

PROSTATE CANCER

Effective Date: March, 2015

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Cancer of the prostate is the most common cancer among men and accounts for about 27% of all new male cancer cases in Canada (age-standardized incidence rate of 123 per 100,000 men).(1) There is approximately 2,500 new cases each year in Alberta.¹ The peak age of diagnosis is between 60 and 69 years.(1) Despite its relatively high incidence, prostate cancer is only the third leading cause of cancer deaths among men and accounts for approximately 440 deaths (mostly among men aged 80 years and over) each year in Alberta.(1) Five-year survival rates are excellent for this disease: 80% of men diagnosed will present with localized prostate cancer, for which the 5-year survival rate is 100%. Approximately 12% will present with regional spread (lymph node metastasis), for which the 5-year survival rate is still 100%, and for men who present with distant spread (4% of all cases), the 5-year survival rate drops to 30%.(2)

Approximately 95% of all prostate cancers are adenocarcinomas.(3,4) Other, far less common subtypes include: mucinous adenocarcinomas, which tend to be more aggressive tumours; small cell carcinomas; duct papillary carcinomas; and transitional cell carcinomas.(5) Staging of prostate cancer is currently based on the seventh edition (2010) of the American Joint Committee on Cancer's AJCC Cancer Staging Manual.(6) A detailed description of the staging can be found in the Appendix. The purpose of this guideline is to describe the appropriate management and follow up strategies for prostate cancer.

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Unit Handbook](#).

This guideline was originally developed in January, 2005. This guideline was revised in January 2009, January 2011, September 2013, and October 2014 and March 2015.

SEARCH STRATEGY

Ovid MEDLINE and EMBASE (1965 to August 2011) and clinical practice guideline databases, including the Cochrane Library and the National Guidelines Clearinghouse, were searched in order to obtain evidence relevant to this topic.

For the 2015 update, no formal literature review was conducted.

For the 2014 update of this guideline, the Pubmed database was searched using the search terms Locally Advanced Prostate Cancer and Metastatic Prostate Cancer from 2010 to 2014. Only phase III trials were evaluated for inclusion.

For the 2012 update of this guideline, Ovid Medline was searched using the term Prostatic neoplasms (MeSH term, subheadings drug therapy, surgery, therapy and radiotherapy), limited to clinical trials involving humans published in English, between August 2011 and August 2012. Articles were excluded if they were not phase II-IV trials, did not include survival or recurrence outcomes, was retrospective.

Cochrane Database of Systematic Reviews was searched using the term “prostate cancer”, published 2011-2012.

Medline & Embase were further searched using the term prostate cancer (keyword), limited to clinical trials related to “therapy (best balance of sensitivity and specificity) involving male humans published in English between August 2011-2012.

RECOMMENDATIONS

EARLY DIAGNOSIS AND SCREENING

Detection

The standard methods of detection include:

- Digital rectal examination (DRE)
- Serum prostate specific antigen (PSA) measurement
 - Serum PSA should be checked in fit men between the ages of 50 and 75 years, where clinically indicated.
 - Serum PSA screening increases the detection rate of early stage clinically significant prostate cancers; early detection may improve overall survival.(7)
 - Fit men between the ages of 50 and 75 years with at least ten years life expectancy should be made aware of the availability of PSA as a detection test for prostate cancer; they should also be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have the test performed.
- Elevated PSA and/or abnormal DRE are not diagnostic of prostate cancer; they *do* serve to risk stratify patients.
 - In early stage prostate cancer, a needle biopsy to confirm a diagnosis is standard and is most accurate when done using ultrasound guided sextant biopsies.
 - Indications for biopsies include a clinical suspicion of prostate cancer based on the PSA and DRE findings.

Investigations for staging(8,9)

Assessment for patients who are being considered for active surveillance or treatment with curative intent should consist of:

- History and physical examination
- Complete blood count (CBC), creatinine, urinalysis
- PSA (which should be done prior to biopsy)
- Radionuclide bone scan is indicated only in patients with high-risk disease
- CT scans are not routinely indicated except in high-risk patients

Definition of risk categories for clinical staging(10-12)

Low- must have all of the following: T1- T2a and Gleason score ≤ 6 and PSA < 10 ng/mL.

Intermediate- tumors not meeting criteria for low- or high-risk: T2b-T2c or Gleason 7 or PSA 10-20 ng/mL.

High- must have any one of the following: T3a or higher; Gleason score ≥ 8 ; or PSA > 20 ng/mL.

In patients taking dutasteride (Avodart), measured PSA should be doubled for the purposes of risk stratification.

Consideration for staging(11)

% of involved cores, based on a 10 core biopsy

Low Risk: <33%

Intermediate Risk: 33% – 50%

High Risk: >50%

LOW-RISK DISEASE

Patients need to see an urologist to discuss surgical options for treatment (e.g. prostatectomy and cryotherapy) and a radiation oncologist to discuss brachytherapy or EBRT. These treatments have equivalent cancer-specific outcomes.

Management(13-26)

1. Active surveillance:

- This is an option in a select group of low risk patients with the understanding that curative treatment will be offered if follow-up demonstrates either worrisome PSA elevation or worsening biopsy characteristics (e.g. Gleason grade and/or volume) or if the patient chooses.
- Curative intervention may be required later and patients may be candidates for randomized controlled trials (RCTs).
- Patients with “indolent prostate cancer” harbor prostate cancers that are clinically insignificant and not expected to compromise their quality of life. Indolent prostate cancer is defined as having all of the following characteristics:
 - Low risk (clinical stage <T2b and PSA <10 and Gleason score <7);
 - AND ≤3 cores involved with disease (minimum sampling of 10 cores);
 - AND no cores with >50% of core involved with disease.
- Patients with localized, low risk prostate cancer can consider an active surveillance protocol to monitor their disease for signs of disease progression. A reasonable surveillance protocol would include:
 - PSA assessment every 3-6 months and DRE annually, at the physician’s discretion.
 - Consider repeat biopsies 1-2 years after initial diagnosis, then consider further biopsies every 2-3 years or as clinically indicated.
- Disease progression
 - Progression can be characterized by one of the following criteria:
 - Pathological progression: presence of Gleason pattern ≥4. Any core with >50% of core involved with disease.
 - Clinical progression: increase in clinical stage from baseline status.
 - Biochemical progression: PSA doubling time <3 years.
 - If there are signs of disease progression, intervention is recommended with curative therapy (radical prostatectomy, external beam radiotherapy, brachytherapy or cryotherapy).
 - Patients may also choose to proceed with curative therapy due to personal preference at any time during surveillance.
 - For patients that will not benefit from curative therapy, other therapy (i.e. hormonal therapy or radiotherapy) can be considered at the time of clinical/symptomatic progression of disease.

- 2. Intervention:** if intervention is being considered, treatment should begin no more than 6-8 weeks from the time of diagnosis.

Radical prostatectomy is an option in all low risk prostate cancer, assuming a normal life expectancy >10 years and no severe medical co-morbidities.

Options include:

- Open retropubic prostatectomy.
- Robotic assisted laparoscopic surgery.
- Both treatments have similar oncological outcomes; furthermore, a wait time of up to 3 months for treatment in low-risk prostate cancer is not associated with worse outcomes.
- Pelvic lymph node dissection in this group is optional, but yield is very low in low risk patients.

External beam radiotherapy (EBRT) is an option for all low risk prostate cancer patients.

- 3D conformal radiotherapy or intensity modulated radiation therapy (IMRT) should be utilized to deliver an International Commission on Radiation Units (ICRU) dose of 70–74 Gy at 1.8–2.0 Gy per fraction.
- Daily image guidance is the standard of care.
- The clinical target volume (CTV) is defined as the prostate alone.

Low dose rate (LDR) brachytherapy: option for low risk prostate cancer patients.

- Patients with pubic arch interference may not be eligible for brachytherapy.
- Patients with borderline pubic arch interference may be considered for a short course of hormones to reduce gland size.
- Patients with a prior transurethral resection (TURP) should be assessed on an individual basis.
- Patients with significant baseline obstructive symptoms may not be eligible for brachytherapy (i.e. American Urological Association symptom score >20).

Cryosurgery should be presented to patients as a treatment option for low risk disease.

High Intensity Focused Ultrasound (HIFU) should be considered investigational therapy for low risk prostate cancer and appropriate only in a randomized clinical study.

Follow-up(11,27)

- PSA every six to twelve months for five years, then yearly
- Digital rectal examination yearly, but may be omitted if PSA undetectable.
- Evaluation of treatment morbidity and/or complications.

INTERMEDIATE-RISK DISEASE

Patients need to see an urologist to discuss surgical options for treatment (e.g. prostatectomy and cryotherapy) and a radiation oncologist to discuss brachytherapy (in select cases) and external beam radiotherapy. There are no good quality randomized controlled trials comparing radical prostatectomy (RP) versus radiotherapy (RT).

Management(28-33)

Radical prostatectomy

- The urologist should discuss the risk of a positive margin and its implications.
- Patient selection should include consideration for the risk of margin involvement.
 - While adjuvant/salvage radiation improves progression free outcome following prostatectomy, there is no evidence to suggest intentional combination of surgery followed by radiation is superior to either treatment alone in appropriately selected patients (see recommendations

- below for post-prostatectomy RT).
- Avoid radical prostatectomy in patients with evidence of extraprostatic disease from biopsies.
- Situations in which surgery is the preferred treatment:
 - Patients with normal life expectancy >20 years.
 - Patients with significant lower urinary tract symptoms (LUTS).
 - Absolute or relative contraindications include: previous pelvic radiotherapy and surgery, inflammatory bowel disease, and collagen vascular disease.

Note: Neoadjuvant hormonal therapy prior to radical prostatectomy is not recommended outside of a clinical trial.

EBRT

- Data from several clinical trials indicates an advantage with dose escalated RT for intermediate risk prostate cancer, but only for PSA endpoints. More mature data from randomized studies is needed to show if this translates into survival benefits.(14)
- Based on current evidence, the recommended prescribed dose to the target is 74-78 Gy in standard fractionation.(28-30)
 - In order for this dose to be given safely, some form of image guidance is always required.
 - Specific details regarding these parameters may vary from patient to patient, depending on individualized clinical circumstances.
- Short term (neoadjuvant + concurrent) hormones may be used for patients undergoing radiotherapy.(33,34)
 - Improvement in all-cause mortality was demonstrated in men randomized to RT 66.6- 70 Gy ± 6 months of hormones; in one study the subgroup analysis showed this effect was only in men with minimal comorbidity, while another study found the benefit to be primarily for intermediate risk patients.

Brachytherapy

- Brachytherapy is a potential treatment option for low-intermediate risk patients with favourable characteristics or with these parameters: Gleason <7 and PSA 10-15(31-33)
- Low Dose Rate (LDR) Brachytherapy:
 - Patients with pubic arch interference may not be eligible for brachytherapy.
 - Patients with borderline pubic arch interference may be considered for a short course of hormones to reduce gland size.
 - Patients with a prior transurethral resection of the prostate (TURP) should be assessed on an individual basis.
 - Patients with significant baseline obstructive symptoms may not be eligible for brachytherapy (i.e. American Urological Association symptom score >20).
- The role of High Dose Rate (HDR) brachytherapy in conjunction with external beam RT is considered investigational.

Cryosurgery

- Cryosurgery is available for selected T1-T3 patients with gland volume <60 cubic centimeters, PSA <20, and any Gleason score.
- There is a lack of evidence demonstrating cryosurgery's equivalence to other treatment modalities. One clinical trial compared cryosurgery to EBRT and reported no difference in cancer related outcomes reported in that study (35).

Follow-Up(11,27)

- PSA every six to twelve months for five years, then yearly.

- Digital rectal examination yearly.
- Evaluation of treatment morbidity and/or complications.

HIGH-RISK DISEASE

Preparation for Therapy

- Baseline complete blood count (CBC), creatinine (Cr), urinalysis
- Liver function tests (LFTs) if considering non-steroidal anti-androgens
- Baseline mineral density study if considering androgen deprivation therapy (ADT)
- Bone scan and CT abdomen/pelvis
- Referral to a radiation oncologist prior to making a treatment decision

Management

Clinical Trials

Patients should first be considered for multimodality discussion and clinical trials.

EBRT and Androgen Deprivation Therapy (ADT)

- It is strongly recommended that all patient with high risk localized prostate cancer be referred to a radiation oncologist for a discussion about treatment options and available clinical trials
- Radiotherapy should treat the prostate planning target volume with 74- 78Gy. Consider including regional lymph nodes within the radiotherapy treatment volume.
- ADT should be administered for at least 18 months and may be initiated prior to radiotherapy or concurrently with EBRT.
- An anti-androgen could be co-administered with a LHRH agonist and be continued for at least 7 days for possible flare in testosterone with initial LHRH agonist alone.

Radical Prostatectomy ± Post-Operative EBRT and/or ADT

- Can be considered in highly selected cases with low volume disease without fixation to adjacent organs. Ideally this should be in the context of a clinical trial.
- Procedure should include regional lymph node dissection.
- Post-operative radiotherapy should be delivered according to guidelines described below for post-operative radiotherapy.(36-44)
- Post-operative ADT should be considered for patients with node-positive disease, either on an adjuvant or salvage basis.

Cryotherapy

- Cryotherapy can be considered in selected patients with high grade (GS 8 – 10) prostate cancer with organ confined disease and PSA <20, after a full discussion of the risks of systemic failure with a purely local treatment option.

Androgen Deprivation Therapy (ADT) (selected patients)

- In patients not being considered for external-beam radiotherapy with ADT (i.e. patients with extensive nodal metastasis, locally advanced disease T3b-T4, or short life expectancy), ADT alone can be considered.
- If ADT alone is considered, the patient must understand that the omission of RT for high risk prostate cancer is associated with significantly worse overall survival (45,46) based on results from 2 randomized controlled clinical trials.

- Counsel patients and primary care physician regarding the effects of prolonged testosterone suppression.
 - Baseline mineral density study should be repeated every 2-3 years.
 - Refer to Bone Health guidelines below.

Post Prostatectomy Radical RT (36-44,47,48)

- Patients with any of the following pathological risk factors for local recurrence require referral to a radiation oncologist for a discussion regarding adjuvant therapy
 - Positive surgical margins
 - Seminal vesicle involvement (pT3b)
 - Capsular perforation (pT3a)
- Salvage radiotherapy can be considered at the time of PSA relapse (ideally, PSA <0.5 ng/mL) in those patients who initially refuse adjuvant radiotherapy, those who wish to defer expected radiotherapy-induced toxicity, and those who are referred outside of the adjuvant window 4 months after prostatectomy. Salvage radiotherapy can also be considered in patients with local recurrence after prostatectomy but no evidence of distant metastatic disease.
- The potential benefit of adjunctive hormonal therapy is not established.

Follow-up PSA

- First post-operative PSA should be done 4-12 weeks after surgery.
- Routine PSA should be done every 6 months, unless otherwise specified.
- Low-risk patients (pT2, Gleason ≤ 3+4, margins negative) may have PSA done yearly.

Other factors for consideration

- PSA relapse within 12 months of surgery is strong predictor of adverse long term outcome.
- PSA doubling time appears to have prognostic power.

ADVANCED DISEASE

Stage T1-4, N1-3, M0

Staging

- Pathologically node positive (N1-3, or N+): after radical prostatectomy.
- Radiologically node positive: obviously enlarged lymph nodes on CT scanning, in an appropriate clinical context.

Management

- Radiotherapy should be given to these patients in addition to ADT. A recent randomized phase III trial demonstrated a significant benefit in overall survival.(42)
- RT for clinical, radiologic nodal involvement (enlargement) could be considered on a case-by-case basis in pathologic N+ disease or radiologic N+ disease for those with normal life expectancy of ≥10 years.(48)
- Intermittent hormone therapy is not inferior to continuous long-term hormonal therapy in relation to cancer-specific outcomes and may be associated with better quality of life or less treatment toxicity.^{48,52}
- Semi-annual clinical evaluation and PSA should be done if it will affect management.

Follow-up

- Age dependent.
- Investigation at the discretion of the physician.

Stage T1-4, N1-3, M+ Hormone Sensitive Disease

Indications include symptomatic disease or asymptomatic disease.

Staging

- Physical Exam
- PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN)
- Bone scan
- CT scan, (abdomen and pelvis, +/- chest)

Management

- Surgical castration
- Medical castration
 - Treatment with an LHRH analogue (agonist or antagonist)
 - When first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily, flutamide 250 mg three times a day or nilutamide 300mg daily) should be given concurrently with the first administration of LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare.
 - The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward.
 - Medical and surgical castration are equally effective and the risks, benefits, and economic implications should be discussed with the patient.
 - Treatment with gonadotropin-releasing hormone (GnRH)
 - The GnRH antagonist Degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster (49) than GnRH Agonists. Treatment with a GnRH antagonist (Degarelix) avoids the risk of testosterone ‘flare’ that occurs with GnRH agonists (50). Treatment with a GnRH antagonist eliminates the need for concomitant administration of a peripheral anti androgen.
 - PSA reduction occurred significantly faster with Degarelix when compared to GnRH agonists without increases in treatment related side effects (49).
 - No survival benefit has been demonstrated with Degarelix compared to traditional LHRH agonists and injections are administered monthly.
 - Degarelix is not presently funded in Alberta.
 - Single agent antiandrogens
 - Nonsteroidal antiandrogens can be administered to those patients wishing to maintain potency. This may result in a reduction in disease-free survival. To date there is insufficient data to recommend bicalutamide at the 150 mg/day dose and it is not approved by Health Canada.
 - Bicalutamide 50 mg orally once a day.
 - Flutamide 250 mg orally three times daily.
 - Nilutamide 300 mg orally once a day for one month, then decrease to 150 mg daily.
 - Use of intermittent hormone therapy is controversial. Recent data suggests that intermittent is not non-inferior to continuous, which does not necessarily mean intermittent is inferior to

continuous.(46,51)

- Patients undergoing androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.(52)

NOTE: Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended.

- Docetaxel chemotherapy for castrate sensitive disease
 - Data from the CHAARTED trial(53) demonstrated significant overall survival benefit of 13 months when administered to patients with castrate sensitive metastatic prostate cancer who are about to or just recently (within 4 months) started hormonal therapy. The greatest benefit was seen in patients with high volume disease.
 - Patients with high volume disease castrate sensitive metastatic prostate cancer who are about to or just recently started hormonal therapy should be offered 6 cycles of docetaxel chemotherapy at 75 mg/m² every 3 weeks (given without prednisone). Hormone therapy as above is carried throughout and after docetaxel completion.

Follow-up

- 3–6 months following the initiation of therapy to evaluate and then as clinically indicated
- If on chemotherapy, need to be seen every 3 weeks
- Duration: age-dependent.

Stage M+ Castrate Resistant Disease

Indications include symptomatic disease or asymptomatic metastatic disease.

Staging

As clinically indicated:

- Bone scan
- CT scan
- MRI
- Serum PSA, serum testosterone (to ensure that testosterone is in the castrate range)

Management

The benefits of treatment are primarily palliative and related to quality of life, although some systemic therapies confer a small survival advantage.

Palliative Radiotherapy

- EBRT to symptomatic sites
- Strontium 89 (Metastron®) not recommended for routine use, but available for appropriate indications, including:
 - Multiple painful sites of bone metastases on both sides of diaphragm
 - Patient and/or tumor factors contraindicating the use of multiple fields of EBRT for palliation
 - Adequate bone marrow reserve (NB: Platelet count > 100)
 - No evidence of impending spinal cord compression
 - No plans for systemic chemotherapy

Systemic Therapy

Clinical trials should be given first consideration where appropriate. Currently, there is no data to support one of these agents/sequences over the other.

- 1st line options:
 - Abiraterone acetate 1g oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.(54,55)
 - Docetaxel 75mg/m² IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.⁵⁴
 - Enzalutimide (pending approval by Health Canada) (PREVAIL).(56)
 - 2nd line options:
 - Post progression on docetaxel chemotherapy:
 - Abiraterone acetate⁵⁵ or enzalutimide (AFFIRM).(57,58)
 - Cabazitaxel 25mg/m² IV every 3 weeks in combination with prednisone 10 mg oral daily.⁵⁶
 - Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).(59,60) Ra 223 is administered upon referral to nuclear medicine and given at a dose of 50 kBq (1.35 microcurie) per kg body weight at 4 week intervals for a total of 6 injections. Funding is currently being sought.
 - Patient selection is important. These patients should be discussed in multidisciplinary tumor board rounds.
 - Post progression on Abiraterone or Enzalutamide
 - Docetaxel chemotherapy
 - Subsequent lines:
 - Sequencing with another agent listed above not previously used. For example, abiraterone → docetaxel → enzalutamide → cabazitaxel is a reasonable sequence. There are many others. There is no data to suggest the preferred sequence.
 - Docetaxel rechallenge or Mitoxantrone 12mg/m² every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.
 - Sipuleucel-T is not Health Canada approved
- Mitoxantrone 12mg/m² every 3 weeks in combination with prednisone 5 mg oral twice a day can provide adequate palliation in 2nd or subsequent line.
 - Bone targeted therapy: treatment with bisphosphonates bone targeted agents will be discussed below for patients with metastatic castrate resistant prostate cancer.
 - It is important to note that chemotherapy is NOT indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA.

Table 1. Recent Systemic Therapy Trials for the Treatment of Metastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Abiraterone (61,62)	COU-AA-301 (NCT00638690)	Post Docetaxel	5 mg of prednisone twice daily with 1000mg (4x 250mg) of abiraterone acetate (797 patients) or placebo (4x 250mg) daily	Abiraterone group: 5.6mo Placebo: 3.6 mo	p <0.001	Abiraterone group: 14.8mo Placebo: 10.9mo Median follow-up: 12.8mo	p<0.001, HR: 0.65, 95%CI: 0.54-0.77
Abiraterone (54,55)	COU-AA-302 (NCT00887198)	Pre Docetaxel	Abiraterone acetate 1000mg (4 x 250mg) plus prednisone (5mg twice daily) (544 patients) vs placebo plus prednisone (544 patients)	Radiographic PFS Abiraterone group: 16.5mo vs placebo: 8.2mo median follow-up 22.2mo	p<0.0001, HR: 0.52, 95%CI: 0.45-0.61	Abiraterone: 35.3mo Placebo: 30.1 mo	p=0.0037 HR: 0.80; 95%CI: 0.69-0.93
Enzalutamide (56)	PREVAIL (NCT01212991)	Pre Docetaxel	872 in the enzalutamide group, 845 in the placebo group	Radiographic PFS at 12 months was 65% in the enzalutamide group compared to 14% in the placebo group	p<0.001, HR: 0.19, 95%CI: 0.15-0.23	OS was 72% (626 patients) in the enzalutamide group vs 63% (532 patients) in the placebo group	p<0.001, HR: 0.71, 95%CI: 0.60-0.84
Enzalutamide (57,58)	AFFIRM (NCT00974311)	Post Docetaxel	Enzalutamide 160mg once daily (four capsules) (800 patients) vs placebo (399 patients).	Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo	p<0.001, HR: 0.40	Enzalutamide group: 18.4mo Placebo: 13.6mo	p=0.0151, HR: 0.79, 95%CI: 0.66-0.95
Docetaxel (63-65)	TAX 327	Metastatic CRPC	Docetaxel 75 mg/m ² q3 weekly + prednisone 5 mg bid vs. Mitoxantrone 12 mg/m ² + prednisone 5 mg bid (3rd arm of weekly docetaxel demonstrated no benefit)	N/A	N/A	Docetaxel 18.9 vs Mitoxantrone 16.5 months	p=0.009, HR: 0.76, 95%CI: 0.62-0.94)
Cabazitaxel (66,67)	TROPIC (NCT00417079)	Post Docetaxel	10mg oral prednisone daily and 12mg/m ² mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m ² cabazitaxel intravenously over 1h (378 patients) every 3 weeks	cabazitaxel group:2.8mo mitoxantrone group:1.4mo	p<0.0001, HR:0.74 95%CI: 0.64-0.86	Cabazitaxel group: 15.1mo Mitoxantrone group: 12.7mo	p<0.001, HR: 0.63, 95%CI: 0.53-0.75
Sipuleucel-T (144)	IMPACT (NCT000065442)	Asymptomatic or minimally symptomatic CRPC	Sipuleucel-T (341 patients) vs placebo (171 patients).	Similar	p=0.40, HR: 0.92, 95%CI: 0.75-1.12	Sipulencel-T group: 25.8mo Placebo: 21.7mo	p=0.03, HR 0.78, 95%CI: 0.61-0.98
Radium-233 (Xofigo) (59,60)	ALSYMPCA (NCT00699751)	Post docetaxel or non-docetaxel candidates	Radium-233- six injections (1 every 4 weeks), 50kBq/kg of body weight, intravenously vs matching placebo	Time to First Symptomatic Skeletal Event (median): Radium-223: 15.6mo Placebo: 9.8mo	p<0.001, HR: 0.66, 95%CI: 0.52-0.83	Radium-233: 14.9mo Placebo: 11.3mo	p=0.03, HR: 0.78, 95%CI: 0.61-0.98

Follow-up

- As clinically indicated to evaluate response to therapy.
- Patients on docetaxel should have PSA evaluated for response after two to three courses and symptomatic response; treatment should be continued for as long as a response is occurring and the morbidity of treatment is manageable.
- Patients who have responded well to docetaxel chemotherapy can be rechallenged in the case of subsequent progressive disease.
- Duration: as clinically indicated

Biochemical Recurrence(68)

Following prostatectomy

- Any rise in PSA.

Following radiotherapy with or without hormonal therapy

- Rise by 2 ng/mL (mcg/L) or more above the nadir PSA (defined as the lowest PSA achieved).
- Date of failure should be determined “at call” and not backdated.
- Patients not meeting these PSA criteria for failure who undergo salvage therapies should also be declared as failures at the time a positive biopsy is obtained or salvage therapy is administered.

Patients with Rising PSA after Curative Intent Treatment without Metastases

It is recommended that patients be referred to a cancer clinic or re-referred to their treating urologist. Please refer to definition of biochemical recurrence above.

Staging

- Bone scan
- CT scan
- MRI
- Consideration for prostate re-biopsy

Post-radical prostatectomy recurrence

- Radiotherapy with or without concurrent or adjuvant ADT is recommended
- Observation is also an option, depending on the findings during staging

Post- radiotherapy recurrence

Recommended options include:

- Active surveillance within a cancer clinic
- Cryosurgery
- Brachytherapy
- ADT

Bone Health(69-76)

All patients should ensure adequate calcium and vitamin D intake, using supplements if necessary.

For patients being treated for prostate cancer, an assessment of risk for osteoporosis should be performed:

- The WHO Fracture Risk Assessment Tool (FRAX) is recommended for calculating the ten year

probability of fracture with BMD. It is available at <http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19>.

- *Low risk for osteoporosis:* no high-risk characteristics.
- *High risk for osteoporosis:* any of the following:
 - ADT > 6 months
 - Previous fracture
 - Family history of osteoporosis
 - Low body weight
 - Smoker
 - Excessive alcohol intake
 - Steroid use
 - Low vitamin D levels

Management options:

Non-metastatic patients

1. Calcium 1500mg and Vitamin D 2000 IU daily for all men on ADT.
2. Baseline DEXA scan for all patients.
3. If DEXA reveals osteoporosis (T-score <-2.5) then bisphosphonate therapy should be initiated as per standard treatment protocols. Treatment of osteoporosis with bisphosphonates should be undertaken with oral agents that have been approved by Health Canada.
4. If DEXA reveals osteopenia (T-score -1 to -2.5) or normal findings then close F/U as suggested below and initiate treatment with bisphosphonates only if osteoporosis is diagnosed.
5. Concurrent bisphosphonate treatment at the initiation of ADT to prevent bone loss and the development of osteoporosis cannot be recommended at this time. Studies of immediate bisphosphonate use concurrent with ADT have been undertaken and in small sample sizes have been shown to increase bone mineral density (BMD). However, this has not been translated into a change in fracture risk, hence, the lack of recommendation to routinely use bisphosphonates prophylactically.
6. The diagnosis and treatment of osteoporosis may be undertaken by the person most familiar with the treatment of this condition. This may be the family physician but the individual who prescribes ADT (urologist, MO, RO) should raise the issue and notify the family physician, through the consult note, of the recommendations regarding the management of bone health.

Metastatic patients, hormone sensitive

1. All men being placed on ADT for metastatic prostate cancer should have a baseline assessment of osteoporosis risk and have a DEXA scan.
2. The routine use of any prophylactic bone targeted therapy (in the absence of DEXA scan proven osteoporosis) for the prevention/delays of osteoporotic skeletal complications cannot be recommended at this time.
3. The use of a bone targeted therapy in this clinical setting cannot be claimed to alter SREs or survival. Should men develop metastatic castrate resistant disease, then consideration should be given to more specific bone targeted therapies (see “metastatic patients, castrate resistant” below).

Metastatic patients, castrate resistant

1. For patients with castrate resistant and evidence of bony metastatic disease, zoledronic acid 4 mg IV every 4 weeks(74) or denosumab 120 mg subcutaneously every 4 weeks.(77) Zoledronic acid can be considered for reduction in SREs.
2. Denosumab has demonstrated non-inferiority and superiority over zoledronic acid in prevention of

SREs and can/should be considered as the first line option.(77) There is no documented survival benefit noted with either of these agents.

3. Dosing of zoledronic acid should be tailored to the patient's kidney function (starting dose to be based on creatinine clearance as per the CPS).
4. Patients should be continuously monitored to ensure adequate renal function.
5. If patient clinic condition deteriorates and severe pain develops (narcotic analgesics are required) the routine administration of zoledronic acid bone targeted agents should be reviewed and potentially stopped.
6. Osteonecrosis of the jaw has and hypocalcemia have been reported in association with the administration of zoledronic acid. Patients have to be monitored and with the appropriate precautions these complications can be prevented or managed in a timely fashion.

DISCUSSION

Early Diagnosis and Screening

Prostate cancer is detected with digital rectal examination (DRE) and serum prostate specific antigen (PSA) measurement. Prostate cancer has a low overall incidence in men younger than 50 years of age, who represent less than 0.1% of all affected patients.(78) Although the value of serum PSA screening in detecting early stage disease is clear, with a lead-time of 4-8 years,(79) it is only recently that there is data to link early detection to improved overall survival.(7) A study among men who were randomized to either PSA testing every 2 years (n=7,578) or to no screening (n=10,000) showed that over a median follow-up of 14 years, PSA testing led to a diagnosis of prostate cancer in 1138 men (12.7%) in the screening group and in 718 men (8.2%) in the control group. However, the absolute cumulative risk reduction of death from prostate cancer was 40% (95% CI 0.17-0.64) and 293 (95% CI 177-799) men needed to be invited for screening and 12 be diagnosed to prevent one prostate cancer death.(7)

While elevated PSA and/or abnormal DRE are not diagnostic of prostate cancer; they do serve to risk stratify patients.(80) Vickers et al. (2010) analyzed data from five European and three U.S. cohorts of men undergoing biopsy for prostate cancer (n=25,772). For a given PSA level, a greater number of biopsy cores increased the risk of cancer (odds ratio for >6- vs. 6-core biopsy, 1.35; 95% CI,1.18-1.54; p<.0005).(81) In early stage prostate cancer, a needle biopsy to confirm a diagnosis is standard and is most accurate when done using ultrasound-guided sextant biopsies. Indications for biopsies include a clinical suspicion of prostate cancer based on the PSA and DRE findings.

Treatment is based on an assessment of patient risk for biochemical failure following treatment. Categories of risk are dependent on clinical tumour stage (determined from digital rectal exam), Gleason score (determined from biopsy), and PSA level.(10-12,82,83)

Patients stratified to the low risk level must have ALL of the following:

- T1-T2b tumour
- Gleason score of 6 or less
- PSA level of less than 10 ng/mL

High risk patients must have ONE of the following:

- T3a or higher tumour
- Gleason score of 8 or more
- PSA level above 20 ng/mL

Intermediate risk patients are those that do not meet the criteria for low or high risk (i.e. T2c tumour, a Gleason score of 7 or a PSA level of 10-20 ng/mL).

The proportion of involved cores, based on a 10-core biopsy is also predictive of risk (i.e. <33% is indicative of low-risk, 33-50% is indicative of intermediate risk, and >50% is indicative of high risk).(11)

Low-Risk Disease

Active surveillance is an option for some low risk patients.(13,84,85)

Eligible patients include those with less than 30% of cores involved and no cores with more than 50% of the core involved, until such time as ANY of the following:

- T3a or higher tumour
- An accelerated elevation in PSA level (i.e. a PSA doubling time of less than 3 years)(86)
- An increase in Gleason grade and/or volume (i.e. pattern of 4 or greater or any core with >50% of the core involved)(87)
- An increase in clinical stage(88)
- The patient chooses to pursue an intervention

The National Prostate Cancer Register of Sweden Follow-up Study analyzed data from men aged 70 years or younger who were diagnosed with low risk prostate cancer: clinical stage T1, Gleason score 2-6, and serum PSA level of <10 ng/mL (n=2686). Among men treated with active surveillance and watchful waiting (n=1,085), versus radical prostatectomy or radiation therapy (n=1,601), the calculated cumulative 10-year prostate cancer-specific mortality was 2.4% (95% CI 1.2- 4.1%) and 0.7% (95% CI 0.3- 1.4%), respectively.(89)

For patients who show signs of disease progression on active surveillance or who are not candidates for active surveillance at diagnosis, intervention is recommended with curative therapy (i.e. radical prostatectomy, external beam radiotherapy, brachytherapy, or cryotherapy). Patients who opt out of active surveillance due to personal preference are also candidates for curative therapy. Patients must see an urologist to discuss surgical options for treatment (i.e. prostatectomy and cryotherapy) and a radiation oncologist to discuss brachytherapy. Radical prostatectomy, external beam radiotherapy, and brachytherapy have been shown to be equivalent, in terms of cancer-specific outcomes.(18,90-93) However, if intervention is being considered, treatment should begin no more than 6 to 8 weeks from the time of diagnosis.

Radical prostatectomy is an option for patients with low risk prostate cancer, assuming a normal life expectancy of greater than ten years and no severe medical co-morbidities. Options include an open retropubic prostatectomy (ORP) or a robotic assisted laparoscopic prostatectomy (RALP). Both treatments have similar oncological outcomes. A recent systematic review of 37 studies comparing prostatectomy approaches found that RALP was more operatively time consuming than ORP. However, blood loss, transfusion rates, catheterization time, hospital stay, and complication rates favored laparoscopic prostatectomy. There were no differences in functional results (e.g. continence and potency rates) or oncologic outcomes (e.g. positive surgical margin rates).(94) A subsequent non-randomized prospective study among patients undergoing RALP (n=103) or ORP (n=105) for localized prostate cancer also found no differences in positive margin rates (P=.70). However, urinary continence was better in patients undergoing RALP (68.9% vs. 41% at catheter removal, p<.001; 97% vs. 88% at 12 months, P=.01).(95) It should also be noted that a wait time of up to 3 months for treatment in low-risk prostate cancer is not associated with worse outcomes. Pelvic lymph node dissection in this group is optional.

External beam radiotherapy (EBRT) is delivered as 3D conformal radiotherapy (3DCRT) or intensity

modulated radiation therapy (IMRT) and should be utilized to deliver a dose of 70–74 Gy at 1.8–2.0 Gy per fraction to the prostate alone, with use of daily image guidance. A study of patients with low risk T1b-T2b prostate cancer (n=227) with a median follow-up of 8.9 years demonstrated that a dose of 79.2 Gy was superior to a dose of 70.2 Gy, in terms of local failure rate (HR=0.57) and 10-year ASTRO biochemical failure rate (7.1% vs. 28.2%; p<.0001). Nevertheless, the overall survival rates were not significantly different (83.4% vs. 78.4%; p=.41) and incidence of grade 3 or higher genitourinary or gastrointestinal toxicity was much more frequent in those patients who received 79.2 Gy.(96) Among low risk patients after a median follow-up of 8.3 years, administration of IMRT (5-field, 81 Gy) resulted in a 10-year actuarial PSA relapse-free survival rate of 81%, a 10-year distant metastases-free rate of 100%, and a 10-year cancer-specific mortality rate of 0%.(97) Overall, there is good evidence that patients with low risk disease (i.e. PSA < 10, Gleason score ≤6, stage ≤T2b) have similar outcomes when treated with external beam radiotherapy or surgery.(98)

Low dose rate (LDR) brachytherapy is a good option for low risk patients. However, some individuals may not be eligible for this treatment, including those with pubic arch interference,(98,99) those with a prior transurethral resection of the prostate (TURP),(100,101) and those with significant baseline obstructive symptoms (i.e. American Urological Association symptom score >20). A study among low risk patients undergoing low dose rate prostate brachytherapy (n=140) with a median follow-up of 50 months demonstrated a 7% biochemical failure rate and a 91% overall survival rate. The median biologically effective dose was 148 Gy (range 46-218 Gy) and the overall 5-year biochemical relapse-free survival rate was 90.1%.(102) A study of 1006 consecutive implants in British Columbia with a median follow-up of 54 months demonstrated a 5 year freedom from biochemical recurrence rate of 95.6% and a 5 year overall survival rate of 95.2%.(32) Furthermore, a multi-institutional trial of brachytherapy for localized prostate cancer resulted in a 5 year biochemical failure rate of 6% and overall survival of 96.7%.⁹² Similar outcomes have been reported elsewhere.(103-105)

Cryosurgery should be presented to patients as a treatment option for low risk disease. Several studies have demonstrated that cryosurgery is equivalent to external beam radiotherapy in terms of oncologic outcomes(35) and favorable in terms of quality of life outcomes.(106,107) One study demonstrated that men with newly diagnosed localized disease who underwent cryosurgery following neoadjuvant antiandrogen therapy (n=122) had similar rates of progression at 36 months as compared to those who received radiotherapy following neoadjuvant antiandrogen therapy (23.9% vs. 23.7%). No differences between overall or disease-specific survival were observed. However, more patients in the radiotherapy arm had a cancer-positive biopsy (28.9%) than those in the cryosurgery arm (7.7%) at 36 months.(35) It should be noted, however, that only a small proportion of patients included in these studies were low risk.

High Intensity Focused Ultrasound (HIFU) should be considered investigational therapy for low risk prostate cancer and appropriate only in a randomized clinical study. Recto urethral fistula has been reported as a rare but serious complication associated with HIFU.(108) A retrospective review of patients who underwent HIFU (n=53), over half of which were low-risk patients, demonstrated a 5-year biochemical-free and disease-free survival rates of 21.7% and 13.5%, respectively, after a mean follow-up of 45.4 months.(109) Further study is needed to determine which patients would obtain the greatest benefit from HIFU.

Intermediate-Risk Disease

As with low risk patients, intermediate risk patients need to see a urologist to discuss surgical options for treatment (i.e. prostatectomy and cryotherapy) as well as the risk of a positive margins and their implications.(110) Furthermore, the patient must see a radiation oncologist to discuss brachytherapy (in

select cases) and external beam radiotherapy. Cryosurgery is an option for intermediate risk patients. Radical prostatectomy, EBRT, and brachytherapy appear to be equally efficacious in this group of patients, with 5-year biochemical recurrence free survival rates of 79.9% for retro pubic radical prostatectomy, 85.7% for EBRT, and 89.5% for brachytherapy, reported among 979 patients with a median follow-up of 65 months. Median time to initiation of salvage therapy from time of treatment was 26.1 months for radical prostatectomy, 47.8 months for EBRT, and 47.4 months for brachytherapy.(111,112) However, quality of life may vary according to treatment modality.(112)

Patient selection for radical prostatectomy should include consideration for the possible risk of margin involvement. Radical prostatectomy is the preferred treatment option in patients with a normal life expectancy of greater than 20 years and those with significant lower urinary tract symptoms (LUTS). However, radical prostatectomy is contraindicated for individuals with previous pelvic radiotherapy and surgery (given the risk of worse functional outcomes),(113,114) individuals with inflammatory bowel disease, individuals with collagen vascular disease, and individuals with extraprostatic disease on the biopsies. As compared with radical retro pubic prostatectomy, robotic-assisted laparoscopic prostatectomy was shown in a retrospective study to achieve similar rates of positive surgical margins: 12 cases (14%) for radical retro pubic prostatectomy versus 11 cases (13%) for robotic-assisted laparoscopic prostatectomy.(115) While adjuvant/salvage radiation improves progression-free outcomes following prostatectomy,(116,117) there is only limited evidence that the combination of surgery followed by radiation is superior to either treatment alone in appropriately selected patients. A randomized controlled trial among patients with pT3N0M0 prostate cancer who received either 60 to 64 Gy adjuvant radiotherapy (n=214) or observation (n=211) following radical prostatectomy, showed that metastasis-free survival was significantly greater with radiotherapy (HR for death 0.71; 95% CI 0.54-0.94; p=.016). Overall survival was also improved significantly with adjuvant radiation (HR for death 0.72; 95% CI 0.55-0.96; p=.023).(37) Another study (SWOG) showed that adjuvant radiotherapy is effective in patients with seminal vesicle involvement. However, this study was conducted among patients with high risk disease.(118) At this time, neoadjuvant hormonal therapy prior to radical prostatectomy has not been proven efficacious and is therefore not recommended outside of a clinical trial.(119)

Among intermediate risk patients, PSA outcome advantage has been demonstrated with dose escalated RT.(28-30,120) Regardless, there is no evidence to suggest any survival benefit from high dose RT. A recent randomized trial showed that among intermediate risk T1b-T2b patients (n=144), 79.2 Gy (high dose) produced a lower biochemical failure rate (30.4% vs. 42.1%; p=.06) than 70.2 Gy (conventional dose), after a median follow-up of 8.9 years. However, there was no difference in overall survival between the treatment arms (78.4% vs. 83.4%; p=.41).(96) Based on current evidence, the recommended prescribed dose to the target is 78 Gy in standard fractionation.(28,30,96,120) Short term neoadjuvant and concurrent hormone therapy may be used in patients undergoing radiotherapy.(33) Improvement in all-cause mortality was demonstrated in men randomized to a radiotherapy dose of 70 Gy with or without 6 months of hormones, after a median follow-up of 8.2 years. In spite of this, subgroup analysis showed this effect was largely noted in men with minimal comorbidity.(121,122)

Brachytherapy is a potential treatment option for intermediate risk patients with favourable characteristics or a Gleason score of less than seven and PSA of 10-15ng/mL.(31,33) As with low risk patients, patients with intermediate risk disease may not be eligible for low dose brachytherapy if they are found to have pubic arch interference,(98) have had a prior transurethral resection of the prostate,(100,101) or have significant baseline obstructive symptoms (i.e. American Urological Association symptom score >20). At this time, high dose rate brachytherapy in conjunction with EBRT is considered investigational.(123-125)

Cryosurgery is available for selected T1-T3 patients (i.e. those with gland volume <60 cubic centimeters,

PSA <20, and any Gleason score). However, there is a lack of rigorous evidence showing equivalence to other treatment modalities. A retrospective study among patients treated who underwent cryosurgery (n=2,427; all risk levels) from the Cryo On-Line Data Registry showed that at 60 months post-cryoablation, the 5-year biochemical disease-free survival was 76% for intermediate risk patients with a PSA level of <0.1 ng/mL and 67% for those with a PSA level of 0.1-0.5 ng/mL. The 2-year biochemical relapse-free rate was 56.1% for those with a PSA level of 0.6-1.0 ng/mL and the 12-month failure rate was 38% for those with a PSA level of 1.1- 2.5 ng/mL.(126,127)

High-Risk Disease

All patients with high-risk prostate cancer should be referred to a radiation oncologist prior to treatment decisions being made. Patients should be considered for multimodality discussion and clinical trials. Options for high risk patients include EBRT with androgen deprivation therapy, radical prostatectomy with lymph node dissection with the option of post-operative EBRT and/or androgen deprivation therapy, or androgen deprivation therapy alone. A long-term study among high risk patients with a median follow-up of at least six years demonstrated that the 10-year cancer-specific survival rate was not significantly different (p=.06) among patients who underwent radical retro pubic prostatectomy (n=1,238; 92%) versus those who received EBRT alone (n=265; 88%) or with androgen deprivation therapy (n=344; 92%). Nevertheless, risk of all-cause mortality was higher among those who received EBRT and hormone therapy as compared to those who underwent prostatectomy (HR 1.60; 95% CI 1.25-2.05; p=.0002).(128) Analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry (including 7,538 men with localized disease) also suggests that absolute differences in cancer-specific mortality between prostatectomy and radiation therapy (favoring prostatectomy) are increased for men at intermediate and high risk.(129)

Radiotherapy should treat the prostate to a planning target volume of 74-78 Gy. Superior long-term cancer control was demonstrated in men with localized prostate cancer receiving high-dose versus conventional-dose radiotherapy.(96) RT up to 78 Gy is well tolerated.(130) Consider including regional lymph nodes within the radiotherapy treatment volume. Androgen deprivation therapy should be administered for at least two years, as demonstrated by the RTOG 92-02 study that showed significant improvements with long-term (2 years) versus short term (4 months) therapy. In that study, 10-year rates of disease-free survival (22.5 vs. 13.2%; p<.0001), disease-specific survival (88.7 vs. 83.9%; p=.0042), local progression (12.3 vs. 22.2%; p<.0001), distant metastasis (14.8 vs. 22.8%; p<.0001), and biochemical failure (51.9 vs. 68.1%; p<.0001) were all significantly better in the group receiving ADT for 2 years. Ten-year overall survival was significantly better only among a subgroup of patients with a Gleason score of 8-10 (45.1 vs. 31.9%; p=.0061).(130) If ADT alone is considered, the patient must understand that the omission of RT for high risk prostate cancer is associated with significantly worse overall survival(42,45) based on results from 2 randomized controlled clinical trials. In a phase III study by Warde, P. et al.(2011), the addition of RT to ADT improved overall survival at 7 years (HR=0.77, p=0.033).(42) Widmark et al. (2009) also conducted a randomized phase III study comparing ADT with ADT and RT. The cumulative incidence at 10 years for prostate-cancer-specific mortality was 23.9% for the group that received ADT alone, and 11.9% for the group that received RT and ADT; a 12% difference.(45)

In highly selected patients, radical prostatectomy with regional lymphadenectomy can be considered with the option of adjuvant EBRT and/or androgen deprivation therapy. Patients that are appropriate for this treatment include those with low volume disease without fixation to adjacent organs. Patients that could be considered for adjuvant or salvage androgen deprivation therapy include those with node-positive disease. Randomized trials have provided strong evidence for the role of adjuvant radiotherapy (post-op PSA < 0.2 ng/mL) for patients with positive surgical margins, seminal vesicle invasion, or capsular

perforation, with respect to biochemical and clinical progression-free survival.(32,131) A recent update of the SWOG study(44) has now shown a significant improvement in metastasis-free survival and overall survival at a median follow-up of 12.6 years. The 10-year estimated benefit from radiotherapy with respect to metastasis free survival was 10% (71% vs. 61%) and 8% with respect to overall survival (74% vs. 66%). Nevertheless, the relative merits and implications of immediate RT for all such patients have to be judiciously considered. Recently reported adjuvant randomized controlled trials were conducted before the role of salvage radiotherapy was well appreciated, especially if salvage radiotherapy is initiated when PSA is well below 0.5 ng/mL. PSA outcomes following salvage radiotherapy have been reported by retrospective multi-institutional case series.(41) Trablusi et al. (2008) conducted a multi-institutional matched-control analysis of adjuvant versus salvage postoperative radiation therapy for pT3-4N0 prostate cancer. The five-year freedom from biochemical failure from the end of RT was 73% after adjuvant RT, compared with 66% after salvage RT.(132) Budhiarto et al. (2010) conducted a multi-institutional analysis comparing adjuvant and salvage RT, and found that salvage RT was a significant predictor of decreased biochemical relapse-free survival in patients negative for lymph node invasion and surgical margins, positive for lymph node invasion and negative for surgical margins, and positive for both lymph node invasion and surgical margins.(117) Current ultra-sensitive PSA measurements allow more timely early salvage radiotherapy and/or systemic treatment than previous trials had offered. The potential value of early salvage radiotherapy for rising PSA at levels of ~ 0.1 ng/mL was not represented on protocol in the reported randomized trials.(133) The difficulty remains in defining a window of opportunity when a detectable PSA represents localized disease that is potentially curable with salvage local therapy, before malignant cells metastasize. The applicability of randomized trials data must be interpreted within the clinical context, experience, and expertise of the health care providers the region, with a goal to provide unambiguous recommendations in the best interest of the patient. It is assumed that synoptic surgical pathology examination and reporting is available to the consultants. There is strong evidence indicating review by central/reference pathologist provides more reliable pathologic features to predict outcomes.

In patients not being considered for external-beam radiotherapy with androgen deprivation therapy, androgen deprivation therapy alone should be delivered. An analysis of data from the CaPSURE registry showed that patients who received treatment with primary androgen deprivation therapy for clinically localized disease (T1-T3,Nx/N0,Mx/M0; n=993) more frequently had higher risk disease (as defined by PSA level, T classification, and Gleason score) with more comorbidities and tended to be older, less educated, and of a lower average household income than those who received standard therapy. Nevertheless, at 5 years after the initiation of androgen deprivation therapy, 67.3% of patients were still receiving treatment with only androgen deprivation, while 13.8% had gone on to receive definitive secondary treatment (radical prostatectomy, external beam radiotherapy, brachytherapy, or cryotherapy) and 3.9% underwent second-line therapy (chemotherapy or alternative hormone-deprivation therapy). Another 4.1% died of prostate cancer and 19% died of all causes.(134) Patients should be counseled regarding the effects of prolonged testosterone suppression. In particular, cardiovascular health(135,136) and bone health (69-76,137,138)should be monitored closely in these patients.

Advanced Disease

Stage T1-4, N1-3, M0

Radiotherapy should be given to these patients in addition to ADT. A recent randomized phase III trial demonstrated a significant benefit in overall survival.(42) RT for clinical, radiologic nodal involvement could be considered on a case-by-case basis in pathologic N+ disease or radiologic N+ disease for those with normal life expectancy of ≥ 10 years.(48) Intermittent hormone therapy is not inferior to continuous long-term hormonal therapy in relation to cancer-specific outcomes and may be associated with better

quality of life or less treatment toxicity.(46,51) Semi-annual clinical evaluation and PSA should be done if it will affect management. Follow-up is age dependent, and investigations done at the discretion of the physician.

Stage T1-4, N1-3, M+ Hormone Sensitive Disease

Options for management include surgical castration or medical castration. Medical castration can include treatment with an LHRH analogue. When first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily, flutamide 250 mg three times a day or nilutamide 300mg daily) should be given concurrently with the first administration of LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare. The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward. Another option is single agent antiandrogens. Nonsteroidal antiandrogens can be administered to those patients wishing to maintain potency. This may result in a reduction in disease-free survival. To date there is insufficient data to recommend bicalutamide at the 150 mg/day dose and it is not approved by Health Canada. These treatments are equally effective and the risks, benefits, and economic implications should be discussed with the patient. Ongoing total androgen blockade (e.g. castration with LHRH agonist plus a nonsteroidal antiandrogen) is not recommended. Use of intermittent hormone therapy is controversial. Recent data suggests that intermittent is not non-inferior to continuous, which does not necessarily mean intermittent is inferior to continuous. (46,51) Patients undergoing androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.(52)

Stage M+ Castrate Resistant Disease

The benefits of treatment are primarily palliative and related to quality of life, although some systemic therapies confer a small survival advantage. Palliative radiotherapy (EBRT) can be given to symptomatic sites. Strontium 89 (Metastron®) is not recommended routinely, but appropriate indications include: multiple painful sites of bone metastases on both side of diaphragm, patient and/or tumour factors contraindicating the use of multiple fields of EBRT for palliation, adequate bone marrow reserve (Platelet count>100), no evidence of impending spinal cord compression, and no plans for systemic chemotherapy.

With regards to systemic therapy, it is important to note that chemotherapy is not indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA. It is recommended that first line chemotherapy consist of docetaxel, 75mg/m² IV every 3 weeks in combination with prednisone (5mg) twice daily.(63) In a study comparing this regimen with mitoxantrone (12mg/m² every 3 weeks) resulted in a median overall survival in the docetaxel group of 18.5 months versus 16.5 months.⁵² Post-progression on docetaxel, systemic therapy options include: abiraterone (pending approval by Health Canada), cabazitaxel, or enzalutamide (pending approval by Health Canada). Abiraterone should be given orally (1g) daily in combination with prednisone (5mg oral, twice daily). In a randomized trial, abiraterone and prednisone was compared with a placebo and prednisone. Abiraterone resulted in a significantly longer overall survival (14.8 months versus 10.9 months, p<0.001).(61) Abiraterone is not yet approved by Health Canada. Cabazitaxel should be given in 25mg/m² IV every 3 weeks in combination with prednisone (10mg oral daily). A randomized phase III trial compared this regimen with mitoxantrone (12mg/m² IV every three weeks).(66) The hazard ratio for death of men treated with cabazitaxel compared with mitoxantrone was 0.70 (95% CI 0.59-0.83, p<0.0001). (66) Enzalutamide was recently approved by the FDA but is pending Health Canada approval. A phase III, double-blind, placebo-controlled trial demonstrated that enzalutamide (160mg per day) resulted in a overall survival of 18.4 months in castration-resistant prostate cancer versus 13.6 months in patients who

received placebo.(57) Currently, there is no data showing preference for one of these agents over the other. In the third line, clinical trials should be the first consideration where appropriate. If clinical trials are not an option, abiraterone or cabazitaxel can be used, provided the choice agent was not used for second line. Docetaxel can also be re-challenged as third line. Mitoxantrone 12mg/m² every 3 weeks with prednisone 5 mg oral twice a day can provide adequate palliation in 2nd or subsequent line.

An abstract presented at the ASCO 2012 Genitourinary Symposium reported on the use of radium-223 in patients with castration-resistant prostate cancer. These preliminary results of the ALSYMPCA trial demonstrated a significantly improved overall survival among patients treated with radium-223 and best standard of care versus those treated with a placebo and best standard of care (14 months versus 11.2 months, HR 0.695 p=0.00185). Furthermore, Ra-223 demonstrated highly favorable safety and tolerability, showing low levels of myelosuppression.(139) Radium-223 is currently under review by the FDA, and is a promising agent for the treatment of metastatic castrate-resistant prostate cancer.

Biochemical Recurrence

Biochemical recurrence is defined using the Phoenix definition; any rise in PSA following a prostatectomy and a rise of 2ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) after radiotherapy with or without hormone therapy.(68) For the purposes of reporting, dates of failure should be determined “at call” and not backdated. Patients not meeting these PSA criteria for failure who undergo salvage therapies should also be declared failures at the time a positive biopsy is obtained or salvage therapy administered.(68)

Patients with Rising PSA after Curative Intent Treatment without Metastases

For patients with biochemical failure after radical prostatectomy, radiotherapy with or without concurrent or adjuvant ADT is recommended. A retrospective study by Stephenson et al. (2004) presented a single-centre experience of patients with PSA rise after radical prostatectomies that were given a median dose of 64.8 Gy of radiotherapy. Seven year disease-specific survival was 90%, and seven year overall survival was 82%.(39) There is debate regarding when and under what circumstances androgen deprivation therapy should be delivered. Souhami et al. (2010), in their secondary analysis of RTOG 85-31, found that within a sample of patients where most had previously undergone a radical prostatectomy and were negative for distant metastases, radiotherapy and early hormone therapy (PSA <10ng/mL) led to a significantly higher 11 year overall survival (41% versus 27%, p=0.002).(140)

For patients with biochemical failure after radiotherapy, recommended options include active surveillance within a cancer centre, cryosurgery, brachytherapy or androgen deprivation therapy. An estimated 10-60% of men initially treated with curative intent radiotherapy may experience biochemical recurrence.(141) No consensus currently exists for treatment of recurrences thought to be confined to the prostate. A prospective phase II trial by Bales et al. (1995) of cryosurgery in patients who underwent previous radiotherapy and had a biopsy proven recurrence resulted in a decrease in positive prostate biopsies by 86% at 3 months after surgery (only 14% positive).(142) With regards to brachytherapy, the review and case series presented by Allen et al. (2007) appears to indicate that salvage brachytherapy is at least as effective as other options with comparable or potentially fewer treatment related side effects.(141) ADT can be given on either an intermittent or continuous basis. Intermittent hormone therapy is not inferior to continuous long-term hormonal therapy in relation to cancer-specific outcomes and may be associated with better quality of life or less treatment toxicity.(46,51)

Bone Health

All patients who have prostate cancer are at risk for osteoporosis.(69) This risk may be further increased depending on the type of therapy required. Patients requiring androgen deprivation therapy (ADT) are at particular risk of developing osteoporosis. Part of the integrated management plan for patients being treated for prostate cancer is to consider long-term bone health.(138) The concern is that osteoporosis is associated with a significantly higher risk of fracture and that fractures are themselves associated with higher mortality.(69)

In metastatic hormone-sensitive patients, those presenting with *de novo* metastatic bone disease or those who become metastatic after primary therapy should undergo ADT as part of standard management. Continuous and intermittent ADT are both viable options for patients with metastatic hormone sensitive disease. An assessment of bone health and risk should be undertaken, including a DEXA scan to assess BMD. Several bisphosphonates have been studied in the setting of overt metastatic disease when patients are still hormone sensitive. Pamidronate and clodronate have both been shown to be statistically no better than placebos in delaying or reducing skeletal related events (SREs), altering overall survival or reducing bone pain.(71,72) Studies of zoledronic acid are currently being performed in the setting of bone metastatic hormone sensitive prostate cancer. There are currently no study results that demonstrate the use of any bisphosphonate in hormone sensitive metastatic prostate cancer will alter SREs or survival.(76)

Far more work has been done examining the role of bisphosphonates for castrate resistant disease. Bisphosphonates have been compared to placebos either as monotherapy or in conjunction with chemotherapy. Endpoints have included overall survival, skeletal-related events (SREs), pain control, and quality of life (QOL) improvement. Studies using less potent bisphosphonates, such as clodronate and pamidronate, have been negative for all endpoints.(72) Only zoledronic acid has been shown to improve outcomes by delaying median time to SRE and number of SREs without any effect on patient-rated QOL.(74,137) However, it should be noted that the treatment effect was relatively small, and only patients with no pain or mild to moderate pain were eligible. Conclusions regarding the utility of zoledronic acid to reduce bone morbidity and improve QOL in patients with severe pain cannot be drawn. Nevertheless, with high quality evidence to support a reduction in SREs by administering zoledronic acid, it should be available to patients and patients and their physicians should discuss the issue on a case by case basis.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ADT	androgen deprivation therapy
BMD	bone mineral density
CBC	complete blood count
CT	computed tomography
CTV	clinical target volume
DEXA	dual-energy x-ray absorptiometry
DRE	digital rectal examination
EBRT	external beam radiotherapy
GnRH	Gonadotropin-releasing hormone
Gy	radiotherapy dosage units
HDR	high dose rate
HIFU	high intensity focused ultrasound
ICRU	International Commission on Radiation Units
IMRT	intensity modulated radiation therapy
LDR	low dose rate
LHRH	luteinizing hormone-releasing hormone
LUTS	lower urinary tract symptoms
MO	medical oncologist
MRI	magnetic resonance imaging
NOS	not otherwise specified
PE	physical examination
PFS	progression free survival
PSA	prostate specific antigen
QOL	quality of life
RCT	randomized controlled trials
RO	radiation oncologist
RP	radical prostatectomy
RT	radiotherapy
SRE	skeletal related events
TURP	transurethral resection of the prostate

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

- (1) Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2012. 2012; Available at: <http://cancer.ca/~media/CCS/Canada%20wide/Files%20List/English%20files%20heading/PDF%20-%20Policy%20-%20Canadian%20Cancer%20Statistics%20-%20English/Canadian%20Cancer%20Statistics%202012%20-%20English.ashx>. Accessed 04/03, 2013.
- (2) Alterkruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W. SEER Cancer Statistics Review, 1975-2007. National Cancer Institute 2007. Available at: http://seer.cancer.gov/archive/csr/1975_2007/. Accessed 07/16, 2014.
- (3) Ellis WJ, Lange PH. Prostate cancer. *Endocrinol Metab Clin North Am* 1994 Dec;23(4):809-824.
- (4) Gilliland FD, Key CR. Male genital cancers. *Cancer* 1995 Jan 1;75(1 Suppl):295-315.
- (5) Losi L, Brausi M, Di Gregorio C. Rare prostatic carcinomas: histogenesis and morphologic pattern. *Pathologica* 1994 Aug;86(4):366-370.
- (6) Edge SB, Byrd DR, Compton CC. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
- (7) Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010 Aug;11(8):725-732.
- (8) Freedland SJ, Aronson WJ, Terris MK, Kane CJ, Amling CL, Dorey F, et al. Percent of prostate needle biopsy cores with cancer is significant independent predictor of prostate specific antigen recurrence following radical prostatectomy: results from SEARCH database. *J Urol* 2003 Jun;169(6):2136-2141.
- (9) Quinn DI, Henshall SM, Brenner PC, Kooner R, Golovsky D, O'Neill GF, et al. Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. *Cancer* 2003 Apr 15;97(8):1884-1893.
- (10) Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L, et al. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001 Aug;8(4):1314-1322.
- (11) National Comprehensive Cancer Network. Clinical Practice Guidelines In Oncology: Prostate Cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 07/16, 2014.
- (12) Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009 Mar 26;360(13):1320-1328.
- (13) Choo R, Klotz L, Danjoux C, Morton GC, DeBoer G, Szumacher E, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol* 2002 Apr;167(4):1664-1669.
- (14) Brachman DG, Thomas T, Hilbe J, Beyer DC. Failure-free survival following brachytherapy alone or external beam irradiation alone for T1-2 prostate tumors in 2222 patients: results from a single practice. *Int J Radiat Oncol Biol Phys* 2000 Aug 1;48(1):111-117.

- (15) Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009 Oct;27(5):607-612.
- (16) Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001 Sep 1;51(1):31-40.
- (17) Koper PC, Stroom JC, van Putten WL, Korevaar GA, Heijmen BJ, Wijnmaalen A, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *Int J Radiat Oncol Biol Phys* 1999 Mar 1;43(4):727-734.
- (18) Kupelian PA, Elshaiikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol* 2002 Aug 15;20(16):3376-3385.
- (19) Keyser D, Kupelian PA, Zippe CD, Levin HS, Klein EA. Stage T1-2 prostate cancer with pretreatment prostate-specific antigen level < or = 10 ng/ml: radiation therapy or surgery? *Int J Radiat Oncol Biol Phys* 1997 Jul 1;38(4):723-729.
- (20) Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999 Jan 23;353(9149):267-272.
- (21) Nguyen LN, Pollack A, Zagars GK. Late effects after radiotherapy for prostate cancer in a randomized dose-response study: results of a self-assessment questionnaire. *Urology* 1998 Jun;51(6):991-997.
- (22) Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001 Dec;58(6):843-848.
- (23) Pollack A, Zagars GK, Starkschall G, Childress CH, Kopplin S, Boyer AL, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996 Feb 1;34(3):555-564.
- (24) Robinson JW, Moritz S, Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2002 Nov 15;54(4):1063-1068.
- (25) Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2000 Oct 1;48(3):635-642.
- (26) Zelefsky MJ, Wallner KE, Ling CC, Raben A, Hollister T, Wolfe T, et al. Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. *J Clin Oncol* 1999 Feb;17(2):517-522.
- (27) Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999 May 5;281(17):1591-1597.
- (28) Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008 Jan 1;70(1):67-74.
- (29) Zietman AL, DeSilvio ML, Slater JD, Rossi CJ, Jr, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005 Sep 14;294(10):1233-1239.
- (30) Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006 May 1;24(13):1990-1996.
- (31) Morris WJ, Keyes M, Palma D, McKenzie M, Spadinger I, Agranovich A, et al. Evaluation of dosimetric parameters and disease response after 125 iodine transperineal brachytherapy for low- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009 Apr 1;73(5):1432-1438.
- (32) Morris WJ, Keyes M, Palma D, Spadinger I, McKenzie MR, Agranovich A, et al. Population-based study of biochemical and survival outcomes after permanent 125I brachytherapy for low- and intermediate-risk prostate cancer. *Urology* 2009 Apr;73(4):860-5; discussion 865-7.
- (33) D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008 Jan 23;299(3):289-295.
- (34) Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011 Jul 14;365(2):107-118.
- (35) Donnelly BJ, Saliken JC, Brasher PM, Ernst SD, Rewcastle JC, Lau H, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. *Cancer* 2010 Jan 15;116(2):323-330.
- (36) Thompson IM, Middleton RG, Optenberg SA, Austenfeld MS, Smalley SR, Cooner WH, et al. Have complication rates decreased after treatment for localized prostate cancer? *J Urol* 1999 Jul;162(1):107-112.

- (37) Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009 Mar;181(3):956-962.
- (38) Jani AB, Kao J. Postprostatectomy adjuvant versus salvage radiotherapy: a complication-adjusted number-needed-to-treat analysis. *Cancer* 2005 May 1;103(9):1833-1842.
- (39) Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004 Mar 17;291(11):1325-1332.
- (40) van der Kwast TH, Collette L, Van Poppel H, Van Cangh P, Vekemans K, DaPozzo L, et al. Impact of pathology review of stage and margin status of radical prostatectomy specimens (EORTC trial 22911). *Virchows Arch* 2006 Oct;449(4):428-434.
- (41) D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol* 2005 Aug 1;23(22):4975-4979.
- (42) Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011 Dec 17;378(9809):2104-2111.
- (43) Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007 May 20;25(15):2035-2041.
- (44) Zhou P, Chen MH, McLeod D, Carroll PR, Moul JW, D'Amico AV. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol* 2005 Oct 1;23(28):6992-6998.
- (45) Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009 Jan 24;373(9660):301-308.
- (46) Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Urological Group. *Eur Urol* 2009 Jun;55(6):1269-1277.
- (47) Valicenti RK, Thompson I, Jr, Albertsen P, Davis BJ, Goldenberg SL, Wolf JS, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. *Int J Radiat Oncol Biol Phys* 2013 Aug 1;86(5):822-828.
- (48) Zagars GK, Pollack A, von Eschenbach AC. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. *Urology* 2001 Aug;58(2):233-239.
- (49) Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008 Dec;102(11):1531-1538.
- (50) Frampton JE, Lyseng-Williamson KA. Degarelix. *Drugs* 2009 Oct 1;69(14):1967-1976.
- (51) Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012 Sep 6;367(10):895-903.
- (52) Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2003 May 1;21(9):1653-1659.
- (53) Sweeney C, Chen Y, Carducci M, Liu G, Jarrard D, Eisenberger M, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPRCA): An ECOG-led phase III randomized trial. *J Clin Oncol* 2014;32(5s):suppl; abstr LBA2.
- (54) Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013 Jan 10;368(2):138-148.
- (55) Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). *Eur Urol* 2014 Nov;66(5):815-825.
- (56) Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014 Jul 31;371(5):424-433.
- (57) Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012 Sep 27;367(13):1187-1197.

- (58) Fizazi K, Scher HI, Miller K, Basch E, Sternberg CN, Cella D, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol* 2014 Sep;15(10):1147-1156.
- (59) Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013 Jul 18;369(3):213-223.
- (60) Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol* 2014 Jun;15(7):738-746.
- (61) de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011 May 26;364(21):1995-2005.
- (62) Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012 Oct;13(10):983-992.
- (63) Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004 Oct 7;351(15):1502-1512.
- (64) Berthold DR, Pond GR, de Wit R, Eisenberger M, Tannock IF, TAX 327 Investigators. Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa. *Ann Oncol* 2008 Oct;19(10):1749-1753.
- (65) Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock AI, et al. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res* 2008 May 1;14(9):2763-2767.
- (66) de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010 Oct 2;376(9747):1147-1154.
- (67) Bahl A, Oudard S, Tombal B, Ozguroglu M, Hansen S, Kocak I, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol* 2013 Sep;24(9):2402-2408.
- (68) Roach M,3rd, Hanks G, Thames H,Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006 Jul 15;65(4):965-974.
- (69) Higano CS. Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician. *Urol Clin North Am* 2004 May;31(2):331-352.
- (70) Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003 Nov 1;21(21):4042-4057.
- (71) Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* 2003 Sep 3;95(17):1300-1311.
- (72) Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003 Sep 1;21(17):3335-3342.
- (73) Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003 Dec 1;21(23):4277-4284.
- (74) Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004 Jun 2;96(11):879-882.
- (75) Brown JE, Neville-Webbe H, Coleman RE. The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer* 2004 Jun;11(2):207-224.
- (76) Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SR. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003 Aug 30;327(7413):469.

- (77) Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011 Mar 5;377(9768):813-822.
- (78) Patel AR, Klein EA. Risk factors for prostate cancer. *Nat Clin Pract Urol* 2009 Feb;6(2):87-95.
- (79) Finne P, Fallah M, Hakama M, Ciatto S, Hugosson J, de Koning H, et al. Lead-time in the European Randomised Study of Screening for Prostate Cancer. *Eur J Cancer* 2010 Nov;46(17):3102-3108.
- (80) Vickers AJ, Cronin AM, Aus G, Pihl CG, Becker C, Pettersson K, et al. Impact of recent screening on predicting the outcome of prostate cancer biopsy in men with elevated prostate-specific antigen: data from the European Randomized Study of Prostate Cancer Screening in Gothenburg, Sweden. *Cancer* 2010 Jun 1;116(11):2612-2620.
- (81) Vickers AJ, Cronin AM, Roobol MJ, Hugosson J, Jones JS, Kattan MW, et al. The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group. *Clin Cancer Res* 2010 Sep 1;16(17):4374-4381.
- (82) Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009 Mar 26;360(13):1310-1319.
- (83) Huang Y, Isharwal S, Haese A, Chun FK, Makarov DV, Feng Z, et al. Prediction of patient-specific risk and percentile cohort risk of pathological stage outcome using continuous prostate-specific antigen measurement, clinical stage and biopsy Gleason score. *BJU Int* 2011 May;107(10):1562-1569.
- (84) Hardie C, Parker C, Norman A, Eeles R, Horwich A, Huddart R, et al. Early outcomes of active surveillance for localized prostate cancer. *BJU Int* 2005 May;95(7):956-960.
- (85) Eggener SE, Mueller A, Berglund RK, Ayyathurai R, Soloway C, Soloway MS, et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. *J Urol* 2009 Apr;181(4):1635-41; discussion 1641.
- (86) Venkitaraman R, Norman A, Woode-Amisssah R, Dearnaley D, Horwich A, Huddart R, et al. Prostate-specific antigen velocity in untreated, localized prostate cancer. *BJU Int* 2008 Jan;101(2):161-164.
- (87) Venkitaraman R, Norman A, Woode-Amisssah R, Fisher C, Dearnaley D, Horwich A, et al. Predictors of histological disease progression in untreated, localized prostate cancer. *J Urol* 2007 Sep;178(3 Pt 1):833-837.
- (88) Dall'Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer* 2008 Jun 15;112(12):2664-2670.
- (89) Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst* 2010 Jul 7;102(13):950-958.
- (90) Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, et al. Radical prostatectomy, external beam radiotherapy or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004 Jan 1;58(1):25-33.
- (91) Potters L, Klein EA, Kattan MW, Reddy CA, Ciezki JP, Reuther AM, et al. Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004 Apr;71(1):29-33.
- (92) Sharkey J, Cantor A, Solc Z, Huff W, Chovnick SD, Behar RJ, et al. 103Pd brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer: a 12-year experience from a single group practice. *Brachytherapy* 2005;4(1):34-44.
- (93) Stokes SH. Comparison of biochemical disease-free survival of patients with localized carcinoma of the prostate undergoing radical prostatectomy, transperineal ultrasound-guided radioactive seed implantation, or definitive external beam irradiation. *Int J Radiat Oncol Biol Phys* 2000 Apr 1;47(1):129-136.
- (94) Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. *Eur Urol* 2009 May;55(5):1037-1063.
- (95) Ficarra V, Novara G, Fracalanza S, D'Elia C, Secco S, Iafrate M, et al. A prospective, non-randomized trial comparing robot-assisted laparoscopic and retropubic radical prostatectomy in one European institution. *BJU Int* 2009 Aug;104(4):534-539.
- (96) Zietman AL, Bae K, Slater JD, Shipley WU, Efsthathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010 Mar 1;28(7):1106-1111.

- (97) Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011 Apr 1;117(7):1429-1437.
- (98) Sejpal SV, Sathiaselvan V, Helenowski IB, Kozlowski JM, Carter MF, Nadler RB, et al. Intra-operative pubic arch interference during prostate seed brachytherapy in patients with CT-based pubic arch interference of $< \text{or} = 1\text{cm}$. *Radiother Oncol* 2009 May;91(2):249-254.
- (99) Gibbons EP, Jacobs BL, Smith RP, Beriwal S, Krishna K, Benoit RM. Dosimetric outcomes in prostate brachytherapy: is downsizing the prostate with androgen deprivation necessary? *Brachytherapy* 2009 Jul-Sep;8(3):304-308.
- (100) Cesaretti JA, Stone NN, Stock RG. Does prior transurethral resection of prostate compromise brachytherapy quality: a dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2004 Oct 1;60(2):648-653.
- (101) Moran BJ, Stutz MA, Gurel MH. Prostate brachytherapy can be performed in selected patients after transurethral resection of the prostate. *Int J Radiat Oncol Biol Phys* 2004 Jun 1;59(2):392-396.
- (102) Miles EF, Nelson JW, Alkaiissi AK, Das S, Clough RW, Broadwater G, et al. Biologically effective dose (BED) correlation with biochemical control after low-dose rate prostate brachytherapy for clinically low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010 May 1;77(1):139-146.
- (103) Miles EF, Nelson JW, Alkaiissi AK, Das S, Clough RW, Anscher MS, et al. Equivalent uniform dose, D(90), and V(100) correlation with biochemical control after low-dose-rate prostate brachytherapy for clinically low-risk prostate cancer. *Brachytherapy* 2008 Apr-Jun;7(2):206-211.
- (104) Momma T, Saito S, Toya K, Yoroza A, Dokiya T, Murai M. Three-year results of treatment for prostate cancer with low-dose rate temporary iridium-192 brachytherapy. *Int J Urol* 2006 Mar;13(3):218-223.
- (105) Khaksar SJ, Laing RW, Henderson A, Sooriakumaran P, Lovell D, Langley SE. Biochemical (prostate-specific antigen) relapse-free survival and toxicity after 125I low-dose-rate prostate brachytherapy. *BJU Int* 2006 Dec;98(6):1210-1215.
- (106) Robinson JW, Donnelly BJ, Siever JE, Saliken JC, Ernst SD, Rewcastle JC, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. *Cancer* 2009 Oct 15;115(20):4695-4704.
- (107) Hubosky SG, Fabrizio MD, Schellhammer PF, Barone BB, Tepera CM, Given RW. Single center experience with third-generation cryosurgery for management of organ-confined prostate cancer: critical evaluation of short-term outcomes, complications, and patient quality of life. *J Endourol* 2007 Dec;21(12):1521-1531.
- (108) Netsch C, Bach T, Gross E, Gross AJ. Rectourethral fistula after high-intensity focused ultrasound therapy for prostate cancer and its surgical management. *Urology* 2011 Apr;77(4):999-1004.
- (109) Ripert T, Azemar MD, Menard J, Barbe C, Messaoudi R, Bayoud Y, et al. Six years' experience with high-intensity focused ultrasonography for prostate cancer: oncological outcomes using the new 'Stuttgart' definition for biochemical failure. *BJU Int* 2011 Jun;107(12):1899-1905.
- (110) Coelho RF, Chauhan S, Orvieto MA, Palmer KJ, Rocco B, Patel VR. Predictive factors for positive surgical margins and their locations after robot-assisted laparoscopic radical prostatectomy. *Eur Urol* 2010 Jun;57(6):1022-1029.
- (111) Vassil AD, Murphy ES, Reddy CA, Angermeier KW, Altman A, Chehade N, et al. Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010 Nov;76(5):1251-1257.
- (112) Klein EA, Ciezki J, Kupelian PA, Mahadevan A. Outcomes for intermediate risk prostate cancer: are there advantages for surgery, external radiation, or brachytherapy? *Urol Oncol* 2009 Jan-Feb;27(1):67-71.
- (113) Colombo R, Naspro R, Salonia A, Montorsi F, Raber M, Suardi N, et al. Radical prostatectomy after previous prostate surgery: clinical and functional outcomes. *J Urol* 2006 Dec;176(6 Pt 1):2459-63; discussion 2463.
- (114) Masterson TA, Wedmid A, Sandhu JS, Eastham JA. Outcomes after radical prostatectomy in men receiving previous pelvic radiation for non-prostate malignancies. *BJU Int* 2009 Aug;104(4):482-485.
- (115) Laurila TA, Huang W, Jarrard DF. Robotic-assisted laparoscopic and radical retropubic prostatectomy generate similar positive margin rates in low and intermediate risk patients. *Urol Oncol* 2009 Sep-Oct;27(5):529-533.
- (116) Kruser TJ, Jarrard DF, Graf AK, Hedican SP, Paolone DR, Wegenke JD, et al. Early hypofractionated salvage radiotherapy for postprostatectomy biochemical recurrence. *Cancer* 2011 Jun 15;117(12):2629-2636.
- (117) Budiharto T, Perneel C, Haustermans K, Junius S, Tombal B, Scalliet P, et al. A multi-institutional analysis comparing adjuvant and salvage radiation therapy for high-risk prostate cancer patients with undetectable PSA after prostatectomy. *Radiother Oncol* 2010 Dec;97(3):474-479.

- (118) Swanson GP, Goldman B, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. *J Urol* 2008 Dec;180(6):2453-7; discussion 2458.
- (119) Yee DS, Lowrance WT, Eastham JA, Maschino AC, Cronin AM, Rabbani F. Long-term follow-up of 3-month neoadjuvant hormone therapy before radical prostatectomy in a randomized trial. *BJU Int* 2010 Jan;105(2):185-190.
- (120) Al-Mamgani A, Heemsbergen WD, Levendag PC, Lebesque JV. Subgroup analysis of patients with localized prostate cancer treated within the Dutch-randomized dose escalation trial. *Radiother Oncol* 2010 Jul;96(1):13-18.
- (121) Nguyen PL, Chen MH, Renshaw AA, Loffredo M, Kantoff PW, D'Amico AV. Survival following radiation and androgen suppression therapy for prostate cancer in healthy older men: implications for screening recommendations. *Int J Radiat Oncol Biol Phys* 2010 Feb 1;76(2):337-341.
- (122) Nguyen PL, Chen MH, Beard CJ, Suh WW, Renshaw AA, Loffredo M, et al. Radiation with or without 6 months of androgen suppression therapy in intermediate- and high-risk clinically localized prostate cancer: a postrandomization analysis by risk group. *Int J Radiat Oncol Biol Phys* 2010 Jul 15;77(4):1046-1052.
- (123) Prada Gomez PJ, de la Rúa Calderon A, Romo Fonseca I, Evia Suarez M, Abascal Garcia JM, Juan Rijo G, et al. High dose brachytherapy (real time) in patients with intermediate- or high-risk prostate cancer: technical description and preliminary experience. *Clin Transl Oncol* 2005 Oct;7(9):389-397.
- (124) Orio P, Wallner K, Merrick G, Herstein A, Mitsuyama P, Thornton K, et al. Dosimetric parameters as predictive factors for biochemical control in patients with higher risk prostate cancer treated with Pd-103 and supplemental beam radiation. *Int J Radiat Oncol Biol Phys* 2007 Feb 1;67(2):342-346.
- (125) Wallner K, Merrick G, True L, Sherertz T, Sutlief S, Cavanagh W, et al. 20 Gy versus 44 Gy supplemental beam radiation with Pd-103 prostate brachytherapy: preliminary biochemical outcomes from a prospective randomized multi-center trial. *Radiother Oncol* 2005 Jun;75(3):307-310.
- (126) Jones JS, Rewcastle JC, Donnelly BJ, Lugnani FM, Pisters LL, Katz AE. Whole gland primary prostate cryoablation: initial results from the cryo on-line data registry. *J Urol* 2008 Aug;180(2):554-558.
- (127) Levy DA, Pisters LL, Jones JS. Primary cryoablation nadir prostate specific antigen and biochemical failure. *J Urol* 2009 Sep;182(3):931-937.
- (128) Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, Horwitz EM, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer* 2011 Jul 1;117(13):2883-2891.
- (129) Cooperberg MR, Vickers AJ, Broering JM, Carroll PR. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. *Cancer* 2010 Nov 15;116(22):5226-5234.
- (130) Matzinger O, Duclos F, van den Bergh A, Carrie C, Villa S, Kitsios P, et al. Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. *Eur J Cancer* 2009 Nov;45(16):2825-2834.
- (131) Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005 Aug 13-19;366(9485):572-578.
- (132) Trabulsi EJ, Valicenti RK, Hanlon AL, Pisansky TM, Sandler HM, Kuban DA, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. *Urology* 2008 Dec;72(6):1298-302; discussion 1302-4.
- (133) Thompson IM, Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006 Nov 15;296(19):2329-2335.
- (134) Kawakami J, Cowan JE, Elkin EP, Latini DM, DuChane J, Carroll PR, et al. Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). *Cancer* 2006 Apr 15;106(8):1708-1714.
- (135) Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol* 2009 Jan 1;27(1):92-99.
- (136) Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010 Jan 6;102(1):39-46.

(137) Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002 Oct 2;94(19):1458-1468.

(138) British Columbia Cancer Agency. Prostate Cancer. Cancer Management Guidelines- Genitourinary 2009. Available at:

<http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/Brachytherapy.htm>. Accessed 07/16, 2014.

(139) Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: Results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases. (Abstract) 2012 Genitourinary Cancers Symposium. Available at:

<http://meetinglibrary.asco.org/content/89142-116>. Accessed 07/16, 2014.

(140) Souhami L, Bae K, Pilepich M, Sandler H. Timing of salvage hormonal therapy in prostate cancer patients with unfavorable prognosis treated with radiotherapy: a secondary analysis of Radiation Therapy Oncology Group 85-31. *Int J Radiat Oncol Biol Phys* 2010 Dec 1;78(5):1301-1306.

(141) Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. *Cancer* 2007 Oct 1;110(7):1405-1416.

(142) Bales GT, Williams MJ, Sinner M, Thisted RA, Chodak GW. Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy. *Urology* 1995 Nov;46(5):676-680.