason ≥ 8 points and / or PSA ≥ 20 and / or clinical stage ≥ T2c

These high-risk tumors are at high risk for recurrence, either local or remote, so they are also traditionally called "locally advanced" (12) or "poorly differentiated" (13). If the patient has the 3 items they are considered "very high risk" and have a high probability to die from prostate cancer (14).

Another factor that has been added as a fourth factor is pretreatment *PSA velocity* which if greater 2ng/ml/year is included as criteria for high-risk disease (15,16).

The simplification of the term "risk" has led many doctors to select patients and improperly included in high-risk groups. Also, following the analysis of these high-risk criteria, we can not quantify the individual risk to a patient, for example, with stage T2c and Gleason 8 would have the same risk that a patient with a PSA 70 and stage T3a (17). That is why this classification system is inadequate and we must use another tool to individualize the risk of each patient; this tool are *Nomograms* which individually allow to analyze and quantify the risk presented by each patient in response to multiple risk factors or variables, integrated in a complex mathematical formula (18). There are plenty of nomograms (19) that have been designed for use in prostate cancer in recent years and could be classified into 3 groups:

*Diagnostic nomograms*: those who pretend to estimate the probability of a patient developing prostate cancer. For example, the Vienna nomogram (20) that analyzes the number of cylinders to take a biopsy of the prostate.

*Staging nomograms*: such as the Partin tables (21), which indicates the likelihood of organ-confined disease. Or A. Borque neural network for predicting pathological stage in men undergoing radical prostatectomy. (22)

*Prognostic nomograms*: are tools that estimate the probability of success in applying a certain treatment to analyze different variables. The most famous and globally applied is Kattan nomogram (23). It analyzes a combination of three factors to determine the probability of PSA relapse after local therapy. These factors are: PSA, Gleason score and clinical stage. They apply both to radical prostatectomy, radiotherapy and brachytherapy. Nomograms derived from the results of treating thousands of patients. The statistical probability of relapse depends on the presence of pre-existing micro metastases at the time of local therapy (23). Hence the likelihood of relapse determined by the Kattan nomograms can be taken as an indication of the presence of micro metastases at the time of local therapy, resulting in an estimate to calculate the probability of success / failure when applying a certain treatment.

In summary, nomograms are useful modern tools that exist today, which may help us making treatment decisions in patients with prostate cancer, especially those with high-risk prostate cancer. As well as providing more information to the patient.

### **2.1 Locally advanced prostate cancer cT3a**

When the disease has overpassed the prostate capsule, it is a T3a stage. Typically, when a patient is at this stage we are advise against radical prostatectomy (24) as primary treatment based on the high rate of positive surgical margins and lymph node metastases (25,26). Numerous studies have shown that the risk/benefit of a radical prostatectomy is even more clear in the treatment of high risk prostate cancer (27-32), but unfortunately, there are not studies comparing combination therapy (radiotherapy plus hormones) with RP.

Between 13% and 27% of patients diagnosed with stage T3 are overestimated (31,32).

The development of CT imaging or MRI, as well as directed needle biopsies of lymph nodes or seminal vesicles (32), help identify patients who have less probability to benefit from a surgical treatment (33) as well as to plan surgery upon results.

Due to an increased sophistication and experience of the different surgical techniques, there has been a decreased in operative morbidity and better functional outcomes after RP in stage T3 cancer than before (31,33). Urinary incontinence and erectile dysfunction remain the two major consequences of the surgery, but due to surgical expertise and experience, as well as a proper surgical planning, an improvement in functional results has been shown (35).

### **2.2 High grade prostate cancer: Gleason score 8-10**

Patients with high Gleason score 8-10 tumors, which are confined to the prostate on histopathological examination, they still have a good prognosis after RP (36). The differences between the Gleason score biopsy and the Gleason score regarding the surgical specimen are between 36 and 60% of cases, although a study by Dr. Grossfeld (37) shows that 39% of patients had Gleason 8-10 in the biopsy specimen, showed a Gleason score of 7 or less in the prostatectomy specimen.

In a recent publication (38) in which the outcome of 781 patients undergoing RP clinically localized stages T1-T2 was analysed, they divided into 2 groups according to Gleason: Gleason patients 2-7 and another group with Gleason 8-10. Over all, they showed a worse prognostic features and higher PSA relapse. (Table 2)

Patients with Gleason score 8-10 prostate cancer have a higher likelihood of recurrence, but due to the PSA era, many of these patients are diagnosed with an early stage and therefore a potential local curative treatment is applicable successful (38).



Various studies such as those of Mian et al (39), Lau et al (40) and Soloway et al (41) analyze and study the survival in these patients concluded similarly.

The clinical Gleason 8-10 is an independent prognostic factor for biochemical progression-free survival. The radical prostatectomy remains one of the most valid treatments for these short of patients and providing good oncological and functional outcomes.

	Group Gleason 2-7	Group Gleason 8-10	P value
N° of patients	673	108	
PSA (ng/ml)	Av 13,48 Median 9,8	Av. 16,89 Median 12	<0,01
T1c	55%	50%	<0,0001
>T1c	45%	50%	
<pT3b	69%	44%	<0,0001
pT3b	30%	56%	
Surgical Margin-	67%	48%	<0,0001
Surgical Margin +	33%	53%	
Biochemical Progression -	74,3%	52,5%	<0,0001
Biochemical Progression +	25,7%	47,5%	

Table 2.

2.3 Prostate cancer with PSA > 20

Different studies show that the RP in patients with a PSA> 20 is associated with a high recurrence rate, D'Amico and colleagues found that males with a PSA level higher than 20 ng/ml had risk recurrence of 50% at 5 years after RP (42). Similarly, Yossepowitch published the results of their series of patients with PSA> 20ng/ml who underwent radical prostatectomy, showing a PSA recurrence rate of 44 and 53% at 4 and 20 years respectively (10). It is perhaps the high preoperative PSA, the factor that best relates to a worse prognosis preoperatively.

On the other hand, Inman and colleagues, in their series of patients with PSA> 50ng/ml who underwent RP with multimodal adjuvant therapy, had biochemical progression-free survival at 10 years of 83% with a cancer-specific survival 87% (43). These highlights the potential benefit of surgery with in a multimodal approach.

3. Therapeutic options in “high risk” prostate cancer

3.1 Introduction

Localized prostate cancer

The lack of evidence regarding the effectiveness of treatment options for clinically localised prostate cancer continues to impact on clinical decision-making. The two such options are radical prostatectomy (RP) and active surveillance (AS). (44)

For the majority of men with favorable-risk localized disease, older than 65, surveillance will be an attractive option that avoids adverse effects of treatment(45). But the existing trials,

provide insufficient evidence to allow confident statements to be made about the relative beneficial and harmful effects of RP and AS for patients with localised prostate cancer.(44) Klotz L et al. assure that active surveillance with treatment reserved for evidence of rapid PSA progression or increase in tumor volume or grade is associated with about a 3% risk of prostate cancer death at 10 years. (46)

### **Advanced prostate cancer**

In the other hand, patients with prostate cancer continue to present with metastatic disease or to relapse following initial hormone therapy; for these men, the optimal combination and sequencing of new medical treatments must be defined. (45)

### **High risk prostate cancer**

For these patients, (T2c-T3-T4 or PSA >20 or Gleason score  $\geq 8$ ) it is very important to give information about the different treatment options, and trying to adequate them to their live expectancy and quality of live.

Urologist, traditionally recommended radiotherapy or androgen deprivation therapy over RP, not because oncologic outcomes were better with radiotherapy, but because incontinence and impotence rates with RP were higher, and cure rates was discouraging. (47)

Actually, RP and radiotherapy have potential benefits and cumulative toxicities that must be matched to disease characteristics and patient expectations in selecting a treatment course. (48)

## **3.2 Pre-treatment management in high risk prostate cancer**

A critical assessment of the location, size, and extent of the primary tumor provides prognostic information, is essential for treatment planning.

D'Amico and colleagues have defined high-risk prostate cancer as that associated with any 1 of 3 risk factors: biopsy Gleason score  $\geq 8$ , PSA  $\geq 20$  ng/mL, or clinical stage  $\geq T2c$ . (11)

More recently, D'Amico and colleagues refined their high-risk definition to incorporate an absolute number of high-risk features (stage  $\geq T2b$ , biopsy Gleason score  $\geq 7$ , and pre-treatment PSA >20 ng/mL). (14) Patients are classified into 1 of 3 high-risk groups, defined by the presence of 1, 2, or all 3 features. Probability of death from prostate cancer was highest among men with 3 high-risk features.

High-risk patients with aggressive tumors (PSA >20 ng/mL and Gleason sum >7), advanced local lesions (T3-T4), or patients with symptoms suggestive for metastatic disease, should have imaging studies. (17)

While not uniformly accurate, there are some imaging studies that help us to identificate the high risk disease:

- DRE provides some evidence of the cancer's size and pathologic stage.
- Transrectal ultrasonography (TRUS) is extremely useful for guiding needle biopsies.
- Computed tomography (CT) scans poorly the prostate and lack of sensitivity and specificity for detecting extraprostatic extension.
- Magnetic Resonance Imaging (MRI) provides additional information about the local lesion, it has largely replaced CT in the local staging of prostate cancer.
- MRI has been used primarily to determine local disease extent. Body MRI has a role in identifying seminal vesicle involvement, but not extra capsular extension.
- Bone Scan, which is highly sensitive but relatively nonspecific because areas of increased radiotracer uptake are not always secondary to osteoblastic activity from metastases. (17)

An alternative to patients risk-grouping with similar but not identical risk features is use of multivariable models such as nomograms. These models incorporate data from all risk factors relevant to the probability of treatment failure and proportionately weigh their relative contribution in order to calculate a risk score. (48)

Eastham et al. demonstrate that high-risk patients were more likely to exhibit adverse pathologic features and to have biochemical progression. Nevertheless, roughly one-third of high-risk patients (22% to 63%, depending on the definition) had organ-confined cancers and roughly half (41% to 74%) remained progression-free 10 years after surgery alone. These results confirm that current definitions of high risk disease are unreliable in identifying patients who cannot be cured by local therapy. (48)

### 3.3 Objectives of treatment in high risk prostate cancer

The actual objectives of the treatment of high prostate cancer are:

1. To offer a radical treatment
2. Trying to decrease prostate cancer progression
3. To increase metastatic disease free interval
4. To provide a proper quality of life.

Men with high-volume lesions or high-stage yet clinically localized disease must receive multimodal therapy. More advances will require concerted efforts through clinical trials. (45)

Neoadjuvant Androgen Deprivation Therapy may indeed provide no additional benefit over surgery alone for patients with clinically localized prostate cancer. Recent studies have demonstrated the feasibility of neoadjuvant chemotherapy prior to RP in patients with high-risk prostate cancer. (17). If such a strategy was shown to be effective, future clinical practice could be altered significantly. A randomized phase 3 clinical trial, CALGB 90203, is currently investigating whether neoadjuvant chemo-hormonal therapy followed by RP reduces the risk of biochemical recurrence when compared to RP alone.

### 3.4 Actual treatment in high risk prostate cancer

Actually, the optimal treatment are:

- radical prostatectomy (RP) + radiation therapy (RT)
- radical prostatectomy + hormone therapy
- radiation therapy + hormone therapy

There is no consensus regarding the optimal treatment of men with high-risk PCa.

Surgery is showing good results, but decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. (49)

On the other hand, it has been recently assessed the effect of RP and RT on the rate of distant metastases in patients with clinically localized prostate cancer on the study from Memorial Sloan Kettering Cancer Center comparing patients whom underwent surgery versus radiotherapy (50). Patients with clinical stages T1c-T3b prostate cancer treated with intensity-modulated RT (81 Gy) from 1998 to 2002 were compared with similar cohort of men treated with RP.

This study, showed that patients with higher-risk disease, treated with RP had a lower risk of metastatic progression and prostate cancer-specific death, than men treated with RT. The metastatic progression is infrequent in men with low-risk prostate cancer, treated with either RP or RT.

These results, despite being from retrospective review of patients treated at a single institution, certainly suggest that RP should be considered as a treatment option in men with clinically localized, high-risk prostate cancer. (50)



As mentioned above, the multimodal treatment is achieving good results, and to corroborate this, several randomised studies of radiotherapy combined with androgen-deprivation therapy (ADT) versus radiotherapy alone have shown a clear advantage for combination treatment, but no trial has ever proven combined treatment to be superior to RP.

4. Radical prostatectomy in high risk CaP

4.1 Introduction

Actually radical prostatectomy is accepted as an election treatment in both low and high risk prostate cancer with different evidence level, and even for very high risk prostate cancer. (Table 3)

INDICATIONS	LE
In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20) and a life expectancy > 10 years	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 yr or Gleason score 7	3
Selected patients with low-volume high-risk localised PCa (cT3a or Gleason score 8-10 or PSA > 20)	3
Highly selected patients with very high-risk localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment	3
Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years.	3

Table 3.

The goals of RP are to remove the cancer completely with negative surgical margins, minimal blood loss, no serious perioperative complications, and complete recovery of potency and urinary continence. From an oncologic standpoint, obtaining negative surgical margins is paramount. A positive surgical margin has been associated with as much as 4-fold higher risk of biochemical recurrence, even after adjusting for other prognostic factors such as Gleason grade, extracapsular extension, seminal vesicle invasion, and lymph node metastasis. (48)

On the same way, there are good results in terms of morbidity and survival when radical prostatectomy is offered as a radical treatment.

4.2 Evidence of RP in HR.PC

RP in locally advanced PCa: cT3a

Is defined, as cancer that has perforated the prostate capsule. Surgical treatment has traditionally been discouraged, mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse

In recent years, there has been renewed interest in surgery for locally advanced PCa, and several retrospective case-series have been published. In general, 33.5-66% of patients will have positive section margins, and 7.9-49% will have positive lymph nodes.

On the other hand, excellent 5-, 10- and 15-year overall survival (OS) and cancer-specific survival (CSS) rates have been published.

Therefore, it is increasingly evident that surgery has a place in treating locally advanced disease (45)

The problem remains on patient selection before surgery: Nomograms, nodal imaging with CT and seminal vesicle imaging with magnetic resonance or directed specific puncture biopsies of the nodes or seminal vesicles can help to identify those patients unlikely to benefit from a surgical approach. (17)

In addition, it is extremely important that radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep an acceptable morbidity level.

#### **RP in High-grade PCa: Gleason score 8-10**

In this group of patients, the incidence of organ-confined disease is around 26% to 31%. The PSA value and percentage of positive prostate biopsies may help to select men with high-grade PCa most likely to benefit from RP.

Rioja Zuazu J. et al. (38) analyzed the characteristics of the clinical Gleason 8-10 group of patients within their series of patients diagnosed with prostate cancer and treated by means of radical prostatectomy, and tried to ascertain which were the influence factors within this group, upon progression and progression free survival. They conclude, that Clinical Gleason Score 8-10 is a negative independent prognostic factor on the progression free survival, but its prognosis is better if they present a PSA prior surgery lower than 11 ng/ml and the pathological stage is a pT2. So, these kind of patients could be beneficed of RP.

#### **RP in PCa with PSA > 20**

Yossepowitch et al. (19) and D'Amico et al. (15) have investigated the results of RP in these patients. In all cases, very good results were seen, with a cancer-specific survival of up to 91% in 10 years in patients treated with RP.

More recently, Inman and co-workers (43) described the long-term outcomes of RP with multimodal adjuvant therapy in men with PSA > 50. Systemic progression-free survival rates at 10 years were 83% and 74% for PSA 50-99 and > 100, respectively, while CSS was 87% for the whole group. These results argue for aggressive management with RP as the initial step.

#### **RP in cT3b-T4 N0**

Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume.

In 2005, The Mayo Clinic reported a series of patients with seminal invasion, treated with RP + HT adjuvant. They had a progression free survival at 5, 10 and 15 years, of 85%, 73% and 67% respectively, and a cancer specific survival of 95%, 90% and 79%.

Despite this, management decisions should be made after all treatments, and should be discussed by a multidisciplinary team, and after balancing benefits and side-effects of each therapy modality by the patient, with regard to his own individual circumstances, decision has to be taken.

### **4.3 Optimal surgical technique for high risk cancer**

Surgeons must understand the important anatomical and surgical principles that will allow them to improve their own technique, particularly when operating in the high-risk setting. Certain principles are important, and apply equally to open, laparoscopic and robotic surgical techniques.

Even in a patient with a high risk of extra prostatic disease, a portion of the neurovascular bundle can often be preserved. (17)

This approach has been facilitated by recent anatomical descriptions of the periprostatic anatomy. (51)

Dissection of the neurovascular bundles can be done in an intrafascial plane (directly adjacent to the prostatic capsule; complete nerve sparing), an interfascial plane (within the lateral prostatic fascia; partial nerve sparing) and extrafascial plane (outside the lateral prostatic fascia; nerve resection)

Deep dissection beneath Denonvilliers' fascia posteriorly should be performed routinely, as few nerves are present in this area and deep dissection will reduce the incidence of posterolateral margins.

Large, high-grade cancers, near the base of the prostate, or in the anterior transition zone often invade the bladder neck. For anterior cancers, begin division of the bladder neck a centimeter or more from its junction with the prostate. For large posterior tumors or those with seminal vesicle invasion, include the posterior bladder distal to the interureteral ridge in the specimen. (48)

## 5. Pelvic lymph node dissection

For patients with low risk disease, PLND is not necessary and is not recommended, because the chance of metastasis is low.

For patients with high and intermediate risk disease, extended PLND at least for external iliac, obturator and hypogastric lymph nodes should be performed during radical prostatectomy. Removing at least 10 lymph nodes is recommended to detect LNI. (52)

Prostate cancer lymphatic spread ascends from the pelvis up to the retroperitoneum invariably through common iliac lymph nodes. PC lymphatic spread can be divided in two main levels: pelvic and common iliac plus retroperitoneal lymph nodes. (53)

So the technique try to remove all lymphatic tissue between the external iliac vein and hypogastric vein above and below the obturator nerve, including the hypogastric and obturator lymph nodes.

Therefore may assert that an eLND should be performed in all high-risk cases, as the estimated risk for positive lymph nodes will be in the range 15-40%. (10)

However, despite the above, some authors like Bubley are not so categorical in affirming this.

Although it is generally accepted that eLND provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, capsular perforation of the node) that cannot be matched by any other current procedure, consensus has not been reached as to when eLND is indicated and to what extent it should be performed. When making such decisions, many physicians rely on nomograms based on pre-operative biochemical markers and biopsies. (54)

### 5.1 Role of RT in high risk prostate cancer

#### Indications for RT after RP

As stated earlier, currently, a multimodal treatment is chosen to increase survival and reduce biochemical progression. In this sense the RT play an important role.

There are two important studies about this:

The EORTC Trial 22911 included 1,005 patients with positive surgical margins or pT3 disease (extracapsular extension and seminal vesicle involvement) and randomized them to adjuvant EBRT (50 Gy to the prostatic fossa and periprostatic tissue plus a 10-14 Gy

boost to the prostatic fossa only) versus no immediate treatment. (55) The cumulative rate of loco regional failure was significantly lower in the irradiated group ( $P < 0.0001$ ). However, other clinically important endpoints were not improved. In particular, 5-year metastasis-free survival, cause-specific survival, and overall survival were not affected by adjuvant RT.

The Southwest Oncology Group (SWOG) trial 8794 included 425 patients with high-risk localized disease, who were randomized to receive either 60–64 Gy to the prostatic fossa or observation only. (56) Biochemical control, disease-free survival, cancer-specific mortality, and overall survival were significantly increased in the adjuvant irradiation arm at a median follow-up of 10.6 years.

Both the EORTC and SWOG randomized trials, provide evidence that adjuvant post-prostatectomy irradiation reduces the risk of biochemical recurrence and local clinical failure. It remains uncertain, whether administration of radiation immediately after PSA is detected, could provide equally effective long-term outcomes to patients receiving adjuvant therapy, while sparing such patients from unnecessary irradiation. (17) (48)

### Salvage radiotherapy

The efficacy of radiotherapy in the setting of a rising PSA after RP is unproven, and its use is highly controversial. Stephenson et al. reported on a large retrospective analysis of salvage irradiation of 501 patients from 5 institutions. (57)

Positive surgical margins, Gleason scores  $< 8$ , or PSADT  $> 10$  months. In such patients, PSA relapse-free survival outcomes were in the range of 70% to 80% at 3 years.

## 6. Survival

Regarding cancer-specific survival rate, and the overall survival rate, there are many studies, with different results (table 4).

First, in terms of morbidity, Berglund and colleagues (58) showed, that recovery from surgery, duration of catheterization, and the overall return of continence were essentially similar to those observed in the low-risk population.

Another important factor to consider when analyzing survival, is the overstaging sometimes happens in the T3. Therefore, Ward et al report a long-term experience with radical surgery in patients presenting with locally advanced (cT3) prostate cancer, as the best management of such patients remains a problem. They found that, significantly many patients with cT3 prostate cancer were over-staged (pT2) in the PSA era, and RP as part of a multimodal treatment strategy for patients with cT3 disease offers cancer control and survival rates approaching those achieved for cT2 disease. (31)

For short term survival, Loeb et al (35) reported a complication rate of 11% in 288 consecutive high-risk patients treated by RP, which was not different from the rate in a previous study from the same group that included 3,477 consecutive patients with prostate cancer (59) when analyzing intermediate-term cancer control, and quality-of-life outcomes after radical retropubic prostatectomy (RRP), and concluded that RRP offers excellent intermediate-term cancer control for selected men, of all ages, who present with high-risk or locally advanced disease. Both, continence and potency, were preserved in most patients, although the potency rates were significantly greater for the younger men. RRP with appropriate postoperative radiotherapy and/or hormonal therapy is a reasonable treatment option for selected men with high-risk or locally advanced disease. (35) (Table 4)

	↑Risk	N° Patients	% 5 years BR free survival	% 10 years cancer especif survival
Van de Ouden (29)	T3 clínic	136	39	72
Hsu (26)	T3 clínic	235	60	92
Ward (20)	T3 clínic	841	58	90; 15 y 79
Lau (23)	Gleason 8-10	407	49	85
Berglund (19)	PSA ≥15 or Gleason 8-10	281	65	NR
Loeb (21)	T2 and Gleason 8-10 or PSA ≥15 o T3	288	39-53	70-93
Van Poppel (27)	T3a y PSA ≤20 and Gleason ≤7	32	3mo:90	NR

BR: Bioquimical recurrence  
NR: No results.

Table 4.

For long term survival, Van Poppel (60) showed in 2006, that in patients with locally advanced disease, the cancer-specific survival rate after RP at 5- and 10-years of follow-up, was 85-100% and 57-91.6%, respectively. The overall survival rate at 5 and 10 yr was, 75% and 60%, respectively. In patients with high-grade prostate cancer (Gleason score> or =8), the biochemical recurrence-free survival, after RP at 5 and 10 yr of follow-up was, 51% and 39%, respectively.

Van Der Ouden et al. determined the progression and survival rates, and investigate subgroups of patients who may not benefit from this treatment. Defining that Radical prostatectomy as monotherapy, in patients with locally advanced non-metastatic prostate cancer (T3) produces acceptable results, in those with well or moderately differentiated tumors. The results of progression and survival, are not significantly different from those patients with organ confined prostate cancer. (29)

Yossepowitch describe the results of RP in their patient’s serie, classify patients in risk groups: (61) he studied pathological and clinical outcomes among high-risk patients treated with RP. To identify high-risk subsets, eight definitions from the medical literature were applied. Depending on the criteria, high-risk patients comprised 3% to 38% of the entire study population, highlighting the immense variability among available high-risk definitions. High-risk patients were more likely to exhibit adverse pathological features (35%–71% with extra capsular extension, 10%–33% with seminal vesicle invasion, and 7%–23% with lymph node involvement), but roughly one third (22%–63%) had organ-confined cancers and nearly half (41%–74%) remained progression-free 10 years after surgery alone. (Table 5)

More recently the group from the Mayo Clinic, has reported their long-term result after radical prostatectomy versus external bean radiotherapy for patients with high-risk prostate cancer. (62) The 10-year cancer specific survival rate was 92%, 92% and 88% after RRP, EBRT plus ADT and EBRT alone. After adjusting for case mix, no significant differences in the risks of systemic progression or prostate cancer death were observed between patients who received EBRT plus ADT and patients who underwent RRP. However, the risk of all causes of mortality was greater, and statistically significant, after EBRT plus ADT than after RRP.



Criterion ↑R	N° patients	% confined organ	% free survival in 5 years	% cancer specific survival in 10 years
Gleason 8-10	274	35	53	88
PSA > 20	275	33	56	91
T3c(*year 1992)	144	22	49	89
Nomogram PFP 5 years ≤50%	391	28	53	92
PSA velocity >2 ng/mL/year	952	63	80	97
PSA≥ 20 o ≥T2c o Gleason 8-10	957	43	68	93
PSA≥15 o T2Bc o Gleason 8-10	1752	51	73	95

Table 5.

7. Local control

Local control, main objective with both techniques, is better achieved with surgery. Local relapse rates between 3-30%(63-65) Depends on clinical stage (pT2: 2-7%; negative margins 7%; pT3-4: 40%; positive margin 27%) While with Radiotherapy, local recurrence rate is for T1: 17-22% (Standford); 4.6% (Schelhamer); T2: 19%-35%.

The rate of positive biopsies is between 20-70%, although is difficult to classify its meaning, they highlight disease and progression. It depend on clinical stage (B=17%, C=59%) and Gleason score. A valuable biopsy is at 18 months after finishing treatment.

Frequency of positive prostate biopsies on patients whom underwent radiotherapy, is around 38% on average.

In the study (66) with 100 patients, with biopsy every 6 months showed following results T-1b: 21%; en T-2a: 24%; en T-2b-c: 28%.

There is no doubt regarding its prognostic value. Although the pioneers showing these results were Rhamy (1972) and Sewel (1975) Scardino has been reporting, and highlighting its value (67). At Baylor-Colleague (Houston) 147 patients treated with Au 198 and external bean radiotherapy, clinical stage A2, B, C with pelvic lymphadenectomy. They had a positive biopsy rate of 42%, 36%, 28% at 6, 12 and 18 months. The chance of local recurrence at 5 years for positive and negative biopsies is around 52% and 12%, and at 10 years of 72% and 30%.

8. Conclusions

Many cancers, categorized clinically as high risk, are actually pathologically confined to the prostate, and most men with such cancers who undergo RP, are free of additional therapy long after surgery.

For men with high-risk, clinically localized prostate cancer, decisions on whether to elect surgery as local definitive therapy should be based on the best available clinical evidence rather than on an individual practitioner’s experiences and biases.

Patients classified with high-risk prostate cancer, by commonly used definitions, are at increased risk of PSA failure, need for secondary therapy, metastatic progression, and death from systemic disease. Nevertheless, such high risk patients do not have a uniformly poor prognosis after RP.

- If the prostate cancer risk has a high probability of progression to metastasis or death, we must offer aggressive treatment, which achieves high cure rate, and eliminate the illness onset.
- Radical prostatectomy is proving a very valid option with high success rate, for which we must select patients appropriately
- The success of RP in high-risk patients, with stage T3 resection depends entirely local tissue containing the tumor and include the resection of seminal vesicles and extended lymphadenectomy.

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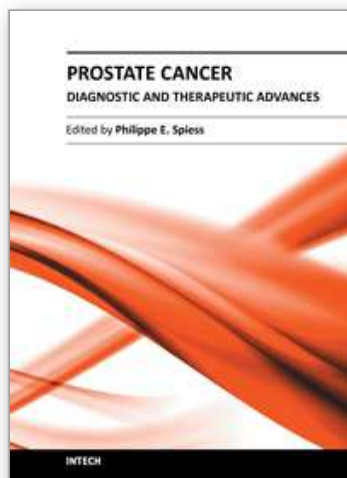
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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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