Clinical Practice Guideline for Prostate Cancer Treatment

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

Plan de Calidad para el Sistema Nacional de Salud

Instituto Aragonés de Ciencias de la Salud

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This CPG is healthcare decision aid. It is not mandatory, and it is not a substitute for the clinical judgement of healthcare personnel.

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Presentation

Care practice is becoming more and more complicated due to many different factors. One of the most relevant factors is the exponential increase of scientific information.

To make clinical decisions that are adequate, safe and effective, practitioners need to devote a lot of effort in continously updating their knowledge.

In 2003, the Interterritorial Council of the Spanish NHS created the GuiaSalud Project whose final aim is to improve clinical decision-making based on scientific evidence, via training activities and the configuration of a registry of Clinical Practice Guidelines (CPG). Since then, the GuiaSalud project has assessed dozens of CPGs in agreement with explicit criteria stipulated by its scientific committee. It has registered them and has disseminated them over the Internet.

At the beginning of 2006, the D.G. of the Quality Agency of the National Health System prepared the Quality Plan for the National Health System, which was divided into in 12 strategies.

The purpose of this Plan is to increase the cohesion of the National Health System and help guarantee maximum quality health care for all citizens regardless of their place of residence.

As part of the Plan, different agencies and expert groups in prevalent pathologies related to health strategies were entrusted with the preparation of eight CPGs. This prostate cancer treatment guideline is the fruit of this assignment.

The definition of a common methodology to prepare the guidelines for the NHS was also requested and this has been prepared as a collective effort of consensus and coordination among the Spanish CPG expert groups. This methodology was used as the basis to prepare this prostate cancer treatment guideline.

In 2007, the project prepared CPGs in depth and included other Evidence-Based Medicine services and products. It also aims to favour the implementation and assessment of the use of CPGs in the National Health System.

Prostate cancer is one of the main health problems affecting the male population. It is highly prevalent and is one of the leading causes of death of men in Spain as well as affecting the patients' quality of life.

The choice of the most appropriate thereapetic option in men with prostate cancer is complex due to different factors. The patient's clinical situation must be considered, but it is also very important to consider the adverse effect profiles of the different therapeutic alternatives that sometimes represent a great impact on the quality of life of the person concerned.

The existing variability in the treatment of prostate cancer that currently exists has meant that this "Clinical Practice Guideline for Prostate Cancer Treatment" is essential to provide practitioners with recommendations based on scientific evidence to address the

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management of this process, offering therapeutic alternatives that adapt to each clinical situation.

This guideline is the result of the work of a group of professionals linked to different fields and disciplines of health care and who represent the healthcare continuity with all it variants, for men with prostate adenocarcinoma. The scientific societies directly involved in this health problem have collaborated in this guideline.

Answers to many of the questions raised when caring for patients with prostate cancer will be found in this guideline. These questions are given in the form of systematic recommendations and with the best available scientific evidence. We hope that this will lead to a more homogeneous and higher quality health care for these patients and their families.

PABLO RIVERO CORTE
DG, NHS Quality Agency

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Questions to be answered

LOCALISED PROSTATE CANCER

1. What are the prognostic factors in localised prostate cancer?
2. In patients with clinically localised prostate cancer, what is the safety and efficacy of different treatment options?
3. In patients with clinically localised prostate cancer in which surgery is indicated, what is the safety and efficacy of different types of radical laparoscopy surgery (transperitoneal or extraperitoneal, robot-assisted or not) in comparison with open radical prostatectomy?
4. In a patient with clinically localised prostate cancer who is indicated radical surgery with intent to cure, does lymphadenectomy increase the cure rates of the disease? If performed, which is better, extended or limited lymphadenectomy?
5. In patients with clinically localised prostate cancer where a radical prostatectomy is indicated, what percentage of positive surgical margins are obtained when it is decided to keep or not keep the neurovascular bundles (uni- or bilaterally)? And what results are obtained regarding urinary incontinence and erectile dysfunction?
6. In patients with clinically localised or locally advanced prostate cancer in which radiation is indicated (external and/or brachytherapy), what volume, dose and fractionation have the best safety and efficacy according to the risk?
7. In patients with clinically localised prostate cancer treated with intent to cure, does implementation of a neoadjuvant or adjuvant hormonal treatment improve the disease cure rates?
8. When can surveillance be stopped for a patient with localised prostate cancer after attempting a cure (radical prostatectomy and radical radiotherapy)? What tests are performed and how often do they take place?

LOCALLY ADVANCED PROSTATE CANCER

9. What is the safest treatment and most effective option for a patient with prostate cancer at the locally advanced clinical stage?
10. In a patient who has undergone radical prostatectomy in which locally advanced prostate cancer and/or positive microscopic surgical margins are demonstrated, is it safer and more effective to establish an adjuvant treatment (radiation) or not?
11. In patients with prostate cancer at a locally advanced clinical stage in which surgery is indicated, does carrying out a lymphadenectomy increase cure rates for the disease? And if carried out, which is better, extended or limited lymphadenectomy?
12. In patients with locally advanced prostate cancer subjected to local treatment (such as radiation or surgery) associated with hormone therapy, which form of hormone treatment is the safest and most effective: monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgenic blockade?

PROSTATE CANCER IN PSA RELAPSE

13. In patients with prostate cancer subjected to prostatectomy or radiotherapy with intent to cure, what would be the best analytical criteria for the diagnosis of PSA relapse?
14. In patients with PSA relapse after radical prostatectomy, what kind of salvage intervention is safer and more effective?

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15. In patients with PSA relapse after radiotherapy or brachytherapy with intent to cure, what kind of salvage intervention is safer and more effective?
16. In those patients subjected to curative treatment who are in PSA relapse and for whom hormone therapy (active treatment) is indicated, when should this start?
17. In those patients subjected to curative treatment who are in PSA relapse and for whom hormone treatment is indicated, is it safer and more effective to apply this continuously or intermittently?

DISSEMINATED PROSTATE CANCER

18. In patients with disseminated prostate cancer, which is the safer and more effective treatment: complete androgen blockade or castration (surgical or chemical)?
19. In patients with disseminated prostate cancer (affecting the lymph node and/or metastasis), which is safer and more effective: immediate hormone therapy or deferred hormone treatment?
20. In patients with disseminated prostate cancer, which hormone treatment is safer and more effective: continuous or intermittent? And with what treatment guidelines?
21. In patients with disseminated prostate cancer where first line hormone therapy has failed (androgen suppression, complete androgen blockade) and the PSA is beginning to increase, which is safer and more effective: continuing to follow lines of hormonal treatment or start chemotherapy?
22. In patients with androgen-independent disseminated prostate cancer, which is safer and more effective for the improvement of overall survival, clinical or biochemical response, progression-free survival and reduced side effects: oestramustine, mitoxantrone, docetaxel, docetaxel-oestramustine, vinorelbine or etoposide?
23. In patients with androgen-independent prostate cancer who are going to receive chemotherapy, is it safer and more effective to start when biochemical progression is seen or to wait for clinical progression?
24. In patients with disseminated prostate cancer in progression who have received hormone treatment and are going to receive chemotherapy, does removing the LH-RH agonists affect the safety and efficacy of the treatment?
25. In patients with disseminated prostate cancer, does intervention with bisphosphonates (zoledronic acid), compared with doing nothing, improve event-free survival for bones, bone pain and the quality of life, and does it allow a reduction in painkiller dosage?
26. In patients with disseminated prostate cancer, does allowing the administration of radiopharmaceuticals lead to a better control and/or a reduction of metastatic bone pain?

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Summary of recommendations

5. LOCALISED PROSTATE CANCER	
5.2 Initial choice of treatment	
B	In patients with clinically localised prostate cancer with a life expectancy exceeding 10 years, radical prostatectomy or external beam radiotherapy is recommended.
A	For patients with clinically localised prostate cancer treated with external beam radiotherapy, it must be three-dimensional conformation radiotherapy, as this allows administration of higher radiation doses with greater safety.
D	In patients with clinically localised prostate cancer who receive external beam radiotherapy, it may be associated with brachytherapy to be able to escalate the dose.
D	In patients with clinically localised prostate cancer at low risk (cT1 - cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), low or high dosage brachytherapy as a monotherapy is an alternative treatment intended as a cure for prostate volumes less than 50 cm^3.
B	In patients with clinically localised prostate cancer with a life expectancy exceeding 10 years, watching and waiting is a possible alternative.
D	In patients with clinically localised prostate cancer at low risk, Gleason < 3 + 3, < 50% of affected cylinders in the biopsy and PSA density < 15 ng/ml, active monitoring can be offered as an alternative to immediate radical treatment.
√	Active monitoring for patients will be done in the following way: - PSA determinations and rectal examinations every three months during the first 2 years, then every six months. - Prostate biopsy after 1 year, 4 years and 7 years (there must be at least 10 cylinders per biopsy).
√	In patients with active monitoring, radical treatment will be considered when any of the following appear: PSA velocity > 1 ng/ml/year, a greater degree or extent of the tumour in repeated biopsies, or evidence of locally advanced disease in a rectal examination.
A	Primary cryotherapy and high intensity focused ultrasound are experimental techniques in patients with clinically localised prostate cancer.
A	RESEARCH RECOMMENDATION: Randomised trials should be started comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with clinically localised prostate cancer.
5.3 Surgery	
B	In clinically localised prostate cancer with an indication of radical prostatectomy, both laparoscopic surgery as well as open can be used.
C	In patients with clinically localised prostate cancer at low risk (cT1 - cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), lymphadenectomy is not necessary when performing radical prostatectomy.
D	In patients with clinically localised prostate cancer of intermediate or high risk treated with radical prostatectomy, lymphadenectomy should be performed.
D	In patients with clinically localised prostate cancer with radical prostatectomy indicated, it is recommended to retain the neurovascular bundles when intraoperatory findings permit.
5.4 Radiotherapy	
B	In patients with clinically localised prostate cancer of low risk (cT1 - cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), the dose of external beam radiotherapy should be 72-74 Gy.

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B	In patients with clinically localised prostate cancer of intermediate risk [cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)], the dose of external beam radiotherapy should be 76-78 Gy.
B	In patients with clinically localised prostate cancer of high risk (cT2c or PSA > 20 ng/ml or Gleason > 7) or with prostate cancer in the locally advanced clinical stage (cT3), the dose of external beam radiotherapy must be at least 78 Gy.
B	In patients with localised prostate cancer at low risk, irradiation of the pelvis is not recommended.
C	In patients with prostate cancer and a risk of lymph node invasion ≥ 15%, irradiation of the prostate and seminal vesicles is recommended.
√	RESEARCH RECOMMENDATION: Randomised trials should be started to assess the usefulness of modified fragmentations (hypofragmentation, etc) of radiotherapy for prostate cancer.
5.5 Hormone therapy	
A	In patients with clinically localised prostate cancer of low risk (cT1 - cT2a and Gleason < 7 and PSA ≤ 10 ng/ml) or intermediate risk [cT2b or Gleason = 7 or (PSA> 10 and ≤ 20 ng/ml)], neoadjuvant hormone therapy with radical prostatectomy should be avoided.
B	In patients with clinically localised prostate cancer of low or intermediate risk, adjuvant hormone therapy with radical prostatectomy should be avoided.
A	In patients with clinically localised prostate cancer of low risk, neoadjuvant hormone therapy with radiotherapy should be avoided.
B	In patients with clinically localised prostate cancer of low risk, adjuvant hormone therapy with radiotherapy should be avoided.
√	In patients with clinically localised prostate cancer of intermediate risk, neoadjuvant hormone therapy concomitant with radiotherapy is recommended.
√	In patients with clinically localised prostate cancer of high risk (cT2c or PSA> 20 ng/ml or Gleason > 7), the criteria used in patients with locally advanced prostate cancer will continue to be used for the use of neoadjuvant and adjuvant hormone therapy with radical prostatectomy or radiation therapy.
5.6 Monitoring	
D	The singular case of a reported combined Gleason score between 2-4 in the specimen from a prostatectomy should be viewed with caution until reviewed by another expert.
D	Patients with a confirmed combined Gleason score of between 2-4 in the specimen from a prostatectomy do not require monitoring for cancer.
D	Prostate cancer patients in clinical stages T1a subjected to a radical prostatectomy do not require monitoring for cancer.
D	Prostate cancer patients in clinical stages T1b-T1c subjected to a radical prostatectomy require monitoring for 10 years.
D	For the remainder of patients with clinically localised prostate cancer (T2), after treatment with radical prostatectomy, the follow-up period should be 15 years.
D	The minimum monitoring period for patients with clinically localised prostate cancer after radiotherapy intended to cure it should be 8 years.
D	For patients with clinically localised prostate cancer treated with radical prostatectomy or radiation therapy, the only monitoring required is PSA control, as long as no PSA relapse is detected.
D	The recommended frequency for PSA monitoring in patients with clinically localised prostate cancer is as follows: at 3, 6 and 12 months after a treatment intended to cure; then 18, 24, 30 and 36 months, then annually after the third year.

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6. LOCALLY ADVANCED PROSTATE CANCER	
	6.1 Initial choice of treatment
√	In patients with prostate cancer at a locally advanced clinical stage and with a life expectancy exceeding 10 years, 3-dimensional conformal external beam radiotherapy or conformal external beam radiotherapy + brachytherapy is recommended.
D	In patients with prostate cancer at a locally advanced stage requiring radiotherapy treatment, 3-dimensional conformal radiotherapy is an alternative in centres where intensity modulated radiotherapy (IMRT) is not available.
√	In patients with prostate cancer at a locally advanced stage with a life expectancy exceeding 10 years and a low risk of it affecting the lymph node (cT3a + Gleason < 8 + PSA < 20 ng/ml), treatment with radical prostatectomy could be considered.
√	In patients with prostate cancer at a locally advanced stage with a life expectancy less than 10 years, watching and waiting or hormone therapy may be therapeutic alternatives.
A	Neoadjuvant hormonal therapy should be administered to patients with prostate cancer at a locally advanced clinical stage where radiotherapy treatment is indicated.
C	The normal duration of neoadjuvant hormonal treatment with radiotherapy in patients with prostate cancer at a locally advanced stage is 3 months.
A	Hormonal adjuvant radiotherapy is recommended in patients with prostate cancer at a locally advanced clinical stage.
D	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.
B	Neoadjuvant hormone therapy is not recommended in patients with prostate cancer at a locally advanced clinical stage who will receive radical prostatectomy.
B	Adjuvant hormone treatment with prostatectomy is not recommended in patients with prostate cancer at a locally advanced clinical stage, unless spreading to the lymph node is demonstrated.
A	In patients with prostate cancer at a locally advanced clinical stage, primary cryotherapy and high intensity focused ultrasound are experimental techniques.
A	RESEARCH RECOMMENDATION: Randomised trials should be started comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with prostate cancer at a locally advanced clinical stage.
√	RESEARCH RECOMMENDATION: Randomised trials should be started to assess the usefulness of docetaxel administered as a concomitant or adjuvant to radiotherapy after local treatment.
6.2 Adjuvant radiotherapy[a]	
√	In patients with locally advanced prostate cancer and/or microscopically positive surgical margins after radical prostatectomy, systematic use of adjuvant radiotherapy is not recommended.
6.3 Lymphadenectomy	
A	Lymphadenectomy would be indicated in patients with prostate cancer at a locally advanced clinical stage who underwent radical prostatectomy, as a staging and post-evaluation of adjuvant treatment
√	In patients with prostate cancer at a locally advanced clinical stage with radical surgery indicated, carrying out an extended lymphadenectomy may be of therapeutic interest.

[a] Section 5.4 responds to a question about the volume, dose and fractioning of radiotherapy for patients with localised or *locally advanced* prostate cancer.

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6.4 Neo or adjuvant hormone therapy	
A	For patients with prostate cancer at a locally advanced clinical stage where hormone therapy is suggested as an addition to surgery or radiotherapy, the appropriate hormone treatment (monotherapy with antiandrogens, LHRH agonist monotherapy or complete androgen block) cannot be determined.
√	RESEARCH RECOMMENDATION: Randomised trials should be started to determine the appropriate hormone treatment (monotherapy with antiandrogens, LHRH agonist monotherapy or complete androgen block) in patients with prostate cancer at a locally advanced clinical stage.
7. PROSTATE CANCER IN PSA RELAPSE	
7.1. Definition of PSA relapse	
D	In prostatectomised patients, biochemical recurrence of the disease will be considered when the serum levels of PSA exceed 0.4 ng/ml.
D	In those patients who have received radiotherapy or brachytherapy as curative intent, biochemical recurrence of the disease will be considered when the serum levels of PSA increase by 2 ng/ml above the PSA nadir.
7.2 Salvage treatment after surgery	
D	In patients with PSA relapse of the disease after radical prostatectomy, with no distant metastasis or other risk factors, early salvage radiotherapy should be offered before the PSA exceeds 2.5 ng/ml.
D	Salvage hormonal therapy may be indicated for those men with PSA relapse after radical prostatectomy who also exhibit symptomatic local progression, existence of distant metastases or doubling of PSA levels in less than 10 months.
	7.3 Salvage treatment after radiotherapy
D	Salvage radical prostatectomy can be offered after radiotherapy treatment in patients with local recurrence showing few associated comorbidities, a life expectancy of at least 10 years, with cT1-T2, Gleason < 7 and a pre-surgical PSA < 10 ng/ml.
D	Hormone therapy should be considered as a salvage therapeutic option for patients treated by radiotherapy and local recurrence of the disease who cannot be offered salvage radical prostatectomy.
D	The adoption of other salvage therapeutic alternatives (cryotherapy or high intensity focused ultrasound) should be considered within the field of experimentation.
D	RESEARCH RECOMMENDATION: Clinical trials should be launched to evaluate local salvage therapies in terms of survival and quality of life in men with biochemical recurrence after radiotherapy or brachytherapy.
7.4 Hormone therapy	
D	In patients with PSA relapse after radical prostatectomy for whom hormone treatment has been decided, if they have Gleason > 7, PSA ≤ 5 ng/ml and a PSA duplication time of less than 1 year, it is recommended that the hormone treatment be applied early.
√	In patients with PSA relapse after radical radiotherapy or brachytherapy in which hormone treatment is indicated, the decision on the timing of its application should be on an individual basis.
7.5 Intermittent v continuous hormone therapy	
A	In patients in PSA relapse after radical treatment for whom hormone therapy has been decided, it cannot be determined whether continuous or intermittent application is better.

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8. DISSEMINATED PROSTATE CANCER	
8.1 Hormone therapy	
A	In patients with disseminated prostate cancer for whom hormone therapy has been indicated, castration (surgical or chemical) is recommended as a first-line treatment.
D	In patients with symptomatic disseminated prostate cancer, hormone treatment is recommended.
B	In patients with asymptomatic disseminated prostate cancer, hormone therapy which is immediate or deferred (until the onset of symptoms) may be offered.
√	In patients with disseminated prostate cancer and low tumour load, intermittent androgen suppression may be assessed as an alternative to continuous androgen suppression if there is a good response to the initial hormone treatment.
√	To be able to indicate intermittent hormone therapy, the patient must have received androgen deprivation for at least 7 months and have reached a PSA < 4 ng/ml (stable or in decline during the sixth and seventh month) or a 90% reduction in the levels previous to treatment. Monitoring will be performed every 6 months. Patients who interrupt androgen deprivation will receive another cycle of androgen suppression when requested, when the PSA increases or when showing clinical signs of disease progression. If, after the new cycle of androgen deprivation, the PSA returns to normal, the hormone therapy can be interrupted again.
√	In patients with androgen-independent disseminated prostate cancer (those for whom androgen suppression and complete androgen blockade have failed), second-line hormone therapy can be offered before starting chemotherapy treatment.
√	RESEARCH RECOMMENDATION: Patients with androgen-independent disseminated prostate cancer (those for whom androgen suppression and complete androgen blockade have failed) should be offered inclusion in clinical trials to evaluate the efficacy and safety of second-line hormone therapy, comparing it with chemotherapy that has proven effective.
8.2 Chemotherapy	
B	In patients with androgen-independent prostate cancer (AIPC) and metastatic prostate cancer, when chemotherapy is suggested, docetaxel (75 mg/m^2 every 3 weeks) with corticoid is recommended.
√	In patients with AIPC and metastatic prostate cancer, it is not recommended to systematically combine docetaxel/oestramustine.
√	In patients with biochemical relapse, androgen-independence, asymptomatic and without documented metastatic disease, they can be offered an early start for chemotherapy, especially within the framework of randomised clinical trials.
√	RESEARCH RECOMMENDATION: Patients with biochemical relapse, androgen-independence, asymptomatic and without documented metastatic disease should be offered inclusion in clinical trials that compare early and delayed start chemotherapy.
√	In patients with androgen-independence, LHRH agonists may continue to be applied.
√	RESEARCH RECOMMENDATION: Patients with androgen-independent disseminated prostate cancer for whom chemotherapy treatment has been decided, should be offered inclusion in clinical trials to compare the safety and efficacy of exclusive chemotherapy to that for chemotherapy associated with LHRH agonists.

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	8.3. Bisphosphonates and radiopharmaceuticals
B	The systematic use of bisphosphonates (zoledronic acid) as a preventive treatment in bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected hormone-independent patients with demonstrated metastasis.
A	In men with androgen-independent prostate cancer (AIPC), treatment with Sr-89 or Sm-153 can be proposed when there is bone pain that requires third step analgesics which are not adequately controlled. To administer them, a correct haematological formula (> 3,500 leukocytes and > 150,000 platelets) and a bone scan showing bone metastasis are necessary.

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1. Introduction

Prostate cancer is one of the major health problems of the male population. Its frequency increases with age: 90% of cases are diagnosed in people older than 65. The aetiology is not entirely clear, although it is known to be related to factors such as environmental, lifestyle, family history and genetic[1,2].

It is estimated that in 2000 there were 1,555,000 cases in the world of men with prostate cancer[3]. For men, it is the third most common cancer in the world and in Spain[1,3], and represents approximately 11% of all neoplasias in European men[4].

The estimated prevalence in Spain in 2001 was 157.9 cases/100,000 inhabitants. Of these, 21% had been diagnosed within the previous year; 46%, within the previous 4 years; 23%, between 5 and 10 years beforehand; and 10% had been ill for over 10 years[5].

The prevalence of prostate cancer is increasing, and it is expected that this trend will continue due to several factors, such as the detection of more cases at earlier stages of the disease, increased survival thanks to diagnostic and therapeutic improvements and the longer life expectancy of the population[1]. We also know that many prostate tumours remain dormant, as only one-third of those discovered in autopsies were clinically discovered[2].

It is difficult to study the incidence of prostate cancer, given the limited number of cancer population records[1]. Based on available data, it is estimated that in the year 2000, 543,000 new cases of prostate cancer appeared in the world[3]. The incidence in Spain in 1998 was 10,659 new cases, with a rate[b] of 45.33 per 100,000 inhabitants. This is one of the lowest rates in the European Union, which that year had 68 cases per 100,000 inhabitants[1,2]. During the period 1997-2000, the incidence in Spain was 13,212 new cases a year, with an annual rate of 56.29 per 100,000 inhabitants-year[1].

The incidence of prostate cancer increased in all Spanish records (1983-97), which may be explained partly by better quality information, but mainly by three factors: increased life expectancy (which increases the age population), the use of prostate-specific antigen (PSA) measurements since the late eighties, which allows the detection of the disease at earlier stages, and the existence of more and better image diagnostic methods[1].

It is estimated that in 2000 there were 204,000 deaths in the world from prostate cancer[3]. In European Union males, prostate cancer accounts for 3% of all deaths and 9-10% of deaths from neoplasia[1,4]. It is the third leading cause of cancer death in Spain and Europe[1,2,4,6]. The mortality rate in Spain rose progressively up to 1998, until reaching a rate[c] of 24 deaths per 100,000, corresponding to 5,728 deaths[1,2,7]. Subsequently, this rate began to decline, probably due to improvements in diagnosis and certification of the cause of death[2]; reaching a rate of 18.22 per 100,000 inhabitants in 2005, with approximately 5,500 mortalities[7].

[b] Incidence rates adjusted to the European population.
[c] Rate adjusted to the European population.

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The survival rate in Spain in 2003 was around 86% for the year of diagnosis and 65.5% after 5 years, figures comparable to those of neighbouring countries[1,2].

With regard to decision-making in the clinical management of prostate cancer, we know that there is variability. For example, in the choice of radical or expectant treatment at the time of initial diagnosis, the amount of radiotherapy applied, clinical management after treatment with intent to cure and in rates of prostatectomy[8-13].

Within Spain, geographical differences for the risk of death from prostate cancer are not very pronounced, and no geographical pattern is clear[1,2,7].

The Clinical Practice Guidelines (CPG) are a set of "recommendations developed in a systematic manner to help professionals and patients to make decisions on the most appropriate health care, and to select the most appropriate diagnostic or therapeutic options when dealing with a health problem or a specific clinical condition"[14].

Since 2006, the Ministry of Health and Consumer Affairs in Spain has promoted the development of a Programme for preparing clinical practice guidelines based on scientific evidence in the Quality Plan for the National Health Service (SNS). A collaboration agreement between the Ministry, through its SNS Quality Agency, and the Carlos III Health Institute was established in the framework of this programme, with different health technology evaluation agencies and bodies. A common methodology for preparing a CPG was defined in this agreement, which was embodied in a methodology manual[14] and which also prompted several evidence-based guidelines to be produced.

Several international CPGs on prostate cancer have been developed, for example by the European Association of Urology[4], the National Comprehensive Cancer Network (NCCN) in the United States [4] or the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom[16,17]. By contrast, there are hardly any clinical practice guidelines on prostate cancer in our resources. The Prostate CancoGuide by the Catalan Health Agency for Technological Evaluation in Medical Research, 2004, is based on the revision and compilation of other clinical practice guidelines on the same subject.

As a result, and taking into account the high prevalence of this neoplasia and the existing variations in clinical management, within the framework of the collaboration agreement with the health technology evaluation agencies and units, the Ministry commissioned the Aragon Institute of Health Sciences, I+CS, to prepare the current guideline based on the evidence of prostate cancer treatment, with the aim of boosting the cancer health strategy adopted by the Interterritorial Council [4].

This document is the complete version of the *Clinical Practice Guidelines for Prostate Cancer Treatment* (http://www.guiasalud.es).

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2. Scope and Objectives

The *objective* of this CPG is for it to be used as a tool to improve the clinical management of men with prostate cancer, which in Spain is usually decided in specialised care, in addition to providing relevant information on this subject for other health professionals attending to people with this disease, the patients and their families.

The guideline summarises the evidence available for the key issues in prostate cancer clinical management, and is aimed at provide healthcare professionals and patients with the means to share decision making. It is not mandatory nor does it replace the clinical judgment of health personnel.

The *target population* for the guideline is adult males with a histological check or clinical diagnosis in accordance with a primary prostate adenocarcinoma. In other words, it is not designed for asymptomatic men with elevated levels of prostate-specific antigen (PSA) without a histopathological diagnosis of prostate cancer, nor for patients with metastasis in the prostate from other tumours, nor for children and adults with other malignant tumours in the prostate, both epithelial and non-epithelial, such as the cell carcinoma and rhabdomyosarcoma.

The *health area* involved is specialist care.
The recommendations are presented depending on their *clinical situation*:

- Localised prostate cancer: definition, risk factors, clinical management and monitoring following treatment with intent to cure.
- Locally advanced prostate cancer: definition and clinical management.
- Prostate cancer in PSA relapse after treatment with intent to cure: definition and clinical management.
- Disseminated prostate cancer: definition and clinical management.

The guideline aims to advise on different *clinical management alternatives*, such as surgery (open or laparoscopic prostatectomy), external radiation therapy (including 3D-CRT, IMRT) and/or brachytherapy; expectant management (watchful waiting or active surveillance), hormonal manipulation, which includes androgen ablation (orchiectomy, oestrogen, LHRH agonists), antiandrogens (steroidal and non-steroidal) and combined hormone therapies; and other treatments, such as chemotherapy (cytotoxic agents), bisphosphonates, radiopharmaceuticals, cryotherapy and high intensity ultrasound (HIFU).

We have not provided information on how to go about early detection (screening), diagnosis or staging of these patients.

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3. Methodology

The methodology employed is included in the following document: "Preparation of Clinical Practice Guidelines in the National Health System. Methodology Manual", from the Ministry of Health and Consumer Affairs and the Aragon Institute of Health Science[14].

The steps to be followed are:

- Forming the *guidelines preparation group*, composed of specialists in urology, radiotherapy, medical oncology and pathology, nursing in urology and methodologists.
- Formulation of clinical questions using the format: Patient/intervention/comparison/ outcome or PICO.
- Bibliographic Search in: The Cochrane Library, DARE, Medline-PubMed, Embase, Trip Database, IME and manual search. Languages of studies elected: English, French, Italian, Portuguese and Spanish. As a first phase, a preliminary search of the CPG and systematic reviews was carried out. Two CPGs on prostate cancer were identified which were rated with the instrument AGREE[20]. One was then chosen[16,17] as a secondary source of evidence to help with specific sections in the guideline, according to the methodology of preparation-adaptation-update used in the Basque Country clinical practice guideline on asthma[21]. As a second phase, an extended search of original studies (controlled and randomised clinical trials, observational, prognostic and case series studies) was carried out.
- Evaluating the quality of the studies and a summary of the evidence for each question, following the SIGN recommendations (Scottish Intercollegiate Guidelines Network)[22].
- Preparing recommendations based on "formal evaluation" or "reasoned judgment" in SIGN. The classification of evidence and the grading of the recommendations was done with the SIGN system (see Appendix 1) [22]. Controversial recommendations or those with an absence of evidence were resolved by consensus during several meetings of the preparation group.
- Expert collaborators participated in the revision and drafting of the recommendations and the external reviewers supplied notable contributions to the draft guidelines revision.
- Collaboration from the following scientific organisations was received: the Spanish Association of Urology (AEU), Spanish Society of Radiotherapeutic Oncology (SEOR), Spanish Society of Medical Oncology (SEOM) and the Spanish Association of Nursing in Urology (AEEU), who were represented by members of the preparation group, the expert collaborators and the external reviewers.
- The detailed information with the CPG methodological process is available at http://www.guiasalud.es.

An update is planned for the guideline every three years, or less if new scientific evidence (that could modify some of the recommendations offered in this guideline) appears. Updates will be made on the electronic version of the guideline, available at http://www.guiasalud.es.

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4. Classification of prostate cancer

There are different ways of classifying patients with prostate cancer: according to the extension of the tumour (TNM), the histopathological grade (Gleason), the clinical or histopathological stage, or its risk.

4.1 TNM Classification[4]

T: Primary tumour[d]

Tx		Unable to assess the primary tumour.
T0		No evidence of primary tumour.
T1		Tumour not clinically apparent, not palpable or visible using imaging techniques.
	T1a	Tumour detected by chance in an extension less than or equal to 5% of the tissue removed.
	T1b	Tumour detected by chance in an extension greater than 5% of the tissue removed.
	T1c	Tumour identified by fine needle biopsy (for example, as a consequence of a high PSA).
T2		Tumour confined to the prostate.
	T2a	Tumour covers half of a lobe or less.
	T2b	Tumour covers more than half of a lobe but not both lobes.
	T2c	Tumour covers both lobes.
T3		Tumour extends beyond the prostatic capsule.
	T3a	Extracapsular extension unilateral or bilateral
	T3b	Tumour invades the seminal vesicle(s).
T4		Tumour is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, upper anus muscles and/or pelvic wall.

N: Regional lymph nodes[e]

Nx	The regional lymph nodes cannot be assessed.
N0	Regional lymph node metastasis is not shown.
N1	Metastasis in regional lymph nodes.

M: Distant metastasis[e]

Mx	Distant metastasis cannot be assessed.
M0	There is no distant metastasis.
M1	Distant metastasis.
M1a	Non-regional lymph node(s).
M1b	Bone(s).
M1c	Other location(s).

d prostate adenocarcinoma.
e The regional lymph nodes are those in the lower pelvis (mainly, the iliopelvic lymph nodes located below the bifurcation of the primitive iliac arteries)[4].

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4.2 Histopathological grading

The grading system proposed by Gleason *et al* [23] is recognised internationally, and is based on a pathological examination of prostate tissue obtained by a biopsy. The result is an average index of abnormality for the tissue, for which values between 2 and 10 can be taken[17]. The classification according to Gleason is as follows[4]:

Gx	The degree of differentiation cannot be assessed.
G1	Well differentiated (weak anaplasia): Gleason 2-4.
G2	Moderately differentiated G2 (moderate anaplasia): Gleason 5-6.
G3-4	Poorly differentiated/undifferentiated (marked anaplasia): Gleason 7-10.

In 2005, the International Society of Urological Pathology (ISUP) 24 established an international consensus on the diagnosis of a Gleason 2-4, deciding that such a score should be an exception (only in tumours of the transition zone), and will therefore always have to be compared with another expert.

4.3 Classification according to the clinical or pathological stage

In prostate cancer, the stage at which the patient is found is *clinically* defined (ie, a stage which is suspected before removing the prostate, taking into account the clinical and analytical information available at that time, which may be inaccurate or incomplete: cT1 to cT4) or *pathologically* defined (a stage defined on the basis of information provided by the analysis of a piece surgically extracted by radical prostatectomy: pT1 to pT4). There are different definitions for these phases[4,15,17,18]. For example, many studies talk about *advanced* prostate cancer[25-30] to refer generally to the locally advanced or disseminated form. This guideline uses the following definitions:

Localised prostate cancer

From an *anatamopathological* point of view, localised prostate cancer is the verified presence of prostate adenocarcinoma without extension to the prostate capsule (pT1-pT2), without lymphatic invasion (N0) and without metastasis (M0).

The patient with *clinically* localised prostate cancer is consistent with the stage cT1-cT2, N0-Nx, M0-Mx.

Locally advanced prostate cancer

From an *anatamopathological* point of view, locally advanced prostate cancer is the verified presence of prostate adenocarcinoma with extracapsular invasion (pT3a) or invasion to the seminal vesicles (pT3b), but without lymphatic invasion (N0) nor metastasis (M0).

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The patient with locally advanced prostate cancer at a *clinical stage* corresponds with the stage cT3, N0-Nx, M0-Mx.

Prostate cancer in PSA relapse

The patient with prostate cancer in PSA relapse is one who, having received primary treatment with intent to cure, has an increased PSA (prostate specific antigen) defined as "biochemical recurrence" (section 7.1 of this guideline).

Disseminated prostate cancer

From an *anatamopathological* point of view, the patient with disseminated prostate cancer is the verified presence of prostate adenocarcinoma with lymphatic invasion (N1) and/or metastasis (M1) and/or a primary tumour which is fixed or invades adjacent structures other than the seminal vesicles (pT4).

The patient with *clinically* disseminated prostate cancer spread corresponds to a stage N1, M1 or cT4.

4.4. Classification according to risk

The TNM clinical stage is insufficient to establish the most appropriate treatment for patients with localised prostate cancer.

Patients diagnosed with prostate cancer at localised or locally advanced clinical stages can fall into risk or prognosis subgroups on the basis of known risk factors, primarily PSA and Gleason.

This guideline uses the D'Amico classification[31,32]:

- Low risk: cT1-cT2a, Gleason < 7 and PSA ≤ 10 ng/ml.
- Intermediate risk: cT2b, Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml).
- High risk: cT2c or PSA > 20 ng/ml or Gleason > 7.

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5. Localised prostate cancer

From an *anatamopathological* point of view, localised prostate cancer is the verified presence of prostate adenocarcinoma without extension to the prostate capsule (pT1-pT2), without lymphatic invasion (N0) and without metastasis (M0).

The patient with *clinically* localised prostate cancer is consistent with the stage cT1-cT2, N0-Nx, M0-Mx.

5.1. Prognostic factors

Questions to answer:

• What are the prognosis factors in localised prostate cancer?

The majority of prostate cancers never progress to be clinically significant. A minority of clinically relevant cases remain confined to the prostate for many years, while others rapidly transform into a life-threatening disease[33].

The clinical TNM stage is insufficient to establish the most appropriate treatment for patients with localised prostate cancer, as it does not reflect the prognostic situation in full. Patients diagnosed with clinically localised prostate cancer should be categorised into risk or prognosis subgroups on the basis of known risk factors, primarily PSA and Gleason.

There are several prognostic factors used in routine clinical practice, since there is evidence from observational studies that they are risk factors which are independent of mortality in patients with localised prostate cancer. The most used are the Gleason grade and PSA pre-treatment, but others have also been proposed whose importance is much discussed, including extension of the tumour beyond the prostate capsule, the invasion of the seminal vesicles, the tumour volume, etc[33].

5.1.1. Gleason Grade

Univariate and multivariate analysis of prognostic factors for prostate cancer identify the Gleason grade as one of the most significant prognostic markers, with the worst results for survival, tumour extension and disease-free period the more undifferentiated the tumour[34-47]. The use of combined Gleason indices (relative proportion of samples with a high degree of cancer) provide more accurate prognostic information[48].

If the Gleason grade is evaluated along with the clinical stage even more accurate prognoses can be made[38]. However, it has been found that when the tumour is of a high degree, the prognosis is poor even when there is organ-confinement[39].

The most accurate Gleason grade is obtained with a sample from radical prostatectomy. When it is attempted with a fine needle biopsy sample, a high error rate is found, often higher

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then 50%[49,50]. Some studies suggest that the most common error occurs when the fine needle biopsy suggests a Gleason < 7, which, after analysing a surgical sample, in many cases is classified as Gleason ≥ 7[51,52].

5.1.2. Prostate specific antigen (PSA)

Prostate cancer causes the release of a number of substances in the blood, including prostate specific antigen (PSA). There are three forms of circulating PSA: free PSA, PSA covalently linked to alpha-1 antichymotrypsin (PSA-ACT) and PSA combined with alpha-2 macroglobulin (PSA-MG). The total PSA is the sum of these three values[33].

Normal blood tests measure total PSA. Irrespective of other factors, a high value during diagnosis means worse survival results, more likelihood of PSA relapse and an increased risk of death[41,42,45,53-55]. It is associated with other unfavourable circumstances, such as extracapsular extension, seminal vesicle invasion, increased tumour or positive surgical margins.

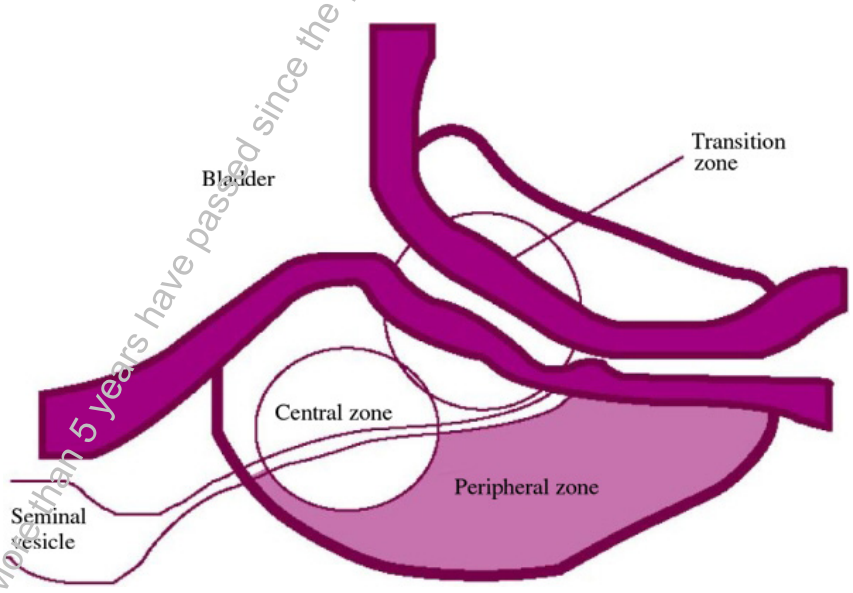
A post-treatment increase also indicates a deterioration in survival results[54] and always precedes the clinical recurrence of cancer[44]. Therefore, total PSA has become the most relevant information for monitoring patients with prostate cancer.

Values of free PSA and PSA-ACT are also independent prognostic survival factors in patients with prostate cancer[41].

5.1.3. Focus of origin

The prostate is divided into three parts: the peripheral zone, the transition zone and the central zone[33] (see Figure 1). Several studies have found that the tumours of the transition zone data have a better prognosis (malignancy, extension of the tumour, biochemical recurrence-free survival) than those in the peripheral zone[34,56-59].

Figure 1. Parts of the prostate



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5.1.4. Multifocality

A high proportion (67%) of prostate cancers have multiple locations, which can have different histological degrees (heterogeneity)[37,60].

Multifocality is associated with higher rates of recurrence, and with a more advanced degree and stage[60].

5.1.5. Extracapsular extension

Extracapsular extension is an indicator of poor prognosis, with higher rates of PSA relapse and progression of the disease[35,61,62]. This unfavourable relationship increases when there is an increased level of invasion and penetration of the capsule by the tumour[61,63].

Some authors believe that the prognostic significance of extracapsular extension is due to its association with other variables, such as tumour size or infiltration of the seminal vesicules[34,35,64,65], but others found worse outcomes in patients with capsular penetration, regardless of the possible associated locoregional variables[61,62].

5.1.6 Invasion of the seminal vesicles

Invasion of the seminal vesicles is a poor prognosis factor associated with higher rates of progression of the disease and PSA relapse[40,62,64].

Several authors argue that this increased risk of adverse outcomes is due to its association with other poor prognosis markers, such as the Gleason grade, extra-capsular extension, tumour volume, positive surgical margins or pre-operation PSA levels[53,62,64].

In addition, Debra *et al* believe that the meaning of the prognosis in the invasion of seminal vesicles is not constant, and depends on the vesicle zone affected: if the invasion is in the distal portion, the prognosis is worse than when it occurs in the proximal zone[66].

5.1.7 Positive surgical margins

Some studies have found that positive surgical margins are a predictor of increased risk of disease progression or PSA relapse[36,40,43,62].

Although for some authors this effect of positive surgical margins is due to its association with other variables that worsen the prognosis, such as seminal vesicle invasion, extracapsular extension, preoperative PSA, Gleason grade or tumour volume[36,62], others have found prognostic significance independently[40,43.62].

5.1.8 Tumour volume

A greater tumour volume in the prostatectomy sample is associated with increased risk of progression of the disease and PSA relapse[35,36,62]. However, several studies have found that

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this adverse effect is due to its association with several prognostic factors[35,36,40,67], including the existence of capsular penetration, positive surgical margins, seminal vesicle invasion or an advanced Gleason grade[34-36,62,67].

5.1.9 Age

Different publications have concluded that a lower age is a favourable prognosis factor. In one study of men treated with radical radiotherapy[68], it was found that the rate of distant metastasis after 5 years was significantly higher in patients older than 65 years. In another publication[69], the time of PSA relapse after radical prostatectomy was significantly higher for those less than 70 years of age. And in a third study[70], the rate of PSA relapse after radical prostatectomy was significantly higher in the over-70 age group, compared to rates found with those under 51 and with those in the 51-70 age group.

However, not all authors came to the same conclusions on the influence of age. One study found no differences between different age groups in a cohort of 6,890 patients[71]. In addition, Austin *et al* suggested that race is an important modifier on the effect of age on prognosis. In their study, with black men, younger patients had more advanced tumours at diagnosis and poorer outcomes for survival, while the study showed the opposite for white men[72].

5.1.10 Microvascular Density

The growth of a tumour of a certain size requires angiogenesis, and when it starts to form new vessels, the risk of metastasis is also increase[33] Some authors maintain that the increase in microvascular density is a poor prognosis factor in clinically localised prostate cancer, with a higher risk of progression of the disease or PSA relapse[62,73-75].

Other authors have found no association between microvascular density of the tumour and the prognosis of patients with prostate cancer[76].

5.1.11 Morphometric findings

Several studies have been used histological nuclear morphometry (analysis of the shape and size of cell nuclei) to make predictions on the prognoses in prostate cancer[33]. Some authors[37,38] have stated that the amount of the elliptically shaped nuclei is a very important prognostic factor. Others have analysed the size of nuclei[79-84] and other morphometric factors[79-81] to make prognostic predictions about localised prostate cancer.

5.1.12 E-cadherin

E-cadherin is an important molecule in maintaining tissue adhesion[33]. The low immunohistochemical expression of E-cadherin in patients with prostate cancer represents a poor prognosis factor, leading to lower survival, a more advanced disease or a higher risk of recurrence[85-89].

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5.1.13 Insulin-like growth factors (IGFs)

There are two forms of IGF (insulin-like growth factors, formerly called somatomedins): IGF-I and IGF-II. To exercise their function, they bind to two specific sites, IGFR-I and IGFR-II. In the plasma, they are bound to specific proteins, IGFBP (IGFBP 1 to 6)[33].

The imbalance in IGF production of the proteins it binds to is linked with different pathological conditions. The increase in IGF-II or IGFBP5 is associated with the pathological stage, the appearance of lymph node metastases, malignant tissue and levels of PSA, in contrast to the increase in IGF-I and IGFBP3. There are some doubts about the significance of the IGFBP2[90-92] serum levels.

5.1.14 p53

Mutation of the gene suppressor p53 gene may cause disproportionate cell growth and has been associated with many malignant tumours[33]. The appearance of mutations in p53 is a poor prognosis factor associated with lower biochemical progression-free survival, increased risk of clinical progression or the appearance of metastasis, resistance to radiotherapy itself or lower overall survival[93-101].

5.1.15 p27

The protein p27 can inhibit the cell cycle and it may have some effect on tumour suppression. Low levels of p27 expression have been associated with worse prognoses in several tumours[33].

Yang *et al* found that low or undetectable levels of p27 expression are an adverse prognostic factor in patients with clinically localised prostate cancer treated with prostatectomy, especially in the pathological stages pT2-pT3b[102].

5.1.16 p21

The protein p21/WAF1 is able to disrupt the cell cycle in the G1 phase by inhibiting the replication of DNA[33]. Its overexpression in patients with prostate cancer, paradoxically, indicates an increased risk of poorer clinical outcomes[103]. The greater expression of another type of p21 (Ras p21), is associated with lower survival after 5 years[104].

5.1.17 DNA diploid

Several authors have found that patients with prostate cancer with DNA diploid have better prognosis results (longer survival and disease-free periods, less advanced Gleason stage, lower risk of metastasis, better response to treatment) than those with non-diploid tumours. Patients with aneuploid tumours have worse results[43,50,105-112].

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5.1.18 Ki-67

Ki-67 is a cell cycle regulatory protein[33]. The increase in the Ki-67 index (the fraction of positive nuclei with Ki-67 in immunohistochemistry) is associated with earlier progression and greater risk of prostate cancer recurrence[113-115].

5.1.19 Percentage of cells in the S phase

The increase in the proportion of cells in the S phase of the cell cycle is associated with shorter survival and disease-free periods in clinically localised prostate cancer[116,117].

5.1.20 Gene expression profiles

Some gene expression profiles are associated with poorer survival outcomes or treatment response in breast cancer[118,119], and studies are being performed to find out whether the same is true for prostate cancer[33].

5.1.21 Androgen receptors

Androgen receptors are found in the nucleus. Their function is to mediate the biological effects of male sex hormones in target cells, by activating the transcription of androgen-dependent genes. The gene for these receptors is in the X chromosome and contains a series of repeated CAG nucleotide triplets. The length of these repetitions varies among individuals and is associated with the transcriptional activity of the androgen receptors[33].

It has been suggested that the existence of alterations in the expression of the androgen receptors is a risk factor for less biochemical progression-free and overall survival in patients with *advanced* prostate cancer (locally advanced or disseminated)[25-30].

5.2 Initial choice of treatment

Question to answer

• For patients with clinically localised prostate cancer, what is the safety and efficacy of different treatment options?

The treatment options normally considered in patients with localised prostate cancer are:

- Treatment with intent to cure[4, 17]: can be done with radical prostatectomy or radiation therapy. It is applied with the aim of completely removing the tumour.
- Observation of the patient or expectant treatment[4, 120]:
  - This term is normally referred to as watchful waiting (WW): a choice of patient management which consists of not doing anything until the progression of the disease

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or appearance of symptoms are seen; at which point the application of a palliative treatment is considered.

• There is another, non-standard expectant management option, which is active surveillance/monitoring. This consists of not doing anything until the aggressiveness of the tumour increases; at which point treatment with intent to cure is started.

- Other treatments, usually considered experimental[4, 17], are cryotherapy or HIFU (high intensity focused ultrasound). They treat the tumour locally.

5.2.1. Radical prostatectomy v other treatments

Radical prostatectomy v Watchful waiting

The watchful waiting attitude is the conscious decision not to provide any kind of treatment until the progression of the disease or presence of symptoms is apparent. In the latter situation, hormonal or palliative treatment could be started, but any radical treatment option is excluded. This attitude is often adopted with men of an advanced age or with significant comorbidities, with a low probability that the cancer will progress in any meaningful way during their expected lifetime[17].

RCT (1+) The randomised clinical trial of Bill-Axelson *et al*[121] compared the efficacy of radical prostatectomy with watchful waiting in patients with localised prostate cancer. The study showed the results with an analysis with intent to treat. The results (accumulated over 10 years) for both groups (radical prostatectomy v watchful waiting) are 19.2% [95% CI = 15.0-24.6] v 44.3% [95% CI: 38.8-50.5] for local progression (RR = 0.33; [CI 95%: 0.25-0.44]); 15.2% [95% CI 11.4-20.3] v 25.4% [95% CI 20.4-31.5] for distance metastasis (RR = 0.60; [CI 95%: 0.42-0.86]), 9.6 % [95% CI 6.5-14.2] v 14.9% [95% CI 11.2-19.8] for cancer-specific mortality (RR = 0.55; [CI 95%: 0.36-0.88]) and 27% [95% CI: 21.9-33.1] v 32% [95% CI: 26.9-38.2] for overall mortality (RR = 0.74: [95% CI: 0.56-0.99]). In other words, surgery is a statistically significant more effective treatment than watchful waiting.

RCT (1+) The clinical trial of Steineck *et al*[122] compared the quality of life for radical prostatectomy v watchful waiting in patients with localised prostate cancer. The results for both groups (radical prostatectomy v watchful waiting) are 80% v 45% for erectile dysfunction (RR = 1.78 [95%: 1.49-2.12], number needed to treat, NNT = 3 for watchful waiting), 29.1% v 39.6% for difficulties in urination (RR = 0.74 [95%: 0.55-0.98], NNT = 10 for surgery), 15.9% v 1.6% for the losses of urine (RR = 9.89 [95% CI 3.07-31.86], NNT = 7 for watchful waiting), 23.3% v 15% for moderate or severe urinary pain (RR = 1.55 [CI 95%: 1.01-2.39], NNT = 12 for watchful waiting), and 33.9% v 36.4% for perceived quality of life (RR = 0.93 [95% CI: 0.71-1.23]). It is believed that the only clinically significant differences for quality of life between the two treatment s are those relating to the sexual sphere, where there are better results for watchful waiting.

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Radical prostatectomy v Active surveillance

The aim of active surveillance is to avoid unnecessary treatment for patients with very slow tumour progression (with a low probability of having clinical progression during their lifetime), and treating only those cancers that show early signs of progression, where treatment with intent to cure could benefit the patients. In this management option, patients are monitored and offered a radical treatment when progression of the disease is apparent[17, 120].

Series of cases (3)

Klotz *et al*[120] evaluated a series of 299 patients with clinically localised prostate cancer and proposed active surveillance for those meeting the following criteria:

- Age < 70 years: Gleason < 7 and PSA ≤ 10 ng/ml (definition similar to low risk).
- Age > 70 years: Gleason ≤ 7 (3 +4) and PSA <15 ng/ml.

These patients received treatment with intent to cure when the PSA doubling time was less than 2-3 years, when a Gleason ≥ 7 appeared in a prostate biopsy or when the patient requested it.

After a follow-up of 5.3 years, 15% of patients experienced early biochemical progression; 3%, clinical progression; 4%, histological progression, and 12% requested radical treatment. After 8 years, overall survival was 85% and cancer-specific survival 99.2% (100% of the deaths from prostate cancer had a PSA doubling time of < 2 years).

Revision of series of cases (3)

The systematic revision of Martin *et al*[123] compared active surveillance protocols for patients with localised prostate cancer, including 5 series of cases. They agreed only in the PSA determination and digital rectal examination in active surveillance, with initial checks after each quarter, then every 6 months.

Expert opinions (4)

The clinical practice guideline on prostate cancer from the United Kingdom's National Institute for Health and Clinical Excellence (NICE)[16,17] recommended special active surveillance in patients with clinical stage cT1, Gleason 3 + 3, PSA < 0.15 ng/ml and less than 50% of biopsy cylinders affected. It also proposed offering active surveillance to other low risk patients and considered it as an alternative for patients at intermediate risk.

Expert opinions (4)

The initial draft of this guideline recommended following up patients who opt for active surveillance with the following measurements[124,125]:

- Repeated yearly biopsies, after 4 years and 7 years, with at least 10 cylinders in each biopsy.
- PSA determinations every 3 months during the first 2 years, and every 6 months thereafter.
- Estimation of the PSA speed with linear regression, using at least 5 PSA determinations extending over at least a year.

It also suggested radical treatment in patients with any of the following data: PSA velocity > 1 ng/ml/year, higher degree or greater extension of the tumour in repeated biopsies, or evidence of locally advanced disease during a rectal examination[124,125].

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Radical prostatectomy v Radiotherapy

The studies that have been performed so far analysing radiotherapy as a treatment for prostate cancer have a follow-up period less than the surgery series.

Efficacy

SR different types of study (3)

In the systematic review of Nilsson *et al*[126] on the effects of radiotherapy for prostate cancer, the effects of radiotherapy alone are compared with radiotherapy associated with an intervention. It concludes that there are a large series of patients with efficacy results for external beam radiotherapy (ERT) and brachytherapy (BT) which are similar to those for radical prostatectomy (RP) for patients with localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml).

SR different types of study (2-)

In the systematic review of the Medical Services Advisory Committee (MSAC) in the Australian Ministry of Health, which includes systematic revisions, retrospective cohort studies and a series of cases, brachytherapy was evaluated with permanent I-125 implants in patients with localised prostate cancer at low risk. The review concluded that the available evidence did not demonstrate any differences in survival or disease progression in these patients compared with ERT v RP v BT.

Series of cases (3)

In another systematic review of the Norway Health Technologies Evaluation Centre (SINTEF)[128], which analysed brachytherapy in patients with localised prostate cancer, a series of cases of men with low or intermediate risk [cT2b or Gleason = 7 or (PSA> 10 and ≤ 20 ng/ml)] when treated with BT or RP was studied. No differences were found in progression-free biochemical survival (PFBS) after 5 years, although the groups were not entirely comparable in terms of age and clinical stage. They also looked at 3 other studies (one cohort study of 2,222 patients, a case-control study and a series of cases) comparing BT with ERT, and in those where there were no differences found in PFBS at 5 and 7 years, although the groups were not entirely comparable in the case studies and controls, and the follow-up time was very short for the series of cases. When comparing BT + ERT v ERT, a case-control study found a greater PFBS after 5 years for the combined treatment (67% v 44%), although in this study the follow-up was incomplete and the average age of the control group was 5 years older. The authors concluded that BT compared with ERT or RP seems to provide comparable results, although the evidence is scant.

SR different types of study (3)

In the systematic revision of Nilsson *et al*[126], the use of high dose rate brachytherapy (HDR) in patients with prostate cancer was also studied. This consists of the application of brachytherapy at a high dose rate with Ir-192 in combination with ERT to provide a boost in the prostate. It must be done through transperineal ultrasound guided biopsy (TRUS). The review concluded that the total minimum dose obtained with this technique is far superior to those achieved with 3D-CRT, with an acceptable toxicity, and it induces local healing in most patients, even those at high risk.

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Safety

SR different types of study (2-)

The systematic revision of the MSAC[127] also compares the toxicity of brachytherapy vs external beam radiation vs radical prostatectomy. It found that, in the short term, brachytherapy is equal to or less toxic than ERT and RP in the area of sexual function (p = 0015); and that, for urinary incontinence, BT is better than RP (p < 0.0001); for urethral obstruction, BT is worse than ERT (p < 0.0001); and for rectal toxicity, BT and ERT have similar results, both being worse than RP (p = 0.03). In other words, the toxicity profiles for RP, ERT and BT are different. The authors of this revision concluded that, although it needs more evidence on the safety and efficacy of BT as a treatment for prostate cancer, its use can be recommended for patients with localised prostate cancer at low-risk, with a glandular volume less than 40 cm^3 and availability of treatment (it is not possible to implement it in all Spanish public establishments).

Cohort study (2+)

The study by Potosky *et al*[129] is a retrospective cohort study comparing the adverse effects of RP vs ERT, with 5 years of follow-up. After 2 years, the (adjusted) percentage of patients with impotence is significantly higher in patients who underwent RP (82.1%) than in those treated with ERT (50.3%). Between 2 and 5 years, sexual function in patients who underwent ERT gets worse, although at 5 years there are still significant differences between the two treatments (erectile dysfunction 79.3% for RP v 63.5% for ERT; odds ratio, OR = 2.5 [CI 95%: 1.6-3.8]). There are significant differences in urinary incontinence (14-16% for RP v 4% for ERT; OR = 4.4 [95% CI: 2.2-8.6]), rectal tenesmus (35% for ERT v 20% for RP; OR = 0.56 [95% CI: 0.36-0.87]) and painful haemorrhoids (16% for ERT v 11% for RP; OR = 0.43 [95% CI: 0.25-0.74]).

Case-control study (2+)

In the SINTEF systematic review[128], which analyses brachytherapy in patients with localised prostate cancer, a case-control study comparing BT vs ERT was investigated. Higher rates of urinary obstruction were found in patients treated with BT, but no differences with regard to sexual function or proctitis were found. A series of cases comparing BT with BT + ERT was also analysed. It found more patients with rectal complications in patients treated with only BT (grade 1: 10.5% v 8.9%; grade 2: 7.1% v 6.5 %; Grade 3: 0.7% v 0,4%).

Series of cases (3)

SR different types of study (2-)

The study by Robinson *et al*[130] is a systematic review comparing rates of erectile dysfunction after RP with preservation of neurovascular bundles (PNB) with other treatments. The results are derived from non-randomised studies of low sample size which may be biased, because they allowed neoadjuvant hormonal therapy (which can block testosterone for up to one year after finishing treatment). It was found that the probability of maintaining erectile function one year after treatment, adjusting for age, was as follows: for BT, 0.80 [95% CI: 0.64-0.96]; for BT + ERT, 0.69 [95% CI: 0.51-0.86]; for ERT, 0.68 [95% CI: 0.41-0.95]; for RP + PNB it was 0.22 [95% CI: 0-0,53]; and for RP without PNB, 0.16 [95% CI: 0.0-0.37].

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5.2.2 Different Radiation Therapy techniques

Conformal radiotherapy vs Conventional radiotherapy

Efficacy

SR different types of study (1+)

In the systematic review of Morris *et al*[131], which includes randomised and non-randomised trials, conformal radiotherapy is compared with conventional for the treatment of localised prostate cancer. In terms of efficacy, the conclusion was that, at similar doses, there were no statistically significant differences for local control of the disease, disease-free survival, biochemical progression-free survival or overall survival. Similar conclusions were found even with added hormonal treatment in both groups.

Safety

In the Morris review[131], the acute toxicity induced by similar doses of radiation applied by conventional and conformal radiotherapy was also reviewed, and three randomised studies with revealing information were identified:

RCT (1+)

In the study by Dearnaley *et al* from 1999[132], statistically significant differences ($p = 0.01$) were found in the incidence of acute gastrointestinal toxicity grade ≥ 2 (proctitis with bleeding), with a frequency of 5% for conformal radiotherapy and 15% for conventional, at a dose of 64 Gy. No significant differences were found in bladder function.

RCT (1+)

In the trial by Koper *et al*[133], which applied a dose of 66 Gy in both groups, a gastrointestinal toxicity of grade 2 was observed in 32% for conventional radiotherapy and 19% for conformal radiotherapy, characterised by anal toxicity and proctitis ($p = 0.02$).

RCT (1+)

The randomised study by Storey *et al*[134], which compares conventional and conformal radiotherapy with escalating doses, identified no statistically significant differences in acute rectal or bladder toxicity ($p = 0.6$).

SR different types of study (2-)

In addition, the Morris review identified 15 non-randomised articles for which no statistically significant differences were found in toxicity when comparing the equivalent dose application of conformal radiotherapy with conventional radiotherapy. This included a minimum follow-up period of 2 years.

RCT (1-)

In another clinical trial by Dearnaley *et al* from 2007[135], improved results were seen for intestinal toxicity (adverse effect frequencies of 8% and 5%, but without statistically significant differences) for the conformal radiotherapy group with escalating doses.

IMRT vs 3-Dimension conformal RT

SR different types of

The systematic review of the Galicia Health Technologies Evaluation Agency, evaluation-t[136] analysed the safety and efficacy of treatment with

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study (2-) intensity modulated radiation therapy (IMRT). This is a (more advanced) 3-dimensional conformal radiotherapy technique, evaluated on patients with localised and locally advanced (T1-T3) prostate cancer. Three retrospective localised prostate cancer studies of poor quality were found which compare IMRT and 3D-CRT. No statistically significant differences were found regarding efficacy. As for safety, better (and statistically significant) results were found for IMRT on the quality of life related to the sexual sphere (p = 0003). Patients treated with IMRT also obtained more favourable (and statistically significant) results in connection with late rectal toxicity grade 2-3 (p < 0.001).

IMRT is available in few Spanish health centres. Its use can be beneficial for patients with localised prostate cancer of intermediate or high risk. Giving a dose > 78 Gy has rectal toxicity problems with 3D-CRT[137, 138], as described more comprehensively in section 5.4 of this guideline. In addition, IMRT allows dose escalation. For patients at low risk, IMRT slows the process without adding any benefits to 3-dimensional conformal radiotherapy.

5.2.3 Adjuvant/neoadjuvant hormone treatment

The scientific evidence examining the safety and efficacy of adjuvant/neoadjuvant hormonal therapy treatment in localised prostate cancer is discussed in detail in section 5.5 of this guideline.

5.2.4 Experimental treatments

SR different types of study (3) The systematic review of Hummel *et al*[139] attempts to assess the clinical efficacy of new and emerging technologies for localised prostate cancer. With regard to cryotherapy (cryoablation of the prostate) and HIFU (high intensity focused ultrasound), analysed using non-comparative studies, it concludes that there is no evidence to support their use as a first line of treatment.

SR different types of study (3) Another systematic review of the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom[140] evaluates the safety and efficacy of HIFU for the treatment of prostate cancer. The localised prostate cancer studies were case series with short follow-up periods (less than 2 years). It also concluded that it is an experimental procedure, and not a first choice treatment.

SR different types of study (2-) The systematic revision of Shelley *et al*[141] compared the efficacy and adverse effects of cryotherapy with those of other primary treatments (radical prostatectomy, radiation therapy and observation) for the management of patients with T1-T3 prostate cancer. A comparative study only was found. Separate results for localised prostate cancer were not found. It considers cryotherapy to be an experimental procedure, and therefore not a first choice treatment.

In other words, different, well-performed systematic reviews[141] have not been able to identify high-quality scientific literature that would support HIFU or cryotherapy as first-line treatment in patients with localised prostate cancer, which leads to the conclusion that there is insufficient evidence in this regard.

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Summary of evidence

1+	For the management of patients with clinically localised prostate cancer, radical prostatectomy (RP) is more effective than watchful waiting[121].
1+	For the management of patients with clinically localised prostate cancer, watchful waiting does not improve the quality of life in a clinically significant manner when compared with RP, except in the sexual area[122].
3	In patients with clinically localised prostate cancer who received active surveillance, with an average follow up of 5.3 years, 15% of patients experienced early PSA relapse, 3% clinical progression, 4% histological progression and 12% sought radical treatment. After 8 years, overall survival was 85% and cancer-specific survival was 99.2% (100% of the deaths from prostate cancer had a PSA doubling time of < 2 years)[120].
3/2-/2+[f]	There are no statistically significant differences found when comparing the efficacy of external beam radiation (ERT), RP and brachytherapy (BT) for clinically localised prostate cancer risk at low or intermediate risk[126-128].
2+	The Association of BT with ERT may have better biochemical progression-free survival results (BPFS) at 5 years than exclusive application of ERT in patients with clinically localised prostate cancer[128].
3	The minimum total dose obtained with high dose rate (HDR) BT is much higher than that achieved with 3D-CRT, with an acceptable toxicity, inducing local healing in the majority of patients with clinically localised prostate cancer, including those at high risk[126].
2-/2+/2+	In patients with clinically localised prostate cancer, those treated with BT have a greater risk of urethral obstruction, while those treated with RP are more likely to suffer urinary incontinence. Treatments with ERT have an intermediate risk of both adverse effects[127-129].
2-/3/2+	Patients with clinically localised prostate cancer treated with BT or ERT have similar rectal toxicity which is higher than that for patients undergoing RP. ERT has more risk of rectal tenesmus and painful haemorrhoids than RP. The combination of BT + ERT may decrease the rate of rectal complications with respect to treatment with BT[127-129].
2-/2+	In patients with clinically localised prostate cancer, BT may have an equal or better toxicity profile in the area of sexual function than RP and ERT[127,128].
2+/2-	In patients with clinically localised prostate cancer, the probability of maintaining erectile function one year after treatment is highest for BT (0.80), followed by BT + ERT (0.69), ERT (0.68), RP with neurovascular bundle preservation (0.22) and RP without bundle preservation (0.16). After 5 years, the probability is still less for RP than for ERT[129,130].

[f] When the evidence presented corresponds to a number of bibliographic references with different levels of evidence, each will be presented in the same order as they are listed.

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1+	When comparing the efficacy of conformal and conventional radiotherapy, no statistically significant differences can be found for similar doses in clinically localised prostate cancer[131].
1+/1+/1+ 1-	In patients with clinically localised prostate cancer, rectal toxicity with conformal radiotherapy (RT) is equal to or less than conventional RT[132-135].
2-	For the management of patients with clinically localised prostate cancer, there is no difference in the efficacy of IMRT (intensity modulation radiotherapy) and 3-dimensional conformal RT. IMRT provides better results in the sexual sphere (p = 0.003), and allows higher doses to be given with less rectal toxicity[136].
1+	There is no evidence to support high-intensity focused ultrasound (HIFU) or cryotherapy as first-line treatment in patients with clinically localised prostate cancer[139-141].

Recommendations

B	In patients with clinically localised prostate cancer with a life expectancy exceeding 10 years, radical prostatectomy or external beam radiotherapy is recommended.
A	In patients with clinically localised prostate cancer treated with external beam radiotherapy, it must be 3-dimensional conformal, as this allows the administration of higher doses of radiation with greater safety.
D	In patients with clinically localised prostate cancer treated with external beam radiation, brachytherapy may be associated to allow escalating dosages to be achieved.
D	In patients with clinically localised prostate cancer at low risk (cT1-cT2a, Gleason < 7 and PSA ≤ 10 ng / ml), low or high dose brachytherapy as a monotherapy is an alternative treatment with intent to cure for prostate volumes less than 50 cm^3.
B	In patients with clinically localised prostate cancer with a life expectancy below 10 years, watchful waiting may be an alternative.
D	In patients with clinically localised prostate cancer at low risk, Gleason < 3 + 3, < 50% affected cylinders in the biopsy and PSA < 15 ng/ml, active surveillance can be offered as an alternative to immediate radical treatment.
√	Monitoring of patients with active surveillance will be as follows: - PSA determinations and rectal examination every three months during the first 2 years, then later, every six months. - Prostate biopsy at 1 year, at 4 and at 7 years (there must be at least 10 cylinders per biopsy).
√	In patients with active surveillance, radical treatment will be considered when any of the following data appear: PSA velocity > 1 ng/ml/year, higher degree or greater extension of the tumour in repeated biopsies, or evidence of locally advanced disease in a rectal examination.
A	Primary cryotherapy and high intensity focused ultrasound techniques are experimental in prostate cancer patients at a clinically localised stage.
A	RESEARCH RECOMMENDATION: Randomised trials should be started comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with clinically localised prostate cancer.

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5.3 Surgery

Questions to answer:

- In patients with clinically localised prostate cancer for which surgery is indicated, what is the safety and efficacy of different types of laparoscopic radical surgery (transperitoneal or extraperitoneal, robot-assisted or not) in comparison with open radical prostatectomy?
- In a patient with clinically localised prostate cancer for which radical surgery with intent to cure is indicated, does lymphadenectomy increases cure rates for the disease? And which is better, extended or limited lymphadenectomy?
- In patients with clinically localised prostate cancer for which radical prostatectomy is indicated, what percentage of positive surgical margins are obtained when keeping or not keeping neurovascular bundles (uni- or bilaterally)? And what results are obtained with regard to urinary incontinence and erectile dysfunction?

5.3.1 Laparoscopic radical prostatectomy

Radical prostatectomy can be done with a retropubic or perineal incision with or without a laparoscopic technique. Radical prostatectomy with a laparoscope eliminates the need for large incisions in the body. It allows lymphadenectomy and conservation of neurovascular bundles, as well as the use of robotic arms to facilitate the operation. It can be done via a transperitoneal or extraperitoneal route[142-146].

For the incorporation of a minimally invasive method, the oncological and functional results obtained with the new technique must be at least equivalent to the test reference[142].

The evaluation of the rate of positive surgical margins is essential for proper evaluation for different surgical procedures from the oncological point of view[147]. Finding positive surgical margins in prostatectomised patients is associated with higher rates of PSA relapse, local and systemic progression[148].

RCT (1+)

The Guazzoni *et al* study[147] is a randomised clinical trial of 120 patients with clinically localised prostate cancer subject to open (ORP) or laparoscopic radical prostatectomy (LRP)[g] carried out by the same surgeon with extensive experience in both techniques. No differences in the rates of positive surgical margins could be found when comparing both groups (ORP v LRP), but there are better results with laparoscopic for blood loss (mean ± standard deviation: 853.3 ± 485 v 257.3 ± 177 cm^3; $p < 0.001$); catheter removal rate within 5 days (33.4% v 13.4%); operating time (mean ± standard deviation: 170 ± 34.2 v 235 ± 49.9 min; $p < 0.001$), and post-operative pain on the first day ($p = 0.250$). No data were available for long-term safety and efficacy.

[g] transperitoneal.

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SR different types of study (2-)

A systematic review by the United Kingdom National Institute for Health and Clinical Excellence[143] evaluated the safety and efficacy of LRP, in comparison with ORP, for localised prostate cancer. It included non-randomised and case series studies. No statistically significant differences were found between LRP (transperitoneal - TLRP, extraperitoneal - ELRP or robot-assisted: RALRP) and ORP for either biochemical progresion free-survival or urinary incontinence with a follow-up of less than 3 years. There are no statistically significant differences with regard to urinary continence. And, although not significant (due to low sample size), there are differences with regard to sexual impotence, with a tendency to get better results for LRP in different studies.

SR different types of study (2-)

A systematic review of Tooher *et al*[149] compares LRP (transperitoneal, extraperitoneal or robot-assisted) and ORP. It includes non-randomised comparative studies. The safety and adverse effects, including urinary incontinence, are very similar for the different types of LRP and ORP: TLRP v ORP, similar (complications average 2% v 0%); ELRP v ORP, similar; RALRP v ORP, higher complication rate for ORP.

Besides relying on clinical criteria, whether LRP is used or not depends on the resources available in the hospital. For example, robot LRP exists in very few Spanish public centres.

The learning curve for laparoscopic radical prostatectomy is much longer than for the open, but the robot type is much less than conventional laparoscopic methods[149].

Cohort study (2+)

The study of Hu *et al*[146] included 2,702 men treated with LRP v ORP. Those treated with laparoscopic prostatectomy were found to be younger ($p < 0.001$). This study offered no information on other relevant clinical or anatamopathological data (pre-operative PSA, Gleason score, clinical stage). A lower rate of preoperative complications was found with the minimally invasive treatment (29.8% v 36.4%; $p = 0.002$), in addition to shorter hospital stays (1.4 v 4.4 days; $p < 0.001$). However, patients who received LRP received salvage treatment more frequently than for ORP (27.8% v 9.1%; p <0001). Regarding the need for salvage treatment, better results were obtained by surgeons who had performed more laparoscopic prostatectomies the previous year (OR = 0.92; [95% CI: 0.88-0.99]), although the need for subsequent salvage treatment was still higher for ORP. The results of this study in light of the clinical or pathological patient data were not analysed.

5.3.2 Lymphadenectomy

Performing pelvic lymphadenectomy in patients receiving radical prostatectomy has been justified for two possible objectives[150-152]:

- The elimination of microscopic lymph node metastases, which could theoretically increase patient survival and disease-free periods.

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- The most accurate identification of patients with positive lymph nodes, which would allow a better staging for the cancer, and thus the application of a more appropriate treatment for the patient.

Extended[h] pelvic lymphadenectomy includes a larger number of lymph nodes than the limited or standard[i] treatment.

Cohort study (2+) The Bhatta-Dhar *et al* study[153] is a cohort study with a 6-year follow-up of 336 patients with clinically localised prostate cancer, PSA < 10 ng/ml and Gleason < 7 (low risk) who underwent prostatectomy. The decision to perform a lymphadenectomy (LN) or not was taken by the surgeon. After 6 years no significant difference was found in PSA relapse-free survival between patients with or without LN.

Cohort study (2-) The study by Allaf *et al*[150] is a retrospective cohort study involving 4,000 patients with clinically localised prostate cancer, comparing extended lymphadenectomy (n = 2,135) v limited (n = 1,865), with each technique applied by a different surgeon. No statistically significant differences in the results for biochemical progression-free survival at 5 years were found. No differences were found when comparing extended vs limited for biochemical recurrence-free survival in patients with positive lymph nodes, although there was a trend for improved survival results in patients who underwent extended dissection (p = 0.07). More positive lymph nodes were detected with the extended treatment (mean 14.7 v 12.4; p = 0.15) as well as more patients with lymph node affectation (p < 0.0001).

Cohort study (2+) The 2003 study from Bader *et al*[151] is a cohort study involving 367 men with clinically localised prostate cancer subjected to prostatectomy, with a comparison of results with and without LN. 25% (92 patients) had positive lymph nodes. 43% of the patients had a pathological stage pT3 (infra staging), this group had a greater chance of having positive lymph nodes than those who were in stages pT1-T2 (39% v 13%). The existence of positive lymph nodes is statistically significantly associated with increased risk of progression, decreased cancer-specific survival (74% at 5 years) and a greater probability of relapse.

RCT (1+) The study by Clark *et al*[152] is a clinical trial that compares extended and limited lymphadenectomy in 123 patients with clinically localised prostate cancer. In this study, the same patient received an extended LN on one side and a limited LN on the other side. No statistically significant differences were found between both groups with respect to unilateral surgical complications. Positive lymph nodes were found in only 8 patients, making it impossible to find any statistically significant differences between each group.

[h] Includes the removal of all fibrous, fatty and lymphatic tissue in an area extending (from top to bottom) 2 cm above the bifurcation of the common iliac artery to the Cloquet's ganglion, and (at the sides) from the genitofemoral nerve to the vesicle wall[152].

[i] Includes the lymph nodes from the external iliac veins (from the deep circumflex iliac vein to the bifurcation of the common iliac artery), plus all the connective tissue that lies between the internal and external iliac arteries, and that surrounds the obturator nerve[153].

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If the aim is to increase cure rates, it seems that extended lymphadenectomy is not indicated for patients with localised prostate cancer, except in clinical studies. In patients at intermediate or high risk, it could be used only to improve the staging of the patient.

5.3.3 Preservation of neurovascular bundles

The preservation of the neurovascular bundles surrounding the prostate after performing radical surgery is intended to functionally improve the patient, especially in the sexual sphere but also with regard to urinary incontinence[148,154,155]. However, it must not be forgotten that the purpose of giving radical prostatectomy is to completely remove the tumour[4,17,148], and that the discovery of positive (microscopic) surgical margins in prostatectomised patients is associated with higher rates of biochemical, local and systemic progression[148].

Cohort study (2-)

The study by Sofer *et al*[148] is a retrospective cohort study evaluating the effect of radical prostatectomy (RP) with the preservation of neurovascular bundles (PNB) vs RP without PNB (the surgeon applies PNB when he feels that it is technically feasible, which can skew the results, because patients with PNB may be less at risk). The number of losses is not specified. The percentage of positive surgical margins was 24% in patients with PNB and 31% in those without PNB (no statistically significant differences were found). The cumulative risk of PSA relapse (BF) with PNB at 3 and 5 years of surgery was 9.7% and 14.4%, respectively. No statistically significant differences were found when comparing the BF of patients with PNB v patients without PNB after 3 years of surgery (not even when stratifying according to preliminary risk), nor when comparing unilateral PNB v bilateral PNB v patients without PNB. After adjusting for a number of variables (age, PSA and Gleason), there was no statistical difference in the probability of positive surgical margins between the two groups: OR = 0.89 [95% CI: 0.61-1.31].

SR different types of study (2-)

The study by Robinson *et al*[130] is a systematic review comparing the rates of erectile dysfunction after RP with PNB vs other treatments. The results were obtained from non-randomised studies, with low sample size, and may be biased because they allow neoadjuvant hormonal therapy (which can block testosterone for up to a year after finishing the treatment). It was found that the probability of maintaining erectile function after RP + PNB 1 year after treatment is 0.34 [95% CI: 0.30-0.38], and after 2 years was 0.25 [95% CI: 0.18-0.33]. After adjusting for age, the probability 1 year after treatment is 0.22 [95% CI: 0-0.53]. The probability of erectile dysfunction for RP without PNB is 0.16 [95% CI: 0.0-0.37]. In other words, for patients with localised prostate cancer who have undergone a prostatectomy, the probability of erectile function is greater if the neurovascular bundles are preserved.

Cohort study (2+)

The study of Kundu *et al*[154] includes 1,834 patients who underwent retropubic RP with or without PNB, whether uni- or bilaterally. The neurovascular bundles were retained in only 5% of patients (91 out of 1,834). No statistically significant differences were found (p = 0.3) in the recovery of urinary continence when comparing RP and PNB v RP without PNB (minimum follow-up of 18 months).

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Cohort study (2-)

The study of Wille *et al*[155] is a small sample size retrospective cohort study which analyses post-RP urinary continence results according to a number of variables. It consists of a questionnaire completed by 81% of those requested. It concludes that PNB (both uni- and bilateral) does not affect urinary continence results (no statistically significant difference between the performance or not of PNB in RP).

In conclusion, the various studies suggest that there is no difference between preserving the bundles or not with respect to the margins and incontinence, but there is a difference with regard to sexual potency, in studies with a minimum follow-up of 1 year.

Prostatectomy patients are getting younger, so the maintenance of erectile function (in addition to urinary incontinence) is an important aspect to consider when deciding on treatment.

Summary of evidence

1+	There are no differences in the rates of positive surgical margins between both groups (laparoscopic vs open prostatectomy) in patients with clinically localised prostate cancer[147].
2+	Patients treated with laparoscopic radical prostatectomy (LRP) need salvage treatment more frequently than those who have had open radical prostatectomy (ORP): 27.8% v 9.1%; $p < 0.001$. These differences were reduced by surgeons who performed a greater number of LRPs. These results are not adjusted for clinical or anatomopathological data[146].
2+/1+	There are better results for LRP (compared with ORP) in reducing blood loss, early withdrawal of the catheter, postoperative pain on the first day, length of hospital stay and preoperative complication rate in patients with clinically localised prostate cancer[146, 147].
2-	No significant differences were found for urinary continence when comparing different types of LRP and ORP in patients with clinically localised prostate cancer[143, 149].
2-	With regard to impotence, there is a tendency to get better results with LRP in patients with clinically localised prostate cancer, although there are no significant differences between the two techniques (small sample size)[143].
2+	In patients with clinically localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng / ml) carrying out pelvic lymphadenectomy did not affect the PSA relapse-free survival 6 years after surgery[153].
2-	In patients with clinically localised prostate cancer, comparing extended vs limited lymphadenectomy, no differences were found in biochemical progression free survival after 5 years[150].
2-	No differences were found when comparing extended vs limited for biochemical progression-free survival in patients with positive lymph nodes and clinically localised prostate cancer, although there was a tendency for better survival in patients who underwent the extended dissection ($p = 0.07$) [150].

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2-	In patients with clinically localised prostate cancer, extended lymphadenectomy allows more patients with lymph node affectation and more positive lymph nodes to be detected than the limited[150].
2+	In patients with clinically localised prostate cancer, patients with pathological stage pT3 are more likely to have positive lymph nodes than those with stages pT1-pT2[151].
2+	In patients with clinically localised prostate cancer, the existence of positive lymph nodes was associated with significantly increased risk of progression, decreased cancer-specific survival and a greater probability of relapse[151].
1+	In patients with clinically localised prostate cancer, there were no differences in unilateral surgical complications when comparing extended vs limited lymphadenectomy[152].
2-	In patients with clinically localised prostate cancer subjected to radical prostatectomy, the preservation or not of neurovascular bundles has no significant effect on biochemical progression at 3 years nor on the percentage of positive microscopic surgical margins[148].
2-	For patients with clinically localised prostate cancer who had a prostatectomy, there was a tendency to maintain erectile function when neurovascular bundles were preserved[130].
2+/2-	In patients with clinically localised prostate cancer who underwent radical prostatectomy, there were no statistically significant differences in urinary continence results if the neurovascular bundles were preserved or not[154,155].

Recommendations

B	In clinically localised prostate cancer with radical prostatectomy indicated, either laparoscopic or open surgery can be employed.
C	In patients with clinically localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), lymphadenectomy is not necessary when performing radical prostatectomy.
D	In patients with clinically localised prostate cancer risk at intermediate or high risk treated with radical prostatectomy, a lymphadenectomy must be performed.
D	In patients with clinically localised prostate cancer with radical prostatectomy indicated, it is recommended to preserve the neurovascular bundles when intraoperative findings permit.

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5.4 Radiotherapy

Question to answer:

- In patients with clinically localised or locally advanced prostate cancer for which radiotherapy is indicated (external and/or brachytherapy), what volume, dose and fractionation have the best safety and efficacy depending on the risk?

According to the previous risk of the patient, previous studies suggest that changes in the dose, volume and fractionation of radiotherapy received by men with localised and locally advanced prostate cancer can have an impact on survival and disease control, and can also affect the toxicity of the treatment[126,156].

In this CPG, patients with prostate cancer are divided into the following categories, proposed by D'Amico[31,32], according to risk:

- Low risk: cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml
- Intermediate risk: cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)
- High risk: cT2c or Gleason > 7 or PSA > 20 ng/ml.

5.4.1. Dosage

In a randomised clinical trial carried out by Peeters *et al*[137] which compared a dose of 68 Gy vs 78 Gy in 664 patients with prostate cancer T1b-T4, it was found that there were statistically significant differences between the two groups for biochemical progression-free survival (BPFS) at 5 years: 54% v 64% (p = 0.01).

Low Risk

Cohort study 2++ The Khuntia *et al* study[157] is a prospective cohort study, which includes T1-T3 patients treated with external radiotherapy (RT). For patients with T1-T3 and low risk, biochemical progression-free survival at 5 years depending on the dose was 52% (≤ 68 Gy), 82% (68-72 Gy), 93% (≥ 72 Gy); p < 0.001.

Cohort study 2++ The Kupelian *et al* publication[158] is a prospective dose escalation cohort study that analyses 292 patients with localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml) treated with external beam radiotherapy (ERT). Statistically significant differences were found in the BPFS at 96 months when comparing ≤ 72 Gy vs > 72 Gy (77% v 95%; p = 0.01). When analysing by dosage subgroups at 4 years, again statistically significant differences were found when comparing <74 Gy (77%) vs > 74 Gy (94%), with p = 0.09. There were no differences when comparing 74 Gy (94%) vs 78 Gy (96%), with p = 0.90.

RCT (1-) In a randomised clinical trial by Peeters *et al*[137] with T1b-T4 patients, it was found that there were no statistically significant differences for BPFS after 5

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years when comparing 68 Gy vs 78 Gy in the low risk group. One cannot rule out that there were no differences, however, because the study had insufficient statistical power to analyse the subgroups and because some patients received a lesser dose than was planned initially.

RCT (1++) In another clinical trial by Pollack *et al*[159], 70 Gy was compared to 78 Gy in patients with T1-T3 prostate cancer, where the minipelvis and prostate with vesicles were radiated. The results are shown according to different risk groups. In patients with PSA <10 ng/ml, there were no statistically significant differences in the BPFS.

Intermediate risk

Cohort study (2++) The article by Hanks *et al*[160] is a prospective dose escalation cohort study, which analyses patients with localised prostate cancer treated with external RT (median 9 years of follow-up). For a PSA between 10-20 ng/ml, statistically significant differences were found in the BPFS when comparing 71.5 Gy vs 75.6 Gy vs > 75.6 Gy (19% vs 31% vs 84%); p = 0.0003.

RCT (1-) The Peeters *et al* trial[137], which analysed patients T1b-T4 and the intermediate risk group, found that there are statistically significant better results for the BPFS at 5 years in the higher dose when comparing 68 Gy vs 78 Gy.

Intermediate and high risk

Cohort study (2++) In the Khuntia *et al* study[157] of T1-T3 patients of intermediate risk, the BPFS at 5 years depending on the dose was 27% (≤ 68 Gy), 51% (68-72 Gy), 83% (≥ 72 Gy, median dose 78 Gy); p < 0.001. It also found that for T1-T3 patients at high risk, the BPFS at 5 years depending on the dose was 21% (≤ 68 Gy), 29% (68-72 Gy), 71% (≥ 72 Gy; median dose 78 Gy); p < 0.001. Moreover, by increasing the median dose from 70 Gy to 78 Gy, the greatest improvement was found in the intermediate and high risk group. In other words, in patients with T1 and T3 prostate cancer and intermediate and high risk, the best BPFS results at 5 years were in the ≥ 72 Gy group (median 78 Gy).

RCT (1++) In the Pollack *et al* study[159], in T1 and T3 patients with PSA > 10 ng/ml, comparing 70 Gy vs 78 Gy, statistically significant better results at 5 years were found for the BPFS: 48% vs 75% (p = 0.011).

High Risk

RCT (1-) In the test Peeters *et al* study[137], in the high-risk group for BPFS at 5 years, there is a tendency to find better results for the higher dose when comparing 68 Gy vs 78 Gy.

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Toxicity

RCT (1-) In another Peeters article[138], the same patients as in the previous study[137] are included, but toxicity results are offered instead of efficacy results. It includes patients with T1-T4 prostate cancer. In this study, different volumes and dose limits (VD) are compared and different institutions are involved. When comparing 68 Gy vs 78 Gy (with a volume that includes the anus), no statistically significant differences were found for gastrointestinal toxicity grades 2 and 3 (p = 0.2; p = 0.4). However, statistically significant differences were found for rectal bleeding (3% vs 7%; p = 0.02) and anal incontinence (for faeces, mucus or blood, which require disposable pads more than twice a week; 6% vs 10%; p = 0.03). In other words, a dose of 78 Gy maintains anal bleeding and losses below 10% in patients with T1-T4 prostate cancer.

5.4.2 Volume

The studies that examine differences in the radiation volume refer to the "planning target volume", which is the required dose that is prescribed.

The fields that are used vary according to different studies. Some authors[161,162] deal only with the prostate (POV, with a maximum volume of 10 x 10 cm), partial pelvis or minipelvis (MPV, which includes the prostate, seminal vesicles and periprostatic lymph nodes and obturators, with a typical size of 10 x 14 cm), and total pelvis (TPV, which includes the prostate, seminal vesicles and external iliac lymph nodes). In other studies[163], the pelvis area (PV) is defined. This includes both the MPV and TPV. Other authors[164] irradiate a volume which includes the prostate and seminal vesicles (PSSV field).

Low Risk

In patients with localised and locally advanced prostate cancer at low risk, no evidence has been found that irradiation of the pelvis improves results.

Intermediate and high risk

Cohort study (2+) The publication by Vargas *et al* study[164] is a multicentre study which includes patients with clinically localised (86.5%) and locally advanced (13.5%) prostate cancer and a high risk of lymph node invasion, ie, above 15% (calculated according to the formula[j] proposed by Roach *et al*[163]). ERT plus TPV (n = 312) is compared with ERT with PSSV (n = 284). The choice of volume to be used in the study depended on the centre treating the patient: TPV in two centres, PSSV in

[j] The Roach formula to calculate the risk of lymph node invasion: (2/3) PSA + [(Gleason-6) x 10]. There are other ways of calculating this probability, such as the nomogram of Borque *et al*[165], validated for the Spanish population.

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another centre. When comparing the two groups with a follow-up of 15 years, statistically significant differences were found in clinical failure (univariate p = 0.04, multivariate p = 0.9), but not for PSA relapse (univariate p = 0.8), clinical disease-free survival (p = 0.06), cancer-specific survival (p = 0.8) and overall survival (p = 0.6). In other words, for patients with clinically localised prostate cancer and a high risk of metastasis (greater than 15% risk), when comparing pelvic irradiation with prostate and seminal vesicles, no statistically significant differences for clinical control and cancer-specific survival with a follow-up period of up to 15 years were found.

Cohort study (2+)

The study by Jacob *et al*[161] includes 420 men with prostate cancer and pre-treatment PSA of <100 ng/ml, treated with 3-dimensional conformal ERT with or without Androgen deprivation of short duration. The patients had a lymph node invasion risk of ≥ 15% or a cT2 stage with Gleason 6-10. POV fields were applied in 48 cases, MPV in 74, and TPV in 298. In this study, the irradiated volume was not a significant predictor of outcome.

RCT (1-)

The 2003 study by Roach *et al*[163] is a random clinical trial comparing RT with PV + neoadjuvant hormone therapy (HT) vs RT with PV + adjuvant HT vs RT with POV + neoadjuvant HT vs RT with POV + adjuvant HT in patients with prostate cancer (67% were pT2c-pT4). When comparing PV vs POV at 4 years, statistically significant differences for progression-free survival were found (54.2% vs 47.0%; p = 0.02) and biochemical progression-free survival (40.7% vs 33.5%; p = 0.007), but not for overall survival (84.7 vs 84.3%; p = 0.94), PSA relapse rate (34% vs 40%; p = 0.089), lymph node failure nor metastasis at a distance.

RCT (1-)

In the article by Lawton *et al*[166], the results from the 2003 Roach study[163] were updated with 1,292 cases and a longer follow-up period, of up to 10 years (with a median of 7 years). When comparing PV with POV, no statistically significant differences were found in progression-free survival (p = 0.99) nor for biochemical progression-free survival (p = 0.93).

RCT (1-)

In another article by Roach *et al*[166], published in 2006, an analysis was done of the patient subgroups who received neoadjuvant HT from the 2003 Roach study[163] (those who had obtained the best results for larger volumes), with a longer follow-up (up to 9 years, with a median of 7).

In this article from 2006, the patients were divided into 3 groups according to the volume received: TPV (n = 309) vs MPV (n = 170) vs POV (n = 131). Of the patients studied, 67% were pT2c-pT4, and all of them received neoadjuvant HT.

Statistically significant differences were found (p = 0.024) for progression-free survival at 9 years when comparing the 3 groups: 40% (TPV), 35% (MPV) and 27% (POV), and also when comparing TPV vs POV (p = 0.010; in favour of TPV), but not for TPV vs MPV (p = 0.06).

No statistically significant differences were found (p = 0.06) for biochemical progression-free survival at 9 years when comparing the 3 groups, nor when comparing TPV vs MPV (p = 0.12). However, statistically significant differences were found for TPV when compared with POV (p = 0025).

Statistically significant differences were also found for TPV in the percentage of PSA relapse at 9 years when comparing the 3 groups with each other (p = 0.025), when comparing TPV with POV (p = 0.029) and with MPV (p = 0.022).

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RCT (1-) When analysing the results at 4 years according to the type of hormone therapy received in the 2003 article by Roach[163], when PV + neoadjuvant HT was compared with POV + neoadjuvant HT, statistically significant differences were found in progression-free survival (54.2% vs 47.0%; p = 0022), but not for overall survival (84.7% vs 84.3%; p = 0.94), local progression (9.1% vs 8.0%; p = 0.78), lymph node failure (1.3% vs 2.5%; p = 0.12) nor distant metastasis (8.2% vs 6.6%; p = 0.54).

RCT (1-) Lawton[166] did not find statistically significant results for biochemical progression-free survival at 10 years according to the type of HT received, nor when comparing PV + neoadjuvant HT with POV + neoadjuvant HT (p = 0.066), or PV + adjuvant HT against POV + adjuvant HT (p = 0.057). These results were only offered for a definition of biochemical progression different to the global analysis[k]. Regarding overall survival, there is no statistical difference when comparing PV +neoadjuvant HT with POV + neoadjuvant HT (p = 0.9629). However, POV + adjuvant HT has better results than PV + adjuvant HT (p = 0.01).

To summarise, in patients with localised or locally advanced prostate cancer at high-risk, there is no evidence that irradiation of the pelvis (TPV) when compared with irradiation of a field that includes the seminal vesicles (MPV or PSSV) improves the results in a clinically significant manner.

Toxicity

RCT (1-) In the 2003 article by Roach *et al*[163], when comparing the different groups (RT with PV + neoadjuvant HT vs RT with PV + adjuvant HT vs RT with POV + neoadjuvant HT vs RT with POV + adjuvant HT), no statistically significant differences in the following types of toxicity were found: grade ≥ 3, acute (p = 0.06) and late (p = 0.09) gastrointestinal; and acute (p = 0.39) and late (p = 0.85) genitourinary.

RCT (1-) In the 2006 article by Roach *et al*[162], the following toxicity results were found when comparing TPV vs MPV vs POV: Acute gastrointestinal toxicity ≥ grade 2 was 46.5% vs 36.7% vs 20.2%; p < 0.001. The late was 15.2% vs 8.5% vs 7%; p = 0.002. Acute genitourinary toxicity of grade ≥ 2 was 31.4% vs 37.7% vs 22.1%; p = 0.016. The late was 14.9% vs 14.7% vs 5.6%; p = 0.03.

In patients with prostate cancer (with more than 67% T2c-T4) and neoadjuvant hormone therapy, genitourinary and gastrointestinal toxicity (both acute and late) ≥ grade 2 is higher in patients who received the radiation volume TPV.

5.4.3 Fractionation

There are some randomised studies[167,168] that compare hypofractionation with standard, but the dosages were too low (maximum 66 Gy) for a comparison to be valid.

[k] Here, biochemical progression is considered when 2 consecutive increases in PSA, separated by 1 month, are found (the elevation must be at least 20% greater than the previous PSA value, with a minimum of 0.3 ng/ml). In the rest of the results in this section, biochemical progression is regarded as an increase of serum PSA levels of 2 ng/ml on the PSA nadir, which is the definition used in this guideline (see section 7.1).

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The study by Kupelian *et al*[169] is a series of cases of 770 patients treated with hypofractionation for 5 years, with a biochemical progression-free survival of 82% [95% CI: 79-85]. In addition, there is another set of 300 cases treated with hypofractionation, from Higgins *et al*[170], who also received neoadjuvant hormone therapy, which found a biochemical progression-free survival of 57.3%, and cancer-specific survival rate of 83.2% at 5 years.

It is believed that at present there is not enough evidence to reach any conclusion on the safety and efficacy of hypofractionation, compared with standard fractionation.

Summary of evidence

1-	In patients with prostate cancer treated with radiotherapy, for the biochemical progression-free survival (BPFS) at 5 years, 78 Gy has better results than 68 Gy[137].
2++	In patients with prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), doses ≥ 72 Gy improve BPFS at 5 and 8 years compared with lesser doses[157,158].
1-/2++/1++	In patients with prostate cancer at low risk, doses > 74 Gy do not improve BPFS when compared with lesser doses[137,158,159].
2++	In patients with prostate cancer at intermediate risk [cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)], doses > 75.6 Gy improve BPFS at 9 years when compared with lesser doses[160].
1-	In patients with prostate cancer at intermediate risk, doses ≥ 78 Gy improve BPFS at 5 years compared with 68 Gy doses[137].
2++/1++	In patients with prostate cancer at intermediate or high risk (cT2c or PSA > 20 ng/ml or Gleason > 7), doses ≥ 78 Gy improve BPFS at 5 years when compared with lesser doses[157,159].
1-	In patients with prostate cancer at high risk, doses ≥ 78 Gy improve BPFS at 5 years compared with 68 Gy doses[137].
1-	Doses of 78 Gy keep rectal bleeding and losses below 10% in patients with T1-T4 prostate cancer, without increasing the gastrointestinal toxicity grades 2 and 3[138].
2+	For patients with clinically localised prostate cancer and a high risk (> 15%) of lymph node invasion, there are no differences for clinical control or cancer-specific survival (with a follow-up of up to 15 years) when comparing RT volumes in total pelvis (TPV) vs RT in prostate + seminal vesicles (PSSV)[164].
2+	For patients with prostate cancer and a high risk (> 15%) of lymph node invasion or a cT2 stage with Gleason 6-10, the irradiated volume is not a significant predictor for results[161].
1-	For patients with pT2c-pT4 prostate cancer, when comparing RT in the pelvis (PV) vs RT only in the prostate (POV), there are differences for progression-free survival after 4 years (p = 0.02) and biochemical progression-free survival (p = 0.007), but not for overall survival (p = 0.94), local progression (p = 0.78), PSA relapse rate (p = 0.089), lymph node failure or distant metastasis[163].
1-	For patients with pT2c-pT4 prostate cancer, when comparing PV vs POV, no differences are found at 10 years for progression-free survival (p = 0.99) or biochemical progression-free survival (p = 0.93)[166].

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1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant hormone therapy (HT), there are no significant differences between TPV and POV with respect to progression-free survival at 9 years (p = 0.010)[162].
1-	For patients with pT2c-pT4 prostate cancer, and neoadjuvant HT, there are better results for those treated with TPV than POV for biochemical progression-free survival at 9 years (p = 0.025) and percentage of PSA relapse (p = 0.029)[162].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant HT, there are no significant differences between TPV and MPV with respect to progression-free survival (p = 0.06) and biochemical progression-free survival at 9 years (p = 0.12)[162].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant HT, there are significant differences between TPV and MPV with regard to percentage of PSA relapse at 9 years (p = 0.022), with better results for VPT[162].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant HT, there are significant differences at 4 years between PV and POV with respect to progression-free survival (p = 0.022), but not for overall survival (p = 0.94), local progression (p = 0.78), lymph node failure (p = 0.12) or distant metastasis (p = 0.54) at 9 years[163].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant HT, there are no significant differences at 10 years between PV and POV with respect to progression-free survival (p = 0066) or overall survival (p = 0.9629)[166].
1-	For patients with pT2c-pT4 prostate cancer and adjuvant HT, no significant differences are found at 10 years between PV and POV with respect to progression-free survival (p = 0057). However, POV shows better results for overall survival (p = 0.01)[166].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant hormone therapy, no differences were found in gastrointestinal or genitourinary toxicity ≥ grade 3 when comparing RT with PV vs RT with VOP[163].
1-	For patients with pT2c-pT4 prostate cancer and neoadjuvant hormone therapy, gastrointestinal and genitourinary toxicity grade ≥ 2 is higher in patients who received RT with TPV than those who received RT with MPV, with the exception of acute genitourinary toxicity[162].
3	It is believed that at present there is not enough evidence to lead to any conclusion on the safety and efficacy of hypofractionation compared to standard fractionation[169,170].

Recommendations

B	In patients with clinically localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml), the dose of external beam radiation should be 72-74 Gy.
B	In patients with clinically localised prostate cancer at intermediate risk [(cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)], the dose of external beam radiation should be 76-78 Gy.
B	In patients with clinically localised prostate cancer at high risk (T2c or PSA > 20 ng/ml or Gleason ≥ 7) or with prostate cancer at the locally advanced clinical stage (cT3), the dose of external beam radiation must be at least 78 Gy.

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B	In patients with localised prostate cancer at low risk, only the prostate must be radiated.
C	In patients with prostate cancer and a ≥ 15% risk of lymph node invasion, radiation of the prostate and seminal vesicles is recommended.
√	RESEARCH RECOMMENDATION: Randomised trials to assess the usefulness of modified fractionation (hypofractionation, etc) of radiotherapy in prostate cancer should be started.

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5.5 Hormone therapy

Question to answer:

- In patients with clinically localised prostate cancer subjected to treatment with intent to cure, does the implementation of neoadjuvant or adjuvant hormone treatment improve cure rates for the disease?

Because hormone therapy induces prostate cell apoptosis[4,10], patients with prostate cancer often choose to combine a local treatment (usually prostatectomy or radiation therapy) with a general treatment when having hormone therapy. In such cases, HT can be applied[17,171] before the primary treatment (neoadjuvant HT), at the same time (concomitant HT) or afterwards (adjuvant HT).

RCT SR (1+) The study by Kumar *et al*[171] compared the effectiveness and side effects of hormone therapy added to local treatment (radical prostatectomy or radiotherapy) vs local treatment in patients with localised and locally advanced prostate cancer (sometimes without separating the two groups).

5.5.1 HT + RP vs RP

Neoadjuvant HT + RP vs RP

RCT SR (1+) In the review by Kumar *et al*[171], for patients with T1 and T2 disease with localised prostate cancer risk at low and intermediate risk [cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)] who received radical prostatectomy, the addition of neoadjuvant HT did not improve overall survival (OR = 1.11 [95% CI: 0.67-1.85]; p = 0.69). There was no available data on disease-associated survival (DAS). A significant limit reduction on relapse rates was found (OR = 0.74 [95% CI: 0.55-1.0]; p = 0.05).

Adjuvant HT + RP vs RP

RCT (1+) In the only article about the Kumar review[171] which analysed patients with T1-T2 Nx localised prostate cancer who received radical prostatectomy (McLeod *et al*[172]), the addition of adjuvant HT (bicalutamide 150 mg/day) did not improve survival.

5.5.2 HT + RT vs RT

Neoadjuvant HT + RT vs RT

RCT (1++) The study by D'Amico *et al*[173] is a high-quality randomised clinical trial that includes localised prostate cancer patients (most of them at low risk, cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml) in which (3-dimensional conformal) radiation treatment + neoadjuvant androgen suppression HT is compared with 3D-CRT; in both cases at a dose of 30 Gy. The overall survival at 5 years in the group treated with RT + HT was 88% [95% CI: 80-95%] and 78% [95% CI: 68-88%] in those treated with RT. In other words, no statistically significant difference in overall survival between the two groups was found 5 years after treatment.

Adjuvant HT + RT vs RT

RCT (1+) In the McLeod *et al* study[172] for patients with localised prostate cancer who received radical radiotherapy the addition of adjuvant HT (bicalutamide 150 mg/day) did not improve survival.

5.5.3 Neoadjuvant/adjuvant hormone treatment

SR different types of study (3) The Hummel *et al* study[139] is a systematic review comparing different treatments for localised prostate cancer. In the comparison of local treatment + neoadjuvant HT v local treatment, no differences were identified in terms of biochemical progression-free survival (BPFS), and when comparing local treatment + adjuvant HT vs local treatment, no differences were identified in terms of survival, although there were indications that high-risk patients could benefit from HT added to local treatment.

5.5.4 HT toxicity

SR of RCT and RCT (1+/1++) In the Kumar review[171] and the D'Amico study[173], for patients with localised prostate cancer who received radical treatment, the addition of HT (neoadjuvant or adjuvant) increased adverse events (hot flushes, diarrhoea, fatigue, gynecomastia).

Specifically, bicalutamide appears to cause high levels of gynecomastia (sometimes painful) among those studied.

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Summary of evidence

1+	In patients with clinically localised prostate cancer at low and intermediate risk [cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)] who received radical prostatectomy, the addition of neoadjuvant hormone therapy did not improve overall survival[171].
1+	In patients with clinically localised prostate cancer who received radical prostatectomy, the addition of adjuvant HT (with bicalutamide 150 mg/day) did not improve survival[172].
1++	In patients with localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml) who received radical radiotherapy, the addition of neoadjuvant HT did not improve overall survival at 5 years[173].
1-	In patients with clinically localised prostate cancer at intermediate risk [cT2b or Gleason = 7 (PSA > 10 and ≤ 20 ng/ml)] who received radical radiotherapy, the addition of neoadjuvant HT did not improve overall survival at 5 or 8 years[173].
1+	In patients with clinically localised prostate cancer who received radical radiotherapy, the addition of adjuvant HT (with bicalutamide 150 mg/day) did not improve survival[172].
3	In patients with clinically localised prostate cancer treatment with intent to cure, patients at high risk (cT2c or PSA > 20 ng/ml or Gleason > 7) may benefit from the addition of neoadjuvant and/or adjuvant HT[139].
1+/1++	In patients with clinically localised prostate cancer who received radical treatment, the addition of HT (neoadjuvant or adjuvant) increases adverse events[171,173].
1+	In patients with prostate cancer, the addition of bicalutamide seems to cause high rates of gynecomastia[172].

Recommendations

A	In patients with clinically localised prostate cancer at low risk (cT1-cT2a and Gleason < 7 and PSA ≤ 10 ng/ml) or intermediate risk [cT2b or Gleason = 7 or (PSA > 10 and ≤ 20 ng/ml)], neoadjuvant hormone therapy with radical prostatectomy should be avoided.
B	In patients with clinically localised prostate cancer at low or intermediate risk, hormone therapy adjuvant to radical prostatectomy should be avoided.
A	In patients with clinically localised prostate cancer at low risk, neoadjuvant hormone therapy with radiotherapy should be avoided.
B	In patients with clinically localised prostate cancer at low risk, hormone therapy adjuvant to radiotherapy should be avoided.
√	In patients with clinically localised prostate cancer at intermediate risk, the use of neoadjuvant or concomitant hormone therapy to radiotherapy is recommended.
√	In patients with clinically localised prostate cancer at high risk (cT2c or PSA > 20 ng/ml or Gleason> 7), the criteria used in the patient with locally advanced prostate cancer will be followed for the use of neoadjuvant or adjuvant hormone therapy to radical prostatectomy or radiotherapy.

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5.6 Monitoring

Question to answer:

- When can the monitoring of a patient with localised prostate cancer after treatment with intent to cure (radical prostatectomy and radical radiotherapy) be completed? What tests should be performed, and how often?

Some patients with localised prostate cancer receive radical treatment with intent to cure[4,17], which is aimed at completely removing the tumour. This is usually done with radical prostatectomy or radical radiotherapy (external beam radiotherapy and/or brachytherapy).

PSA relapse is said to occur when the prostate cancer patient who has received a treatment with intent to cure exceeds a certain level of total PSA, indicative of a significantly higher risk of morbidity and mortality[4]. PSA relapse is followed in a few years by clinical recurrence[174].

Case series (3)

To assess how to monitor men with localised prostate cancer subjected to radical prostatectomy, firstly, the Han *et al* case series[171] was investigated. The study followed 2,404 such patients over 15 years. It found that no patient experienced local or distant recurrence without the PSA level increasing. In addition, patients with clinical stage T1a or Gleason 2-4 (a subgroup of 50 cases) experienced no PSA relapse[l]. Patients with clinical stage T1b-T1c did not experience PSA relapse within 10 years of monitoring. In the rest of the clinical stages, no patient had PSA relapse after 15 years.

Cohort study (2+)

Another publication by Kupelian *et al*[175] compared patients with localised prostate cancer treated with prostatectomy vs radiotherapy[m]. The percentage of the 1,467 prostatectomised patients with biochemical progression-free survival (BPFS)[n] was 79% [95% CI: 77-81%] at 5 years and 67% [95% CI: 64-71%] at 10 years. While the percentage of the 1,049 irradiated patients was 66% [95% CI: 63-69%] at 5 years and 62% [95% CI: 58-65%] at 10 years. The survival curve stabilised around 6.5 years after radiotherapy treatment and 13 years after the operation.

Cohort study (2++)

The Hanks *et al* study[160] is a series of 229 cases of localised prostate cancer treated with 3-dimensional conformal external beam radiation (3D-CRT), which was the standard radiotherapy treatment for these patients. Biochemical progression-free survival[o] was 55% at 5 years, 48% at 10 years and 48% at 12 years, with no statistically significant differences when compared with each other. The BPFS curve stabilised around 7.2 years. When stratified into different prognosis groups according to the pre-treatment PSA level, no statistically

[l] Definition of biochemical progression with a cut-off level of 0.2 ng/ml.
[m] RT: 57% conformal, 43% conventional; RT: 54% > 72 Gy, 46% ≤ 72 Gy.
[n] Definition of biochemical progression: the ASTRO[176] definition was used for irradiated patients; for those who received surgery, a cut-off of 2 ng/ml.
[o] ASTRO definition of biochemical progression.

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significant differences for BPFS were found. In patients who had pre-treatment PSA <10 ng/ml, the biochemical progression-free survival at 8 years was between 68% and 74%.

Case series (3) The Albertsen *et al* case series[47] followed 767 patients with localised prostate cancer who did not receive treatment with intent to cure, and found that the cancer-specific survival curve for these patients stabilised at 15 years. This result is considered extrapolable to the rest of the patients who did receive treatment.

In addition to the survival data, another factor to take into account when deciding the maximum length of follow-up, is that normally patients with localised prostate cancer who opt for radiotherapy are older than those who choose surgery when diagnosed; this was also found in these studies[160,174]. The average age was 70 years for those treated with radiotherapy and 58.2 years for those who underwent prostatectomy.

Expert reviews (4) Since no studies have been found comparing the PSA monitoring frequency guidelines, it is proposed to follow the recommendations of the 2007 prostate cancer clinical practice guideline from the European Association of Urology[4], which proposes reviews at 3, 6 and 12 months after treatment with intent to cure, then every 6 months after the 1st year and annually after the 3rd year.

Expert reviews (4) To be able to establish the recommendations, the 2005 consensus of the International Society of Urological Pathology (ISUP)[24] was also taken into account. It was agreed that the diagnosis of a Gleason summation grade 2-4 in the prostatectomy sample should be an exception (only in transition zone tumours) and should always be confirmed.

Summary of evidence

4	Diagnosing a Gleason score of 2-4 in the prostatectomy sample is something so exceptional that it must be checked[24].
3	Patients with a clinical stage T1a or Gleason 2-4 treated with surgery did not experience biochemical progression[174].
3	Patients with a clinical stage T1b-T1c treated with surgery did not experience biochemical progression after 10 years of monitoring[174].
2+	The survival curve for patients with clinically localised prostate cancer subjected to radical prostatectomy stabilised about 13 years after treatment[175].
3	In the rest of the clinical stages for clinically localised prostate cancer treated with surgery, no patient had biochemical progression after 15 years[174].
3	The cancer-specific survival curve for patients with clinically localised prostate cancer who did not receive treatment with intent to cure stabilised at 15 years[47].
3	No patient with clinically localised prostate cancer treated with surgery experienced local or distant recurrence without the PSA level increasing first[174].
2++/2+	The survival curve for patients with clinically localised prostate cancer who received radiotherapy stabilised after about 7 years after treatment[160.175].
2++/3	Patients with clinically localised prostate cancer who underwent radiotherapy treatment were older at diagnosis than those who received surgery[160,174].

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Recommendations

D	The unusual case of a Gleason score of 2-4 being found in the prostatectomy sample should be viewed with caution until reviewed by another expert.
D	Patients with a confirmed Gleason score of 2-4 in the prostatectomy sample do not require monitoring for cancer.
D	Patients with prostate cancer in clinical stages T1a who have undergone radical prostatectomy do not require monitoring for cancer.
D	Prostate cancer patients in clinical stages T1b-T1c who have undergone radical prostatectomy require monitoring within 10 years.
D	For the rest of the patients with clinically localised prostate cancer (T2) after treatment with radical prostatectomy, the monitoring period should be 15 years.
D	The minimum period of monitoring for patients with clinically localised prostate cancer after radiotherapy with intent to cure should be 8 years.
D	The only monitoring for patients with clinically localised prostate cancer treated with radical prostatectomy or radiotherapy are PSA controls, providing biochemical progression is not detected.
D	The recommended PSA monitoring frequency for patients with clinically localised prostate cancer is 3, 6 and 12 months after treatment with intent to cure, then every 6 months after the 1st year, and annually after the third year.

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6. Locally advanced prostate cancer

From the *anatomopathological* point of view, patients with locally advanced prostate cancer are those with the confirmed presence of prostate adenocarcinoma with extracapsular invasion (pT3a) or of the seminal vesicles (pT3b) without lymphatic invasion (N0) or metastasis (M0).

Locally advanced prostate cancer patients at the *clinical stage* are those with a stage cT3, N0-Nx, M0-Mx.

6.1 Initial choice of treatment

Question to answer:

- What is the safest and most effective treatment for a patient with prostate cancer at the locally advanced clinical stage?

The following options[4] may arise when considering the treatment of patients with locally advanced prostate cancer:

- Local treatment: radiotherapy or prostatectomy
- Observation of the patient (watchful waiting)
- Combination of local treatment (radiation or prostatectomy) and hormone therapy
- Hormone therapy exclusively
- Other experimental treatments: cryotherapy or HIFU

6.1.1 Prostatectomy vs other treatments

Prostatectomy vs watchful waiting

No studies were found comparing prostatectomy with watchful waiting (WW) in patients with locally advanced prostate cancer.

Prostatectomy vs Radiotherapy

No studies were found comparing prostatectomy with radiotherapy in patients with locally advanced prostate cancer. However, for these patients, it is known that:

Cohort study (2 +)

- Due to the very nature of locally advanced cancer, it is unlikely that a prostatectomy would completely remove the tumour. The worst side effect of this treatment is urinary incontinence, which affects the quality of life of those operated upon (in patients with localised prostate cancer[129], the risk of incontinence is 14-16%).
- Radiation therapy has similar efficacy to that of prostatectomy, but greater safety. The most significant side effects with this treatment are related to the

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rectum (in localised prostate cancer[129] when lower doses are employed, the risk of tenesmus is 35% and painful haemorrhoids, 16%).

6.1.2 IMRT vs 3-dimensional conformal RT

SR different study types (2-)

The systematic review of the Health Technology Evaluation Agency of Galicia, avalia-t[136], aims to analyse the safety and efficacy of treatment with intensity modulated radiation therapy (IMRT), which is an advanced form of 3-dimensional conformal radiotherapy, in patients with localised and locally advanced prostate cancer (T1-T3). It concludes that scientific evidence on the safety and efficacy of IMRT compared to conformal radiotherapy is limited and of low quality, and that studies using IMRT have not found any statistically significant differences in disease control or survival of patients with locally advanced prostate cancer when compared with the equivalent dose of 3D-CRT. Regarding safety, the review concluded that IMRT has less late rectal and sexual toxicity compared with 3D-CRT in patients with localised prostate cancer.

6.1.3 Neoadjuvant/adjuvant hormone treatment

Kumar *et al*[171] compared the safety and efficacy of hormone therapy added to local treatment (radical prostatectomy or radiotherapy) vs local treatment in patients with localised and locally advanced prostate cancer (on occasions without separating the two groups).

HT + WW vs WW

RCT (1+)

In the study by McLeod *et al*[172] comparing HT (with bicalutamide 150 mg/day) added to WW vs WW in patients with locally advanced prostate cancer at the clinical stage, bicalutamide obtained better results for biochemical progression-free survival (HR = 0.60; [95% CI: 0.49-0.73]; p < 0.001), in addition to a tendency to improving overall survival (HR = 0.81 [95% CI: 0.66-1.01]; p = 0.06).

HT + RT vs RT

Neoadjuvant HT + RT vs RT

SR of RCT (1+)

The studies analysed by Kumar *et al*[171] comparing RT + neoadjuvant HT vs RT in the treatment of locally advanced prostate cancer give the following relevant results:

- With regard to overall survival at 8 years, no better results were found with neoadjuvant HT, but improvement was seen in those with tumours with a Gleason score of 2-6 (70% vs 52%; p = 0.015).
- For disease-free survival at 5 years, a statistically significant hazard ratio (HR) (0.65 [95% CI: 0.52-0.80]; p = 0.0001) was found[177]. At 8 years,

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the percentage of disease-free patients was higher in the neoadjuvant treatment group (33% vs 21%; $p < 0.004$)[178].

- For biochemical disease-free survival, a highly significant pooled OR for neoadjuvant HT was found (1.93; [95% CI: 1.45-2.56]), with heterogeneity between the studies.

SR different types of study (1+)

The systematic review of Jereczek-Fossa *et al*[156] was intended to study radiotherapy treatment for nonmetastatic prostate cancer. It found that the addition of neoadjuvant hormone treatment to radiotherapy increased disease-free survival in T1-T4 patients with an OR = 1.64 [95% CI: 1.12-2.4]. The duration of hormone treatment in these studies was variable, but in most cases was about 3 months.

Adjuvant HT + RT vs RT

The studies identified by the Kumar review[171] which addressed adjuvant hormone therapy and radiotherapy gave the following results:

SR different types of study (1+)

When LHRH analogues were used as adjuvants, results improved significantly with respect to overall survival, disease-free survival, risk of distant metastasis and biochemical progression-free survival at 5 and 9 years[179, 180]. Regarding locoregional failure, the best results were seen at 5 years[179]. For cancer-specific survival, there was significant improvement with the combined treatment at 5 years[179] but not at 12 years[180].

Adjuvant hormone therapy with bicalutamide, with a median follow-up of 7.4 years showed better results for the combined treatment with regard to overall survival and disease-free survival[181].

SR different types of study (1 +)

The systematic review of Sharifi *et al*[182] found that in patients with locally advanced prostate cancer, androgen deprivation adjuvant to radiotherapy improves overall survival at 5 years (in two separate studies) and 10 years (53 % v 38%; $p < 0.004$) statistically significantly.

SR different types of study (2 +)

In studies of adjuvant hormone therapy after radiotherapy which appeared in the systematic review of Jereczek-Fossa *et al*[156], the usual duration of adjuvant hormone treatment in patients with locally advanced prostate cancer was 2-3 years.

HT + prostatectomy vs prostatectomy

Neoadjuvant HT + prostatectomy vs prostatectomy

The articles included in the Kumar *et al* review[171] comparing these treatments included T1-T3 N0 M0 patients, but the patients had predominantly T1 and T2 disease and the results were not shown as separate, so they cannot be used to draw conclusions about locally advanced prostate cancer patients.

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Adjuvant HT + prostatectomy vs prostatectomy

RCT (1+) The only article in the Kumar *et al* review[171] that analyses patients with locally advanced prostate cancer (McLeod *et al*[172]), includes T1-T4 Nx patients for whom the administration of bicalutamide (150 mg/day) as adjuvant to local treatment (prostatectomy or RT) or watchful waiting (WW) was compared with local treatment or WW. For prostate cancer patients at the locally advanced clinical stage, when comparing bicalutamide with prostatectomy vs prostatectomy, bicalutamide obtained better results for biochemical progression-free survival (HR = 0.75 [95% CI: 0.61-0.91]; p = 0.004), but no statistically significant difference was found for overall survival with a maximum follow-up of 10 years (HR = 1.09 [95% CI: 0.85-1.39]; p = 0.51).

SR different types of study (1 +) The systematic review of Sharifi *et al* [182] was aimed at analysing the risks and benefits of androgen deprivation in locally advanced prostate cancer and in localised prostate cancer at high risk. It found that in prostate cancer patients at the locally advanced clinical stage who were subjected to prostatectomy where lymph node affectation was detected, adjuvant androgen deprivation improved overall survival at 10 years (72.4% v 49%; p = 0.025).

Prostatectomy + HT vs RT + HT

RCT (1-) The Akakura *et al* study[183] is a randomised clinical trial that seeks to identify the safety and efficacy of prostatectomy + neoadjuvant and adjuvant HT vs RT + neoadjuvant and adjuvant HT in 95 patients with cT2b-T3 N0 M0 prostate cancer. 37% (17/46) of the patients operated upon and 27% (13/49) of those who received radiation therapy in this study were clinically localised cases (T2b), and their results were not separated from the locally advanced results. It found that in patients with cT2b-CT3 N0 M0 prostate cancer, patients who received prostatectomy + HT had equivalent long-term (10 years) results when compared with those who received RT + HT.

HT toxicity

SR of RCT (1+) In the Kumar *et al* review[171], more adverse events (hot flushes, diarrhoea, asthenia, gynecomastia) were found in the groups receiving local and hormonal treatment than for patients who received only local treatment.

RCT (1+) Green *et al*[184] clearly demonstrated the quality of life for patients treated for non-localised prostate cancer. It showed an impairment of sexual function during hormonal treatment, and concerned elderly or persons of an advanced age with a low-medium sexual function beforehand.

6.1.4 Hormone therapy alone

No studies have been found comparing the hormone therapy alone with local treatment in patients with locally advanced prostate cancer.

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6.1.5. Experimental treatment

No studies have been identified to assess the usefulness of docetaxel administered simultaneously or as an adjuvant to radiotherapy after local treatment.

SR different types of study (1+)

The UK National Institute for Health and Clinical Excellence (NICE) has carried out two systematic reviews that evaluate the use of cryotherapy[186] and HIFU[140] as primary interventions for non-metastatic prostate cancer. They conclude that the available scientific evidence on the importance of these treatments for locally advanced prostate cancer is scarce and of poor quality.

SR different types of study (2-)

The systematic review of Shelley *et al*[141] compared the efficacy and side effects of cryotherapy with other primary treatments (radical prostatectomy, radiotherapy and observation) for the management of T1-T3 prostate cancer patients. Only one comparative study was found, and this did not show separate results for locally advanced prostate cancer. It also concluded that it was an experimental procedure and not, therefore, first-choice.

In short, different thorough systematic reviews[140,141,186] have not been able to identify high-quality scientific literature that would support the use of HIFU or cryotherapy as a first line treatment in patients with locally advanced prostate cancer, which leads to the conclusion that there is insufficient evidence in this regard.

Summary of evidence

-	No studies have been found comparing prostatectomy with watchful waiting (WW) in prostate cancer patients at the locally advanced clinical stage.
-	No studies have been found comparing prostatectomy with radiotherapy in prostate cancer patients at the locally advanced clinical stage.
2+	Prostatectomy alone is unlikely to completely eliminate the tumour. The most important adverse effect of this treatment is urinary incontinence[129].
2+	In patients with clinically localised prostate cancer, RT has similar efficacy results to prostatectomy but better safety results. The most important side effect of this treatment is rectal toxicity[129].
2-	There were no statistically significant differences between intensity modulated radiation therapy (IMRT) and conformal radiotherapy with respect to efficacy at the same dose. IMRT has less late rectal and sexual toxicity than conformal RT[136].
1+	Better results are obtained for HT (with bicalutamide 150 mg/day) plus WW, when compared with WW alone in prostate cancer patients at the locally advanced clinical stage, for biochemical progression-free survival (BPFS), as well as showing a tendency to improve overall survival[172].
1+	The addition of neoadjuvant HT to radiotherapy treatment in patients with prostate cancer at the locally advanced clinical stage can improve results for biochemical progression-free survival, disease-free survival and overall survival at 8 years in patients with Gleason 2-6[156,171].
1+	The usual duration of neoadjuvant HT in patients with prostate cancer at the locally advanced clinical stage is around 3 months[156].
1+	LHRH analogues used as adjuvants significantly improve results with respect to overall

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	survival, disease-free survival, the risk of distant metastasis and biochemical progression-free survival at 5 and 9 years[179,180]. With regard to loco-regional failure, better results were seen at 5 years[179]. For cancer-specific survival, there was significant improvement with the combined treatment at 5 years[179] but not at 12 years[180].
1+	Adjuvant hormone therapy with bicalutamide with a median follow-up of 7.4 years showed better results for the combined treatment with respect to overall survival and disease-free survival[181].
1+	In patients with prostate cancer at the locally advanced clinical stage, adjuvant HT added to radiotherapy (with androgen deprivation) improved overall survival[182]
2+	The usual duration of adjuvant HT in patients with prostate cancer at the locally advanced clinical stage is 2-3 years[156].
-	No studies have been found comparing neoadjuvant HT + prostatectomy vs prostatectomy in patients with prostate cancer at the locally advanced clinical stage.
1+	Patients with prostate cancer at the locally advanced clinical stage who received radiation therapy, showed improved biochemical progression-free survival with the addition of adjuvant HT (bicalutamide 150 mg/day), but not overall survival[172].
1+	Patients with prostate cancer at the locally advanced clinical stage who underwent prostatectomy which detected lymph node affectation, showed improvement at 10 years regarding overall survival with adjuvant androgen deprivation[182].
1-	Adjuvant/neoadjuvant HT to prostatectomy shows equivalent results at 10 years compared with adjuvant/neoadjuvant HT to RT in patients with cT2b-cT3 prostate cancer[183].
1+	There are more adverse events (hot flushes, diarrhoea, asthenia, gynecomastia) in patients with prostate cancer who receive local and hormonal treatment than those who receive only receive local treatment[171].
1+	The sexual function of patients with prostate cancer at the locally advanced clinical stage is affected by hormone treatment. They were elderly patients or those of advanced age with previous low-middle sexual function[184].
1+	No studies have been found comparing the use of hormone therapy alone with local treatments in patients with prostate cancer at the locally advanced clinical stage[140,141,186].
1+	There is no evidence to support the use of high intensity focused ultrasound (HIFU) or cryotherapy as a first-line treatment in patients with prostate cancer at the locally advanced clinical stage[140,141,186]

Recommendations

√	In patients with prostate cancer at the locally advanced clinical stage with a life expectancy exceeding 10 years, treatment with 3-dimensional conformal radiotherapy or conformal radiotherapy + brachytherapy is recommended.
D	In patients with prostate cancer at the locally advanced clinical stage who require radiotherapy treatment, 3-dimensional conformal radiotherapy is an alternative in centres where IMRT (intensity modulated radiation therapy) is not available.
√	In patients with prostate cancer at the locally advanced clinical stage with a life expectancy exceeding 10 years and a low risk of lymph node affectation (cT3a + Gleason < 8 + PSA < 20 ng/ml), radical prostatectomy could be considered as treatment.
√	In patients with prostate cancer at the locally advanced clinical stage with a life expectancy below 10 years, watchful waiting or hormone therapy may be therapeutic alternatives.

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A	Neoadjuvant hormone treatment must be given to patients with prostate cancer at the locally advanced clinical stage indicated with radiation treatment.
C	The usual duration of neoadjuvant hormone treatment to radiotherapy in patients with prostate cancer at the locally advanced clinical stage is 3 months.
A	Adjuvant hormone treatment to radiotherapy is recommended for patients with prostate cancer at the locally advanced clinical stage.
D	The usual duration of adjuvant hormone treatment after radiotherapy in patients with prostate cancer at the locally advanced clinical stage is 2-3 years.
B	Neoadjuvant hormone treatment is not recommended in patients with prostate cancer at the locally advanced clinical stage who are going to have radical prostatectomy.
B	Adjuvant hormonal treatment in prostatectomy is not recommended for patients with prostate cancer at the locally advanced clinical stage, unless lymph node dissemination is demonstrated.
A	In patients with prostate cancer at the locally advanced clinical stage, primary cryotherapy and high intensity focused ultrasound are experimental techniques.
A	RESEARCH RECOMMENDATION: Randomised trials comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with prostate cancer at the locally advanced clinical stage should be started.
√	RESEARCH RECOMMENDATION: Randomised trials evaluating the usefulness of docetaxel administered simultaneously or as an adjuvant to radiotherapy after local treatment should be started.

6.2 Adjuvant radiotherapy

Question to answer[p]:

- For patients who have undergone radical prostatectomy which shows locally advanced prostate cancer and/or microscopic positive surgical margins, is it safer and more efficacious to establish an adjuvant treatment (radiotherapy) than not?

The objective of radical prostatectomy is to completely remove the tumour[4,17,148]. Patients with locally advanced prostate cancer have a greater risk of positive surgical margins (33.5-66%), lymph node metastasis and/or distant recurrence than those clinically localised[4]. Finding positive surgical margins in prostatectomised patients is associated with higher rates of PSA relapse, local and systemic progression[148].

[p] Section 5.4 responds to a question about the volume, dose and fractioning of radiotherapy for patients with localised or *locally advanced* prostate cancer.

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RCT (1+) The randomised clinical trial of Bolla *et al*[187,188] includes patients at the *localised* or locally advanced clinical stage, with positive surgical margins or pathological stage pT3 after radical prostatectomy, comparing the results in patients treated with post-operative (adjuvant) RT with those receiving RT at PSA relapse or clinical progression. The results at 5 years were significantly better in the group who received post-operative RT for biochemical progression-free survival (74.0% vs 52.6%; $p < 0.0001$), clinical progression-free survival ($p = 0.0009$) and the locoregional failure rate ($p < 0.0001$). Grade 2 or 3 adverse effects were significantly more frequent in the postoperative RT group ($p = 0.0005$), but there were no significant differences for severe toxicity ($p = 0.0726$), which also appeared in a small percentage of patients (2.6% vs 4.2%).

SR different types of study (1-) In the systematic review of Nilsson *et al*[126] on the effects of radiotherapy for prostate cancer, it was found that post-operative (adjuvant) external radiotherapy in pT3 patients prolonged biochemical progression-free survival and disease-free survival in the long term compared to salvage RT (at PSA relapse or clinical progression). These results are repeated in several studies.

SR different types of study (2-) The Lennernas *et al* review[189] 189 evaluated the potential benefits of adding adjuvant radiotherapy (> 65 Gy) for patients with pT3-T4 prostate cancer who had received radical prostatectomy. It found that post-operative radiotherapy improves local control of the disease in patients with positive surgical margins or local recurrence (especially in small tumours or with a PSA < 1-2 ng/ml) or with multiple positive margins. In these patients, the probability of local recurrence after 5 years when adjuvant RT was applied was 0-23%; without adjuvant RT, the probability was 17-30%. There seems to be no evidence that it improves overall survival. On the other hand, adverse effects are increased when using adjuvant RT.

Case series (3) In the MacDonald *et al* study[190], which analysed patients with prostate cancer treated with radical prostatectomy and which had a 5 year follow-up, overall survival and metastasis-free survival were described as better when RT was performed at PSA relapse compared with RT at palpable local recurrence ($p = 0.02$; $p = 0.05$), although differences for biochemical progression-free survival were not found ($p = 0.1$).

Summary of evidence

1-/1+/1+/2-	In patients with prostate cancer at the clinical *localised* stage or locally advanced and with a high risk of disease progression after radical retropubic prostatectomy, postoperative radiotherapy (dose on prostate > 65 Gy) gives better results than those receiving radiotherapy at clinical progression, for biochemical progression-free survival, clinical progression-free survival and local control of the disease, without significantly increasing the risk of serious side effects. There seems to be no evidence of improved global survival[126,187-189].

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3	In patients with prostate cancer treated with radical prostatectomy, overall survival and metastasis-free survival at 5 years were better when radiotherapy was applied at biochemical recurrence than when given at palpable local recurrence, although no differences were found for biochemical progression-free survival[190].

Recommendation

√	In patients with locally advanced prostate cancer and/or positive microscopic surgical margins after radical prostatectomy, systematic adjuvant radiotherapy is not recommended.

6.3. Lymphadenectomy

Question to answer:

- In patients with prostate cancer at the locally advanced clinical stage in which surgery is indicated, does a lymphadenectomy increase cure rates for the disease? If so, which is better, extended or limited lymphadenectomy?

Carrying out a pelvic lymphadenectomy in prostate cancer patients at the locally advanced clinical stage who have had a prostatectomy has been justified with the same objectives as for clinically localised prostate cancer[151,191]: removal of microscopic lymph node metastasis and more accurate identification of patients with positive lymph nodes.

No studies have been located which directly address the need for implementing lymphadenectomy in patients with locally advanced prostate cancer.

Cohort study (2-) The study by Bader *et al*[151] included patients with clinically localised prostate cancer subjected to prostatectomy, which compares results with or without lymphadenectomy. It includes patients with pathologic stages T1-T3 (56% were pT1-T2, 43% were pT3, 1% were pT4) and does not separate the results. There was a statistically significant association between the existence of positive lymph nodes and an increased risk of progression, decreased cancer-specific survival (74% at 5 years) and increased probability of relapse. It found that some patients with minimum metastasis stay free of relapse of the disease 10 years after prostatectomy. Positive lymph nodes are more likely to be found in patients with prostate cancer in stages pT3 than in stages pT1-T2 (39% v 13%).

Cohort study (2-) The retrospective study by Allaf *et al*[150] included patients with clinically localised prostate cancer, and compared extended lymphadenectomy (n = 2,135) with limited (n = 1,865), with each technique being performed by a surgeon. There were no statistically significant differences in the results for

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biochemical progression-free survival at 5 years (short follow-up time). In patients with positive lymph nodes, although there was a trend towards better survival for extended dissection (p = 0.07), no differences were found for biochemical progression-free survival.

Furthermore, extended lymphadenectomy allowed more patients with lymph node affectation to be identified (p < 0.0001) and more positive lymph nodes than the limited method (mean 14.7 v 12.4; p = 0.15).

SR different types of study (1+)

The systematic review of Sharifi *et al*[182] was intended to analyse the risks and benefits of androgen deprivation in locally advanced and localised prostate cancer at high risk. It found that in patients with locally advanced prostate cancer who underwent prostatectomy where lymph node affectation was detected, adjuvant androgen deprivation improved overall survival at 10 years (72.4% vs 49%; p = 0.025).

RCT (1 +)

The study by Clark *et al*[152] compared extended and limited lymphadenectomy in 123 patients with clinically localised prostate cancer. In this study, each patient received an extended lymphadenectomy (LN) on one side and a limited LN on the other. There were no statistically significant differences between groups with respect to unilateral surgical complications.

Summary of evidence

2-	The existence of positive lymph nodes is associated with increased risk of progression, reduced cancer-specific survival and greater probability of recurrence[151].
2-	In patients with clinically *localised* prostate cancer, there were no differences in biochemical progression-free survival at 5 years when comparing extended lymphadenectomy with limited, not even in those with positive lymph nodes. Although, in this subgroup there was a trend towards better survival results with extended dissection (p = 0.07)[150].
2-	In patients with clinically *localised* prostate cancer, extended lymphadenectomy identified more patients with lymph node affectation and more positive lymph nodes than the limited[150].
1+	In patients with prostate cancer at high risk (cT2c-T3 or PSA > 20 ng/ml or Gleason > 7) who underwent radical prostatectomy which detected lymph node affectation, adjuvant androgen deprivation improved overall survival at 10 years[182].
1+	In patients with clinically *localised* prostate cancer, there are no differences in unilateral surgical complications when comparing extended and limited lymphadenectomy[152].

Recommendations

A	Lymphadenectomy should be indicated in patients with prostate cancer at a locally advanced clinical stage who have undergone radical prostatectomy, as a staging and subsequent evaluation of adjuvant treatment.
√	In patients with prostate cancer at a locally advanced clinical stage where radical surgery is indicated, extended lymphadenectomy may be of therapeutic interest.

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6.4 Adjuvant/neoadjuvant hormone therapy

Question to answer:

- In patients with locally advanced prostate cancer subjected to local treatment (such as radiation or surgery) associated with hormone therapy, what form of hormone treatment is safer and more effective: monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade?

Hormone therapy induces prostatic cell apoptosis[4,171]. Hormone treatment of prostate cancer can be established with different drugs[4]: LHRH agonists, gonadotropin-releasing hormone (so-called "chemical castration"), antiandrogens, or a combination of both (complete androgen blockade).

No sufficiently-well designed studies have been identified to determine what type of hormone treatment (monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade) is safest or most effective.

Summary of evidence

-	No studies with a sufficiently robust design have been identified to determine what type of hormone treatment is most effective (antiandrogen, LHRH agonists or complete androgen blockade) in prostate cancer patients at the locally advanced clinical stage.

Recommendation

√	The appropriate hormonal treatment (monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade) cannot be determined for patients with prostate cancer at the locally advanced clinical stage for whom the addition of hormone therapy has been suggested.
√	RESEARCH RECOMMENDATION: It would be necessary to start randomised trials to determine the appropriate hormone treatment (monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade) in prostate cancer patients at the locally advanced clinical stage.

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7. Prostate cancer in PSA relapse

A patient with prostate cancer in PSA relapse is one who, having received a primary treatment with intent to cure, has a raised PSA (prostate-specific antigen) level defined as "biochemical progression".

7.1. Definition of PSA relapse

Question to answer:

- In patients with prostate cancer undergoing prostatectomy or radiotherapy with curative intent, what would be the best analytical approach for the diagnosis of biochemical failure?

Prostate-specific antigen (PSA) is a protein produced by prostate epithelial cells, whether benign or malignant. Measuring the PSA level is a key aspect in monitoring after treatment with intent to cure, as very low levels of PSA are indicative of a successful removal of the tumour[4,17].

It is known that, if the PSA level increases after a radical treatment, clinical recurrence of the tumour will be seen within a few years[174,185,192-195].

The challenge is to find out how this increase in PSA levels after radical treatment involves a significantly higher risk of morbidity or mortality, which is called progression, relapse or PSA relapse. There has been much debate about the PSA limit indicative of the greatest risk[4,185,196,197].

7.1.1 After radical surgery

Retrospective case series (3)

In the study by Stephenson *et al*[185], different definitions of PSA relapse after radical prostatectomy were evaluated. It found that the best indication of metastatic progression was an increased PSA value ≥ 0.4 ng/ml, which gives a probability of PSA progression in the following 4 years of 91 %, and secondary treatment failure or clinical failure in the following 7 years of 62%. It also concludes that if the serum PSA cut-off level is increased to above 0.4 ng/ml, the probability that the patient will still be disease-free within the following 10 years is 74% [95% CI: 70-78%], which is equivalent to an increase of false negatives for biochemical progression.

Some groups choose to adhere to values of 0.2 ng/ml or higher due to the greater sensitivity of the serum PSA measurement method. Choosing a lower cut-off level results in a higher rate of secondary interventions for patients with a high probability of remaining disease-free for 10 years (false positives).

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7.1.2 After Radiotherapy

Several types of studies (2-/3/3/4)

There are several studies that examine the best definition of biochemical progression after radiation therapy (external or brachytherapy), such as the Horwitz *et al* retrospective cohort study[194], two prospective case series published by Kuban *et al*[197,198] and the consensus document from the American Society for Therapeutic Radiology and Oncology (ASTRO), published by Roach *et al*[196]. They conclude that for external beam radiotherapy, the 2005 ASTRO definition agreed by consensus (PSA 2 ng/ml above the nadir value) has the best values for sensitivity (72-74%) and specificity (71-83 %) for clinical failure and at a distance. For brachytherapy, it also found that the definition offered the best sensitivity and specificity. The false positive rate is 2% for external beam radiation therapy (with or without neoadjuvant and/or adjuvant hormonal treatment) and for brachytherapy with hormone therapy. For brachytherapy without hormone treatment, the false positive rate reaches 4%.

Summary of evidence

3	In patients who received radical prostatectomy, obtaining an increasing PSA value ≥ 0.4 ng/ml, is the definition of PSA relapse that best correlates with metastatic progression, with a probability of PSA progression in the following 4 years of 91%, and a 62% probability of secondary treatment or clinical failure in the following 7 years[185].
3	If, after defining PSA relapse in patients who received radical prostatectomy, the serum PSA cut-off level is above 0.4 ng/ml, the probability that the patient will still be disease-free after 10 years is 74% [95% CI: 70-78%], which leads to an increase of false negatives. If lower cut-off points are used, there is a higher rate of false positives[185].
2-/4/3/3	In patients who received radical radiotherapy, the ASTRO 2005 definition of PSA relapse (PSA greater than 2 ng/ml above the nadir value) has the best values for sensitivity (72-74%) and specificity (71-83%) for clinical failure and at a distance[194,196-198].
4/3	In patients who received radical brachytherapy, the ASTRO 2005 definition of PSA relapse offers the best sensitivity and specificity[196,197].
2-/4/3/3	In patients who received radical radiotherapy, the rate of false positives using the ASTRO 2005 definition of PSA relapse is 2% for external beam radiation therapy (with or without neoadjuvant and/or adjuvant hormone treatment) and for brachytherapy with hormone therapy. For brachytherapy without hormone treatment, the false positive rate reaches 4%[194,196-198].

Recommendations

D	In prostatectomised patients, biochemical recurrence of the disease will be considered to have occurred when serum PSA levels exceed 0.4 ng/ml.
D	In those patients whose intervention with intent to cure was radiotherapy or brachytherapy, biochemical recurrence of the disease will be considered to have occurred when serum PSA levels increase by 2 ng/ml above the PSA nadir.

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7.2 Salvage treatment after surgery

Question to answer:

- In patients with biochemical failure after radical prostatectomy, what kind of intervention is safest and most effective?

Radical prostatectomy is a frequently used treatment for localised prostate cancer. Local recurrence of the disease occurs in more than 33% of patients within 5 years of surgery. The existence of PSA relapse implies a 34% probability of metastatic disease within 5 years of radical prostatectomy. Following metastasis, median survival is 5 years[199].

Salvage treatment is offered to patients who display PSA relapse with the intention of reducing adverse outcomes caused by *advanced* prostate cancer (locally advanced affectation or disseminated). Proper management depends on the treatment with intent to cure and the status of the patient[200].

No studies directly comparing salvage radiotherapy with immediate hormone treatment have been found.

Case series (3) Two studies examined overall survival after applying salvage radiotherapy in prostatectomised patients with PSA relapse. It found that survival at 5 years was between 87% and 95%[190,199]. When radiation is given as soon as the disease becomes palpable, survival is 76% (p = 0.02)[190].

SR different types of studies (3) In terms of progression-free survival for these patients, different publications[126,200-202] suggest that statistically significant improvement is found when salvage radiotherapy is applied at PSA relapse, defined as PSA levels between 0.5-2.5 ng/ml.

Case series (3) Analysing the Stephenson *et al*[185] and Pazona *et al*[200] case series, several factors were found which increase the probability for these patients not to respond to salvage radiotherapy, such as a pre-treatment PSA doubling time of less than 10 months, the existence of lymph node or seminal affectation or a Gleason > 7. In general, in patients with PSA relapse, to have a PSA doubling time less than 3 months was an adverse prognostic factor for cancer-specific and overall survival in the Freedland *et al*[203] and D'Amico *et al*[204] publications.

Retrospective cohort study (2-) The study published by Moul *et al*[205] analysed early salvage hormone therapy after radical prostatectomy (beginning when PSA values ≤ 5 ng/ml), compared with late salvage hormone therapy (when there are clinical signs and symptoms of progression of the disease). They note that early hormone therapy provides statistically significant improvement only for metastasis-free survival in a subgroup of patients at high risk: those with a pathological Gleason > 7 or PSA doubling of less than 1 year (HR = 2.32 [95% CI: 1.14-4.70]).

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Summary of evidence

3	Overall survival at 5 years in prostatectomised patients with PSA relapse and salvage radiotherapy is between 87% and 95%[190,199]. When radiotherapy is given as soon as the disease is palpable, survival is 76% (p = 0.02)[190].
3	It seems that statistically significant improvement in progression-free survival is seen if salvage RT is applied at PSA relapse after prostatectomy with PSA levels between 0.6-2.5 ng/ml[126,200-202].
3	Risk factors that do not respond to salvage RT after surgery are: a pre-treatment PSA doubling time of less than 10 months, the existence of lymphatic or seminal affectation or a Gleason > 7[185,200].
3	Having a PSA doubling time of less than 3 months was an adverse prognostic factor for cancer-specific and overall survival in groups of men with PSA relapse after prostatectomy[203,204].
2-	Early salvage hormone therapy after radical prostatectomy (beginning when PSA values ≤ 5 ng/ml), compared with late salvage hormone therapy (when there are clinical signs and symptoms of progression of the disease) shows statistically significant improvement only for metastasis-free survival in a subgroup of patients at high risk: those with a pathological Gleason > 7 or PSA doubling of less than 1 year (HR = 2.32 [95% CI: 1.14-4.70])[205].

Recommendations

D	Patients with PSA relapse of the disease after radical prostatectomy without distant metastases or other risk factors, should be given early salvage radiotherapy before the PSA exceeds 2.5 ng/ml.
D	Salvage hormone therapy may be indicated for those men with PSA relapse after radical prostatectomy who also have local symptomatic progression, distant metastasis or duplication of PSA levels in less than 10 months.

7.3 Salvage treatment after radiotherapy

Question to answer:

- In patients with biochemical failure after radiotherapy or brachytherapy with intent to cure, what kind of salvage intervention is safest and most effective?

The use of radiotherapy as a definitive treatment for new cases diagnosed with prostate cancer has increased significantly over the past 30 years. An estimated 76% of patients with a good prognosis (cT1-cT2a and Gleason < 6) and 51% with an unfavourable prognosis (cT2b-cT3 or Gleason ≥ 7) remain free of PSA relapse at 5 years of curative treatment. Biopsy studies have revealed the persistence of neoplastic cells in 20-50% of patients after treatment

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with radiation therapy, which suggests that when adequate local control of the disease is not achieved, there is a deterioration in results with an increase in late distant metastasis[206].

There are no randomised studies showing direct comparisons between different salvage alternatives in patients with PSA relapse after treatment with intent to cure. Furthermore, the retrospective comparison of existing data reveal methodological difficulties due to the different definitions of PSA relapse used in the different studies[207].

7.3.1 Hormone therapy vs watchful waiting

Cohort study (2-) Faria *et al*[208] has results from 178 men with asymptomatic PSA relapse after external beam radiotherapy. Some received salvage treatment with hormone therapy and others chose to wait and see (watchful waiting). There were no deaths among these patients due to prostate cancer. With a median follow-up of 7 years, overall survival was 95% in the hormone therapy group and 89% in the watchful waiting group.

Cohort study (2-) In a study published by Pinova *et al*[209], with 248 male patients who had salvage treatment (hormone therapy vs watchful waiting), the metastasis-free survival rate at 5 years was 88% vs 92% (p = 0.74) in those with a PSA doubling time of ≥ 12 months. In those who had a PSA doubling time of <12 months, results were 78% vs 57% (p = 0.0026).

7.3.2 Prostatectomy

Case series (3) Different series[206,210,211] gave salvage treatment results with prostatectomy. Cancer-specific survival was 73% at 10 years, and 60% at 15 years. When cystoprostatectomy instead of retropubic prostatectomy was practised, cancer - specific survival at 10 years was much lower (38% vs 77%; p <0.001). The proportion of possible complications after salvage radical prostatectomy was: urinary incontinence (48%), urinary extravasation (15%), contraction of the bladder neck (22%), rectal injury (4%) and kidney damage (2%).

Expert reviews (4) The European Association of Urology[4] clinical practice guideline suggests that salvage prostatectomy be considered in patients with few comorbidities, a life expectancy of at least 10 years, cT1-T2, Gleason < 7 and preoperative PSA < 10 ng/ml.

7.3.3 Brachytherapy

Case series (3) In one study (n = 49), overall survival at 5 years after salvage brachytherapy therapy was 56% [95% CI: 36-71%] and the cancer-specific survival rate was 79% [95% CI: 58-91%]. Median follow-up: 2 years (range: 3 months to 6.5 years)[212].

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7.3.4 Cryotherapy

Case series (3)	In another series (n = 116), cancer-specific mortality at 5 years was 8.3% for salvage cryotherapy and 5.4% for radical prostatectomy, with no statistically significant difference between them. Biochemical progression appeared in 66.7% of those treated with cryotherapy and 28.6% of those treated with surgery[213].
Case series (3)	In another group of patients treated with salvage cryotherapy, with an average follow-up of 13.5 months, there was biochemical progression in 58% of patients. 31% of cases had undetectable levels of PSA[214].
Case series (3)	Side effects found between 12-13.5 months after the salvage cryotherapy were common: urinary incontinence (28-73%), obstructive symptoms (67%), impotence (72-90%) and severe perineal pain (8%)[214,215].

7.3.5 HIFU

On the use of high intensity focused ultrasound (HIFU) as a salvage treatment, there is a very small case series with a short follow-up period for which no conclusions about efficacy could be drawn[216].

Summary of evidence

2-	In a group of men with asymptomatic PSA relapse after external radiotherapy and salvage treatment (hormone therapy vs watchful waiting), no death was due to prostate cancer. With a median follow-up of 7 years, overall survival was 95% in the hormone therapy group and 89% in the watchful waiting group[208].
2-	In a group of men with salvage treatment (hormone therapy vs watchful waiting) after radiotherapy, the metastasis-free survival rate at 5 years was 88% vs 92% (p = 0.74) in those with a PSA doubling time of ≥ 12 months. In those who had a PSA doubling time of <12 months, results were 78% vs 57% (p = 0.0026)[209].
3	In those treated with salvage prostatectomy after radiotherapy, cancer-specific survival was 73% at 10 years, and 60% at 15 years[210]. When cystoprostatectomy instead of retropubic prostatectomy was practised, cancer -specific survival at 10 years was much lower (38% vs 77%; p <0.001). The proportion of possible complications after salvage radical prostatectomy was: urinary incontinence (48%), urinary extravasation (15%), contraction of the bladder neck (22%), rectal injury (4%) and kidney damage (2%)[206,211].
4	It is recommended that salvage prostatectomy be considered in patients with few comorbidities, a life expectancy of at least 10 years, cT1-T2, Gleason < 7 and preoperative PSA < 10 ng/ml[4].
3	In a small series (n = 49), overall survival at 5 years after salvage brachytherapy therapy was 56% [95% CI: 36-71%] and the cancer-specific survival rate was 79% [95% CI: 58-91%]. Median follow-up: 2 years (range: 3 months to 6.5 years)[212].
3	In patients with salvage treatment after radiotherapy (prostatectomy vs cryotherapy) and average follow-up: 4.6 years vs 5.1 years, the cancer-specific mortality was 5.4% vs 8.3%, with no statistically significant differences. Patients with PSA relapse: 28.6% vs 66.7%[213].

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3	In those treated with salvage cryotherapy after radiotherapy, with an average follow-up of 13.5 months, there was PSA relapse in 58% of patients. 31% had undetectable levels of PSA[214].
3	In those treated with salvage cryotherapy after radiotherapy, adverse effects between 12-13.5 months were common: urinary incontinence (28-73%), obstructive symptoms (67%), impotence (72-90%) and severe perineal pain (8%)[214,215].
3	On the use of high intensity focused ultrasound (HIFU) as a salvage treatment after radiotherapy, there is a very small case series with a short follow-up period for which no conclusions about efficacy could be drawn[216].

Recommendations

D	Salvage radical prostatectomy can be offered after radiotherapy treatment for patients with local recurrence with few associated comorbidities, a life expectancy of at least 10 years, with cT1-T2, Gleason < 7 and a pre-surgical PSA < 10 ng/ml.
D	Hormone therapy should be considered as a salvage therapeutic option in patients treated with radiotherapy with local recurrence of the disease, who cannot be offered salvage radical prostatectomy.
D	The adoption of other salvage therapeutic alternatives (cryotherapy or high intensity focused ultrasound) should be considered as experimental.
D	RESEARCH RECOMMENDATION: Clinical trials evaluating local salvage therapies for survival and quality of life in men with biochemical recurrence after radiotherapy or brachytherapy should be started.

7.4 When to start hormone therapy

Question to answer:

- In patients who have undergone curative treatment, are in biochemical failure and for whom hormone treatment (active treatment) is indicated, when should it start?

The objectives of disseminated prostate cancer treatment include prolonging survival, preventing the symptoms of progression of the disease, improving the quality of life and reducing morbidity due to the treatment itself[16,217].

Androgen suppression hormone therapy is one possible alternative treatment. It can be started early (when the patient is diagnosed with asymptomatic PSA relapse), or on a deferred basis, (when the signs and symptoms of disease progression appear)[14,217].

RCT systematic review (1+)

There is a Cochrane review of Nair *et al*[217] which compares immediate hormonal therapy with delayed in men with *advanced* prostate cancer (locally advanced or disseminated affectation). No differences were found for cancer-specific survival when comparing the immediate and delayed treatment.

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Retrospective cohort study (2-)	The study of 1,352 patients published by Moul *et al*[205] analysed *early* salvage hormone therapy in patients with PSA relapse after radical prostatectomy (started when PSA values ≤ 5 ng/ml were reached) and compared it with *late* salvage hormone therapy (when there were signs and symptoms of progression). They noted that for metastasis-free survival at 5 and 10 years there were no statistically significant differences [HR = 0.91 (95% CI: 0.58-1.41)]. Statistically significant improvements were seen only a in a subgroup of patients at high risk: those with Gleason > 7 or a PSA doubling in <1 year (HR = 2.32 [95% CI: 1.14-4.70]).

Summary of evidence

1+	In men with *advanced* prostate cancer (locally advanced or disseminated affectation), no differences were found for cancer-specific survival when comparing immediate and deferred treatment[217].
2-	In patients with PSA relapse after radical prostatectomy, no statistically significant differences were found when comparing metastasis-free survival at 5 and 10 years for those who received *early* salvage hormone therapy (started when PSA levels reached levels ≤ 5 ng/ml) *vs late* (when there were signs and symptoms of progression). The only statistically significant improvement was seen in a subgroup of patients: Gleason> 7 or PSA doubling <1 year (HR = 2.32 [95% CI: 1.14-4.70])[205].

Recommendations

D	In patients with PSA relapse after radical prostatectomy in which hormonal treatment is decided, if there is a Gleason > 7, PSA ≤ 5 ng/ml and a PSA doubling time of less than 1 year, it is recommended that hormone treatment be applied early.
√	In patients with PSA relapse after radiotherapy or radical brachytherapy in which hormone treatment is indicated, the decision on when to implement it should be done on an individual basis.

7.5 Intermittent vs continuous hormone therapy

Question to answer:

- In patients who have undergone curative treatment, are in biochemical failure and for whom hormone treatment is indicated, which is safer and more effective: applying it continuously or intermittently?

The use of intermittent androgen suppression hormone therapy has been justified for various reasons[4]:

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- Improving the quality of life in periods without hormone therapy.
- Reduction of costs.
- Possible delayed induction of the onset of androgen-independence in the prostate tumour: after a variable time of hormone treatment (average 24 months), prostate tumours usually return. There is a theory that if androgen deprivation ends before the appearance of androgen-independent cells, any subsequent tumour growth should be due to androgen-dependent cell lines, which would be susceptible to responding to a new cycle of hormone treatment.

RCT (1-) The systematic Cochrane review published by Conti *et al*[218] is a meta-analysis comparing intermittent hormone therapy (HT) (after prostatectomy, radiotherapy or brachytherapy) vs continuous HT in prostate cancer patients. Most studies included patients who had not received radical treatment, except for the Leval *et al* study[219], consisting of men with prostate cancer in PSA relapse after radical prostatectomy. The median progression rate at 3 years was significantly less for intermittent HT (7% vs 38.9%). Cancer-specific mortality was 5.7% for those treated with intermittent HT, and 12.1% for those treated with continuous HT, after a median follow-up of 2.4 years. After analysing the risk of PSA relapse (defined as PSA ≥ 10 ng/ml), no significant differences were found when comparing intermittent and continuous HT. In patients with Gleason> 6, there was a trend towards lower risk of biochemical progression in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; p = 0.53). Most of the patients who received HT experienced mild-moderate side effects due to androgen suppression (hot flashes, loss of libido and erectile dysfunction). These almost always disappeared during the period without hormone treatment in the intermittent HT group. In addition, the emergence of severe gastrointestinal toxicity stopped treatment in 4.4% of the patients who underwent continuous HT treatment and 2.9% for those receiving intermittent HT treatment[219].

RCT (1+) With regard to sexual function, in a trial published by Calais *et al*[220], 50% of the patients included had been sexually active in the previous month. At 15 months of treatment, 40% of the intermittent HT group and 25% of the continuous HT group maintained sexual activity. Similar results were obtained from both groups in this study using the quality of life scales.

Summary of evidence

1-	For patients in PSA relapse subjected to salvage HT after radical prostatectomy, the median progression rate at 3 years was significantly smaller for intermittent HT compared with continuous HT (7% v 38.9%)[219].
1-	For patients with PSA relapse after radical prostatectomy, 5.7% of those treated with intermittent salvage HT died because of the tumour compared with 12.1% for those treated with continuous HT[219].
1-	For patients with PSA relapse subjected to salvage HT after radical prostatectomy, there were no significant differences between intermittent and continuous when analysing the risk of the appearance of biochemical progression (defined as PSA ≥ 10 ng/ml). For Gleason > 6, there was a trend towards lower risk of biochemical progression in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; p = 0.53)[219].

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1-	Most patients who received HT experienced mild-moderate adverse effects due to androgen suppression (hot flushes, loss of libido and erectile dysfunction), which disappeared during the period without hormone treatment in the intermittent HT group[219].
1-	For patients in PSA relapse subjected to salvage HT after radical prostatectomy, severe gastrointestinal toxicity stopped treatment in 4.4% of patients treated with continuous HT and 2.9% of those receiving intermittent HT[219].
1+	In patients with PSA relapse after radical prostatectomy, 50% of men were sexually active in the month prior to the start of the salvage treatment. At 15 months of treatment, sexual activity was maintained in 40% of the intermittent HT group and 25% of the continuous HT group[220].
1+	The quality of life scales had similar results for intermittent and continuous HT in patients with biochemical progression after salvage radical prostatectomy[220].

Recommendations

A	In patients with PSA relapse after radical treatment in which hormone therapy has been decided, it cannot be determined whether it is better to apply it continuously or intermittently.

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8. Disseminated prostate cancer

From the *anatomopathological* point of view, a patient with disseminated prostate cancer is one with the confirmed presence of prostate adenocarcinoma with lymphatic invasion (N1) and/or metastasis (M1) and/or a primary fixed tumour or one that invades adjacent structures other than the seminal vesicles (pT4).

The patient with *clinically* disseminated prostate cancer spread corresponds to a stage N1, M1 or cT4.

8.1 Hormone therapy

Questions to answer:

- In patients with disseminated prostate cancer, what is the safest and most effective treatment: complete androgen blockade or (surgical or chemical) castration?
- In patients with disseminated prostate cancer (lymph node affectation and/or metastasis), what is the safest and most effective treatment: immediate or delayed hormone treatment?
- In patients with disseminated prostate cancer, what is the safest and most effective hormone treatment: continuous or intermittent? And using what treatment guidelines?
- In patients with prostate cancer where the first line hormone treatment (androgen suppression, complete androgen blockade) has failed and the PSA has begun to rise, what is the safest and most effective: continue with the following lines of hormone

8.1.1 Complete androgen blockade vs castration

The goals of treatment in men with disseminated prostate cancer include prolonging life, preventing or delaying the symptoms caused by the disease, improving the quality of life and reducing the morbidity associated with treatment[16,217].

When hormone treatment is suggested in these patients, there are different options. Androgen suppression or ablation (castration) can be done with LHRH agonists (luteinising hormone-releasing hormone) or surgery (orchiectomy). Both options are considered to have comparable survival rates and side effects. The use of chemical castration, compared to surgery, has both advantages (such as the possibility of intermittent application) and disadvantages (greater cost, lack of adherence to treatment)[16].

Another possibility of hormonal treatment in these patients is antiandrogens, which may be non-steroidal (flutamide, nilutamide, bicalutamide) or steroidal (cyproterone acetate)[4,16].

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There is a tendency to obtain better overall survival results with antiandrogen castration. Both treatments have different toxicity profiles: gynecomastia is more common with non-steroidal antiandrogens, while hot flushes and decreased sexual function are more likely with androgen deprivation. The dropout rate is similar for agonists and LHRH antiandrogens[16].

When LHRH agonists are administered in monotherapy, the patient also receives a short period of antiandrogen treatment to prevent the "flare phenomenon"[16]. If this is not done, the chemical castration provokes a regenerative blast reaction in bone metastatic lesions, with at times new lesions appearing[221].

LHRH analogues can also be administered in combination with anti-androgen treatment, which is called "complete androgen blockade (CAB). This alternative therapy can be applied as an initial hormone guidance or exclusively after failing with castration treatment[4,16].

RCT (1++) reviews — Different reviews conclude that CAB provides an improvement (of about 3%) in survival at 5 years when compared with castration[222-227]. It seems that this benefit occurs only in patients taking non-steroidal antiandrogens[223-226].

RCT (1+) review — When estimating the CAB effect of using bicalutamide vs castration, the global mortality hazard ratio showed a small statistically significant difference in favour of the blockade (HR = 0.8 [95% CI: 0.66-0.98])[228].

RCT (1++) reviews — Cancer-specific survival was better with CAB than with orchiectomy, except when the androgen blockade was cyproterone acetate[223,226].

RCT (1++) reviews — In the Schmitt *et al* review[222], CAB was evaluated in patients with *advanced* prostate cancer (locally advanced affectation or disseminated). In the subgroup analysis for patients with *metastatic* disease, a significant OR was seen for overall survival at 5 years for CAB (OR = 1.25; [95% CI: 1.05-1.48]) when compared with castration. However, when this analysis was limited to high quality studies, as identified by the review, the OR was not significant (OR = 1.34 [95% CI: 0.96-1.87])[222].

RCT (1++)/RCT reviews — In various reviews and in a study by Moinpour *et al*[229], CAB was found to be more toxic than castration: diarrhoea (9.7% vs 1.8%), gastrointestinal pain (74% vs 1.6%), ophthalmologic events (29% vs 5.4%), emotional disturbance at 3 and 6 months ($p < 0.003$) and haematological toxicity[223,225,226,229].

8.1.2 Immediate vs delayed hormone therapy

Treatment with androgen suppression can be implemented immediately (when lymph node disease or metastasis is diagnosed) or deferred (when signs and symptoms of clinical development appear)[4,217].

The studies found show the results of patients with *advanced* prostate cancer without differentiating between locally advanced or disseminated affectation.

RCT (1+) — In the Jordan *et al* study[230] immediate and delayed hormone therapy were compared in patients with *advanced* prostate cancer. Subgroup

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analysis of the patients with metastasis showed an overall survival hazard ratio at one year of HR = 1.29 (95% CI: 0.83-2.02), at 5 years it was HR = 1.00 (95% CI: 0.65-1.55) and at 10 years it was HR = 1.88 (95% CI: 0.86-4.07).

RCT systematic review (1+) The Loblaw publication, which contains the recommendations from the American Society of Clinical Oncology (ASCO) on this issue, presents evidence of moderately better results for cancer-specific mortality with the immediate use of androgen deprivation in patients with *advanced* prostate cancer, although there were no differences for overall mortality[231].

RCT systematic review (1+) The review published by Nair *et al*[217] includes studies of patients with *advanced* prostate cancer treated with hormone therapy (as a single treatment or adjuvant with radical prostatectomy) prior to the widespread use of PSA as a diagnostic tool. No differences were found for cancer-specific survival when comparing the immediate and delayed treatments.

RCT systematic reviews (1++/1+) Two publications agree in concluding that delayed HT is more cost-effective than the immediate treatment in patients with *advanced* prostate cancer[223,231].

RCT (1+) The following side effects were found to be more frequent in the immediate HT group than in the delayed HT group: genitourinary (48% vs 13%), hot flushes (59% vs 0%), gynecomastia (22% vs 2%) and incontinence (43% vs 30%)[232]. With regard to cardiovascular deaths, the results were similar for both groups[230,233].

It is considered important to assess the use of immediate HT vs delayed in a different way for symptomatic and asymptomatic patients.

Moreover, as cancer-specific survival tends to be greater in patients with immediate HT[231], the patient's life expectancy is an important factor when considering the type of hormonal treatment to apply.

8.1.3 Intermittent vs continuous hormone therapy

As with patients with prostate cancer in biochemical progression, the use of intermittent androgen suppression hormone therapy in men with disseminated prostate cancer is justified for various reasons, such as improving the quality of life in periods without hormone therapy, reduced costs and the possibility of delaying the appearance of androgen-independence in the prostate tumour[4].

Case series (3) Lane *et al*[234] found that in a number of patients with metastatic prostate cancer subjected to intermittent treatment, overall survival at 5 years was 70%.

RCT (1-) The JDeval *et al* study[219] included patients with *advanced* prostate cancer (locally advanced affectation or disseminated) in biochemical progression after radical prostatectomy. They were subjected to intermittent v continuous hormone therapy. The median progression rate at 3 years was 7% vs 38.9%. A cancer-specific mortality of 5.7% was found in those treated with intermittent HT

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(median follow-up: 2.4 years). No significant differences were found when comparing intermittent vs continuous HT for the risk of PSA relapse (defined as PSA ≥ 10 ng/ml). In patients with Gleason > 6, there was a trend towards lower risk of PSA relapse in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; p = 0.53)[219].

Most patients who received HT experienced mild-moderate adverse effects due to androgen suppression (hot flushes, loss of libido and erectile dysfunction), which almost always disappeared when the hormone treatment stopped[219].

Treatment was stopped because of severe gastrointestinal toxicity in 4.4% of patients who received continuous HT and 2.9% of the intermittent group[219].

RCT (1+) With regard to sexual function, the Hering *et al* study[235] obtained better results for the intermittent HT group when hormone treatment was stopped (those impotent at the end of treatment: 18/25 vs. 18/18; RR = 0.72; [95% CI: 0.56-0.92]; p = 0.008).

Expert reviews (4) With regard to the economic impact of both these treatments, the clinical practice guideline from the United Kingdom National Institute for Health and Clinical Excellence (NICE) suggested that intermittent HT probably has a lower cost than the continuous despite the need for greater monitoring[16].

Case series (3) As to how to administer this treatment, the Lane *et al* case series[234] only considered the application of intermittent HT to patients who had received androgen deprivation for at least 9 months and had reached a PSA < 4 ng/ml or a 90% reduction in the levels prior to treatment. If a patient who had stopped androgen deprivation reached a PSA > 20 ng/ml, another cycle of androgen deprivation was started.

The Hussain *et al* study[236] compared intermittent with continuous hormone treatment, but without any conclusive results. It included patients with metastatic prostate cancer who had received androgen deprivation for at least 7 months and had reached PSA < 4 ng/ml (stable or declining during the sixth and seventh months). Intermittent or continuous treatment was chosen at random. Where deprivation was stopped, the initial pattern was repeated if the PSA of the patient began to rise or clinical symptoms of disease progression appeared. After this cycle of androgen deprivation, if the PSA returned to normal, HT was stopped. Patients were monitored every 6 months.

8.1.4 Second-line hormone therapy

In the therapeutic scheme followed in this guideline, first line hormone therapy is considered as castration (chemical or surgical) or complete androgen blockade. If castration starts to fail, an antiandrogen is added. If CAB becomes less effective, the antiandrogen is removed, which paradoxically has a beneficial effect (known as "antiandrogen withdrawal syndrome")[4,17].

If there is biochemical or clinical progression after exhausting the first line[q] hormone treatment possibilities, androgen-independence[4,16,17] will be considered after checking testosterone is at castration levels.

[q] In some documents the failure of first-line hormone therapy is said to be "hormone refractory", a term that in this guideline indicates failure of any type of hormone therapy (first or second line)[4,16,17].

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In patients with androgen-independent prostate cancer (AIPC), treatment with cytotoxic chemotherapy (CT, such as docetaxel and oestramustine) or second-line hormone therapy: ketoconazole, progestins (such as MPA), oestrogens, corticosteroids, bicalutamide at high doses (150 mg/day) and other hormone manoeuvres can be suggested[4,16.17].

Currently, first-line chemotherapy in patients with prostate cancer includes docetaxel (see section 8.2), although other treatment programmes have been used with drugs such as oestramustine, mitoxantrone, vinorelbine or etoposide[237].

RCT (1+) In a study comparing medroxyprogesterone acetate (MPA) vs oestramustine in patients with AIPC, no differences were found for the progression at 3 months nor for overall survival at 1 year. However, differences were seen in the time to progression: 12 to 56 weeks in 13/51 patients with MPA, while 22 to 28 weeks in 4/51 patients with oestramustine (p = 0.05). The oestramustine treatment was discontinued in 8/51 patients due to side effects (nausea, vomiting and diarrhoea), and in 3/51 patients who received MPA (oedema, cardiovascular toxicity and increased pain)[238].

Expert review (4) The only clinical trial found that was aimed at comparing second-line HT v CT with docetaxel was the ECOG 1899[239], which was stopped early due to inability to attract patients (17 between 2003 and 2005)[240,241]. According to a Ryan *et al* narrative review, this fact indicates that few of these patients agreed to be included in an experimental study that directly compared CT with docetaxel vs second line HT, as they considered it unlikely that there would be a sufficiently robust study to resolve this question in the future[241].

RCT (1++) Some studies have assessed second line hormone therapy or chemotherapy with docetaxel in patients with AIPC, but the two treatments were not compared directly[242-244].

RCT (1++) In the Small *et al* publication, two second-line HT programmes (ketoconazole 400 mg/day + hydrocortisone 40 mg/day + antiandrogen withdrawal vs antiandrogen withdrawal) were evaluated in patients with AIPC. Survival results obtained were 15.3 months vs 16.7 months (difference not statistically significant)[242].

RCT (1++) Petrylak *et al* analysed 2 CT treatment programmes (docetaxel + oestramustine vs mitoxantrone + prednisone) that gave a statistically significant overall survival difference of 17.5 months v 15.6 months[243].

RCT (1++) The Tannock *et al* study compared other CT treatment programmes (docetaxel vs mitoxantrone + prednisone). Statistically significant survival results of 18.9 months v 16.5 months were obtained[244].

Expert review (4) In the Ryan *et al* narrative revision[241], the authors listed a number of arguments that have been used to advocate a strategy of one treatment or another. Among the reasons given for recommending CT as soon as the tumour becomes hormone-resistant are the following:

- It has been proven that early use of CT is effective in other solid tumours (breast, colorectum), where applying it immediately after surgery is considered the standard treatment when the disease is disseminated.

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- According to some authors, in earlier stages of the disease there may be a lower number of androgen-independent cells, which would mean CT would have a greater cumulative effect.
- For some it may be ethically unacceptable to delay offering a treatment that may prolong life and reduce pain.

Expert review (4)

As for arguments that, according to Ryan *et al* have been used to recommend the use of CT alone in patients with advanced and symptomatic disease are the following[241]:

- In the TAX 327[244] study, no significant differences were found in the mortality hazard ratio when comparing symptomatic and asymptomatic patients, which for some authors suggests that delaying CT treatment until there are clinical signs does not alter the results.
- The length of time to disease progression induced by androgen deprivation is important, even in patients with metastasis.
- Secondary hormone treatments, such as ketoconazole have some use.
- Some argue that, although it is possible that the response to second line hormone therapy is slightly less than with chemotherapy, when this response is managed in an individual (by measuring PSA), the final survival of the patient may be lengthened. Therefore, before offering CT, it may be appropriate to first of all try a second-line hormone treatment, particularly in patients with a higher disease burden without significant tumour pain.
- There are authors who believe that early use of chemotherapy may have significant adverse effects, and that for many patients it is not necessary as it does not provide significant benefits.
- As there is no standard second-line CT (currently the alternative may be mitoxantrone), some believe it is better to use only docetaxel when there is no alternative treatment. Failure to do so, according to these authors, means that resistance to this treatment may appear too soon, leaving the patient without further treatment alternatives for palliation once the tumour becomes symptomatic.

In conclusion, with the information available so far, it is difficult to know whether there are differences between the two treatment options in terms of safety or efficacy.

Summary of evidence

1++	CAB provides a 3% improvement in survival at 5 years when compared with castration[222-227]. The benefit seems limited to patients who take non-steroidal antiandrogens [223-226].
1+	The overall mortality hazard ratio showed a small statistically significant difference in favour of the blockade with bicalutamide compared with castration (HR = 0.8)[228].
1++	When comparing CAB vs orchidectomy, better results were found in cancer-specific survival, except when using CAB with cyproterone acetate[223,226].
1++	In a subgroup analysis, patients with metastatic disease had a significant OR for overall survival at 5 years for CAB (OR = 1.25 [95% CI: 1.05-1.48]) when compared with castration. When the analysis was limited to high-quality studies, the OR was not significant (OR = 1.34 [95% CI: 0.96-1.87])[225].

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1++	CAB has more toxic effects than castration: diarrhoea (9.7% v 1.8%), gastrointestinal pain (74% v 1.6%), ophthalmologic events (29% v 5.4%), emotional disturbance at 3 and 6 months ($p < 0.003$) and haematological toxicity[223,225,226,229].
1+	In a subgroup analysis, the relative overall survival (for deferred HT vs immediate) in patients with metastatic prostate cancer at 1 year gave a survival hazard ratio, HR = 1.29, at 5 years HR = 1.00, at 10 years HR = 1.88 (none of the differences were statistically significant)[230].
1+	For cancer-specific mortality, immediate HT had moderately better results in patients with *advanced* prostate cancer (locally advanced or disseminated). For global mortality, there were no differences[231].
1+	In patients with *advanced* prostate cancer treated with immediate or delayed HT (such as single treatment or adjuvant to radical prostatectomy) before PSA was widely used as a diagnostic tool, no differences were found for cancer-specific survival[217].
1++/1+	Delayed HT is more cost-effective in patients with *advanced* prostate cancer (locally advanced affectation or disseminated)[223,231].
1+	Side effects associated with the treatment were more often in the immediate HT group than the deferred HT group: genitourinary (48% vs 13%), hot flushes (59% vs 0%), gynecomastia (22% vs 2%), incontinence (43% vs 30%)[232]. Cardiovascular deaths: similar results were found for the immediate and delayed treatment[230,233].
3	In patients with metastatic prostate cancer subjected to intermittent treatment, overall survival at 5 years was 70%[234].
1-	In patients with *advanced* prostate cancer (locally advanced affectation or disseminated), the median progression rate at 3 years was significantly less for intermittent HT compared with continuous HT (7% vs 38.9%)[219].
1-	In patients with *advanced* prostate cancer, after a median follow-up of 2.4 years, 5.7% of those treated with intermittent HT had died from the tumour[219].
1-	In patients with *advanced* prostate cancer, no significant differences were found when comparing intermittent HT vs continuous HT when analysing the risk of undergoing biochemical progression (defined as PSA ≥ 10 ng/ml). For Gleason > 6, there was a trend towards lower risk of biochemical progression in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; $p = 0.53$)[219].
1-	Most patients who received continuous or intermittent HT experienced mild-moderate adverse effects due to androgen suppression (hot flushes, loss of libido and erectile dysfunction), which in most cases disappeared when the hormone treatment was stopped[219].
1-	Treatment was stopped because of severe gastrointestinal toxicity in 4.4% of patients treated with continuous HT and 2.9% of those receiving intermittent[219].
1+	For impotence rates, better results were found for the intermittent HT group while the treatment was stopped (18/25 vs 18/18, RR = 0.72 [95% CI: 0.56-0.92]; $p = 0.008$)[235].
1+	When comparing medroxyprogesterone acetate (MPA) vs oestramustine in patients with androgen-independent prostate cancer (AIPC), there were no differences for progression at 3 months nor for overall survival at 1 year. However, there were differences for time to progression: 12 to 56 weeks in 13/51 MPA patients, 22 to 28 weeks in 4/51 with oestramustine ($p = 0.05$)[238].

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1+	When comparing MPA vs oestramustine in patients with AIPC, the treatment was discontinued in 8/51 patients receiving oestramustine due to side effects (nausea, vomiting and diarrhoea) and in 3/51 patients receiving MPA (oedema, cardiovascular toxicity and increased pain)[238].
4	The only study that has tried to compare second-line HT vs CT with docetaxel was the ECOG 1899[239], which had to be stopped early due to low patient numbers (17 between 2003 and 2005)[240,241]. It is unlikely to find a sufficiently robust study to directly compare CT vs second-line HT in these patients[241].
1++	The treatment with second-line HT (ketoconazole + antiandrogen withdrawal vs antiandrogen withdrawal) in patients with AIPC, gave survival results of 15.3 months vs 16.7 months (difference not statistically significant)[242].
1++	Treatment with CT (docetaxel + oestramustine vs mitoxantrone + prednisone) in patients with AIPC had survival results of 17.5 months v 15.6 months (a statistically significant difference)[243].
1++	Treatment with CT (docetaxel vs mitoxantrone + prednisone) in patients with androgen-independent prostate cancer (AIPC), had survival results of 18.9 months vs 16.5 months (a statistically significant difference)[244].
4	Some authors have recommended applying CT as soon as the tumour becomes hormone resistant for the following reasons[241]: - This strategy has proven effective in other solid tumours, where applying CT immediately after surgery is the standard treatment in disseminated disease. - In the early stages there may be fewer androgen-independent cells, which would increase the cumulative effect of the CT. - For some it may be ethically unacceptable to delay treatment which may prolong life and reduce pain.
4	Some authors have recommended using CT alone in patients with advanced and symptomatic disease for the following reasons[241]: - In the TAX 327 study[244], no significant differences were found in the mortality hazard ratio when comparing symptomatic and non-symptomatic patients, which some authors suggest means that delaying therapy until clinical signs appear does not alter the results. - The time to disease progression induced by androgen deprivation is substantial, even in patients with metastasis. - Secondary hormone treatment is of some use. - Some argue that, although it is possible that the proportion of responses to second-line hormone therapy is slightly lower than with CT, where this response is achieved in an individual (by measuring the PSA), the possibilities of final survival in the patient may be higher. Therefore, before offering CT, it may be appropriate to firstly try a second-line hormone treatment, particularly in patients with a higher disease burden without significant tumour pain. - As there is no standard second-line CT, some consider it better to be conservative with docetaxel and use it only when CT is really required. If not, they believe that resistance to this treatment may appear too soon, leaving the patient without further treatment alternatives for palliation once the tumour becomes symptomatic.

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Recommendations

A	In patients with disseminated prostate cancer for which hormone therapy is indicated, (surgical or chemical) castration is recommended as a first-line treatment.
D	In patients with symptomatic disseminated prostate cancer, hormone treatment is recommended.
B	In patients with asymptomatic disseminated prostate cancer spread, immediate or deferred hormone therapy can be offered, the latter when symptoms appear).
√	In patients with disseminated prostate cancer and low tumour burden, intermittent androgen suppression can be evaluated as an alternative to continuous androgen suppression if there is a good response to initial hormone treatment.
√	To be able to indicate intermittent hormone therapy, the patient must have received androgen deprivation for at least 7 months and reached a PSA < 4 ng/ml (stable or in decline during the sixth and seventh months), or a 90% reduction from pre-treatment levels. Monitoring will be carried out every 6 months. Patients who have stopped androgen deprivation will receive another cycle on request, when the PSA increases or when clinical symptoms of disease progression appear. If the PSA returns to normal after the new round of androgen deprivation, hormone therapy can be stopped again.
√	Patients with disseminated androgen-independent prostate cancer (when both androgen suppression and complete androgen blockade have failed) can be offered second-line hormone therapy before starting chemotherapy treatment.
√	RESEARCH RECOMMENDATION: Patients with disseminated androgen-independent prostate cancer (when both androgen suppression and complete androgen blockade have failed) should be offered inclusion in clinical trials to evaluate the safety and efficacy of second-line hormone therapy, comparing it to chemotherapy which has proven effective.

8.2 Chemotherapy

Questions to answer:

- In patients with androgen-independent disseminated prostate cancer, what is the safest and most effective treatment for improving overall survival, clinical or biochemical response, progression-free survival and reduction of side effects: oestramustine, mitoxantrone, docetaxel, docetaxel-oestramustine, vinorelbine or etoposide?
- In patients with androgen-independent prostate cancer who are going to receive chemotherapy, is it safer and more effective to start it at biochemical failure or wait for clinical progression?
- In patients with disseminated prostate cancer in progression after hormone treatment who are going to receive chemotherapy, does removing LHRH agonists modify the safety and efficacy?

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8.2.1 Choosing first-line chemotherapy treatment

In men with hormone-refractory prostate cancer, other alternative therapies need to be evaluated. One possibility is systemic cytotoxic chemotherapy (CT), whose results vary depending on the drugs used. Both docetaxel and mitoxantrone associated with corticosteroids are administered as standard. Prednisone or dexamethasone can also be used[237].

The Shelley *et al* review[237] examines the use of CT in patients with androgen-independent prostate cancer (AIPC). It has little in the way of studies comparing these drugs with each other.

Mitoxantrone + corticoid vs corticoid

RCT (1+) The first chemotherapy considered as standard treatment in patients with AIPC was mitoxantrone, which was analysed by several studies comparing mitoxantrone (12-14 mg/m^2 dose every 3 weeks) + corticoid vs corticoid[245-247].

RCT (1+) The use of mitoxantrone achieved a significant decrease in pain intensity (down 2 points on a scale of 6). The percentage of patients achieving pain relief was 29% vs 12% (p = 0.01)[247].

RCT (1+) Mitoxantrone treatment also managed to increase the quality of life in patients, due to the improvement of emotional status (p = 0.04), the decrease of family disruption (p = 0.02), less pain frequency (p = 0.06) and the existence of less intense pain (p = 0.03), although difficulties in sexual and urological function favoured those treated with hydrocortisone only[245].

RCT (1+) In another study, the quality of life scales were generally better in patients who received mitoxantrone and responded to the mitigation of pain[247].

RCT (1+) In asymptomatic patients with a median follow-up of 22 months, the use of mitoxantrone increased the number of patients who achieved a reduction of over 50% in PSA levels (p = 0.007)[246].

RCT (1+) The use of chemotherapy gave a small, but statistically significant, increase in the time to progression of the disease (p = 0.02[245]; p = 0.018[246]).

RCT (1+) None of the three mitoxantrone studies showed a significant increase in overall survival[245-247].

RCT (1+) The major toxicities associated with mitoxantrone included grade 3-4 neutropenia (7%), nausea and vomiting, alopecia (24%) and cardiotoxicity (66%)[247]. In another study, grade 3-4 cardiotoxicity appeared in 5% of patients who received mitoxantrone, and haematological toxicity was significantly higher in patients who received the chemotherapy[245].

Docetaxel + corticosteroid vs mitoxantrone + corticosteroid

RCT (1++) The docetaxel efficacy results were compared with mitoxantrone (the chemotherapy reference at the time) in the 2004 Tannock *et al* study[244], which included 1,006 men with AIPC. There were two different docetaxel administration regimes: some patients received a dose of 75 mg/m^2 every 3 weeks and others a weekly dose (30 mg/m^2/week over 6 weeks). The mitoxantrone was administered at doses of 12 mg/m^2 every 3 weeks.

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When docetaxel was compared with mitoxantrone, the mortality hazard ratios were: (HR = 0.76 [95% CI: 0.62-0.94]; p = 0.009) for docetaxel every 3 weeks and (HR = 0.91 [95% CI: 0.75-1.11]; p = 0.36) for the weekly scheme. This showed a significant improvement in overall survival with the 3 week docetaxel regime, compared with the mitoxantrone (24% reduction in the risk of death).

A significant reduction was also noted in pain in patients who received the 3-week docetaxel regime compared with mitoxantrone (35% vs 22%; p = 0.01) but not with the weekly programme (31 %). The median pain response duration (3.5 vs 5.6 months) was not significant different between the groups.

The quality of life also showed a significant improvement in patients treated with the 3-week docetaxel regime compared with those treated with mitoxantrone (22% vs 13%; p = 0.009).

Degree 3 and 4 neutropenia in patients included in the 3-week regime was statistically significantly more frequent than those who received weekly docetaxel or mitoxantrone (32% vs 2% vs 22%), although the frequency of febrile neutropenia was less than 4% in all groups.

There was a high incidence of nausea and vomiting in all programmes (38% to 42%). Diarrhoea was significantly more frequent in the docetaxel regimes.

Interruption of treatment with docetaxel was due to fatigue, musculoskeletal events, changes in the nails, sensory neuropathy and infection. In the mitoxantrone group, the main reason was due to cardiac dysfunction.

Docetaxel + oestramustine + corticosteroid vs mitoxantrone + corticosteroid

RCT (1++) The combination of docetaxel and oestramustine has also been compared with mitoxantrone in patients with AIPC. The Petrylak *et al* study[243] administered docetaxel to one group (60 mg/m^2 on day 2) then oestramustine (280 mg/m^2 days 1-5) and mitoxantrone (12 mg/m^2 on day 1) to another group. In the Oudard *et al* study[248], there were 3 branches of treatment: one that received docetaxel at a dose of 70 mg/m^2 (administered on day 2 every 3 weeks) and oestramustine (280 mg/m^2 administered 3 times a day on days 1-5); another that received docetaxel at a dose of 35 mg/m^2 (days 2 and 9, repeated over a 3 week cycle) and oestramustine (as above), and another that received mitoxantrone (12 mg/m^2 every 3 weeks).

RCT (1++) In the Petrylak *et al* study there was a significant improvement in overall survival for those treated with docetaxel and oestramustine (17.5 months vs 15.6 months; p = 0.02)[243]. However, in the Oudard *et al* study, although the median overall survival was greater for those treated with docetaxel (18.6 and 18.4 months) than for mitoxantrone (13.4 months), there were no significant differences between the regimes (p = 0.3)[248].

RCT (1++) Regarding disease progression, significant improvements were found for those receiving combination treatment [6.3 months v 3.2; p <0.001 in one study[243]; p <0.00001 in the other[248]].

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RCT (1++) The percentage of patients who achieved a PSA response (at least a 50% reduction in levels) was statistically significantly better in patients treated with docetaxel and oestramustine [50% vs 27%; p <0.001 in one study[243]; p <0.00001 in the other[248]].

RCT (1++) With regard to pain relief, the Petrylak *et al* study found no significant differences between the two groups when evaluated by patients[243]. However, the Oudard *et al* showed a statistically significant improvement in pain index for each of the two docetaxel groups (70 mg/m^2 and 35 mg/m^2) when compared with mitoxantrone (40% and 29% vs 17%)[248].

RCT (1++) There was a significant improvement in the ECOG performance status of patients treated with docetaxel compared with mitoxantrone (60% and 48% vs 28%, respectively)[248].

RCT (1++) With the docetaxel-oestramustine combination, there were more gastrointestinal side effects (p = 0.001), nausea and vomiting (p = 0.001), infection (p = 0.004), metabolic toxicity (p <0.001) and neurological dysfunction (p = 0.001)[243]. In addition, there was oestramustine-induced thrombosis in 7% of the patients treated with docetaxel, despite receiving anticoagulant treatment[248].

RCT (1++) Granulocytopenia grade 3 and 4 was the most common toxicity in patients treated with docetaxel 70 mg/m^2 and mitoxantrone (37% and 48% respectively), but this was not seen with the lower dosage of docetaxel[248].

Docetaxel + oestramustine + corticosteroid vs docetaxel + corticosteroid

RCT (1++) Comparison of docetaxel-oestramustine v docetaxel in patients with androgen-independent prostate cancer (AIPC) and metastatic prostate cancer was evaluated by the Eynard *et al* study[249], which applied docetaxel (70 mg/m^2 on day 2) and oestramustine (280 mg/m^2 administered twice daily on days 1-5) in a group of patients (n = 47) and docetaxel (75 mg/m^2 on day 1) in the other (n = 44).

There was a statistically significant difference in the PSA response (decrease in PSA level in ≥ 50% maintained for ≥ 3 weeks), which was: 68% [95% CI: 55-81] v 30% [95% CI: 16-43]. The median PSA response duration was 6.0 months in both groups.

The median time to progression was 5.7 months [95% CI: 4.7-6.8] vs 2.9 months [95% CI: 2.0-6.9], and the median survival time was 19.3 months [95% CI: 14.6-25.9] vs 17.8 months [95% CI: 11.8-20.9], both without significant differences.

Haematological and non-haematological toxicity plus the quality of life were similar in both groups.

6% of patients treated with the combination had phlebitis, possibly due to the oestramustine. One patient in each group decided to discontinue the study because of toxicity. One treatment-related death (pulmonary oedema) occurred before 30 days in the docetaxel group[249].

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Although the efficacy results seem similar, it must be remembered that, in the Petrylak *et al* study, 15% of the cardiovascular events appeared in the docetaxel-oestramustine group[243]. Because the patients were elderly and had associated comorbidities, it was necessary to assess the need to add oestramustine to the docetaxel treatment. This was because it only provides an increase in the rate of PSA response[249] at the expense of a possible increase in toxicity.

8.2.2 Chemotherapy start time

An increase in PSA levels is a signal that prostate cancer is in progression, and it also helps to evaluate response to treatment. In patients with androgen-independent prostate cancer (AIPC) for whom it has been decided to administer cytotoxic chemotherapy (CT), this can be started at biochemical recurrence or clinical progression[4,16,17].

No studies have been found that directly compare the use of CT in these two situations, since the effectiveness of chemotherapy has only been assessed at clinical progression[237].

Expert review (4)

The European Association of Urology clinical practice guideline[4] recommends establishing a chemotherapy regime for AIPC patients who have two consecutive PSA increases above the reference values, and a PSA level above 5 ng/ml. It also recommends the decision for the start of the chemotherapy treatment should be done on an individual basis.

8.2.3 Using LHRH agonists with CT

In AIPC patients treated with frontline hormone therapy (androgen suppression or complete androgen blockade) for whom it is decided to apply cytotoxic CT, there is the possibility of maintaining the treatment with LHRH agonists or not[16].

No studies directly comparing these two treatment options have been found, not even in the Cochrane review for Shelley *et al* 2006, which analyses the use of CT in patients with AIPC[237].

Two recent non-systematic reviews[250,251] (2006 and 2007) include a brief comment stating that chemical castration treatment can be continued, but no controlled studies to support this assertion are shown.

The usual strategy for handling these patients is to maintain treatment with LHRH agonists when initiating CT treatment. This is usually justified by health professionals on the grounds that it prevents stimulation of any hormone-sensitive cells the patient may have.

It should be remembered that, when a patient has received treatment with LHRH agonists for a long time and they are removed, testosterone levels may take more than a year to regain their normal values.

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Summary of evidence

1+	A significant reduction in pain intensity with the use of mitoxantrone when compared with corticosteroid was achieved. The percentage of patients achieving palliation was 29% vs 12% (p = 0.01)[247].
1+	An increase in the quality of life was achieved with mitoxantrone + corticosteroid due to an improvement in emotional state (p = 0.04), reduction of family disruption (p = 0.02), less frequent pain (p = 0.06) and less intense pain (p = 0.03). Difficulties in sexual and urological function favoured the hydrocortisone-only option[247]. The quality of life scales were generally better in patients who received mitoxantrone and they responded to pain mitigation[247].
1+	In asymptomatic patients with a median follow up of 22 months, the use of corticosteroid and mitoxantrone increased the number achieving a reduction of more than 50% in PSA levels (p = 0.007), compared with those receiving only corticosteroid[246].
1+	Using mitoxantrone with corticosteroid, a small, but statistically significant, increase was found was in the time to disease progression (p = 0.02; p = 0.018), compared with only corticosteroid[245,246].
1+	Mitoxantrone with corticosteroid, compared with corticosteroid, failed to significantly decrease overall survival[245-247].
1+	Toxicities associated with mitoxantrone include: neutropenia grade 3-4 (7%), nausea and vomiting, alopecia (24%) and cardiotoxicity (66%)[247]. Grade 3-4 cardiotoxicity appeared in 5% of patients who received mitoxantrone. Haematological toxicity was significantly higher for the mitoxantrone group[245].
1++	When docetaxel was compared with mitoxantrone, the mortality hazard ratio was (HR = 0.76; [95% CI: 0.62-0.94]; p = 0.009) for docetaxel every 3 weeks and HR = 0.91; [95% CI: 0.75-1.11]; p = 0.36) for the weekly regime. There was a significant improvement in overall survival with the 3-week docetaxel regime compared with mitoxantrone (24% reduction in the risk of death)[244].
1++	There was a significant pain reduction for patients who received the 3-week docetaxel regime compared with mitoxantrone (35% vs 22%; p = 0.01) but not with the weekly regime (31%). The median pain response duration (3.5 months vs 5.6 months) was not significantly different between the two groups[244].
1++	The quality of life showed significant improvement in patients treated with 3-week docetaxel regime compared with mitoxantrone (22% vs 13%; p = 0.009)[244].
1++	Grade 3-4 neutropenia was significantly more frequent in patients who received the 3-week regime than in those who received docetaxel weekly or mitoxantrone (32% vs 2% vs 22%), although the frequency of febrile neutropenia was less than 4% in all groups[244].
1++	A high frequency of nausea and vomiting was recorded in all docetaxel and mitoxantrone treatment programmes (38% to 42%). Diarrhoea was significantly more frequent with docetaxel[244].
1++	Interruption of treatment with docetaxel was due to fatigue, musculoskeletal events, changes in the nails, sensory neuropathy or infection. In the mitoxantrone group, the main reason was cardiac dysfunction[244].
1++	One study found a significant improvement in overall survival for patients treated with docetaxel-oestramustine (17.5 months vs 15.6 months; p = 0.02), compared with

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	mitoxantrone[243]. However, in another study, although the median overall survival was greater for both groups of patients treated with docetaxel (18.6 and 18.4 months) than for those treated with mitoxantrone (13.4 months), no significant differences between the regimes was found (p = 0.3)[248].
1++	Regarding the time of disease progression, significant improvements were found for patients receiving the docetaxel-oestramustine treatment compared with patients treated with mitoxantrone [6.3 months vs 3.2 months; p < 0.001 in one study[243]; p <0.00001 in another[248]].
1++	The percentage of patients who achieved a PSA response (decrease in PSA levels ≥ 50%) was significantly better in patients treated with docetaxel-oestramustine than in patients treated with mitoxantrone [50% vs 27%; p < 0.001 in one study[243]; p <0.00001 in another[248]].
1++	With regard to pain relief, one study found no significant differences between docetaxel + oestramustine v mitoxantrone when evaluated[243]. However, in another, a significant improvement was found in the pain index for each of the two docetaxel groups (70 mg/m^2 and 35 mg/m^2) when compared with the mitoxantrone group (40% and 29% vs 17%)[248].
1++	There was a significant improvement in the ECOG performance status for patients treated with docetaxel (60% and 48% vs 28%, respectively), when compared with mitoxantrone[248].
1++	Docetaxel-oestramustine was significantly more toxic (than mitoxantrone) with regard to gastrointestinal side effects (p = 0.001), nausea and vomiting (p = 0.001), infection (p = 0.004), metabolic toxicity (p < 0.001) and neurological dysfunction (p = 0.001)[243]. Oestramustine-provoked thrombosis was noted in 7% of patients treated with docetaxel despite receiving anticoagulant treatment[248].
1++	Granulocytopenia grade 3 and 4 toxicity was more common in patients treated with docetaxel 70 mg/m^2 and mitoxantrone (37% and 48%, respectively), although this was not seen with the lower dose of docetaxel[248].
1++	When comparing docetaxel-oestramustine v docetaxel, the PSA response (≥ 50% decrease in PSA level maintained for ≥ 3 weeks) was 68% [95% CI: 55-81] vs 30% [95% CI: 16-43], which was statistically significant. The median PSA response time was 6.0 months in both groups[249].
1++	When comparing docetaxel-oestramustine v docetaxel, the median time to progression was 5.7 months [95% CI: 4.7-6.8] vs 2.9 months [95% CI: 2.0-6.9], with the median survival time of 19.3 months [95% CI: 14.6-25.9] vs 17.8 months [95% CI: 11.8-20.9], both without significant differences[249].
1++	When comparing docetaxel-oestramustine v docetaxel, haematological and non-haematological toxicity as well as the quality of life were similar in both groups[249].
1++	When comparing docetaxel-oestramustine vs docetaxel, 6% of the patients treated with the combined form had phlebitis, possibly due to oestramustine. One patient in each group decided to leave the study due to toxicity. One death occurred before 30 days in the docetaxel-treated group (due to pulmonary oedema)[249].
4	The European Association of Urology clinical practice guideline recommends establishing a chemotherapy regime for patients with AIPC who have two consecutive PSA increases above the reference values, and a PSA level above 5 ng/ml. It also recommends that the time to start chemotherapy should be decided on an individual basis[4].

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4	No studies of a sufficient quality have been found which compare chemotherapy (CT) with CT + LHRH agonists[237].
4	Some authors believe that LHRH agonists may continue to be applied during chemotherapy treatment[250,251].

Recommendations

B	In patients with androgen-independent prostate cancer (AIPC) and metastasis, when chemotherapy treatment is proposed, it is recommended to use docetaxel (a 75 mg/m^2 dose every 3 weeks) with corticosteroid.
√	In patients with AIPC and metastasis, systematic association of docetaxel-oestramustine is not recommended.
√	In patients with biochemical relapse, who are androgen-independent, asymptomatic and without documented metastasis disease, early chemotherapy treatment may be offered, especially within the framework of randomised trials.
√	RESEARCH RECOMMENDATION: Patients with PSA relapse, who are androgen-independent, asymptomatic and without documented metastasis disease, should be offered inclusion in clinical trials comparing early chemotherapy treatment with delayed chemotherapy.
√	In patients with androgen-independence for whom chemotherapy has been decided, LHRH agonists can continue to be applied.
√	RESEARCH RECOMMENDATION: Patients with androgen-independent disseminated prostate cancer, for whom chemotherapy treatment has been decided, should be offered inclusion in clinical trials comparing the safety and efficacy of chemotherapy alone compared to chemotherapy associated with LHRH agonists.

8.3 Bisphosphonates and radiopharmaceuticals

Questions to answer:

- In patients with disseminated prostate cancer, does intervention with bisphosphonates (zoledronic acid) compared with doing nothing improve event-free survival for bone pain and quality of life, and does it allow a reduction in the dose of painkillers?

- In patients with disseminated prostate cancer, does administering radiopharmaceuticals provide better control and/or a reduction of metastatic bone pain?

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8.3.1 Bisphosphonates

Bone metastases appear in over 80% of patients with advanced prostate cancer: in the spine, pelvis, ribs and other locations. The median survival after its occurrence is approximately 3 years and, during this period, patients may suffer pain, hypercalcaemia, fractures and medullary compression[252].

Bone metastases are associated with the occurrence of pain and skeletal events[253]. In prostate cancer, they are predominantly osteoblastic (bone-forming). It seems that before there is abnormal bone formation, osteoclastic resorption activation (bone destruction) appears, which is associated with bone pain. Bisphosphonates act by inhibiting bone resorption[252].

Bone density and skeletal events

RCT (1+) There is consistent evidence from randomised trials that treatment with bisphosphonates increases bone density in the spinal column in men receiving hormone therapy for prostate cancer. In patients treated with bisphosphonates, an average increase in bone density of 1-5% was seen in the first year of hormone treatment. However, a significant reduction of 0.4 - 4.9% was seen in those who received placebo or the standard treatment during the same period. The bisphosphonate group was about 5% greater[254-258].

RCT (1++) In patients with androgen-independent prostate cancer (AIPC), when compared with placebo, bisphosphonates achieved a modest reduction in skeletal events (such as the occurrence of pathological fractures, spinal compression, or the need for surgery or radiotherapy treatment for bone metastases): 37.8% vs 43.0%; absolute risk reduction of 5.2%[252].

RCT (1-) Saad *et al* studied the use of zoledronic acid in patients with AIPC, with a high loss rate (ranging between 62% and 72% depending on the treatment group). Zoledronate at a 4 mg dose caused a statistically significant decrease in the proportion of patients with skeletal events when compared with placebo. However, the difference with zoledronic acid at a dose of 8 mg (subsequently reduced to 4 mg) vs placebo was not significant[259]. In addition, zoledronate reduced the incidence of skeletal events by 36% (RR = 0.640; p = 0.002)[260]. This decrease was highest in patients without pain[261]. The bisphosphonate delayed the first skeletal episode by more than 5 months (p = 0.009, which was a significant difference when compared with placebo)[260]. A significant RR was seen for the proportion of patients with a skeletal event (RR = 0.71 [95% CI: 0.50-0.99]) when zoledronic acid was compared with placebo[262].

RCT (1+/1-) When comparing zoledronic acid with placebo or the standard treatment in patients with AIPC, symptomatic fractures did not appear in the year following the start of hormone therapy. As for asymptomatic fractures, there were no differences in the rates for both groups[258]. In another study with the same design, the relative risk for the proportion of patients with pathological fractures was significant: RR = 0.57; [95% CI: 0.38-0.88][262].

RCT (1+/1+) In patients with AIPC, the rates of spinal compression, bone surgery and bone radiotherapy did not differ significantly when comparing bisphosphonate and placebo[252].

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Pain relief

RCT (1++) In men with AIPC, there was a non-significant trend towards better results with bisphosphonates when compared with placebo for pain relief in bone metastasis[252].

RCT (1-) The use of zoledronic acid at a dose of 8 mg in AIPC produces an improvement in the average pain rating at 15 months of treatment when compared with placebo (p = 0.026), but there were no significant differences when comparing bisphosphonate at a dose of 4 mg to placebo (p = 0.134). There were no significant differences in analgesia levels when comparing each of the bisphosphonate treatments with placebo[259].

RCT (1-) In men with AIPC, zoledronic acid produced significant reductions in bone pain in the long term, when compared with placebo[260].

RCT (1++) The use of bisphosphonates in patients with androgen-independent prostate cancer resulted in a decrease in consumption of painkillers when compared with placebo[252].

Survival

RCT (1-) In patients with AIPC, the median survival time was 464 days for patients treated with placebo, 546 days for patients who received zoledronate at 4 mg (p = 0.091), and 407 days for patients who received a dose of 8 mg (p = 0.386)[259].

Side effects and quality of life

RCT (1+) In men with metastatic prostate cancer treated with androgen deprivation, no significant differences were found in the rate of severe adverse effects when comparing bisphosphonates with placebo[255,257,258].

RCT (1-) In patients with AIPC, zoledronic acid resulted in a deterioration of kidney function: 15.2% of patients treated at a dose of 4 mg and 20.7% of those who received a dose of 8 mg, with 12.5% of those treated with placebo[259].

RCT (1++) In patients with AIPC, the quality of life did not differ significantly when comparing bisphosphonates and placebo[252].

RCT (1++) A systematic review in 2007[263] found only 26 cases of mandibular osteonecrosis in patients treated with bisphosphonates, which had been previously reported. Of the 26 cases found, 87% occurred in women, 78% older than 60 years. For 80%, in the area of osteonecrosis, dental damage already existed or the patients had received treatment prior to surgery. There was no clear link found between the duration of treatment with bisphosphonates and the appearance of mandibular osteonecrosis. It should be remembered that the frequency of this adverse effect is very low: only 1 case appeared in a series of more than 7,000 women treated for 3 years with zoledronic acid. The estimated incidence is 1 case per 10,000-100,000 inhabitants/year in patients treated with bisphosphonates.

Despite this very low frequency, there is a Spanish Medicines Agency warning of mandibular osteonecrosis associated with bisphosphonates. It recommends a dental check-up

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before treatment and that the patient is not subjected to invasive dental interventions while undergoing intravenous treatment with bisphosphonates[264].

8.3.2 Radiopharmaceuticals

The majority of patients with androgen-independent prostate cancer (AIPC) have painful bone metastasis. Strontium-89 (Sr-89) and Samarium-153 (Sm-153) are beta-emitting radioisotopes administered intravenously for these patients[4,16,265].

Pain relief

RCT (1++) When comparing the reduction of pain reported in patients treated with Sr-89 v placebo, no significant differences between the two treatments were found in the long term (1-3 years), but there were differences in the short term (5 weeks)[266,267]. When Sr-89 was compared with local external beam radiotherapy (ERT), some studies found less pain in the group treated with Sr-89 + radiotherapy (RT), although in others there were no differences[268,269]. When Sr-89 + local RT was compared with local RT, the reported pain was similar in both groups, but the appearance of new painful locations was significantly higher in the group receiving external radiotherapy[270,271].

It seems that the Sr-89 is effective for pain control in bone metastasis in up to 70% of patients[17].

RCT (1++) The Sartor *et al* study[272] noted that the use of Sm-153 has positive effects on pain for 1-4 weeks after starting treatment, when compared with placebo (correlation coefficient $r = 0.78$; $p < 0.0001$). In addition, it decreased the use of opioids 3-4 weeks after starting the treatment ($p < 0.0284$).

When compared with placebo, Sm-153 achieved pain reduction in a greater proportion of patients after starting the treatment (38% vs 18%; $p = 0.008$). The same occurred 4 weeks after starting treatment (55% vs 35%)[272].

Survival

RCT (1++) When comparing Sr-89 with local ERT, biochemical progression-free survival was comparable between the two groups, while overall survival was significantly greater in the group receiving ERT[270]. However, when the same comparison was performed in a different trial, overall survival was similar in both groups[271].

RCT (1++) When comparing Sr-89 with placebo, the group treated with Sr-89 had a better overall survival at 2 years[267]. When Sr-89 + local RT was compared with local RT, no differences in global survival were found[268]. However, when Sr-89 + chemotherapy (CT) was compared with CT, better results for overall survival were found in the Sr-89 group[273].

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Side effects and quality of life

RCT (1++) Sr-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30-50% of patients who received it (usually moderate, grade ≤ 2)[17].

In randomised clinical trials that compared Sr-89 v local RT, the rate of adverse effects (haematological toxicity, nausea and vomiting) was similar in both groups[270,271].

Various study types (1++/4) The only statistically significant side effect associated with Sm-153 in a trial was temporary and slight myelosuppression[272]. The European Association of Urology clinical practice guideline found that early use of radioisotopes may make it harder for the administration of chemotherapy, because they cause myelosuppression[4].

RCT (1++) When comparing Sr-89 + local RT v local RT, no significant differences were found regarding the quality of life[269].

In Spain, the use of Sr-89 for bone metastasis is only authorised for prostate cancer. Sm-153 is approved for this and other neoplasias affecting bone, such as in the breast or lung. Therefore, in Spain, the Nuclear Medicine Services usually have more experience in the use of samarium than strontium.

Although both Sr-89 and Sm-153 are beta-emitters[265], Sm-153 also emits gamma radiation. This means that the distribution of this radiopharmaceutical can be checked directly with an image test after the treatment, which cannot be done with strontium.

It seems that, in well-selected patients (when other analgesic treatments have failed), treatment with radiopharmaceuticals is effective in reducing pain. However, before proposing its use, first-line chemotherapy should be suggested first.

Summary of evidence

1+	In patients with metastatic prostate cancer treated with androgen deprivation, bisphosphonates were compared with placebo or the standard treatment. Those treated with bisphosphonates showed an average increase in bone density in the spinal column of 1-5% in the first year of hormone treatment. Those who received placebo or standard treatment showed a significant average decline of 0.4 – 4.9% during the same period. The difference between the two groups was about 5% for the bisphosphonates[254-258].
1++	In patients with androgen-independent prostate cancer (AIPC), there was a modest reduction of skeletal events in those treated with bisphosphonates v placebo: 37.8% vs 43.0%; an absolute risk reduction of 5.2%[252].
1-	In patients with AIPC, zoledronic acid at a dose of 4 mg produced a statistically significant decline in the proportion of patients with skeletal events when compared with placebo. However, when an 8 mg dose of zoledronic acid (subsequently reduced to 4 mg) was compared with placebo, the difference was not significant[259].
1-	In patients with AIPC, zoledronic acid reduced the incidence of skeletal events by 36% (RR = 0.640; p = 0.002)[260]. This decrease was highest in patients without

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	pain[261]. Bisphosphonate delayed the first skeletal episode by more than 5 months (p = 0.009; a significant difference when compared with placebo)[260].
1-	In patients with AIPC treated with zoledronate, the RR for the proportion of patients with a skeletal episode was significant (compared with placebo): RR = 0.71 [95% CI: 0.50 – 0.99][262].
1+/1-	In a study of patients with metastatic prostate cancer treated with androgen deprivation in which zoledronic acid was compared with placebo or the standard treatment, no symptomatic fractures occurred in the year following the start of hormone therapy. No differences in the rates of asymptomatic fractures in either groups was observed[258]. In another test with the same design, the RR for the proportion of patients with pathological fractures was significant: RR = 0.57 [95% CI: 0.38 – 0.88][262].
1++	In patients with AIPC, the rates of spinal compression, bone surgery and radiotherapy did not differ significantly when comparing bisphosphonates with placebo[252].
1++	In patients with AIPC, there was a trend towards better results for bone metastasis pain relief with bisphosphonates than with placebo[252].
1-	In patients with AIPC, zoledronic acid at a dose of 8 mg produced an improvement in pain rating after 15 months of treatment when compared with placebo (p = 0.026). However, no significant differences were found when comparing a 4 mg dose of bisphosphonate with placebo (p = 0.134). There were no significant differences in analgesia levels when comparing each of these doses with placebo[259].
1-	In patients with AIPC, zoledronic acid produced significant reductions in long term bone pain when compared with placebo[260].
1++	The use of bisphosphonates in patients with androgen-independent prostate cancer produced a decrease in consumption of analgesics, when compared with placebo[252].
1-	In patients with AIPC, the median survival time was 464 days for those treated with placebo, 546 days for the group receiving a 4 mg dose of zoledronate (p = 0.091) and 407 days for those who received a dose of 8 mg (p = 0.386)[259].
1+	In patients with metastatic prostate cancer treated with androgen deprivation, there was no significant difference in the rate of severe adverse effects when comparing bisphosphonates with placebo[255,257,258].
1-	In patients with AIPC, the use of zoledronic acid produced a deterioration in renal function: 15.2% of patients treated at a dose of 4 mg, 20.7% of those who received a dose of 8 mg and 11.5% of patients treated with placebo[259].
3	A systematic review in 2007[263] found only 26 cases of mandibular osteonecrosis in patients treated with bisphosphonates, which had been previously reported. Of the 26 cases found, 87% occurred in women, 78% occurred in those older than 60 years and 80% in patients who had been subject to surgery or dental damage in the area of osteonecrosis prior to treatment. There was no clear link found between the duration of treatment with bisphosphonates and the appearance of mandibular osteonecrosis. It should be remembered that the frequency of this adverse effect is very low: only 1 case appeared in a series of more than 7,000 women treated for 3 years with zoledronic acid. The estimated incidence is 1 case per 10,000-100,000 inhabitants/year in patients treated with bisphosphonates.
1++	In patients with AIPC, the quality of life did not differ significantly when comparing bisphosphonate and placebo[252].

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1++	When comparing the reduction of pain reported in patients treated with Sr-89 v placebo, no significant differences between the two treatments were found in the long term (1-3 years), but there were differences in the short term (5 weeks)[266,267]. When Sr-89 was compared with local external beam radiotherapy (RT), some studies found less pain in the group treated with Sr-89 + radiotherapy (RT), although in others there were no differences[268,269]. When Sr-89 + local RT was compared with local RT, the reported pain was similar in both groups, but the appearance of new painful locations was significantly higher in the group receiving external radiotherapy[270,271].
4	Sr-89 is effective for pain control in bone metastases in up to 70% of patients[17].
1++	The use of Sm-153 has positive effects on pain 1-4 weeks after starting treatment, when compared with placebo (correlation coefficient r = 0.78; p <0.0001). In addition, it decreased the use of opioids 3-4 weeks after starting treatment, when compared with placebo (p <0.0284).
1++	The use of Sm-153 manages to reduce pain at the start of the treatment in a greater proportion of patients (38% vs 18%; p = 0.008) when compared with placebo. The same occurred 4 weeks after starting treatment (55% vs 35%)[272].
1++	When comparing Sr-89 v local ERT, biochemical progression-free survival was comparable between the two groups, while overall survival was significantly higher in the group receiving ERT [270]. However, in a different test carrying out the same comparison, overall survival was similar in both groups[271].
1++	When comparing Sr-89 with placebo, the group treated with Sr-89 showed better overall survival at 2 years[267]. When Sr-89 + local RT was compared with local RT, there was no difference in global survival[268], but when comparing Sr-89 + chemotherapy (CT) with CT, overall survival in the Sr-89 group was better[273].
1++	Sr-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30-50% of patients who received it (usually to a moderate degree ≤ 2)[17].
1++	In randomised trials comparing Sr-89 with local RT, the rate of adverse effects (haematological toxicity and nausea or vomiting) was similar in both groups[270,271].
1++/4	The only statistically significant side effect associated with Sm-153 was temporary and slight myelosuppression[272]. Early use of radioisotopes may make the administration of chemotherapy difficult, due to myelosuppression[4].
1++	When comparing Sr-89 + local RT with local RT, no significant differences were found between the two groups regarding the quality of life[269].

Recommendations

B	Routine use of bisphosphonates (zoledronic acid) as a preventive treatment for bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected patients, and those who are hormone-independent or with demonstrated metastasis.
A	Treatment with Sr-89 or Sm-153 can be proposed in men with androgen-independent prostate cancer (AIPC) when third level analgesics are required to adequately control bone pain. A correct haematological formula (> 3,500 leukocytes and > 150,000 platelets) and a bone scan showing bone metastasis are essential before administration.

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9. Dissemination and implementation

The clinical practice guidelines are an attempt to help professionals and patients make decisions about appropriate health care. This involves an investment of effort and resources which is sometimes not sufficiently exploited, due to not being sufficiently used by health professionals or due to not improving the quality of care or health outcomes in the population for which it is intended.

To improve the implementation of this guideline, that is, its use in the clinical setting, a set of strategies should be devised to overcome possible barriers to its adoption[14].

The plan to implement this Prostate Cancer Treatment Guideline includes the following measures:

- Presentation of the guideline by the health authorities to the media.
- Collaboration with the Scientific Organisations involved in the preparation, revision and distribution of this guideline.
- Sending the guideline to different GCP databases to be assessed and included in them.
- Contact with the Spanish Association Against Cancer and other patient groups interested in this guideline.
- Free access to the various versions of this guideline on the Health Guideline web site (http://www.guiasalud.es).
- Spreading information about the guideline in various scientific functions related to prostate cancer (conferences, seminars, meetings).
- Sending a guideline information leaflet to professional places of learning, government health organisations, health centres, local health associations, etc.
- Placing information about the guideline in specialist medical journals and publications.
- Broadcasting the existence and objectives of this guideline via distribution lists for potentially interested practitioners.

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10. Recommendations for future research

This section is a compilation of the different future research recommendations proposed throughout this guideline.

A	Randomised trials should be started comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with clinically localised prostate cancer.
√	Randomised trials should be started to assess the usefulness of modified fragmentations (hypofragmentation, etc) of radiotherapy for prostate cancer.
A	Randomised trials should be started comparing cryotherapy and high intensity focused ultrasound with standard treatments in patients with prostate cancer at a locally advanced clinical stage.
√	Randomised trials should be started to assess the usefulness of docetaxel administered as a concomitant or adjuvant to radiotherapy after local treatment.
√	Randomised trials should be started to determine the appropriate hormone treatment (monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade) in prostate cancer patients at the locally advanced clinical stage.
D	Clinical trials should be launched to evaluate local salvage therapies in terms of survival and quality of life in men with biochemical recurrence after radiotherapy or brachytherapy.
√	Patients with androgen-independent disseminated prostate cancer (those for whom androgen suppression and complete androgen blockade have failed) should be offered inclusion in clinical trials to evaluate the efficacy and safety of second-line hormone therapy, comparing it with chemotherapy that has proven effective.
√	Patients with PSA relapse, androgen-independence, who are asymptomatic and without documented metastatic disease should be offered inclusion in clinical trials that compare early and delayed start chemotherapy.
√	Patients with androgen-independent disseminated prostate cancer for whom chemotherapy treatment has been decided, should be offered inclusion in clinical trials to compare the safety and efficacy of chemotherapy with chemotherapy associated with LHRH agonists.

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Appendices

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Appendix 1. Levels of evidence and grades of recommendation from SIGN[14]

Levels of evidence

1++	High quality meta-analyses, systematic reviews of clinical trials or high quality clinical trials with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials or well-conducted clinical trials with a low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with very low risk of bias and a high probability of establishing a causal relationship.
2+	Well-conducted case control or cohort studies with a low risk of bias and a moderate probability of establishing a causal relationship.
2-	Case control or cohort studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies, eg case reports and case series.
4	Expert opinion.

Grades of recommendation

A	At least one meta-analysis, systematic review or clinical trial rated as 1++, which is directly applicable to the target population of the guideline; or a body of evidence consisting mainly of studies rated as 1+, which demonstrate overall consistency of results.
B	A body of evidence consisting mainly of studies rated as 2++, directly applicable to the target population of the guideline, which demonstrate overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+.
C	A body of evidence consisting of studies classified as 2+, directly applicable to the target population of the guideline, which demonstrate overall consistency of results; or evidence extrapolated from studies rated as 2++.
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

Studies classified as 1- and 2- should not be used in the process of developing recommendations due to their high possibility of bias.

Good Clinical Practice

√* Recommended practice based on clinical experience and the consensus of the development group.

* Sometimes the development group is aware of some important practical aspect which needs to be emphasized but for which there is probably no evidence to support it. Generally, these cases are related to some aspect of the treatment considered as good clinical practice which nobody would normally question. These aspects are evaluated as good clinical practice points. These messages are not an alternative to recommendations based on the evidence, but must be considered only when there is no other way to highlight this aspect.

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Appendix 2. Patient information

Original document: "*Comprendre le cancer de la prostate. Guide d'information et de dialogue à l'usage des personnes malades et de leurs proches* (http://www.sor-cancer.fr), translated with permission of the *Fédération Nationale des Centres de Lutte Contre le Cancer* and adapted for our needs[274].

A2.1 What is the prostate?

The prostate is a *gland* in the male genital apparatus which plays an important role in the production of *sperm*. It is located under the bladder, in front of the rectum, and surrounds the opening of the *urethra*, the tube that allows the removal of accumulated urine in the bladder.

It is shaped like a chestnut, about 3 cm long and 4 cm wide, and is surrounded by a *capsule*. It is composed of a central zone around the urethra and a peripheral zone, near the rectum.

Around the urethra, a set of muscle fibres grouped under the prostate form the urinary *sphincter*, which controls the passage of urine through a process of contraction or relaxation, and is thus responsible for *continence*.

Figure 2. Male reproductive system (from the sagittal plane)



The prostate produces part of the *seminal fluid*, while most of the seminal fluid is produced by the *seminal vesicles*. This liquid is then mixed with sperm, which comes from the testes and passes through the *vas deferens* toward a portion of the *urethra* (prostatic urethra) during ejaculation.

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A2.2 What is a prostate adenoma?

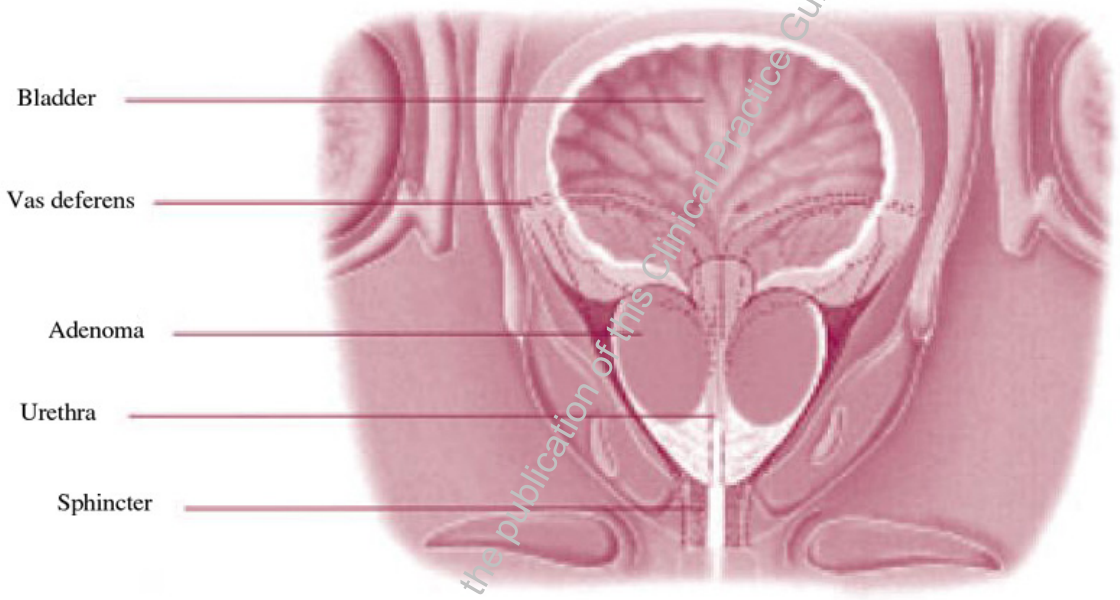
A prostate adenoma is an increase in the volume of the centre of the prostate.

When a man visits a doctor because of urinary problems, normally the problem is due to a prostate adenoma. However, **this is not cancer**. It can also be called benign prostatic hyperplasia. The prostate adenoma presses against the *urethra* and may cause some discomfort and difficulty when urinating.

Usually, no treatment is required, but the *symptoms* should be monitored regularly.

When an adenoma causes great discomfort to the patient or leads to complications (*urinary retention*, for example), the adenoma can be treated with medication or surgery. The surgery consists of removing the central part of the prostate, where the adenoma is found, and leaving the rest of the prostate intact.

Figure 3. Prostate adenoma (front section-facing)



Nowadays, this intervention is often performed through the natural route (via the urethra) and is called *transurethral resection*. However, if the adenoma is very large, it will require a more serious operation, such as an adenectomy, which is surgical removal of the adenoma.

A cancer may develop in the part of the prostate not affected by the adenoma. Even if the adenoma is removed, the prostate must be regularly monitored by a doctor.

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A2.3 What is cancer?

Cancer is a disease of the *cells*.

The cell is the basic unit of life. There are more than 200 different cell types in our bodies (muscle cells, immune cells, nerve cells, etc), and each has a specific role.

A cancer cell is a cell that has been altered during generation. Normally, these changes are repaired by the body, however a cancerous (or *malignant*) cell cannot be repaired. It enters a multiplication phase in the body or human *tissue*. After multiply uncontrollably, the cancerous cells form a mass called a *malignant tumour*.

The cells of malignant tumours have a tendency to migrate to other organs or other parts of the body, where they develop new tumours in a process known as *metastasis*. Such a tumour is said to be a metastatic tumour. In prostate cancer, the metastasis is located mainly in the bones (bone metastasis).

Not all cancers behave in the same way, which is why it is necessary to consider a suitable treatment for each patient. All treatments are aimed at eliminating all the cancer cells. If the cancer is not treated, the tumour can develop and spread to other parts of the body, ie produce metastasis.

A2.4 What is prostate cancer?

Prostate cancer is the development of cancerous cells in the prostate. Most frequently, these cells grow in the peripheral zone of the prostate, and less frequently in the central zone.

How common is this cancer?

It is estimated that in 2000 there were 1,555,000 cases of men with prostate cancer in the world. It is the third most common neoplasm in men in Spain and in the world. It constitutes approximately 11% of all cancers in European men.

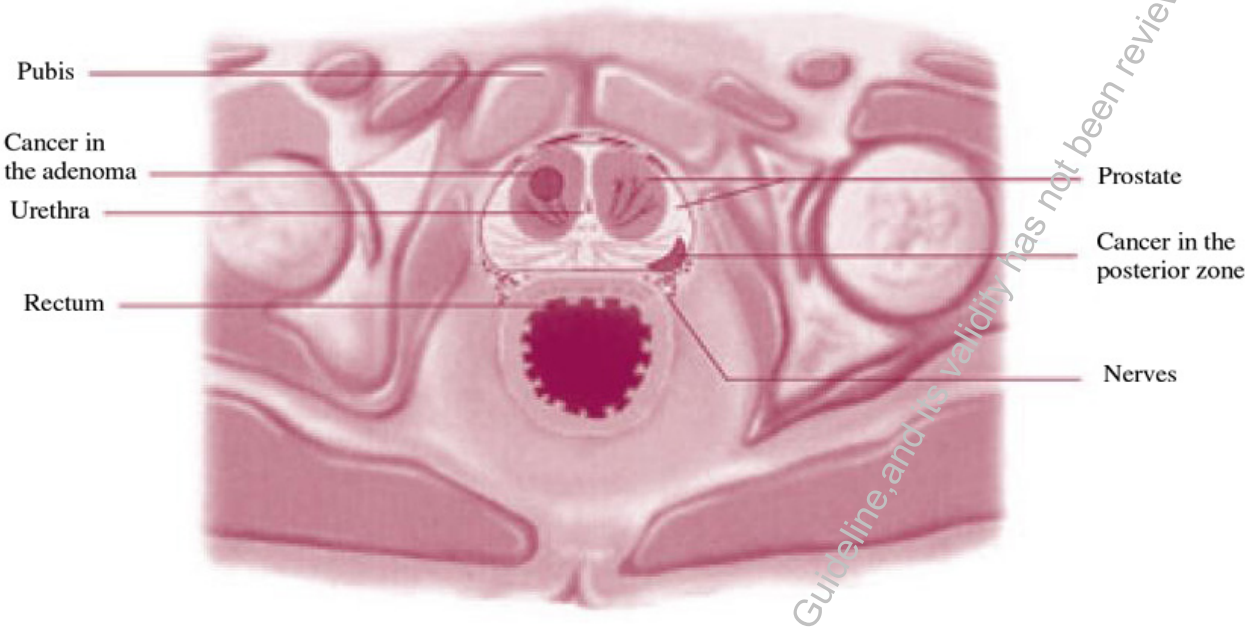
In 2001, it was estimated that in Spain there were 157.9 cases per 100,000 inhabitants. Of these, 21% had been diagnosed the previous year, 46% in the previous 4 years, another 23% between 5 and 10 years beforehand, and 10% of patients had had it for more than 10 years.

There are definitely lots more cases of prostate cancer which go undetected; a number of which are not diagnosed because they are so small. More than half of men over 60 have at least some prostate cancer cells which have not developed sufficiently to affect their health.

Scientific studies show that if a cancer is detected early, the chances of a cure are much better.

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Figure 4. The prostate, adenoma and tumour (transverse-horizontal section)



The role of the physician is to diagnose the cancer, determine whether the cancer poses a risk to the patient's health and if it is really necessary to be treated, which does not always happen.

A2.5 The treatment of prostate cancer

The aim of prostate cancer treatment is to remove all cancer cells or prevent them proliferating. Treatment is more effective the sooner a cancer is detected.

Knowledge about the disease and the best treatment to give patients at different stages of the disease have been identified from a number of scientific studies. These have also helped evaluate new treatments or establish the most effective order for their use. These studies have also enabled comparison of their advantages and disadvantages when compared to the normal treatment used.

Standard treatments are those recognized as the best and those which are systematically proposed in a specific situation. However, it may happen that the doctor cannot apply the standard treatment because of the particular risk for the patient, his illness or because the patient will not accept the consequences linked to the treatment. In these cases, the doctor may suggest one or more other treatments best suited to the situation. For any given situation, there are sometimes different treatments possible, that is, there are treatment *alternatives* or *options*.

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What are the different types of treatment?

There are different types of treatment that can be used alone or associated with each other. The treatment of prostate cancer is adapted to the circumstances of the patient.

Removing the prostate: radical or total prostatectomy
Total prostatectomy is a *local treatment* aimed at removing the entire prostate, along with the *seminal vesicles* via surgery. Radical prostatectomy is a *standard* treatment for non-metastatic prostate cancer. This treatment is performed by a *urologist*, or someone specialising in urology.

External beam radiotherapy
External beam radiotherapy is a *local treatment* aimed at destroying the cancer cells in the prostate by radiation. These rays are produced by an external *radioactive source* and directed towards the prostate. External beam radiation is a *standard* treatment for non-metastatic prostate cancer. This treatment is performed by a *radiotherapist*, or someone specialising in oncological radiotherapy.

Brachytherapy
Brachytherapy is a *local treatment* aimed at destroying the cancer cells in the prostate by radiation. These rays are produced by a *radioactive source* placed inside the prostate (in the form of seeds or wire, for example). Some types of brachytherapy treatment are temporary (eg, iridium wire), but others are permanent (eg, seeds of radioactive iodine-125), depending on whether the radioactive source remains in the body of the patient or not. Brachytherapy is an *alternative*. This treatment is practised by a radiotherapist (often together with a urologist) who specialises specifically in brachytherapy.

High intensity focused ultrasound (HIFU)
High intensity focused ultrasound (HIFU) is a local treatment for prostate cancer aimed at destroying the cancer cells by *ultrasound*. The high intensity ultrasound is directed at the prostate from a *probe* in the rectum. Ultrasound destroys the tumour by applying strong heat in a very particular area. This technique is still under evaluation and is therefore an *alternative*.

Hormone therapy
Testosterone is a male hormone that stimulates the growth of prostate cells, whether normal or cancerous. Hormone therapy prevents the testosterone from acting, and is a *general treatment* acting on the whole body.

Monitoring (with delayed treatment)
Some prostate cancers can develop very slowly, without causing troublesome symptoms for the patient, especially elderly ones. For some patients, therefore, the doctor may suggest merely monitoring the tumour (or *watchful waiting*), thereby avoiding any treatment side effects.

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Cancer development is monitored by regular *clinical examinations* and *PSA* levels. Depending on the progression of the disease and the preferences of the patient, a suitable treatment may be proposed along with patient monitoring.

How is the choice of treatment made?

When choosing treatment, doctors take into account several criteria:

The characteristics of the cancer
The doctor assesses the state of prostate cancer using the international TNM classification. This takes into account three criteria: (1) tumour size - T, (2) the presence of cancer cells in lymph nodes – N, and (3) the presence or absence of metastasis - M.

PSA values give a rough idea of the size of the tumour.

Examination under a microscope of cancer cells obtained from a biopsy allows the aggressiveness of the cancer cells to be assessed. This aggression is defined by a scale called the *Gleason scale*.

The characteristics of the patient
The age of the patient, his illnesses (past or present), any surgery undertaken, the presence of an *adenoma* or urinary infection, as well as the general state of health are factors taken into account when choosing a treatment. These are evaluated together with the risks and benefits expected from the different types of treatment, and therefore have a very important role in the choice of a suitable treatment for the patient.

The characteristics of the prostate
If there is an *adenoma* and a cancer, the prostate will be large, which contraindicates *brachytherapy* or *ultrasound*.

By contrast, although there is an adenoma, the large size of the prostate would not contraindicate a total prostatectomy, which in this case would treat the cancer and the adenoma.

A2.6 Post-treatment monitoring

Why monitor?

The treatment of prostate cancer aims to cure the cancer and reduce the risk of local recurrence or distant *metastasis*. The risk of *relapse* or *progression* of the prostate cancer is highly variable and depends on the *state of evolution* of the cancer at diagnosis. Most relapses occur within 5 years of treatment, and sometimes much later. However, it is possible that the cancer will never appear again.

Monitoring allows the detection of *signs* of disease relapse, so that a modification to the treatment can be offered if necessary. Monitoring also helps to prevent and treat possible *side*

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effects. These depend on the treatment received, in the doses administered, the type of cancer and the way in which the patient has reacted to the disease and treatment.

Regular monitoring, planned and organised in advance, calms the patient. The doctor can answer questions and put the patient in touch with other professionals (nurses, social workers, physical therapists, psychiatrists or psychologists, sexologists, etc) or with patient associations. These professionals and associations can help the patient to resume a normal life as quickly as possible.

What is post-treatment monitoring?

Monitoring consists of regular consultations with a doctor. During the consultation, the doctor interviews the patient, performs a *clinical examination* and requests a *PSA* measurement.

The interview is to find out any *symptoms* which may signal a relapse or side effects of the treatment. It is very important the patient explains and describes anything they consider unusual or strange, especially if the *symptoms* persist.

The doctor may also perform a *rectal examination*.

PSA levels are useful for finding out if everything is normal after treatment. An abnormal PSA value allows a sufficiently rapid detection of any possible relapse and better treatment.

A very low PSA value, ie less than 0.4 ng/ml (nanograms per millilitre), after the operation is a good *sign* of recovery. It is recommended to stop monitoring after a prostatectomy if the PSA value remains low for at least 10 years after the operation.

An increase in the PSA value is a sign that the cancer has returned (relapse).

If the patient reports any abnormal signs or if any become evident after the clinical examination or if there is an increase in PSA which does not reduce, the doctor may consider it necessary to conduct some additional tests: bone scintigraphy, renal and abdominal *ultrasound*, blood and urine analyses. Depending on the results of these tests, if the patient has no symptoms, the specialist will not recommend any more systematic analyses, except for a rectal examination and PSA determination.

Monitoring allows *side effects* to be prevented and treated, especially those related to sexuality. To mitigate these side effects, the doctor may suggest oral medication (tablets) or an injection in the corpora cavernosa (at the base of the penis). A vacuum pump is another means of recovering erections, and, as a last resort, the placement of a prosthesis into the penis may be proposed. Generally speaking, the results are satisfactory.

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How often should monitoring take place?

Prostate cancer specialists recommend regular monitoring, although no studies have established how regular this should be.

After treatment, a monitoring timetable is set up with the patient. The name of the doctor who will perform the monitoring along with the scheduled dates are noted. The doctor who performed the treatment will be informed of the results of this monitoring. It is important that the primary care physician is involved in the surveillance together with the specialist.

Those men treated with prostatectomy, may be monitored by a PSA determination according to the following timetable:

- A PSA determination 3 months after surgery, then every 3 months during the first year.
- Determinations every 6 months until the third year, providing the PSA remains at very low values.
- Annual determinations thereafter.

A *digital examination* is not required as part of the monitoring for patients whose PSA is very low.

Men treated with external beam radiation or brachytherapy are recommended to have a rectal examination and PSA determination at a similar frequency to that for prostatectomy for a period of up to 8 years.

A2.7 Glossary of terms for patients

Adenoma: Anomaly that develops on a gland: a **benign** tumour. A prostate adenoma may lead to a significant increase in the size of the prostate. Also called benign prostatic hyperplasia.

Adenopathy: Increase in the size of **lymph nodes**, hard and sometimes inflamed, which may or may not be painful. An adenopathy may be caused by cancer cells from an organ or tissue adjacent to a lymph node.

Anatomopathologist: medical specialist who examines the tissue cells under a microscope.

Anaesthesia: Act of blocking or temporarily removing sensation in the patient (general anaesthesia) or a part of his body (local anaesthesia) during surgery.

Arteries: Vessels that carry blood from the heart to the tissues.

Benign: A tumour which is not serious. A benign tumour is not cancer.

Biopsy: Extraction of a small piece of tissue from the prostate to examine under the microscope. The prostate biopsy is performed by an ultrasound **probe** through the rectum. The doctor can perform the biopsy with or without anaesthesia (local or general). The fragment of tissue is immediately examined by a medical **anatomopathologist**.

Brachytherapy: Highly localised treatment to destroy cancer cells by radiation from a radioactive substance implanted within the prostate.

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Vas deferens: Duct that conveys sperm from the testicles to the ejaculatory duct.

Cancer: Abnormal **cells** which grow uncontrollably, eventually forming a mass called a **malignant** tumour.

Capsule: External part of the prostate that separates it from neighbouring tissues.

Cell: Component visible under the microscope which is part of every living organism. Plants and animals are composed of very different cells which multiply, renew and die. Organised cells identical to each other form **tissues**. Cancer cells are cells that have been modified and multiply anomalously. See **cancer**.

Surgery: An operation on the patient involving skin incision. This may be aimed at obtaining cells to analyse (**biopsy**) or to remove a tumour (treatment).

TNM classification: International classification allowing the medical specialist to classify the status of prostate cancer:

- T: size of the **tumour**.
- N: indicates whether the **lymph nodes** have been invaded or not.
- M indicates the presence or absence of **metastasis**.

Continence: Ability to retain urine or faeces when not being discharged. Continence is performed by a bladder muscle, which ensures the evacuation of urine and the sphincters which retain urine and faeces.

Ultrasonography: Technique using **ultrasound** that shows images of a part of the body or certain organs. It is type of pain-free radiological examination.

Side effects: The aim of treatment is to cure prostate **cancer**. Sometimes, unpleasant consequences for the patient occur, which are called side effects. Although side effects are common, they do not always occur. They depend on the treatment received, the doses administered, the type of cancer and how the patient reacts to treatment. There are two types of side effects: **early** and **late**.

Early side effects: Short-term adverse effects (diarrhoea, **incontinence**, etc) appear very early and are temporary (they usually disappear after treatment has finished).

Late side effects: Long-term adverse effects (painful scars, **impotence**, etc), which may persist long after treatment has ended (sometimes until the end of life, which is called sequela).

Gleason scale: Results from a microscopic study of cancer cells obtained by biopsy or prostatectomy. This analysis can determine the aggressiveness of the cancer through the establishment of a classification whose range is 2 to 10. A value of 2 corresponds to a tumour which is very similar to **benign** tissue. The higher the value, the more aggressive the tumour.

Sphincter: Muscle that surrounds a natural orifice and opens and closes entry to an organ (bladder, anus). The sphincter allows the retention and disposal of urine and faeces.

Sperm or semen: Whitish liquid emitted during ejaculation. Semen is made up of sperm from the testicles and secretions from various male genital **glands** (prostate, **seminal vesicles**).

State of evolution: See **extension**.

Standard: Examination or treatment whose results are scientifically accepted and are considered beneficial. A standard treatment is always proposed in a specific situation. The standard treatment may not be able to be applied because of the particular characteristics of the patient or his illness. If this happens, the doctor will propose one or more treatments better suited to the particular situation of the patient (**options** or **alternatives**).

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Clinical examination: exploration work carried out by the doctor, who questions the patient about the disease, and examines him (auscultation, palpation, **rectal examination**, etc).

Radiology: Exploration via images of a part of the body or its organs. There are various types of radiological examinations: ultrasound, x-ray, magnetic resonance.

Extension: Development of the cancer. Cancer begins after the development of one or more cancer cells, which multiply and form a tumour. When cancer cells remain in their original location, it is referred to as local extension or evolution of the cancer. The more the cells multiply, the more the tumour grows, and the greater the risk that cells can escape to other parts of the body. If cancer cells reach the lymph nodes, this is called regional affectation or extension. When cancer cells are identified in other organs (liver, bone, lung, etc), this is referred to as metastatic extension or affectation.

Radioactive source: Substance or object that emits **radiation**. A source can be external or internal.

Bone scan: Examination technique showing images of the skeleton. This imaging technique uses products that emit very little radiation and, once injected, attach to the bone. This allows it to be seen whether there are cancer cells in the bone or not.

Lymph node: Small lump-like structure spread throughout the **lymphatic vessels**. Established in certain parts of the body, lymph nodes can be superficial (in the neck, axilla) or interior (in the abdomen, chest). They play an important role in protecting the body against **infections** or cancerous **cells**. Normally, they measure less than one centimetre in diameter. If the size is abnormally large, this is called **adenopathy**.

Gland: Organ whose function is the production of one or more substances. Most of the glands secrete substances outwards and are called exocrine glands, such as those that produce milk or saliva. Other glands produce hormones which are secreted in the blood, such as the ovaries or thyroid. These are called endocrine glands.

Benign prostatic hyperplasia: **Adenoma**.

Impotence: Inability to obtain or maintain an erection of the penis necessary for maintaining a sexual relationship. Impotence is divided into different degrees.

Incontinence: Involuntary loss of urine or faeces. Incontinence can be complete (**micturition** is total) or incomplete, happening during the day (during normal activities, during an effort) or overnight (with normal micturition).

Infection: Presence of a **microbe** in the body.

Lymph: slightly coloured liquid produced by the body that covers the cells. Lymph transports and removes waste from the cells. Like blood, lymph circulates through vessels called lymphatic vessels.

Seminal fluid: Liquid formed by secretions from the **seminal vesicles** and prostatic secretions. It mixes with sperm from the testicles during ejaculation to form part of semen.

Malignant: A cancerous tumour. See **cancer**.

Metastasis: Formation of a tumour elsewhere in the body, due to the migration of cancer cells via the **lymphatic vessels** or **blood vessels** from a primary tumour. Also known as metastatic disease, generalised cancer or secondary location cancer. See **extension**.

Micturition: Action of urination.

Microbe: Micro-organisms invisible to the human eye which can cause diseases (bacteria, viruses).

Microscope: optical instrument used to examine objects which are not visible to the naked eye.

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Medical oncologist: Medical specialist in the treatment of cancer with drugs. Also known as an oncologist.

Oncological radiotherapy: See **Radiotherapy**.

Option or alternative: For a given situation, a therapeutic option is a different choice of treatment, which has no proven advantage over others. See **standard**.

Prostate: **Gland** in the male genital apparatus which plays an important role in the production of **sperm**.

PSA (prostate specific antigen): Substance released by prostate cells. Many factors can cause an increase in the PSA, such as age, infection of the prostate, presence of a prostate adenoma or presence of cancer cells.

Radiation: See **radiotherapy**.

Radiotherapy: **Local treatment** of cancer using a device that releases radiation directed at the tumour to destroy it. It may be emitted by an internal or external source.

Radiotherapist: Medical specialist in the treatment of cancer by **radiotherapy**. Also called **oncological radiotherapists**.

Relapse or recurrence or progression: Reappearance of **signs** or **symptoms** that mean cancer has returned after previous **remission** of the disease.

Remission: Reduction or disappearance of **signs** and **symptoms** of a disease. In the case of cancer, remission occurs when all signs of the cancer have disappeared. After a certain period of time, remission is called cure.

Transurethral resection: Surgical removal of the prostate via the urethra.

Urine retention: Accumulation of urine in the bladder, preventing it from evacuating.

Sign: Anomaly observed by the patient or doctor.

Symptom: Anomaly of the body caused by the disease. A symptom may be perceived differently from one patient to another (feeling of suffocation, burning sensation during urination, discomfort, pain).

Probe: Rigid or flexible tube for exploring a channel or cavity, to remove or insert something. A urinary catheter allows evacuation of urine.

Rectal examination: Examination of the prostate by touching the rectum wall with a finger.

Tissue: A group of **cells** that have the same function (for example, muscular tissue, bone tissue).

Testicles: male organs that produce sperm and testosterone.

General Treatment: Treatment that acts on the tumour and the whole body via a general route (intravenous, oral). Hormone therapy is a general treatment for cancer.

Local Treatment (locoregional): Treatment to remove or act directly on the prostate **tumour**. The aim is to eliminate all cancer **cells** from the tumour region. **Surgery** and **radiotherapy** are locoregional treatments for cancer.

Benign tumour: A tumour that is not cancerous. A prostate **adenoma** is a benign tumour.

Malignant tumour: Mass of cancer cells. See **cancer**.

Ultrasound: Non-audible (to the human ear) sound vibration used for certain imaging examinations (ultrasound) s or certain treatments (high intensity focused ultrasound, HIFU).

Urethra: Tube from the bladder to the tip of the penis. The urethra is used to evacuate urine and to transmit **sperm**.

Urologist: Medical specialist in urinary and genital problems, in particular urological cancers (diagnosis, treatment, monitoring), who operates to remove a tumour.

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Lymph vessels: Channel structures to carry **lymph**. Along with the **lymph nodes**, they form the lymphatic system.

Blood vessels: Channel structures for circulating blood (**arteries** or **veins**).

Veins: Vessels that carry blood to the heart.

Seminal vesicles: male genital glands that produce most of the **seminal fluid**. The vesicles are situated behind the bladder and above the prostate.

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Appendix 3 - Abbreviations

3D-CRT	3-dimensional conformal radiotherapy.
DNA	Deoxyribonucleic acid: the primary chemical component of chromosomes, the material from which genes are encoded.
AEU	Spanish Association of Urology.
AEEU	Spanish Association of Nursing in Urology.
AGREE	An international collaboration designed to assess the methodological quality of clinical practice guidelines.
MPA	Medroxyprogesterone acetate.
ASCO	American Society of Clinical Oncology.
ASTRO	American Society for Therapeutic Radiology and Oncology
CAB	Complete androgen blockade.
BT	Brachytherapy
PNB	Preservation of neurovascular bundles.
AIPC	Androgen-independent prostate cancer.
DARE	Database of Abstracts of Reviews of Effects: a database containing structured summaries of good quality systematic reviews. It is maintained by the Centre for Reviews and Dissemination, a department in the University of York, part of the UK National Institute for Health Research.
EAU	European Association of Urology.
RCT	Randomised clinical trial.
ECOG	Eastern Cooperative Oncologic Group, a leading US organisation devoted to cancer research which has developed an index, the ECOG scale, to measure the quality of life of a cancer patient in a practical way.
CPG	Clinical practice guideline.
HDR	High dose rate brachytherapy.
HIFU	High intensity focused ultrasound.
HR	Hazard ratio.
HT	Hormone therapy.
95% CI	95% confidence interval.
IMRT	Intensity Modulated Radiotherapy.
LHRH	Luteinising-hormone releasing hormone or GNRH (Gondatropin-releasing hormone).
LN	Lymphadenectomy
MSAC	Medical Services Advisory Committee, an Australian Ministry of Health advisory body on the safety, effectiveness and efficiency of new technologies and procedures.
NICE	National Institute for Health and Clinical Excellence, an independent British organisation that provides recommendations on public health, health technologies and clinical practice.
NNT	Number needed to treat.
OR	Odds ratio.
BP	Biochemical progression.
RP	Radical prostatectomy.
ORP	Open radical prostatectomy.
LRP	Laparoscopic radical prostatectomy.

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TP-LRP	Transperitoneal laparoscopic radical prostatectomy.
EP-LRP	Extraperitoneal laparoscopic radical prostatectomy.
RALRP	Robot-assisted laparoscopic radical prostatectomy.
PSA	Prostate specific antigen.
RR	Relative risk.
RT	Radiotherapy.
ERT	External beam radiotherapy.
SEOM	Spanish society of medical oncology.
SEOR	Spanish society of oncological radiotherapy.
OS	Overall survival
SIGN	Scottish Intercollegiate Guidelines Network, Scottish organisation devoted to evidence-based clinical practice guidelines.
BPFS	Biochemical progression-free survival.
Sm-153	Samarium-153.
SNS	National Health System.
Sr-89	Strontium-89.
TNM	Classification of tumour (T) size, regional lymph node (N) status and distant metastasis (M).
TRUS	Transrectal ultrasound-guided biopsy.
MPV	Mini-pelvis volume (of irradiation)
PV	Pelvis volume (of irradiation)
TPV	Total pelvis volume (of irradiation)
PSVV	Prostate + seminal vesicles volume (of irradiation)
POV	Prostate only volume (of irradiation)
WW	Watchful waiting

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Appendix 4 – Glossary

Active surveillance/monitoring: Revisions for cancer patients.

LHRH agonists: Hormones that inhibit the production of androgens (testosterone) by the testicles[16].

Androgen-independence: Situation where the patient is subjected to androgen suppression or complete androgen blockade (first-line hormone therapy) with biochemical or clinical progression.

LHRH analogues: LHRH agonists.

Adjuvant: Application of hormone treatment after main treatment[17].

Fine needle biopsy: aspiration of prostate tissue with a thin needle. The standard method is transrectal guided by ultrasound[4].

Complete androgen blockade: Use of LHRH agonists and antiandrogens[16].

Brachytherapy: Form of radiotherapy in which radioactive "seeds" are inserted directly into the prostate[17].

High dose rate brachytherapy (HDR): Brachytherapy combined with external beam radiation to provide a stimulus (or boost) in the prostate[126].

Advanced prostate cancer: Many studies use this as a general term to refer to locally advanced, lymph node or metastatic affectations[25-30].

Chemical castration: Use of LHRH agonists.

Surgical castration: Orchiectomy[17].

Cryotherapy: Using of freezing techniques (prostate cryoablation) to completely remove the prostate tissue[17].

Dose (radiotherapy): Amount of radiation energy directed and absorbed by a volume or point of biological tissue.

Watchful waiting: Monitoring only until the disease progresses or symptoms appear, whereupon palliative treatment may be suggested[4,120].

Fractionation (radiotherapy): Description of daily and weekly dose distribution. Standard fractionation for prostate cancer is 200 cGy per day, 5 times a week (1000 cGy/week).

Hazard ratio (HR): Indicator that expresses the relative difference between two survival results.

High-intensity focused ultrasound (HIFU): Ultrasound technique modified to reach temperatures > 65°C, resulting in the destruction of the prostate tissue[17].

Hypofractionation (radiotherapy): Fractionation with higher doses than the standard to reduce the number of sessions and usually the total dose.

Hormone-refractory: Some documents regard this as synonymous with androgen-independent. In this guideline, the term is used for a prostate tumour which is refractory to first and second line hormone treatment[17].

First line hormone therapy: In this guideline, the term refers to treatment with androgen suppression or complete androgen blockade.

Second line hormone therapy: In this guideline, this term refers to possible hormone treatment not included in the first line (ketoconazole, progestagens such as MPA, oestrogen, corticoids, bicalutamide at high doses -150 mg/day- and other hormone treatments).

Lymphadenectomy: Surgical procedure to remove lymph nodes for analysis. In prostate cancer, this is usually done alongside radical prostatectomy[17].

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Metastasis: Appearance of cancer away from the primary site due to being transported in blood or lymph vessels[17].

Cancer-specific mortality: Death due to prostate cancer.

Overall mortality: Death from any cause.

PSA nadir: The lowest PSA value reached after any treatment for prostate cancer[275].

Neoadjuvant: Treatment applied before the main treatment[17].

Organ-confined: Tumours found in stages T1-T2[4].

Orchiectomy: Also known as orchidectomy or surgical castration. Surgical removal of the testicles to reduce levels of testosterone[17].

Biological progression: Deterioration of the histological grade in a confirmed biopsy[277].

PSA relapse: Situation where a patient who has received a treatment with intent to cure for prostate cancer exceeds a certain PSA level. This indicates a significantly higher risk of morbidity or mortality due to the cancer.

Clinical progression: There is no single definition, but it is usually considered to be the situation where the prostate cancer patient has a progression in the TNM stage; or an increase in the size of the primary lesion after a rectal examination; radiological evidence of distant metastasis; and/or a clinical picture associated with a worsening of the disease, such as haematuria due to vesicle invasion, urethral obstruction, the need for transurethral resection of the prostate, etc[276,277].

Disease progression: There is no single definition, but it is usually considered to be the situation where the prostate cancer patient experiences clinical progression, biological progression or a rising PSA (evaluated according to the PSA doubling time and/or the total PSA value)[277].

Local progression: For patients who receive treatment with intent to cure, the presence of a tumour in the area of origin of the neoplasia. In patients with expectant treatment: growth of the existing tumour[121,163].

Radical prostatectomy: Complete removal of the prostate, of both seminal vesicles and vas deferens ampullae. It can be done alongside a pelvic lymphadenectomy[144].

PSA (prostate specific antigen): A protein produced by the prostate which is identified in the blood. There are three forms of PSA circulating: free PSA, PSA covalently bonded to alpha-1-antichymotripsin (PSA-ACT) and PSA complexed with alpha-2-macroglobulin (PSA-MG). The PSA value is the sum total for these 3 compounds and is determined via a normal blood test[33].

PSA nadir: Lowest PSA value.

External radiotherapy: Form of radiotherapy which uses electromagnetic radiation (eg, high-energy X-rays) produced in a machine and directed towards the tumour from outside the patient[17].

Radical radiotherapy: The use of radiation techniques near to the limit of tolerance for normal tissue, to completely remove the tumour[17].

Cancer-specific survival: Patients who, after a certain period of time, have not died due to prostate cancer.

Biochemical progression-free survival: Patients who, after a certain period of time, have not experienced biochemical progression.

Clinical progression-free survival: People who, after a certain period of time, have not experienced clinical progression.

General survival: Overall survival.

Overall survival: People who continue to live after a certain period of time.

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Androgen suppression: Androgen blockade.

Rectal examination: Physical examination in which the health practitioner checks for abnormalities by inserting a finger (protected by a lubricated glove) in the patient's rectum[17].

Treatment with intent to cure: Radical treatment.

Salvage treatment: Offered to patients who display biochemical progression with the intention of preventing the occurrence of adverse outcomes caused by disseminated prostate cancer[200].

Expectant treatment: Observation of the patient, usually by following the "watchful waiting" strategy, although sometimes it refers to a non-standard treatment, "active surveillance"[4,120].

General treatment: A systemic treatment (eg, intravenous, oral), ie, not directed at a specific part of the body. For prostate cancer, the general treatments most commonly used are hormone therapy or chemotherapy with antineoplastics[17].

Hormone treatment: For prostate cancer, it is removing and/or blocking the hormones that stimulate the growth of malignant prostate cells[17].

Continuous hormone treatment: Hormone treatment without any treatment-free periods[218].

Intermittent hormone treatment: Hormone treatment which is stopped for a time, until it is decided to restart it. This is usually done when clinical development or changes in the PSA level deem it appropriate[218].

Local treatment: action directly on tumour cells located in a particular area[17].

Radical treatment or treatment with intent to cure: action to try to completely remove the tumour[17].

Nadir value: Lowest PSA value.

Active surveillance/monitoring: Taking no action until the aggressiveness of the tumour increases, whereupon treatment with intent to cure is started[4,120].

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Appendix 5 - Declaration of interest

All members of the development group, collaborating experts and external reviewers have made a declaration of interest.

Joaquín Carballido Ricardo Escó, Elvira García, Antoni Gelabert, Francisco Gómez, Juan Ignacio Martín, José María Mengual, Luis Plaza, Pedro José Prada, Ana Quintanilla, Luis Ángel Rioja, Isabel Rodríguez, Milagros Sagüillo and Martín Tejedor have declared an absence of interest.

Antonio Antón has received funding from Merck Serono, Roche Pharmaceuticals and Lilly to attend meetings, courses and conferences; speaker fees from Sanofi-Aventis and Roche Pharmaceuticals; funding for programmes and courses from Sanofi-Aventis, Roche Pharmaceuticals, Jansen Cilag, Schering-Plough, Lilly, Amgen, Bayer, Merck Serono, Novartis, Astra-Zeneca, Pfizer, GlaxoSmithKline and Pierre Fabre. He is a member of the advisory committees of Roche Pharmaceuticals, Jansen Cilag, Schering Plough and Pfizer; he has received material for an RT-PCR unit from Roche Pharmaceuticals and financial support to hire staff for the unit from Roche Pharmaceuticals and Sanofi-Aventis.

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