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Guideline 26-4 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer

A. Matthew, L.H. Souter, R.H. Breau, C. Canil, M. Haider, L. Jamnicky, R. Morash, D. Smith, M. Surchin, A. Loblaw, and the Prostate Cancer Follow-up Expert Panel

Report Date: June 16, 2015

An assessment conducted in March 2025 placed Guideline 26-4 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 26-4 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/266

For information about this document, please contact Andrew Matthew, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline 26-4: Section 1

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer: Recommendations Summary

Note To Users Of This Summary

This Recommendations Summary may be useful as a quick reference to this guideline. Users are advised to consult the Complete Guideline Report for more information about the evidence base for these recommendations, the quality of the evidence, the interpretation of the evidence and the guideline development process.

GUIDELINE OBJECTIVES

The primary objective of this guideline is to develop recommendations related to the frequency by which prostate-specific antigen (PSA) levels should be tested in men after curative-intent treatment for prostate cancer and to define the most appropriate diagnostic testing if biochemical (BC) recurrence occurs. The secondary objective is to develop recommendations that address psychosocial issues, sexual health, fatigue, urinary health, and bowel heath outcomes associated with treatment for prostate cancer.

TARGET POPULATION

Prostate cancer patients who have undergone curative-intent treatment are the target population for this guideline. For prostate cancer patients who are on active surveillance, please refer to PEBC Guideline 17-9.

INTENDED USERS

This guideline is targeted for radiation oncologists specializing in prostate cancer, family physicians, urologists, nurses, allied health professionals, and any other care provider involved in follow-up care of prostate cancer.

RECOMMENDATIONS

RECOMMENDATION 1

No evidence-based recommendation can be made with respect to follow-up schedule of PSA testing for prostate cancer survivors following curative-intent treatment with surgery.

However, if PSA levels remain undetectable, the Prostate Cancer Follow-up Expert Panel suggests the following as a reasonable schedule. This schedule for PSA testing is in line with PSA kinetics following therapy, other guidelines, and their clinical experience:

- Every three months in year 1
- Every six months in year 2
- Annually thereafter

Qualifying Statements for Recommendation 1

- If PSA levels become detectable, a more frequent PSA surveillance schedule may be appropriate.

- Even though PSA follow-up is recommended annually until end of life, healthcare professionals should use their own discretion in determining the applicability of annual surveillance in patients who are unlikely to benefit from salvage therapy.

RECOMMENDATION 2
No evidence-based recommendation can be made with respect to follow-up schedule of PSA testing for prostate cancer survivors following curative-intent treatment with non-surgery primary therapy, including any form of radiation therapy, cryotherapy, or high-intensity focused ultrasound.

However, the Prostate Cancer Follow-up Expert Panel suggests the following as a reasonable schedule. This schedule for PSA testing is in line with PSA kinetics following therapy, other guidelines, and their clinical experience:

- First test six months after treatment completion
- Every six months until end of year 5
- Annually thereafter

Qualifying Statements for Recommendation 2

- Even though PSA follow-up is recommended annually until end of life, healthcare professionals should use their own discretion in determining the applicability of annual surveillance in patients who are unlikely to benefit from salvage therapy.

RECOMMENDATION 3
Upon biochemical recurrence, the following diagnostic imaging may be considered:

Diagnostic Test	Appropriateness	Notes
When local salvage therapy is planned after radiotherapy:		
Bone scan	Usually appropriate	• Appropriate for all men being considered for local salvage therapy
CT	Usually appropriate	• Appropriate for thorax, abdomen and pelvis imaging
Multiparametric MRI	Sometimes appropriate	• Appropriate when used for targeted biopsy
FDG, NaF, or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental
When salvage radiotherapy is planned after radical prostatectomy:		
Bone scan	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
CT	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
Multiparametric MRI	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
FDG, NaF, or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NaF, sodium fluoride; PET, positron emission tomography; PSA, prostate-specific antigen; RT, radiation therapy.
Note: Salvage therapy refers to follow-up treatment provided after biochemical recurrence.

Qualifying Statements for Recommendation 3

- Diagnostic imaging should only be ordered if that test will result in management decisions; consideration should be given to the appropriateness of the test, coupled with available salvage options.
- Salvage therapies following radiation therapy or ablation therapies need to be performed at specialized centres, with imaging decisions dependent on the local evaluation process.

RECOMMENDATION 4

In men who are not being evaluated through regularly scheduled clinical visits, a PSA test should be performed if the following symptoms develop. Additionally, diagnostic imaging specific to the patient's symptom(s) may be indicated.

- Severe and progressive axioskeletal bone pain
- Unexplained weight loss
- Hematuria
- New urinary symptoms
    - Significant incontinence requiring changing of undergarments, pads, or diapers
    - Urgency
    - Obstructive symptoms
    - Voiding discomfort
    - Nocturia
- Swelling of legs
- New bowel symptoms
    - Rectal bleeding
    - Rectal pain
    - Urgency
    - Change in bowel movement
- Fatigue
    - Tiredness unrelated to sleep disturbance
    - Lack of energy
    - Weakness or lack of muscle strength
    - Physical, emotional and/or cognitive exhaustion

RECOMMENDATION 5

Men experience very specific and oftentimes long-lasting effects after their primary therapy, usually occurring more than three months after surgery or radiation, or during/after androgen deprivation therapy (ADT). Follow-up healthcare providers should be aware of the domains of quality of life potentially affected by treatment for prostate cancer and the management options available to combat them. Research surrounding management options is lacking. Included management options that are based on the clinical standard in Ontario or expert opinion of the Prostate Cancer Follow-up Expert Panel have been denoted with an asterisk (*). The symptoms listed are based on known profiles; however, individual men respond differently to treatments, resulting in individual side-effect profiles. To ensure optimal quality of life in these men, individual patient-reported outcomes should be measured.

Side-Effect	Primary Treatment	Management Options
Sexual Dysfunction		

Side-Effect	Primary Treatment	Management Options
A guideline focusing on the sexual health of cancer patients is under development (PEBC Guideline 19-6) and will provide more in-depth recommendations for sexual dysfunction outcomes.		
Erectile dysfunction	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors as first line treatment* • Men who do not respond to PDE5 inhibitors will need more advanced treatments and should be referred to a urologist* • Men may be referred to penile rehabilitation programs, which include PDE5 inhibitors, vacuum constriction devices, intracorporal or intraurethral therapy, or placement of penile prostheses*
Loss of libido	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling • Testosterone therapy can be considered in men with signs and symptoms of testosterone deficiency and documented low serum testosterone levels provided their cancer is treated and without evidence of persistent or recurrent disease, and if prescribed by the treating oncologist after extensive review of the potential risks*
Anorgasmia	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling*
Dry ejaculate	Surgery, RT, and ADT	• Men should be educated on dry ejaculate*
Climaturia	Surgery, RT, and ADT	• Men should be provided education on self-management strategies, such as emptying the bladder before sexual relations, use of a condom, use of a penile constriction band, and Kegel exercises*
Penile shortening or curvature	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors, intraurethral and intracorporal prostaglandins, vacuum erection device, or penile prostheses*
Infertility	Surgery, RT, and ADT	• Men and their partner should be informed that men treated with rP will become infertile • Men and their partners should be informed that some men treated with RT may remain fertile, even when experiencing sexual dysfunction symptoms*
Urinary Dysfunction		
Obstructive symptoms	Surgery and RT	• Men should be referred to a urologist to determine whether bladder neck dilatation, transurethral resection, or clean intermittent catheterization may be necessary* • Selective alpha antagonists (not in men who underwent rP) may be prescribed*
Urgency symptoms	Surgery and RT	• If the man is able to completely empty his bladder, anticholinergic medications may be appropriate* • All refractory symptoms should result in a referral to a urologist for evaluation and escalation of therapy if appropriate*
Hematuria	RT	• Men with hematuria should be referred to a urologist for evaluation*
Incontinence requiring urinary pads	Surgery and RT	• Men with persistent leakage impacting QoL should be referred to a urologist to evaluate the cause of incontinence (stress, overflow, etc)* • Exercise intervention including resistance, flexibility, and Kegel exercises may improve continence. Specialized physiotherapists may help patients with stress incontinence following rP • In men with post-prostatectomy incontinence who are unable to perform pelvic floor training, urethral slings or artificial urinary sphincters can be considered
Bowel Dysfunction		

Side-Effect	Primary Treatment	Management Options
Rectal bleeding	RT	• All men with rectal bleeding should be referred to a gastroenterologist for colonoscopy if not done within five years* • For men with rectal bleeding post-RT, referral to a gastroenterologist who has experience in managing RT proctitis is recommended. The anterior rectum should only be biopsied when absolutely necessary as this can cause a fistula of the rectum* • For men with bleeding secondary to RT proctitis, the following strategies may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (Salofalk [mesalamine] suppositories, topical formalin, or argon plasma laser treatments) ○ Refractory RT proctitis should be considered for hyperbaric oxygen
Urgency and frequency symptoms	RT	• For men with urgency and frequency symptoms, the following options may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (antidiarrheals, anticholinergics) ○ Pelvic floor muscle therapy
Other Physical Side-Effects		
Anemia	ADT	• Investigation for common sources of anemia should be considered*
Body composition alterations	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Fatigue	Surgery, RT, and ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Gynecomastia/ Mastodynia	ADT	• In severe cases, surgical excision can be considered and patients should be referred to the appropriate specialist*
Hot flushes	ADT	• Treatment with diethylstilbestrol, megestrol acetate, venlafaxine, cyproterone acetate, and medroxyprogesterone have been shown to decrease number of hot flushes, but should be used with caution because treatment with these medications have been associated with adverse side-effects (e.g., gynecomastia, depression, weight gain, muscle spasms, insomnia, nausea, elevated blood pressure)
Physical activity/ function	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Bone health	ADT	• This outcome described in PEBC Guideline 3-14v2 (in development)
QoL and Psychosocial Side-Effects		
Cognitive side-effects	ADT	• Healthcare provider may consider neurocognitive assessment*
Psychological distress (depression and anxiety)	Surgery, RT, and ADT	• In-office psychological therapy and pharmacotherapy as appropriate • Recommendations for depression in cancer survivors are described in PEBC Guideline 19-4v2
General QoL and Psychosocial sequelae	Surgery, RT, and ADT	• During scheduled follow-up clinical visits, the psychosocial status of men should be assessed and distress should result in referral to specialized psychosocial care* • Patients should be encouraged to participate in an exercise program

Side-Effect	Primary Treatment	Management Options
		○ Strategies more thoroughly described in PEBC Guideline 19-5 (in development) • Referral to applicable support groups for coping training for couples, as well as social and emotional QoL well-being, may be considered

Abbreviations: ADT, androgen deprivation therapy; PDE5, phosphodiesterase type 5; QoL, quality of life; rP, radical prostatectomy; RT, radiation therapy.

RECOMMENDATION 6
No diet plan can be recommended because no diet plan or food supplement has been associated with improved cancer outcomes.

RECOMMENDATION 7
For prostate cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by the treating oncologist, urologist, family physician, nurse practitioner, or hospital-based nurses. Models of care are described more thoroughly in PEBC Guideline 26-1.

Qualifying Statements for Recommendation 7

- All healthcare practitioners that provide PSA surveillance should manage PSA as per the current CCO Prostate Cancer Pathway.
- Although the identified literature only evaluated hospital-based nurse-led care and shared care within the hospital setting, expert opinion supports family physicians being involved in all survivorship care models.
- With the greater emphasis on a person-centred approach to care, a multidisciplinary approach to survivorship, which includes a psychosocial focus to recovery, is recommended. Although the shared care model identified by the literature did not include a psychosocial intervention focus, in order to provide person-centred care, expert opinion supports multiple disciplines being involved in shared care models.

Guideline 26-4: Section 2

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer: Guideline

GUIDELINE OBJECTIVES

The primary objective of this guideline is to develop recommendations related to the frequency of which prostate-specific antigen (PSA) levels should be tested in men after curative-intent treatment for prostate cancer and to define the most appropriate diagnostic testing if biochemical (BC) recurrence occurs. The secondary objective is to develop recommendations that address psychosocial needs, sexual health, fatigue, urinary health, and bowel heath outcomes associated with treatment for prostate cancer.

TARGET POPULATION

Prostate cancer patients who have undergone curative-intent treatment are the target population for this guideline. For prostate cancer patients who are on active surveillance, please refer to PEBC Guideline 17-9.

INTENDED USERS

This guideline is targeted for radiation oncologists specializing in prostate cancer, family physicians, urologists, nurses, allied health professionals, and any other care provider involved in follow-up care of prostate cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

RECOMMENDATION 1

No evidence-based recommendation can be made with respect to follow-up schedule of PSA testing for prostate cancer survivors following curative-intent treatment with surgery.

However, if PSA levels remain undetectable, the Prostate Cancer Follow-up Expert Panel suggests the following as a reasonable schedule. This schedule for PSA testing is in line with PSA kinetics following therapy, other guidelines and their clinical experience:

- Every three months in year 1
- Every six months in year 2
- Annually thereafter

Qualifying Statements for Recommendation 1

- If PSA levels become detectable, a more frequent PSA surveillance schedule may be appropriate.
- Even though PSA follow-up is recommended annually until end of life, healthcare professionals should use their own discretion in determining the applicability of annual surveillance in patients who are unlikely to benefit from salvage therapy.

Key Evidence

Both the search for existing systematic reviews and the systematic review of the primary literature did not identify any evidence to inform this research question.

Interpretation of Evidence

Due to a lack of evidence to inform the most appropriate frequency of PSA testing, a consensus approach was used to make a recommendation in the expert opinion of the Prostate Cancer Follow-up Working Group (Working Group). Both the National

Comprehensive Cancer Network (NCCN) [1] and the American Cancer Society [2] have similarly developed a consensus recommendation on PSA testing frequency. For men after initial definitive therapy of any type, both groups have recommended PSA testing every six to 12 months for five years, followed by annually thereafter [1,2]. The NCCN guideline further stipulated that men at high-risk for recurrence should undergo PSA testing every three months [1]. Due to the difference in PSA kinetics following surgery and non-surgical primary therapy, the Working Group chose to propose separate PSA testing schedules for the different therapies. When developing the current suggested PSA testing schedule, the Working Group considered the consensus PSA testing schedule recommended by other clinical practice guidelines, the fact that PSA falls to undetectable levels within two months of prostatectomy, and their clinical experience.

RECOMMENDATION 2

No evidence-based recommendation can be made with respect to follow-up schedule of PSA testing for prostate cancer survivors following curative-intent treatment with non-surgical primary therapy, including any form of radiation therapy, cryotherapy, or high-intensity focused ultrasound.

However, the Prostate Cancer Follow-up Expert Panel suggests the following as a reasonable schedule. This schedule for PSA testing is in line with PSA kinetics following therapy, other guidelines, and their clinical experience:

- First test six months after treatment completion
- Every six months until end of year 5
- Annually thereafter

Qualifying Statement for Recommendation 2

- Even though PSA follow-up is recommended annually until end of life, healthcare professionals should use their own discretion in determining the applicability of annual surveillance in patients who are unlikely to benefit from salvage therapy.

Key Evidence

Both the search for existing systematic reviews and the systematic review of the primary literature did not identify any evidence to inform this research question.

Interpretation of Evidence

Due to a lack of evidence to inform the most appropriate frequency of PSA testing, a consensus approach was used to make a recommendation in the expert opinion of the Working Group. Both the NCCN [1] and the American Cancer Society [2] have similarly developed a consensus recommendation on PSA testing frequency. For men after initial definitive therapy of any type, both groups have recommended PSA testing every six to 12 months for five years, followed by annually thereafter [1,2]. The NCCN guideline further stipulated that men at high-risk for recurrence should undergo PSA testing every three months [1]. Due to the difference in PSA kinetics following surgery and non-surgical primary therapy, the Working Group chose to propose separate PSA testing schedules for the different therapies. When developing the current suggested PSA testing schedule, the Working Group considered the consensus PSA testing schedule recommended by other clinical practice guidelines, the fact that it may take at least six months to establish the PSA nadir, and their clinical experience.

RECOMMENDATION 3

Upon biochemical recurrence, the following diagnostic imaging may be considered:

Diagnostic Test	Appropriateness	Notes
When local salvage therapy is planned after radiotherapy:		
Bone scan	Usually appropriate	• Appropriate for all patients being considered for local salvage therapy
CT	Usually appropriate	• Appropriate for thorax, abdomen and pelvis imaging
Multiparametric MRI	Sometimes appropriate	• Appropriate when used for targeted biopsy
FDG, NaF, or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental
When salvage radiotherapy is planned after radical prostatectomy:		
Bone scan	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
CT	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
Multiparametric MRI	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
FDG, NaF, or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NaF, sodium fluoride; PET, positron emission tomography; PSA, prostate-specific antigen; RT, radiation therapy.
Note: Salvage therapy refers to follow-up treatment provided after biochemical recurrence.

Qualifying Statements for Recommendation 3

- Diagnostic imaging should only be ordered if that test will result in management decisions and consideration should be given to the appropriateness of the test, coupled with available salvage options.
- Salvage therapies following radiation therapy or ablation therapies need to be performed at specialized centres, with imaging decisions dependent on the local evaluation process.

Key Evidence

The identified literature focused on bone scan, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT for appropriate diagnostic imaging after BC recurrence. The eligible studies focused on the diagnostic properties of the tests (e.g., sensitivity and specificity) and not clinical outcomes.

Bone scan: Two comparative cohort studies compared the gold standard bone scan with other imaging modalities for detection of bone metastases after prostate cancer. One study found that whole body MRI demonstrated an increased sensitivity for detection of bone metastases compared with bone scan plus targeted x-ray [3], while the other found that imaging with fluoroethylcholine (FECH) PET/CT did not significantly increase sensitivity beyond a bone scan [4]. A final prospective cohort study assessed the PSA level at which bone scans are positive for men with BC recurrence and found that bone scans are very rarely positive at PSA levels below 5ng/mL [5].

PET/CT: An identified meta-analysis found that choline PET and PET/CT showed high sensitivity (all sites: 85.6%; 95% confidence interval [CI], 82.9-88.1%) and specificity (all sites: 92.6%; 95%CI, 90.1-94.6%) for detection of locoregional recurrence and distant metastatic disease in men with BC recurrence after any primary therapy [6]. A prospective cohort study conducted after the meta-analysis indicated that sodium fluoride (NaF) PET/CT may be a useful diagnostic tool after radical prostatectomy (rP) and external-beam radiation therapy (EBRT) for detection of occult disease with a positive predictive value of 64% and a negative predictive value of 73% [7]. A second prospective cohort study correlated the sensitivity of

fluoromethylcholine (FCH) PET/CT to PSA level and found sensitivity was only 33% for men with a PSA level of less than 0.3ng/mL and 77% for men with a PSA level greater than 0.3ng/mL (p=0.001) [8].

MRI: An identified meta-analysis indicated that MRI had high diagnostic performance and was able to accurately detect local recurrence with a sensitivity of 82% (95%CI, 78-86%) and a specificity of 87% (95%CI, 81-92%) after rP, and sensitivity of 82% (95%CI, 75-88%) and specificity of 74% (95%CI, 64-82%) after EBRT [9]. A cohort study not in our population of interest, but of importance, found that MRI may be promising for targeted biopsies in patients with a rising PSA despite a previous negative biopsy in the pre-diagnostic space [10]. An identified primary study conducted after the Wu et al meta-analysis [9] also indicated that MRI may be beneficial for targeted biopsy after HIFU [11]. While an additional study has shown that MRI can localize local recurrence after rP [12], it is unclear how this knowledge would change the radiotherapy volume or dose fractionation schedule. Additionally, there is no evidence to indicate that biochemical or survival outcomes would be improved as a result. An additional meta-analysis found that MRI has low sensitivity (39%; 95%CI, 22-56%) for detection of lymph node metastases from prostate cancer [13].

Interpretation of Evidence

According to the postoperative radiotherapy guideline jointly published by the American Urological Association and American Society of Radiation Oncology, patients with adverse pathological features, such as seminal vesicle invasive, extracapsular spread, or positive margins, and those with BC recurrence and no evidence of distant metastatic disease, should be offered postoperative radiation therapy (RT) [14]. In this guideline, BC recurrence was defined as a detectable or rising PSA value after surgery of >0.2ng/mL and a second confirmatory level >0.2ng/mL. Given that the vast majority of patients with recurrent disease after prostatectomy will have a PSA of less than 5ng/mL and the fact that salvage RT control rates are poor when PSA is greater than 2ng/mL [15], routine restaging investigations are not warranted.

Local salvage therapies, including prostatectomy and brachytherapy (BT) have been shown to have reasonable BC salvage rates of 54% to 61% [16,17], but generally worse genitourinary and gastrointestinal late side-effects compared with primary therapies, while salvage cryotherapy and HIFU appear to have inferior control rates [17,18]. Therefore, salvage prostatectomy or BT are reasonable options for selected, motivated, and informed patients. Appropriate patients will include those with biopsy-proven local recurrence and an absence of distant metastases, as results seem to be better when relapse PSA is less than 10ng/mL [16,17].

Due to the limited available evidence identified by the systematic review, plus the known data on available salvage therapies, the Working Group decided to summarize the identified diagnostic tests according to their appropriateness for use. The Working Group is concerned about the overuse of diagnostic tests that do not affect patient management. For example, if the treating oncologist suspects BC recurrence after treatment with rP and plans to treat with salvage RT, it is not clear whether a MRI-based diagnosis of local recurrence would affect this decision. Thus, for each diagnostic test, using a consensus process, the Working Group weighed the ability of the test to inform the next stage of treatment against the over-use of the test. Diagnostic tests are defined as usually appropriate, sometimes appropriate, or not usually appropriate in a clinical setting, based on the available evidence and its quality, as well as the clinical experience of the Working Group members.

RECOMMENDATION 4

In men who are not being evaluated through regularly scheduled clinic visits, a PSA test should be done if the following symptoms develop. Additionally, diagnostic imaging specific to the patient's symptom(s) may be indicated.

- Severe and progressive axioskeletal bone pain
- Unexplained weight loss
- Hematuria
- New urinary symptoms
  - Significant incontinence requiring changing of undergarments, pads, or diapers
  - Urgency
  - Obstructive symptoms
  - Voiding discomfort
  - Nocturia
- Swelling of legs
- New bowel symptoms
  - Rectal bleeding
  - Rectal pain
  - Urgency
  - Change in bowel movement
- Fatigue
  - Tiredness unrelated to sleep disturbance
  - Lack of energy
  - Weakness or lack of muscle strength
  - Physical, emotional, and/or cognitive exhaustion

Key Evidence

The literature search did not return any systematic reviews or studies that evaluated common symptoms of clinical prostate cancer recurrence.

Interpretation of Evidence

If men are receiving regular clinical follow-up visits, detection of BC recurrence by PSA should occur before clinical recurrence with associated symptoms. However, if men are not regularly followed, they may present with symptoms that could be consistent with clinical recurrence and require evaluation. Due to the lack of data, the Working Group decided to use a consensus process to list the symptoms of clinical recurrence in their expert opinion.

RECOMMENDATION 5

Men experience very specific and oftentimes long-lasting effects after their primary therapy, usually occurring more than three months after surgery or radiation, or during/after androgen deprivation therapy (ADT). Follow-up health care providers should be aware of the domains of quality of life potentially affected by treatment for prostate cancer and the management options available to combat them. Research surrounding management options is lacking. Included management options that are based on the clinical standard in Ontario or expert opinion of the Prostate Cancer Follow-up Expert Panel have been denoted with an asterisk (*). The symptoms listed are based on known profiles; however, individual men respond differently to treatments, resulting in individual side-effect profiles. To ensure optimal quality of life in these men, individual patient reported outcomes should be measured.

Side-Effect	Primary Treatment	Management Options
Sexual Dysfunction *A guideline focusing on the sexual health of cancer patients is under development (PEBC Guideline 19-6) and will provide more in-depth recommendations for sexual dysfunction outcomes.*		

Erectile dysfunction	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors as first line treatment* • Men who do not respond to PDE5 inhibitors will need more advanced treatments and should be referred to a urologist* • Men may be referred to penile rehabilitation programs, which include PDE5 inhibitors, vacuum constriction devices, intracorporal or intraurethral therapy, or placement of penile prostheses*
Loss of libido	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling • Testosterone therapy can be considered in men with signs and symptoms of testosterone deficiency and documented low serum testosterone levels provided their cancer is treated and without evidence of persistent or recurrent disease, and if prescribed by the treating oncologist after extensive review of the potential risks*
Anorgasmia	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling*
Dry ejaculate	Surgery, RT, and ADT	• Men should be educated on dry ejaculate*
Climaturia	Surgery, RT, and ADT	• Men should be provided education on self-management strategies, such as emptying the bladder before sexual relations, use of a condom, use of a penile constriction band, and Kegel exercises*
Penile shortening or curvature	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors, intraurethral and intracorporal prostaglandins, vacuum erection device, or penile prostheses*
Infertility	Surgery, RT, and ADT	• Men and their partner should be informed that men treated with rP will become infertile • Men and their partners should be informed that some men treated with RT may remain fertile, even when experiencing sexual dysfunction symptoms*
Urinary Dysfunction		
Obstructive symptoms	Surgery and RT	• Men should be referred to a urologist to determine whether bladder neck dilatation, transurethral resection, or clean intermittent catheterization may be necessary* • Selective alpha antagonists (not in men who underwent rP) may be prescribed*
Urgency symptoms	Surgery and RT	• If the man is able to completely empty his bladder, anticholinergic medications may be appropriate* • All refractory symptoms should result in a referral to a urologist for evaluation and escalation of therapy, if appropriate*
Hematuria	RT	• Men with hematuria should be referred to a urologist for evaluation*
Incontinence requiring urinary pads	Surgery and RT	• Men with persisted leakage impacting QoL should be referred to a urologist to evaluate the cause of incontinence (stress, overflow, etc)* • Exercise intervention including resistance, flexibility, and Kegel exercises may improve continence. Specialized physiotherapists may help patients with stress incontinence following rP • In men with post-prostatectomy incontinence who are unable to perform pelvic floor training, urethral slings or artificial urinary sphincters can be considered
Bowel Dysfunction		
Rectal bleeding	RT	• All men with rectal bleeding should be referred to a gastroenterologist for colonoscopy if not done within five years* • For men with rectal bleeding post-RT, referral to a gastroenterologist who has experience in managing RT proctitis is

		recommended. The anterior rectum should only be biopsied when absolutely necessary as this can cause a fistula of the rectum* • For men with bleeding secondary to RT proctitis, the following strategies may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (Salofalk (mesalamine) suppositories, topical formalin or argon plasma laser treatments) ○ Refractory RT proctitis should be considered for hyperbaric oxygen
Urgency and frequency symptoms	RT	• For men with urgency and frequency symptoms, the following options may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (antidiarrheals, anticholinergics) ○ Pelvic floor muscle therapy
Other Physical Side-Effects		
Anemia	ADT	• Investigation for common sources of anemia should be considered*
Body composition alterations	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Fatigue	Surgery, RT, and ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Gynecomastia/ Mastodynia	ADT	• In severe cases, surgical excision can be considered and patients should be referred to the appropriate specialist *
Hot flushes	ADT	• Treatment with diethylstilbestrol, megestrol acetate, venlafaxine, cyproterone acetate, and medroxyprogesterone have been shown to decrease number of hot flushes, but should be used with caution because treatment with these medications have been associated with side-effects (e.g., gynecomastia, depression, weight gain, muscle spasms, insomnia, nausea, elevated blood pressure)
Physical activity/ function	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Bone health	ADT	• This outcome described in PEBC Guideline 3-14v2 (in development)
QoL and Psychosocial Side-Effects		
Cognitive side-effects	ADT	• Healthcare provider may consider neurocognitive assessment*
Psychological distress (depression and anxiety)	Surgery, RT, and ADT	• In-office psychological therapy and pharmacotherapy as appropriate • Recommendations for depression of cancer survivors are described in PEBC Guideline 19-4v2
General QoL and Psychosocial sequelae	Surgery, RT, and ADT	• During scheduled follow-up clinical visits, the psychosocial status of men should be assessed and distress should result in referral to specialized psychosocial care* • Patients should be encouraged to participate in an exercise program ○ Strategies more thoroughly described in PEBC Guideline 19-5 (in development) • Referral to applicable support groups for coping training for couples, as well as social and emotional QoL well-being, may be considered

Abbreviations: ADT, androgen deprivation therapy; PDE5, phosphodiesterase type 5; QoL, quality of life; rP, radical prostatectomy; RT, radiation therapy.

Key Evidence

Treatment-related side-effects were divided into those caused by surgery or any form of RT, and those caused by ADT.

Surgery and RT: An identified systematic review [19], as well as several more current cohort studies [20-26], found that the three most common treatment-related side-effects after curative-intent therapy with surgery or any form of RT are bowel, urinary, and sexual dysfunction. Erectile dysfunction is also common, with an identified meta-analysis indicating that 58% of men report erectile function recovery (EFR) after surgery [27]. Additional cohort studies found that men recovered orgasmic function within 24 months of bilateral nerve-sparing radical retropubic prostatectomy [28], while multiple domains of the International Index of Erectile Function (IIEF) and Expanded Prostate Index Composite (EPIC) QoL questionnaires remain reduced through 24 to 36 months of follow-up after treatment with BT [29,30]. Conversely, a failed-to-accrue phase III trial that collected QoL data reported that men treated with BT experienced more favourable erectile dysfunction recovery than men treated with rP [31]. The identified literature also indicated that after primary therapy for prostate cancer, men have increased fatigue [32], report worse QoL domains [33], and almost 20% are depressed [34]. Intervention strategies that include exercise aided men experiencing fatigue and declining QoL domains [35,36], while psychosocial counselling interventions improved erectile dysfunction [37], and both psychosocial counselling and coping skills training, improved psychological well-being [38,39]. Finally, for urinary dysfunction, cohort studies indicated that men treated with both rP and BT experience urinary incontinence and irritation [30,31], with BT treatment demonstrating more favourable recovery [31]. A meta-analysis assessed male slings and found that most report similar efficacy for improvement and may be a valid option [40], while cohort studies found that pelvic floor muscle training resulted in increased continence rates [41,42].

ADT: When studies that focused exclusively on men undergoing ADT were analyzed, it was determined that these men deal with additional treatment-related side-effects, such as anemia [43], body composition alterations [44-47], cognitive side-effects [48], hot flushes [49], and a decline in physical function [50]. Exercise interventions with this specific subset of patients improved muscle strength [36,51,52] and mass [36], cardiovascular fitness [51,52], lean body mass [51] and fatigue levels [51], as well as social domains of QoL tools [36,52]. A final systematic review evaluated drug therapy for hot flushes and found that diethylstilbestrol, megestrol acetate, and cyproterone acetate resulted in 75% decrease in the number of hot flushes; however, all have adverse side-effect profiles [53]. The systematic review also indicated that venlafaxine and medroxyprogesterone may reduce the incidence of hot flushes, but the results have not been verified in any large randomized controlled trial (RCT) [53]. Many of the studies included in the systematic review did not evaluate the long-term side-effect profiles of the men receiving treatment for hot flushes, but those that did noted adverse effects which included depression, nausea, gynecomastia, weight gain, muscle spasms, insomnia, and elevated blood pressure [53].

Interpretation of Evidence

Following curative-intent treatment, men experience very specific and oftentimes long lasting effects from their treatment. The literature search designed to inform this recommendation focused on both studies that reported rate of side-effect bother and studies that evaluated management strategies to combat the side-effects. Studies that reported rate of bother employed a prospective cohort design and were universally of low quality; however, for these outcomes, this is the best available evidence. For evaluation of management strategies, only RCTs were included. Although these studies were high quality, very few were identified.

For ease of use, the treatment side-effects have been organized to indicate which primary therapy may result in the side-effect and any identified management option.

Prevalence rates for how often each side-effect occurs after a specific primary therapy were intentionally not included in the recommendation. For these studies, data are difficult to compare and summarize because different studies recruited different populations, used different instruments to assess the side-effects, and in many instances, defined the outcomes differently. Each side-effects included in the recommendation table has been reported by a percentage of the population following treatment with each indicated primary therapy.

Given that few management options were evaluated in the literature, the Working Group weighed the benefits and harms of providing consensus guidance for side-effect management without evidence. It was decided that due to the broad intended users for this guideline, providing guidance based on the clinical standard and expert opinion outweighed the negligible harms introduced by the suggested management options.

RECOMMENDATION 6

No diet plan can be recommended because no diet plan or food supplement has been associated with improved cancer outcomes.

Key Evidence

An identified systematic review evaluated the literature that focused on effects of diet and found very weak evidence for a decrease in PSA with low-fat vegan diets, soy beverages, and lycopene supplementation [54]. An RCT that assessed a holistic intervention of intensive diet, exercise, and meditation found that the intervention resulted in decreased saturated fatty acids and total caloric intake, but no change in PSA level [55].

Interpretation of Evidence

The Working Group was unable to provide a recommendation for a specific comprehensive lifestyle management intervention for men following prostate cancer treatment. For this research question, PSA reduction was valued more highly than healthy dietary intake and although exercise is recommended for prostate cancer survivors (see Recommendation 5), there is currently no association between exercise, diet, or food supplement and any cancer outcome improvement.

RECOMMENDATION 7

For prostate cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by the treating oncologist, urologist, family physician, nurse practitioner, or hospital-based nurses. Models of care are described more thoroughly in PEBC Guideline 26-1.

Qualifying Statements for Recommendation

- All healthcare practitioners that provide PSA surveillance should manage PSA as per the current CCO Prostate Cancer Pathway.
- Although the identified literature only evaluated hospital-based nurse-led care and shared care within the hospital setting, expert opinion supports family physicians being involved in all survivorship care models.
- With the greater emphasis on a person-centred approach to care, a multidisciplinary approach to survivorship, which includes a psychosocial focus to recovery, is recommended. Although the shared care model identified by the literature did not include a psychosocial intervention focus, in order to provide person-centred care, expert opinion supports multiple disciplines being involved in shared care models.

Key Evidence

Two RCTs evaluated follow-up care models, with one comparing nurse-led care with traditional urologist-led care [56], and the other comparing a shared care model with usual care [57]. The nurse-led follow-up study indicated that nurse-led care was not inferior to urologist-led care when lag time, amount of hospital care time, depression, anxiety, and satisfaction with care outcomes were compared [56]. The shared care model randomized men to usual follow-up with the treating oncologist, or follow-up visits with the treatment oncologist plus a physical therapist and an oncology nurse, resulting in improved urinary scores and physical component domains of QoL, but no change in incontinence, bowel or sexual scores compared with the usual care group [57].
Interpretation of Evidence
Unfortunately, although the nurse-led follow-up study [56] was of high methodological quality, the study was conducted more than 10 years ago and PSA testing was not mandatory in either arm. The Working Group considered the limited evidence from both studies, plus the patient management limitation of the nurse-led study, and accepts that this is the best available evidence. Additionally, for this research question, QoL, the holistic needs of survivors and satisfaction with care are highly valued. Thus, the Working Group believes that a weak recommendation for health care provided by non-specialists is warranted. The recommendation only includes hospital-based nurses because these nurses are more readily able to order the required follow-up tests.

RELATED GUIDELINES

- PEBC EBS No.: 26-1: Sussman J, Souter LH, Grunfeld E, Howell D, Gage C, Keller-Olaman S, et al. Models of care for cancer survivorship. Toronto (ON): Cancer Care Ontario: 2012 Oct. Program in Evidence-Based Care Evidence-Based Series No.: 26-1. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/246
- PEBC EBS No.: 3-14v2: Alibhai S, Zukotynski K, Walker-Dilks C, Emmenegger U, Finelli A, Morgan S, et al. Bone health and bone targeted therapies for prostate cancer – under development
- PEBC EBS No.: 19-5: Working Panel and the Exercise for Cancer Patients Expert Panel. Exercise for cancer patients – under development

UPDATING

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

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CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix 1.

Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For information about this document, please contact Andrew Matthew,
the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer: Guideline Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO, supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated Programs is editorially independent from the OMHLTC.

Justification for Guideline.

There is substantial variability in the care provided to prostate cancer survivors, both in terms of prostate-specific antigen (PSA) testing timing and diagnostic imaging, as well as management strategies for long-term effects from curative-intent prostate cancer therapy.

Guideline Developers

This guideline was developed by the Prostate Cancer Follow-up GDG (Appendix 1), which was convened at the request of the Survivorship Program.

The project was led by a small Working Group of the Prostate Cancer Follow-up GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, medical oncology, surgical oncology, radiology, psychology, both nursing and advanced practice nursing, patient representation, and health research methodology. Other members of the Prostate Cancer Follow-up GDG served at the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the PEBC *Conflict of Interest Policy*.

Guideline Development Methods

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [58]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [59] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*.

Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

The PEBC external review process includes a Targeted Peer Review that is intended to obtain feedback on the draft report from several content experts, and a Professional Consultation, in the form of a brief online survey, that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: Inventory of Cancer Guidelines (www.cancerguidelines.ca), National Guidelines Clearinghouse (www.guideline.gov).
- Guideline developer websites: Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), American College of Radiology (ACR), and American Cancer Society (ACS).

The following criteria were used to select potentially relevant guidelines:

- Guidelines published after the year 2010.
- Guidelines that included a systematic review of the literature that covered at least one of the outcomes of interest.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [59].

- A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4).

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- Waseem Hijazi for conducting a data audit.
- Sara Miller for copyediting.

Guideline 26-4: Section 4

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer: Evidence Review

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men in Canada and the third leading cause of cancer-related death in men [60]. It is estimated that there will be 23,600 new cases in 2014 and 4,000 deaths [60]. Based on the tumour stage, histology, tumour grade and preferences of the patient, men with prostate cancer are treated with curative-intent, using radical prostatectomy (rP), radiation therapy (RT), androgen deprivation therapy (ADT) and active surveillance. Unfortunately, in addition to late effects of the disease, these curative-intent treatments for prostate cancer leave many men with long-term issues including urinary incontinence, sexual dysfunction, and bowel dysfunction, as well as adverse effects in psychosocial domains of health-related quality of life (QoL).

Even though rP and RT are provided as curative therapy, 30% to 50% of men will develop biochemical (BC) recurrence within five years [61]. Biochemical recurrence is determined by a rise in prostate-specific antigen (PSA) in serum and, in general, no imaging study is necessary after curative treatment for localized prostate cancer unless PSA is elevated. Once BC recurrence is detected by PSA, appropriate diagnostic tests are utilized to determine the location and extent of recurrence or progression so that further disease management may be planned. Thus, PSA testing schedules need to be designed to detect a diagnosis of recurrence or progression at a stage that is potentially curable, while not being overprescribed and negatively impacting prostate cancer survivor QoL.

There is no high-quality evidence to support one surveillance schedule for PSA testing, which results in great variability in guideline recommendations from different organizations. Similarly, there is little high-quality evidence related to which diagnostic tests should be performed on detection of BC recurrence. The current authors sought to create an evidence-based follow-up protocol for men who have received curative-intent treatment following a diagnosis of prostate cancer. The authors also sought to address the level of bother and available management techniques for the commonly experienced long-term effects of prostate cancer therapy.

To make recommendations as part of a clinical practice guideline, the Working Group of the Prostate Cancer Follow-up Guideline Development Group developed this evidentiary base upon which those recommendations are based. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

In survivors who have received curative-intent treatment for prostate cancer:

1. What is the appropriate timing for PSA testing?
2. After biochemical recurrence, what diagnostic tests are effective at detecting progression or occurrence of metastasis and how do they affect patient management? At what PSA threshold are these tests effective? What are the most common symptoms of clinical recurrence?
3. What are the rates and level of distress for common late side-effects of prostate cancer treatment? What interventions are available to manage late treatment effects?

4. Is there a relationship between the model of follow-up care in terms of care provider, setting, and availability of patient navigator or mentor, and the effective detection and management of progression or metastatic disease?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered to be eligible for inclusion. An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for existing systematic reviews on the follow-up care of curatively treated prostate cancer patients. OVID was searched from 2000 to week 32 of 2014 using the following keywords: "prostate cancer", "surveillance", "follow up", "after care", "survivor", "recurrence", "side effects" and "late effects". In addition, websites/databases of specific guideline developers and systematic review producers were also searched, using the same keywords and for the same time period. These websites/databases included: Cochrane Database of Systematic Reviews (CDSR), Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU) and American College of Radiology (ACR). Only the most recent systematic review was chosen for further evaluation when multiple reviews were found with overlapping outcomes.

Identified systematic reviews were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of this guideline. Systematic reviews that were found to be directly relevant to this guideline, and therefore potential foundations for this evidence review, were assessed using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool [62]. The results of the assessments were used to determine whether or not an existing systematic review could be incorporated.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base were reported in the reference list, but not further described or discussed.

Search for Primary Literature

Assuming that no existing systematic review was identified, or that identified reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. This review would be reduced in scope, such as a reduction in subject areas covered, time frames covered, etc., based on the scope of incorporated existing reviews. The criteria described below are written assuming no existing reviews would be incorporated.

Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles related to follow-up care of curatively treated prostate cancer patients, published between 2000 and week 33 of 2014. Due to the variation in the research questions, separate searches were conducted for each question. Common to each search were terms to retrieve articles on prostate cancer and survivor follow-up care. A complete literature search strategy for each question can be found in Appendix 2. In addition to the MEDLINE and EMBASE database searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

All hits from the OVID literature search were input into reference management software (EndNote X6), where duplicate citations were identified and removed. For each research question, only full publications of patients treated with curative-intent therapy for prostate cancer were included. Due to the limited amount of data that was expected to be found and the inability to conduct randomized trials for some of the outcomes of interest, the Working Group searched for randomized controlled trials (RCTs), as well as non-randomized studies. To limit the amount of bias introduced by non-randomized studies, non-randomized studies were only included for outcomes when it was deemed necessary. The study design inclusion criteria and reasons for non-randomized study inclusion/exclusion for each research question by outcome can be found in Appendix 3. For non-randomized studies, retrospective cohort and case series designs were excluded *a priori*. Additionally, prospective cohort studies that enrolled less than 30 patients, as well as studies that enrolled a mixed population and not exclusively prostate cancer survivors, were excluded. Letters and editorials, as well as studies not written in English were excluded from the evidentiary base.

A review of the titles and abstracts that resulted from the search was performed by one reviewer (LS) and verified by a second (AM). For those studies that warranted full-text review, one reviewer (LS) determined whether the inclusion and exclusion criteria were met. The list of proposed studies was verified by a second reviewer (AM) and a final list was approved by the entire Working Group.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by one reviewer (LS) and checked by a second reviewer (AM). All extracted data and information were audited by an independent auditor. Important quality features, such as study design, comparison type, group allocation method, recruitment method, and sources of funding, for each study were extracted. Since randomized and non-randomized, as well as diagnostic studies were included in this review, no specific quality assessment tool was used. Instead, the above quality features were extracted. For diagnostic studies, the quality features extracted were based on a modified form from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. For non-randomized studies, the study designs were defined according to the Cochrane Collaborations schema (Handbook Table 13.2a). The Working Group anticipated that the non-randomized studies would not carry the weight of randomized when creating recommendations, but agreed that this was the best evidence to be found.

Synthesizing the Evidence

Due to the anticipated large variation in study quality and outcomes measured, pooling the data was not planned.

RESULTS

Search for Existing Systematic Reviews

The search for existing systematic reviews identified 80 reviews on the follow-up care of curatively treated prostate cancer patients. Of the 80 systematic reviews identified by the literature search, only 19 met the inclusion criteria, were assessed with the AMSTAR tool and are included in this evidence summary. The AMSTAR tool assesses 11 important features of systematic review methodology. Assessment of the 19 included systematic reviews with the AMSTAR tool can be found in Appendix 4. No systematic review was excluded based on AMSTAR

assessment. However, the AMSTAR tool was designed based on assessing systematic reviews of RCTs and most of the assessed reviews included studies of a lower design quality. Additionally, the majority of the assessed reviews did not fulfill the AMSTAR assessment of publication bias domain.

Search for Primary Literature

The primary literature systematic review was used to address outcomes of interest not covered by the included systematic reviews. Where systematic reviews existed, a search of the primary literature was conducted from the end date of the search in the reviews.

Literature Search Results

Forty-three studies were identified that met the inclusion criteria (Figure 1). Table 1 summarizes the number and types of studies included per research question for each outcome of interest. Both systematic reviews and primary studies were identified for all Research Questions except for Question 1 (Table 1). For Research Question 2, systematic reviews that evaluated magnetic resonance imaging (MRI) for detection or local recurrence and both MRI and computed tomography (CT) for detection of lymph node metastases were identified, so the primary literature was searched for studies using these modalities after the search dates of these systematic reviews, as well the entire original planned search period (2000 – present) for other imaging modalities (Table 1). For Research Questions 3 and 4, where there were multiple outcomes of interest, the primary literature was searched for studies after the search date for those identified systematic reviews that addressed specific outcomes. For outcomes not addressed by systematic reviews, the primary literature was searched for studies within the original planned search dates (Table 1).

Potentially relevant citations identified by initial electronic search:

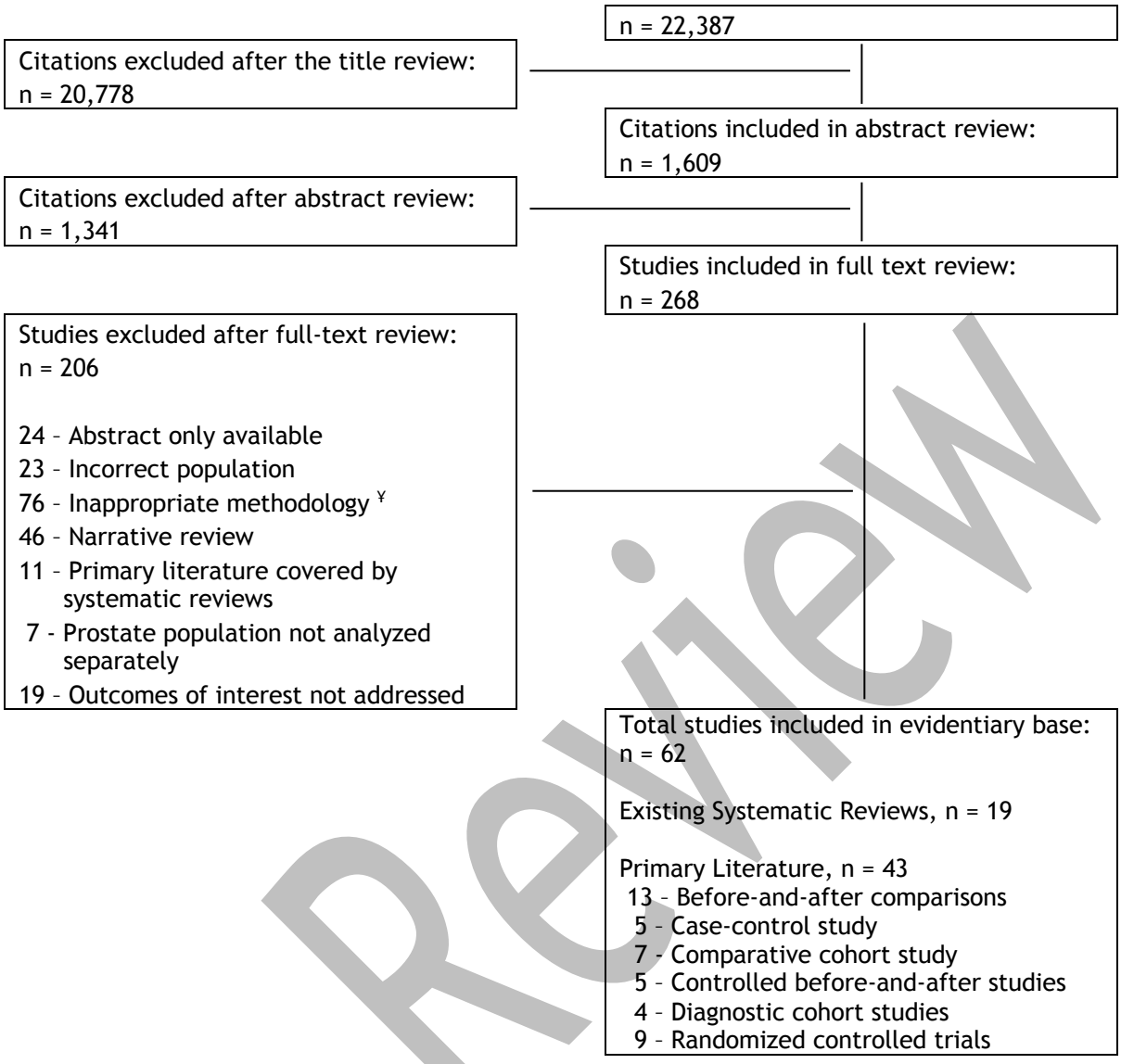

Figure 1. Selection of systematic reviews and primary literature from the search results of MEDLINE and EMBASE.

¥Studies of inappropriate methodology including retrospective studies, surveys, quality of life tool validation studies, preliminary reports, studies that were non-comparative and non-longitudinal, studies enrolling less than 30 patients and prospective cohort studies for outcomes with randomized controlled trial only as inclusion criteria.

Table 1. Studies selected for inclusion according to research question and outcome of interest.

Research Question	Outcome	Number of systematic reviews and studies by type (reference[s])
Q1. Appropriate timing for PSA testing	PSA testing frequency and timing	None
Q2. Diagnostic tests after biochemical recurrence and symptoms of recurrence	Imaging tests if PSA rise	3 – SR [6,9,13] 1 – RCT [5] 2 – CPC [3,4] 4 – Diagnostic cohort study [7,8,11,12]

Research Question	Outcome	Number of systematic reviews and studies by type (reference[s])
	Symptoms of clinical recurrence	None
Q3. Late treatment effects – rate, level of bother and management	Anemia	1 – SR [43]
	Body composition alteration	1 – SR [44] 2 – CCS [45,46] 1 – BAC [47]
	Bowel or gastrointestinal dysfunction	1 – SR [19]* 1 – CPC [20] 3 – BAC [21]*[25]*[22]*
	Cardiovascular side effects	None
	Cognitive side effects	1 – SR [48]
	Depression	1 – SR [34] 1 – CCS [63] 1 – CPC [64] 1 – CBA [33]*
	Fatigue and exercise	2 – SR [36,51] 2 – RCT [35,52] 1 – BAC [32]
	Gynecomastia	1 – SR [65]
	Health-related QoL	3 – CBA [66]*[38,67] 1 – BAC [21]* 2 – CPC [30,31]
	Hot flushes	1 – SR [53] 1 – BAC [49]
	Osteoporosis	None – included in EBS 3-14
	Physical function	1 – CCS [50]
	Psychosocial or emotional problems	1 – SR [68] 1 – RCT [69] 2 – CBA [33,70]* 3 – BAC [71-73]
	Sexual dysfunction	4 – SR [19,27,37]*[74]* 4 – BAC [21,28,29]*[22]*
	Urinary dysfunction	3 – SR [19,40]*[74]* 2 – RCT [41,75] 1 – CCS [26] 5 – BAC [22-24]*[21]*[25]* 1 – CPC [42]
Q4. Models of follow-up care	Available psychosocial care	None
	Holistic needs (exercise, nutrition, return to work)	2 – SR [39,54] 1 – RCT [55]
	Nurse intervention	1 – RCT [56]
	Shared care model	1 – RCT [57]
	Patient care satisfaction	1 – CBA [76]

Abbreviations: BAC, before-and-after comparison; CBA, controlled before-and-after study; CCS, case-control study; CPC, comparative cohort study; EBS, Evidence-based Series; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomized controlled trial; SR, systematic review.
*Denotes studies that appear under more than one outcome.

Study Design and Quality

The primary literature returned 43 studies that met the inclusion criteria. A description of the study design and quality of the studies can be found in Appendix 5. The evidentiary base included nine RCTs, four diagnostic cohort studies and 30 prospective cohort studies (Figure 1, Table 1). When evaluating the quality of diagnostic studies, the PEBC endorses the methods

described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. All four of the diagnostic studies [7,8,11,12] used a cohort recruitment method and fully paired comparison model (all patients received all interventions), minimizing selection bias (Appendix 5). All four diagnostic cohort studies were included in the evidentiary base.

It is well recognized that RCTs provide the best quality evidence and as such, the nine RCTs included in the evidentiary base more strongly informed the recommendations on the follow-up care of prostate cancer survivors. The 30 non-randomized studies were further defined using the Cochrane Collaborations schema (Handbook Table 13.2a) as before-and-after comparisons (13 studies), controlled before-and-after studies (five studies), comparative cohort studies (seven studies) and case-control studies (five studies) (Table 1, Appendix 5). All the included non-randomized studies used prospective data collection and employed a comparison either within the group across time or between the survivor group and a control group (Appendix 5). The controlled before-and-after studies made comparisons between groups as well as across time, resulting in less risk to bias than the before-and-after comparisons, which only compared across time within the group (Appendix 5). However, all non-randomized studies carry an unclear risk of bias, which was considered when drafting the recommendations. In addition, the studies looking at QoL of prostate cancer survivors mostly relied on the use of self-reported QoL tools, which may have resulted in an increased risk of recall bias in these studies, because survivors were required to recall symptoms experienced over a period of time. All nine RCTs and 30 non-randomized studies were included in the evidentiary base.

Question 1: What is the appropriate timing for PSA testing?

The literature search did not return any systematic reviews or prospective studies that evaluated appropriate timing for PSA testing after curative-intent therapy.

Question 2: After biochemical recurrence, what diagnostic tests are effective at detecting progression or occurrence of metastasis? What are the common symptoms of symptomatic recurrence?

The search for existing systematic reviews identified three systematic reviews with meta-analysis to inform this research question. A systematic review of the primary literature, designed to inform outcomes not informed by the existing systematic reviews, identified one RCT, two comparative cohort studies, and four diagnostic cohort studies. All included systematic reviews and primary studies are fully detailed in Table 2 and summarized in the text.

Imaging of Prostate Cancer Progression and Metastasis

Bone Scan (Table 2)

One RCT was identified that evaluated at which PSA level bone scans should be recommended for men after treatment for early prostate cancer [5]. This study was a secondary objective of an RCT, which compared bicalutamide daily with placebo, in addition to standard care [77]. The study was conducted in North America, Europe, and Scandinavia and found that bone scans are very rarely positive at PSA levels below 5ng/mL.

MRI (Table 2)

A meta-analysis conducted by Wu et al [9] assessed the effectiveness of MRI for the detection of local recurrence and found that MRI was able to accurately detect local recurrence with a high sensitivity and specificity after both rP and external-beam radiation therapy (EBRT).

A third meta-analysis, conducted by Hovels et al [13], compared the diagnostic accuracy of CT and MRI for lymph node metastases detection and found that both imaging modalities demonstrated poor diagnostic accuracy.

A diagnostic cohort study evaluated endorectal MRI for detection and localization of recurrent disease in men with BC recurrence after rP [12]. Enrolled men had presented with rising PSA level and were being referred for salvage RT consideration. The study evaluated T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast-enhanced (DCE) MRI and found that endorectal MRI was able to accurately detect local recurrences, with T2W showing the highest diagnostic accuracy.

A second diagnostic cohort study evaluated MRI and MRI targeted biopsy compared with routine biopsy for detection of local recurrence after prostate high-intensity focused ultrasound (HIFU) [11]. Of the 77 suspicious areas found by MRI, 41 (53.2%) lesions in 40 patients were positive for cancer at biopsy. The probability of finding viable cancer on biopsy cores was higher for targeted biopsies than for routine biopsies.

Positron Emission Tomography/CT (Table 2)

A meta-analysis evaluated the diagnostic performance of choline positron emission tomography (PET) or PET/CT in men with a rising PSA level after primary prostate cancer therapy [6]. Evangelista et al [6] found that choline PET and PET/CT showed high sensitivity and specificity for detection of locoregional recurrence and distant metastatic disease in men with BC recurrence. A second meta-analysis, conducted by Hovels et al [13], compared the diagnostic accuracy of CT and MRI for lymph node metastases detection and found that both imaging modalities demonstrated poor diagnostic accuracy.

Two diagnostic cohort studies evaluated the diagnostic accuracy of PET/CT for detection of recurrent disease and metastasis in men with BC recurrence. The study conducted by Jadvar et al [7] compared sodium fluoride (NaF) and fluorodeoxyglucose (FDG) radiotracers, while the study conducted by Beheshti et al [8] evaluated the potential of 18F-fluoromethylcholine (FCH). Irrespective of radiotracer, PET/CT demonstrated limited ability to detect recurrent disease and metastases [7,8].

Bone Scan versus MRI and/or PET/CT (Table 2)

A comparative cohort study investigated the ability of whole body MRI (WBMRI) to replace the two-step system of bone scan with targeted x-rays plus CT (BS/TXR + CT) for detection of prostate cancer metastases [3]. While both WBMRI and BS/TXR demonstrated similar high specificities for detection of bone involvement, WBMRI demonstrated an increased sensitivity compared with BS/TXR. When evaluating detection of lymph node metastases, analysis based on logistic regression models indicated that WBMRI was neither significantly superior nor significantly inferior to CT.

A second comparative cohort study evaluated the efficacy of fluoroethylcholine (FECH) PET/CT for detection of bone metastases compared with bone scan [4]. The study found that imaging with FECH PET/CT did not significantly increase diagnostic accuracy beyond a bone scan.

Table 2. Imaging after PSA rise.

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
Bone Scan					
RCT					
Warren et al, 2006 [5]	• n = 8,113	• <5ng/mL vs. ≥5ng/mL	• rP, RT, or watchful waiting	• Confirmed by x-ray	• Enrolled patients had bone scans irrespective of PSA level at set intervals during follow-up • PSA levels were determined at time of bone scan and divided into subgroups of <5, 5-<10, 10-<20, 20-<50, ≥50ng/mL • Incidence of positive bone scans were calculated for each PSA level subgroup • At PSA levels lower than 5ng/mL, the incidence of positive bone scans was low (0.2 – 1.4%) for men treated with rP or RT • At PSA levels above 5ng/mL, the incidence of positive bone scans appeared to increase; however, the group sizes were much smaller, making it impossible to determine the significance with increasing PSA
Cohort Studies					
Lecouvet et al, 2012 [3]	• n = 100	• Not reported	• Non-defined primary therapy or ADT	• Best value comparator (BVC) – consensus review of all imaging by four reviewers	• Evaluated ability of WBMRI to replace two-step BS/TXR + CT for detection of metastases • Enrolled men at high risk for metastasis, with 44 enrolled at initial prostate cancer diagnosis with a Gleason score of ≥8 and/or a PSA of ≥20ng/mL, 21 enrolled with a rapidly rising PSA level after local therapy, and 35 enrolled with rising PSA while undergoing ADT • WBMRI was able to identify metastases in 11% of patients (5/44) who had a negative BS reading and 35.7% (5/14) with an equivocal BS • For bone metastases, WBMRI showed increased sensitivity (98%; 95%CI, 90-100%) compared with BS/TXR readings (86%; 95%CI, 74-94%; p=0.03) while both modalities showed equivalent specificity (98%; 95%CI, 89-100% for both) • For lymph node metastases, logistic regression models indicated WBMRI was neither superior nor inferior to CT (p>0.05)
Takesh et al, 2012 [4]	• n = 37	• Range: 0.3 – 21ng/dL	• rP, RT, or ADT	• Pathologic confirmation unavailable. Confirmation	• Compared efficacy of FECH PET/CT to bone scan for detection of bone metastases in men with BC recurrence • 9 of the enrolled men were still undergoing ADT or chemotherapy

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
				by clinical follow-up and matched CT or MRI findings	• Of 37 enrolled men with BC recurrence, 18 (49%) were confirmed to have bone involvement • Men positive for bone involvement had higher (p=0.02) median PSA levels (4ng/dL; range, 1 – 21ng/dL) compared with men without bone involvement (median, 1.5ng/dL; range, 0.3 – 19ng/dL) • FECH PET/CT demonstrated a sensitivity of 83.3% and specificity of 100%. NPV was 86.3% and PPV was 100% • Bone scan demonstrated a sensitivity of 94.4% and specificity of 89.4%, with a PPV of 89.4% and an NPV of 94.4%
CT Scan					
Systematic Review with meta-analysis					
Hovels et al, 2008 [13]	• Pooled 24 studies	• Not reported	• Not reported	• Histo-pathologic analysis	• Both CT and MRI demonstrated poor pelvic lymph node metastases detection accuracy • CT scan able to detect lymph node metastases with a sensitivity of 42% (95%CI, 26-56%) and a specificity of 82% (95%CI, 80-83%) • MRI able to detect lymph node metastases with a sensitivity of 39% (95%CI, 22-56%) and a specificity of 82% (95%CI, 79-83%)
MRI					
Systematic Reviews with meta-analysis					
Wu et al, 2013 [9]	• Pooled 14 studies	• Mean: 2.29ng/mL • Range: 0.84 – 6.36ng/mL	• rP only: 5 studies • EBRT only: 7 studies • Either rP or EBRT: 2 studies	• Histo-pathologic analysis and clinical follow-up	• Assessed effectiveness of MRI for detection of local recurrence • After rP, MRI was able to detect local recurrence with 82% sensitivity (95%CI, 79-86%) and 87% specificity (95%CI, 81-92%) • After EBRT, MRI was able to detect local recurrence with 82% sensitivity (95%CI, 75-88%) and 74% specificity (95%CI, 64-82%) • DCE-MRI more accurate than T2W after rP and EBRT
Hovels et al, 2008 [13]	• Pooled 24 studies	• Not reported	• Not reported	• Histo-pathologic analysis	• Both CT and MRI demonstrated poor pelvic lymph node metastases detection accuracy • CT scan able to detect lymph node metastases with a sensitivity of 42% (95%CI, 26-56%) and a specificity of 82% (95%CI, 80-83%)

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
					• MRI able to detect lymph node metastases with a sensitivity of 39% (95%CI, 22-56%) and a specificity of 82% (95%CI, 79-83%)
Cohort Studies					
Lecouvet et al, 2012 [3]	• n = 100	• Not reported	• Non defined primary therapy or ADT	• Best value comparator (BVC) – consensus review of all imaging by four reviewers (agreement measured by Cohen's κ coefficient)	• Evaluated ability of WBMRI to replace two-step BS/TXR + CT for detection of metastases • Enrolled men at high risk for metastasis, with 44 enrolled at initial prostate cancer diagnosis with a Gleason score of ≥8 and/or a PSA of ≥20ng/mL, 21 enrolled with a rapidly rising PSA level after local therapy, and 35 enrolled with rising PSA while undergoing ADT • WBMRI was able to identify metastases in 11% of patients (5/44) who had a negative BS reading and 35.7% (5/14) with an equivocal BS • For bone metastases, WBMRI showed increased sensitivity (98%; 95%CI, 90-100%) compared to BS/TXR readings (86%; 95%CI, 74-94%; p=0.03) while both modalities showed equivalent specificity (98%; 95%CI, 89-100% for both) • For lymph node metastases, logistic regression models indicated WBMRI was neither superior nor inferior to CT (p>0.05)
Liauw et al, 2013 [12]	• n = 88	• Median: 0.30ng/mL • Interquartile range: 0.19-0.72ng/mL	• rP	• Study noted no validated system, so men were scored as 0-4 based on the presence of abnormalities on all scans	• Compared T2W, DWI and DCE MRI for local recurrence detection • Men received all scans • T2W-MRI accurately detected the most local recurrences, followed by DCE and then DWI • 37% of men with PSA over 0.30ng/mL tested positive for local recurrence, compared with 13% of men with PSA levels ≤0.30ng/mL
Rouviere et al, 2010 [11]	• n = 59	• Mean at enrollment: 2.67 ± 2.05ng/mL	• HIFU as primary therapy or as second after EBRT	• Transrectal biopsy	• Men with BC recurrence referred for MRI before transrectal biopsy • Evaluated T2W and DCE MRI for detection of local recurrence • All enrolled men underwent T2W and DCE MRI followed by biopsy by two operators

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
					• Operator 1 was blinded to the MRI results and performed random colour Doppler-guided biopsies to represent a routine biopsy • Operator 2 obtained up to three cores per suspicious area identified by MRI, to represent a targeted biopsy • Probability of finding viable cancer on biopsy cores was higher for targeted biopsies than for routine biopsies (19% vs. 7%; p<0.001), with an odds ratio of 3.35 (95%CI, 3.05-3.64) • 53.2% of suspicious areas identified by MRI were confirmed as cancer upon biopsy
PET/CT					
Systematic Review with meta-analysis					
Evangelista et al, 2013 [6]	• Pooled 19 studies	• Not reported	• Not reported	• Pathology or common imaging modality	• Evaluated diagnostic performance of choline PET or PET/CT for detection of locoregional or distant metastases after BC recurrence • Choline PET/CT able to detect recurrence in all sites of disease with a sensitivity of 85.6% (95%CI, 82.9-88.1%) and specificity of 92.6% (95%CI, 90.1-94.6%) • Choline PET/CT able to detect lymph node metastases with a sensitivity of 100% (95%CI, 90.5-100%) and specificity of 81.8% (95%CI, 48.2-97.7%) • Choline PET/CT able to detect prostatic fossa relapse with a sensitivity of 75.4% (95%CI, 66.9-82.6%) and specificity of 82.0% (95%CI, 68.6-91.4%)
Cohort Studies					
Jadvar et al, 2012 [7]	• n = 37	• Median: 3.2ng/mL • Range: 0.5 - 40.2ng/mL	• rP or EBRT	• Clinical follow-up and further imaging (bone scan, regional MRI, or contrast-enhanced CT of chest, abdomen or pelvis)	• Compared ability of NaF and FDG PET/CT to detect occult metastatic disease in men with BC recurrence • Men underwent PET/CT scans with both radiotracers on two separate days in random order within one week • Scans were read by two experienced radiologists who were blinded to the other paired scan • Irrespective of radiotracer, PET/CT had a PPV of 64% and a NPV of 73% • Median PSA levels for positive PET/CT was 4.4ng/mL and 2.9ng/mL for negative PET/CT scans (p=0.072)

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
Beheshti et al, 2013 [8]	• n = 250	• Mean: 46.9 ± 314.7ng/mL • Range: 0.2 – 4,692ng/mL	• rP, RT or ADT	• Histopath-ologic findings (4.4% of men), increased FCH uptake in follow-up PET studies, or verified by bone scan	• Evaluated diagnostic accuracy of choline PET/CT for detection of recurrent disease or distant metastases • FCH PET/CT correctly diagnosed malignant lesions in 74% (n=185/250) of enrolled men but was negative for 26% of cases (n=65/250) • Scan sensitivity was 77.5% for trigger PSA levels of more than 0.5ng/mL, 80.7% for 1.0ng/mL, 85.2% for 2.0ng/mL and 92.8% for trigger PSA level of at least 4ng/mL (p<0.001) • Sensitivity was 33% in patients with a PSA level less than 0.3ng/mL and 77% for PSA levels over 0.3ng/mL (p=0.001) • Sensitivity was significantly higher (p=0.001) in men who were receiving ADT (85.5%; 95%CI, 80-91%) compared to men not on ADT (59.5%; 95%CI, 50-69%)
Lecouvet et al, 2012 [3]	• n = 100	• Not reported	• Non defined primary therapy or ADT	• Best value comparator (BVC) – consensus review of all imaging by four reviewers (agreement measured by Cohen's κ coefficient)	• Evaluated ability of WBMRI to replace two-step BS/TXR + CT for detection of metastases • Enrolled men at high risk for metastasis, with 44 enrolled at initial prostate cancer diagnosis with a Gleason score of ≥8 and/or a PSA of ≥20ng/mL, 21 enrolled with a rapidly rising PSA level after local therapy, and 35 enrolled with rising PSA while undergoing ADT • WBMRI was able to identify metastases in 11% of patients (5/44) who had a negative BS reading and 35.7% (5/14) with an equivocal BS • For bone metastases, WBMRI showed increased sensitivity (98%; 95%CI, 90-100%) compared to BS/TXR readings (86%; 95%CI, 74-94%; p=0.03) while both modalities showed equivalent specificity (98%; 95%CI, 89-100% for both) • For lymph node metastases, logistic regression models indicated WBMRI was neither superior nor inferior to CT (p>0.05)
Takesh et al, 2012 [4]	• n = 37	• Range: 0.3 – 21ng/dL	• rP, RT or ADT	• Pathologic confirmation unavailable. Confirmation by clinical follow-up and matched CT	• Compared efficacy of FECH PET/CT to bone scan for detection of bone metastases in men with BC recurrence • 9 of the enrolled men were still undergoing ADT or chemotherapy • Of 37 enrolled men with BC recurrence, 18 (49%) were confirmed to have bone involvement

Study	Sample Size	PSA Level	Primary Therapy	Reference Standard	Major Findings
				or MRI findings	• Men positive for bone involvement had higher (p=0.02) median PSA levels (4ng/dL; range, 1 – 21ng/dL) compared with men without bone involvement (median, 1.5ng/dL; range, 0.3 – 19ng/dL) • FECH PET/CT demonstrated a sensitivity of 83.3% and specificity of 100%. NPV was 86.3% and PPV value was 100% • Bone scan demonstrated a sensitivity of 94.4% and specificity of 89.4%, with a PPV of 89.4% and a NPV of 94.4%

Abbreviations: ADT, androgen deprivation therapy; BC, biochemical; BS/TXR, bone scan with targeted x-ray; CI, confidence interval; CT, computed tomography; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted; EBRT, external beam radiotherapy; FCH, fluoromethylcholine; FECH, fluoroethylcholine; FDG, fluorodeoxyglucose; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; NaF, sodium fluoride; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; rP, radical prostatectomy; RT, radiation therapy; T2W, T2-weighted; TRUS, transrectal sonography.

Common Symptoms of Clinical Recurrence

The literature search did not return any systematic reviews or studies that evaluated common symptoms of clinical prostate cancer recurrence.

Ongoing Studies

Ongoing studies were searched through https://clinicaltrials.gov in week 23 of 2014 with no trials found.

Question 3: What are the rates and level of distress for common late side-effects of prostate cancer treatment? What interventions are available to manage late treatment effects?

Both studies that discussed how bothered men are by late side-effects of prostate cancer treatment (bother rates), as well as management strategies, were included to inform this research question. The search for existing systematic reviews identified 14 systematic reviews, the majority of which summarized studies that enrolled men who had received surgery, RT, and/or ADT as treatment for localized prostate cancer and fewer that summarized studies of only men on ADT. A systematic review of the primary literature was designed to inform outcomes not covered by the existing systematic reviews. The systematic review identified 35 studies that evaluated men treated with surgery, any form of RT, or ADT. Systematic reviews and studies that evaluated bother rates in men following any primary treatment are fully detailed in Table 3, while management strategy studies are detailed in Table 4. Systematic reviews and studies that evaluated side-effects of ADT are fully detailed in Table 5, with management strategy studies in Table 6. When studies have evaluated more than one side-effect, tables include study details and the specific side-effect results under each appropriate side-effect heading. All included systematic reviews and studies are summarized in the text under the side-effect evaluated by the publication.

Bowel or Gastrointestinal Dysfunction

Rates of Late Treatment Effects (Table 3)

A systematic review conducted in 2007 by Hsiao et al [19] concluded that the three most common treatment-related symptoms of men after curative-intent therapy are urinary incontinence, sexual dysfunction, and bowel dysfunction. Four additional cohort studies that assessed the rate of bowel or gastrointestinal dysfunction and were published after the Hsiao et al review [19] were identified. A before-and-after comparison followed a large cohort of prostate cancer survivors from diagnosis through four years post-treatment to evaluate their QoL evolution [21]. Enrolled men had undergone rP, EBRT, brachytherapy (BT), combined EBRT plus BT, or ADT. The study found that men who received treatment with rP experienced little change from baseline through follow-up, while men who had received any form of RT experienced a worsening in bowel bother and function during year 1, followed by recovery to baseline levels within the four-year study [21]. A second before-and-after comparison that also enrolled men treated with surgery or RT found that bowel bother rates increased after all treatments [22]. By two years post-treatment, the majority of men (86%) who had undergone surgery reported a return to baseline bowel bother rates, while just over one-half (59%) of men who had received RT or RT plus ADT reported a return to baseline rates [22]. A cohort study that enrolled men after treatment with BT or BT plus EBRT found that 13.1% of the enrolled men reported rectal bleeding following treatment, with higher rates reported for the combination therapy compared with BT alone [20]. The final identified cohort study analysed the rate of bladder and rectal toxicities in men after stereotactic body radiotherapy (SBRT) delivered by CyberKnife [25]. The percent of men who reported minor bowel issues rose from 11% of enrolled men at baseline to 14% of men following treatment [25].

Depression

Rates of Late Treatment Effects (Table 3)

An identified meta-analysis evaluating the prevalence of depression and anxiety in men with prostate cancer found that one in five prostate cancer survivors experience depression or anxiety [34].

Health-related QoL

Rates of Late Treatment Effects (Table 3)

The phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT) closed after two years due to poor accrual [31]. Men who were enrolled in the trial before closing were invited to participate in a QoL study comparing domains after treatment with rP or BT. The study found no difference in bowel or hormonal domains when men treated with rP were compared with men treated with BT; however, men treated with BT scored better in urinary and sexual domains [31]. The Huang et al [21] cohort study, originally discussed under bowel dysfunction, found that treatment with rP, EBRT, BT, BT+EBRT, and ADT all worsened urinary bother, sexual bother, and sexual function. Additionally, age at diagnosis, time since treatment and type of treatment predicted QoL outcomes in all domains assessed by survivor-completed QoL questionnaires [21]. A second cohort study that also enrolled men after treatment with rP, BT, EBRT, or ADT evaluated QoL after treatment and found that following treatment with all included modalities, men reported a decrease in sexual QoL [30]. Additionally, over the two-year follow-up, men treated with BT reported long-lasting urinary irritation, bowel and sexual symptoms, while men treated with rP reported urinary incontinence [30].

Management Strategies (Table 4)

A controlled before-and-after study evaluated the effectiveness of two telephone-based psychosocial interventions for maintaining QoL domains of psychological, physical, social and spiritual well-being [38]. Written materials that covered cancer and health topics, plus weekly telephone calls to review the material resulted in improved depression, stress, fatigue and spiritual well-being compared with standard interpersonal psychotherapy plus cancer education over the telephone.

Fatigue

Rates of Late Treatment Effects (Table 3)

A before-and-after comparison followed men treated with EBRT to determine the long-term fatigue effects due to treatment and found that men experienced a significant increase in fatigue from baseline to five years post-EBRT treatment [32].

Psychosocial/Emotional Problems

Rates of Late Treatment Effects (Table 3)

A systematic review by Wittmann et al [68] summarized studies evaluating psychosocial and emotional problems that arose as a consequence of sexual dysfunction in survivors of prostate cancer. The review concluded that only approximately 50% of men with erectile dysfunction after prostate cancer treatment seek medical help and those that do have low expectations of their care provider. Instead, most men with sexual dysfunction coped by maintaining their professional roles [68]. Five additional cohort studies that were either published after the Wittmann et al [68] review, or covered aspects of psychosocial dysfunction not covered by Wittmann et al, were identified in the primary literature. A controlled before-and-after study assessed the psychological impact of a diagnosis of localized prostate cancer compared with metastatic prostate cancer on men and their partners [70]. Irrespective of the

severity of diagnosis, at six months post-diagnosis all patients reported increased distress, while partners reported decreased distress [70]. Another controlled before-and-after study investigated the psychological impact of early primary treatment compared to watchful waiting (WW) [33]. At 12 months post-treatment, depression and anxiety, as well as physical and psychological aspects of QoL did not differ between men who underwent early treatment and those that chose WW [33]. A cohort study conducted by Ezer et al [71] followed prostate cancer patients for one year to determine their psychological adjustment over the first year post-diagnosis. Over the year follow-up, sexual, domestic, and family relationships declined for the men, while their social environment improved [71]. Two before-and-after comparisons evaluated fear of recurrence in prostate cancer survivors. The first, conducted by Bellizzi et al [72] followed 730 men in the CaPSURE database and found that higher mental component summary scores were associated with improved fear of recurrence. The second study, conducted by Hart et al [73] also followed men enrolled in the CaPSURE database, but this study only included the 333 men who were treated with rP. Similar to the Bellizzi et al study [72], the Hart et al study [73] found that higher mental health QoL scores were predicted by lower fear of recurrence scores.

Management Strategies (Table 4)

An RCT designed to test non-inferiority compared an Internet-based sexual counselling to traditional sexual counselling for couples after treatment for prostate cancer [69]. One year post-treatment both male and female sexual function scores had improved, irrespective of counselling intervention, indicating that the Internet-based program was as effective as brief traditional therapy.

Erectile Dysfunction

Rates of Late Treatment Effects (Table 3)

A meta-analysis published in 2009 reviewed the literature to define erectile function recovery after rP [27]. The overall fixed-effects erectile function recovery (EFR) rate was 58%, but there was significant heterogeneity across the studies pooled. A systematic review that was published in 2011 assessed complications after robot-assisted rP [74]. The review concluded that for men who were potent before treatment, 95% experienced potency again by 18 months post-treatment [74]. Three additional cohort studies were identified by the systematic review of the primary literature. These studies were either conducted after the search date of the identified systematic reviews or included treatment modalities not included in the reviews. The Crook et al [31] QoL data that was collected after SPIRIT closed early, as was described in a previous section, indicated that compared with men treated with rP, men treated with BT demonstrated better erectile function scores, including favourable results for ability to have an erection, quality of erections, frequency of erections, awakening with an erection, and ability to function sexually. A second cohort study evaluated changes in erectile functioning before and after treatment with BT [29]. Erectile function, orgasmic function, sexual desire, and intercourse satisfaction domains were lower at three months post-treatment compared with baseline and remained lower through the 36 months of follow-up [29]. However, within one year of treatment, 33% of men that were potent before BT treatment had maintained function [29]. The final cohort study assessed orgasmic function evolution after bilateral nerve-sparing radical retropubic prostatectomy (BNSRrP) for organ confined prostate cancer [28]. Although orgasmic function fell below baseline at one year post-treatment, scores rose throughout the follow-up period and were the equivalent to baseline scores by two years post-treatment [28].

Sexual Dysfunction

Rates of Late Treatment Effects (Table 3)

As was reported previously, the Hsiao et al [19] systematic review included sexual dysfunction as one of the three most common treatment-related symptoms of men after curative-intent therapy. Systematic review of the primary literature, following the publication date of the Hsiao et al systematic review, identified two cohort studies, which were both also previously discussed under other side-effect headings. The cohort study conducted by Huang et al [21] demonstrated that all men experienced a worsening in sexual bother and function immediately after treatment with rP, EBRT, and BT. Following rP, men reported some recovery after one year, while men in the RT groups reported little or no recovery [21]. Conversely, the Stensvold et al [22] cohort study reported that one-half of men who received treatment with RT had regained baseline sexual bother scores by two years post-treatment, while only 30% of men who received robot-assisted rP had regained baseline bother scores.

Management Strategies (Table 4)

A systematic review evaluated the effectiveness of psychosocial intervention on both sexual and relationship functioning in men treated for prostate cancer [37]. The included studies indicated that psychosocial interventions can improve sexual functioning. The greatest benefit to sexual functioning occurred when interventions were delivered face-to-face, when sexual functioning was a major focus of the intervention, and when more complex strategies that targeted sexuality in men and in relationships were used.

Urinary Dysfunction

Rates of Late Treatment Effects (Table 3)

Two identified existing systematic reviews assessed urinary dysfunction in prostate cancer patients following primary therapy. The Hsiao et al [19] systematic review included urinary dysfunction as one of the three most common side-effects of prostate cancer therapy. The Patel et al [74] systematic review, which was also described previously, assessed complications after robot-assisted rP and found that almost 92% of men regain urinary continence within one year of treatment. A systematic review of the primary literature, designed to address outcomes and years not covered by the existing systematic reviews, identified seven additional cohort studies, four of which have been previously introduced. Quality of life data collected from the failed-to-accrue SPIRIT study [31] demonstrated that compared with men treated with rP, men treated with BT experienced better rates of urine leakage, urinary control, and degree of problem with dripping or leaking urine; however, there was no difference in irritative and obstructive symptoms between the treatment modalities. The Huang et al [21] cohort study found that treatment with rP, EBRT, BT, or BT+EBRT resulted in increased urinary bother in the first year following treatment, but scores returned to baseline levels by year 2 of follow-up. The Stensvold et al [22] cohort study demonstrated lower scores, with 60% of men who received robot-assisted rP regaining baseline urinary bother scores by two years post-treatment, and 79% of men who received RT recovering to baseline scores. A more recent before-and-after comparison sought to evaluate the incidence of urinary incontinence following curative treatment with rP [23]. The study found that all men experienced a decline in continence from baseline to three months post-treatment; however, rates then returned to baseline levels by two years post-treatment [23]. Two studies evaluated urinary dysfunction after SBRT; the King et al [25] cohort study, which analyzed the rate of bladder and rectal toxicities in men after SBRT delivered by CyberKnife, found that the percent of men who reported minor urinary issues rose from 8% of enrolled men at baseline to 23% of men following treatment [25]. Additionally, while 92% of men reported no urinary issues at baseline, only 68% reported no issues following treatment [25]. A second cohort study sought to evaluate the incidences of urinary incontinence following curative treatment for prostate cancer using SBRT

[24]. Urinary incontinence bother increased at one month post-treatment, returned to baseline levels by three months post-treatment, and then increased once again by three years post-treatment [24]. A final case-control study evaluated urethral pain in long-term survivors of prostate cancer and found that after three years, men who had received treatment with EBRT did not experience more urethral pain than population-based controls [26].

Management Strategies (Table 4)

A systematic review evaluated outcomes and adverse events associated with the bone-anchored sling (BA), retrourethral transobturator sling (RTS), and the adjustable retropubic sling (ARS), all of which were designed to aid in urinary incontinence [40]. All three sling designs demonstrated high success rates; however, the review noted that most included studies defined success as either 'dry' or 'improved', while true cure rates were lower and not reported [40]. Three additional studies were identified by the systematic review of the primary literature. An RCT, designed to evaluate the effects of physiotherapist-guided pelvic floor muscle training on urinary continence status after rP, found that by one year post-operation significantly more men in the physiotherapist-guided group experienced continence, compared with men who performed pelvic floor muscles contractions alone [41]. A companion study to the previous RCT [41] found that even though physiotherapist-guided pelvic floor muscle training improved urinary incontinence after rP, this did not lead to a significant difference in QoL domains compared with the control group [75]. Results from another cohort study indicated that men who participated in a physiotherapist-guided pelvic muscle floor and exercise program also experienced superior continence compared with a control group [42].

Physical Function

Management Strategies (Table 4)

A systematic review evaluated whether exercise could reduce symptoms and improve QoL in prostate cancer survivors [36]. The review found strong evidence indicating that exercise may improve muscle mass, muscle strength, functional performance and both social and physical domains of QoL tools [36]. An RCT, published after the search date of the existing systematic review, evaluated the positive effects of a combined exercise intervention for elderly men after rP [35]. After the 12-week intervention, men in the exercise group had better physical function for all evaluated domains of functional physical fitness, flexibility and balance, plus faster improvements for the 24-hour pad test and continence rate, and improvements in QoL scores [35].

Gynecomastia

Management Strategies (Table 4)

An identified meta-analysis examined the literature and determined that both treatment with prophylactic RT and tamoxifen (TMX) resulted in reduced incidences of gynecomastia and breast pain [65].

Table 3. Rates of late treatments effects for surgery and radiation therapy.

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Bowel or Gastrointestinal Dysfunction			
Systematic Review			
Hsiao et al, 2007 [19]	• Reviewed 14 studies	• Any treatment for localized PCa	• Assessed symptom distress at diagnosis, during treatment and post-treatment • Defined symptom distress as the perception of physiological or psychological discomfort resulting from a particular symptom experienced • Three most common treatment-related symptoms after therapy: bowel dysfunction, sexual dysfunction and urinary incontinence
Cohort Studies			
Aoki et al, 2009 [20]	• n = 296	• BT or BT+EBRT	• Study analyzed rate of rectal bleeding after treatment in men followed for more than 36 months • Rectal bleeding reported by 13.1% of total men enrolled • After BT, 9.1% (n=23/252) of men had grade 1 or 2 rectal bleeding • After BT+EBRT, 36.3% (n=16/44) of men reported grade 1 or 2 rectal bleeding • Combination therapy was associated with a significantly higher rate of rectal bleeding compared with monotherapy ($p<0.001$) and a significantly higher percentage of grade 2 bleeding compared with monotherapy ($p=0.0005$)
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years follow-up • QoL assessment included elements from both the SF36 and the UCLA-PCI at baseline and then every six months • After rP, little change from baseline through follow-up • After any form of RT, bowel function and bother worsened in year 1, but recovered to baseline by year 4 • ADT group experienced gradual decrease in function and bother through year 2, then no change
Stensvold et al, 2013 [22]	• n = 462	• Robot-assisted rP (RArP), RT, or RT+ADT	• Study assessed bowel, urinary and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completion of treatment • Bowel, urinary and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the SF-12, and neuroticism was assessed with the appropriate section of the EPQ • By two years post-treatment, 86% of men who received RArP had regained baseline bowel bother rates • By two years post-treatment, 59% of men who received RT or RT+ADT had regained baseline bowel bother rates

Study	Sample Size	Primary Treatment	Rate or Level of Distress
King et al, 2012 [25]	• n = 67	• Stereotactic body radiotherapy (SBRT) delivered by CyberKnife	• Study compared bladder and rectal toxicities before and after treatment • Men followed for a median time of 2.7 years • PSA level and validated QoL questionnaires for urinary and bowel function were obtained at baseline, then every three months post-treatment the first two years, then at six month intervals thereafter • Patient-reported toxicity was scored on the RTOG urinary and rectal toxicity scale at last follow-up • Before treatment 89% of enrolled men reported no bowel issues and 11% reported minor issues (Grade 0-1) • During follow-up, 84% men reported no bowel issues (Grade 0), while 14% had Grade 1 issues and 2% experienced Grade 2 bowel issues
Depression			
Systematic Review with meta-analysis			
Watts et al, 2014 [34]	• Pooled 27 studies	• Any primary therapy for localized prostate cancer	• Meta-analysis that examined literature on prevalence of depression and anxiety at pre-treatment, during prostate cancer treatment and post-treatment • Subgroup analysis indicated that 18.44% (95%CI, 15.18-22.22%) of survivors experience depression post-treatment (13 studies) • Subgroup analysis indicated that 18.49% (95%CI, 13.81-24.31%) of prostate cancer survivors experience anxiety (11 studies)
Health-related QoL			
Cohort Studies			
Crook et al, 2011 [31]	• n = 168	• rP or BT	• Health-related QoL collected from the phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT), which closed after two years due to poor accrual • After initial lack of accrual, the men already enrolled in the study were invited to an educational session on rP and EBRT • Of the 263 men who attended, 190 consented to still participate, with 34 consenting to random assignment, 62 choosing rP and 94 choosing BT • QoL was then evaluated five years later with Expanded Prostate Index Composite (EPIC) and both the physical component scale and the mental component scale of the SF12 questionnaire • Of the 190 men who were sent the questionnaires, 168 responded • There were no difference in bowel (p=0.34) or hormonal (p=0.1) domains for men treated with rP compared with BT • Men treated with BT scored better in urinary (p=0.02) and sexual domains (p=0.001) • Within the urinary domain, compared with rP, men treated with BT showed more favourable results for how often urine leakage occurred (p<0.001), urinary control (p<0.001), and degree of problem with dripping or leaking urine (p<0.001)

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• There were no differences between treatments for irritative and obstructive symptoms • Within the sexual domain, compared with rP, men treated with BT showed more favourable results for the ability to have an erection (p<0.001), the quality of erections (p<0.001), frequency of erections (p=0.003), awakening with an erection (p-0.002), and the ability to function sexually (p=0.003)
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT or ADT	• QoL evolution from diagnosis through four years follow-up • QoL assessment included elements from both the SF36 and the UCLA-PCI at baseline and then every six months • All included treatment modalities worsened urinary bother, sexual bother, and sexual function • Age of diagnosis, time since treatment and type of treatment predicted QoL in all domains (p<0.05)
Sanda et al, 2008 [30]	• n = 1201 PCa patients and 625 spouses	• rP, BT, EBRT, or ADT	• Evaluated QoL after primary treatment and its effects on satisfaction with care in patients and their spouses • At 2 months post-treatment initiation (MPI), 6MPI, 12MPI and 24MPI patients and spouses completed telephone surveys that included the EPIC and Service Satisfaction Scale for Cancer Care • All men reported a decrease in sexual QoL from baseline to follow-up (p<0.001) • Men treated with BT reported long-lasting urinary irritation (p<0.001), bowel and sexual symptoms, as well as transient problems with vitality • Men treated with rP reported urinary incontinence but urinary irritation and obstruction improved
Fatigue			
Cohort Study			
Fransson, 2010 [32]	• n = 407	• EBRT	• Compared fatigue pre-treatment, then at three months, one year, three years and five years post-treatment using the QLQ-C30 questionnaire • Fatigue significantly increased from baseline (15.5; 95%CI, 13.6-17.4) to five years post-EBRT treatment (22.8; 95%CI, 20.5-25.1; p<0.001) • 59% of men experienced fatigue pre-treatment and 66% of men five years after • When looking at clinically relevant change in fatigue, 26% of men reported no change in fatigue over the five years (0-5 points on fatigue scale), 16% reported moderate increase in fatigue (10-20 points on fatigue scale), and 24% reported a large increase (>20 points)
Psychosocial/Emotional Problems			
Systematic Review			
Wittmann et al, 2009 [68]	• Reviewed 102 studies	• Not reported	• Summarized studies that evaluated psychosocial and emotional problems that arise as a consequence of sexual dysfunction in survivors of PCa • 59% of men with erectile dysfunction after PCa treatment seek medical help

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• Men are more likely to seek erectogenic treatment after prostatectomy than after RT, but few of the men actually try the treatments offered and those that do tend to discontinue the treatments early • Most men cope by maintaining their professional/career roles • Studies focused on prostate cancer survivor partners indicated that partners tend to be more distressed than survivors, wish to be included in information gathering and decisions, develop distress as a consequence of the survivor's physical pain and limitations, and benefit from support and inclusion in the recovery process
Cohort Studies			
Couper et al, 2006 [70]	• n = 103 couples	• Not reported	• Compared men diagnosed with localized PCa with those diagnosed with metastatic PCa and assessed depression, anxiety, psychological distress, and marital status at diagnosis (T1) and six months later (T2) • The men's partners were also assessed for the same criteria at the same time points • At T1: o Marital satisfaction was not different between the patient and partner o Partners reported more distress than patients (p=0.004) • At T2: o Partners' marital satisfaction had declined while patients' had not changed (p<0.05) o Patients reported increased distress compared with T1 (p<0.05) o Partners reported decreased distress compared with T1 (p<0.05) o Distress level for patients not different than for partners • Across all outcomes, no difference between couples when men were diagnosed with metastatic PCa compared with localized PCa
Couper et al, 2009 [33]	• n = 211	• rP, ADT or other early treatment (OET; included EBRT and BT)	• Compared psychological domains for men receiving treatment for localized PCa to men who chose watchful waiting (WW) • Depression and anxiety were assessed by the Brief Symptom Index, while physical and psychosocial aspects of QoL were assessed by the Short-Form Health Survey, both at treatment initiation (T1) and 12 months post-treatment (T2) • At T1: o Treatment groups reported greater dysfunction in work roles and daily activities compared with WW controls (p<0.001) o Men scheduled to receive rP reported worse social (p<0.01) and emotional role (p<0.01) than WW controls o Men scheduled to receive ADT or OET reported poorer vitality levels than WW controls (p<0.001 and p<0.01 respectively) o ADT patients reported higher depression scores than WW (p<0.05) • At T2:

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			○ rP and OET groups did not differ from WW controls for depression and anxiety or physical and psychological aspects of QoL ○ Men in ADT group reported higher depression ($p<0.05$) and anxiety scores ($p<0.05$) than WW controls ○ ADT men also reported worse QoL domains including physical function ($p<0.001$), role-physical ($p<0.01$) and vitality ($p<0.01$) compared with controls
Ezer et al, 2012 [71]	• n = 81	• RT or prostatectomy	• Assessed psychological adjustment over first year post-diagnosis • Men were assessed at home prior to treatment (T1), three months later (T2) and one year post-diagnosis (T3) • At T1, predictors of psychological, vocation and domestic domains were mood disturbances, sense of coherence, and couple cohesion and adaptability • At T2, mood disturbances and sexual functioning were predictors of healthcare, vocational, social, psychological and family domains • Sexual relationship of the couple deteriorated from T1 to T2 • Between T1 and T2, men's social environment improved • At T3, urinary function and couple cohesion and adaptability were predictors of vocational, domestic, social and psychological adjustment • Between T1 and T3, sexual, domestic and family relationships declined, while social environment improved
Bellizzi et al, 2008 [72]	• n = 730 from CaPSURE	• rP, BT or EBRT	• Evaluated fear of recurrence, common treatment-related effects and QoL evolution every six months from diagnosis through post-treatment • Physical component summary (PCS) and mental component summary (MCS) were calculated and compared with fear of recurrence and treatment side-effects • Better MCS scores were associated with improved fear of recurrence ($p<0.01$) and improved bowel function ($p<0.01$) • Worse MCS scores were associated with a higher number of post-treatment symptoms ($p<0.01$) • Higher PCS scores were associated with improved urinary bother ($p<0.01$) and a lower number of post-treatment symptoms ($p<0.01$)
Hart et al, 2008 [73]	• n = 333 from CaPSURE	• rP	• Evaluated the impact of fear of recurrence on QoL from diagnoses through 18 months of follow-up • Treatment satisfaction was measured at six months post-rP, while fear of recurrence was measured at six to 12 months post-rP and QoL was measured at 12-18 months post-rP • Higher mental health QoL scores were predicted by lower fear of recurrence scores ($p<0.0001$), and higher treatment satisfaction scores • Higher physical health QoL were predicted by lower fear of recurrence scores ($p<0.01$) • The interaction of treatment satisfaction multiplied by fear of recurrence was associated with both higher mental health QoL scores ($p<0.05$) and higher physical health QoL scores ($p<0.01$)

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Erectile Dysfunction			
Systematic Reviews with and without meta-analyses			
Tal et al, 2009 [27]	• Pooled 22 studies	• OrP, LrP, or RArP	• Pooled studies that reported on EFR or erectile function scores • Overall fixed effects EFR rate was 58% (95%CI, 56-60%) with significant heterogeneity among effects sizes (Q, 164.5; p=0.001) • EFR rates are highest for RArP (EFR, 73%; two studies), followed by LrP (EFR, 56%; 21 studies) and OrP (EFR, 57%; 16 studies; p=0.01) • Patients <60 of age reported higher EFR than those >60 years (77% vs. 61%; RR, 1.26; p=0.001; eight studies) • Studies that reported more than 18 months of follow-up reported higher EFR rates (EFR, 60%; 10 studies) than studies with a shorter follow-up (EFR, 56%; 12 studies; RR, 1.07; p=0.02)
Patel et al, 2011 [74]	• Reviewed 35 studies	• RArP	• Assessed complications after RArP • Measured pentafecta outcomes – attainment of continence, attainment of potency, no evidence of BC recurrence, complications, positive surgical margins • For men potent before treatment, weighted means (range) for potency after surgery were 38.8% (8.3-47.0%) at three months post-operation (MPO), 65.4% (14.7-77.1%) at 6MPO, 73.9% (43.2 – 91.5%) at 12MPO and 95.0% (63.1 – 100.0%) at 18MPO
Cohort Studies			
Crook et al, 2011 [31]	• n = 168	• rP or BT	• Health-related QoL collected from the phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT), which closed after two years due to poor accrual • After initial lack of accrual, the men already enrolled in the study were invited to an educational session on rP and EBRT • Of the 263 men who attended, 190 consented to still participate, with 34 consenting to random assignment, 62 choosing rP and 94 choosing BT • QoL was then evaluated five years later with EPIC and both the physical component scale and the mental component scale of the SF12 questionnaire • Of the 190 men who were sent the questionnaires, 168 responded • Men treated with BT scored better in the sexual domains (p=0.001) • Within the sexual domain, compared with rP, men treated with BT showed more favourable results for the ability to have an erection (p<0.001), the quality of erections (p<0.001), frequency of erections (p=0.003), awakening with an erection (p-0.002), and the ability to function sexually (p=0.003)
Matsushima et al, 2013 [29]	• n = 119	• BT without supplemental therapy (EBRT, ADT or PDE5-I)	• Evaluated changes in erectile function before and after BT • Sexual and erectile function assessed before treatment, then at 3MPO, 6MPO, 12MPO, 12MPO, 18MPO, 24MPO and 36MPO with the IIEF questionnaire • Compared to baseline, at 12MPO:

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			○ A higher percentage of men had severe ED (73.9% vs. 59.7%) ○ Fewer men had moderate (8.4% vs. 9.2%), mild to moderate (4.2% vs. 6.7%), mild (7.6% vs. 11.8%) and no ED (5.9% vs. 12.6%) • Mean total IIEF scores, erectile function, orgasmic function, sexual desire and intercourse satisfaction at 3MPO were lower than before treatment ($p<0.05$) ○ All domains remained lower than baseline through 36MPO ($p<0.05$) • Among men who were potent at baseline, 33% maintained unchanged erectile dysfunction severity at 12MPO ○ Rate of erectile dysfunction deterioration after 12MPO was 50% for men aged 50-59 years, 60% for men 60-69 years, and 87.5% for men 70-79 years of age • Multivariate analysis revealed that age 70 or greater was the only significant predictor for deteriorating erectile function after BT ($p=0.035$)
Salonia et al, 2010 [28]	• n = 334	• BNSRrP	• Assessed orgasmic function evolution from hospital admission through four years at 12 month intervals • Sexual function was assessed with the IIEF for both erectile function (EF) and orgasmic function (OF) • Orgasmic function scores were lower than baseline at 12MPO ($p=0.008$), but rose to be no different by 24MPO • Men were offered PDE5-I for erectile function recovery • At 12MPO, orgasmic function linearly increased with erectile function ($p<0.001$), patient's age ($p<0.001$) and urinary continence ($p<0.001$) • At 24MPO and 36MPO, orgasmic function still linearly increased with erectile function ($p<0.001$), but PDE5-I, rate of continence and patient's age did not significantly affect orgasmic function
Sexual Dysfunction			
Systematic Reviews			
Hsiao et al, 2007 [19]	• Reviewed 14 studies	• Any treatment for localized PCa	• Assessed symptom distress at diagnosis, during treatment and post-treatment • Defined symptom distress as the perception of physiological or psychological discomfort resulting from a particular symptom experienced • Three most common treatment-related symptoms after therapy: bowel dysfunction, sexual dysfunction and urinary incontinence
Cohort Study			
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years follow-up • QoL assessment included elements from both the SF36 and the UCLA-PCI at baseline and then every six months • All men experienced worsened sexual function and bother immediately after treatment

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• After rP, greatest decrease in sexual function reported with some recovery in both function and bother after year 1 • After EBRT, BT, BT+EBRT and ADT, men experienced little or no recovery after decline for both function and bother domains
Stensvold et al, 2013 [22]	• n = 462	• RArP, RT, or RT+ADT	• Study assessed bowel, urinary and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completing of treatment • Bowel, urinary and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the Short Form 12 (SF-12), and neuroticism was assessed with the appropriate section of the Eysenck Personality Questionnaire (EPQ) • By two years post-treatment, 30% of men who received RArP had regained baseline sexual bother scores • By two years post-treatment, 51% of men who received RT had regained baseline bother scores • By two years post-treatment, 47% of men who received RT+ADT had regained baseline sexual bother rates
Urinary Dysfunction			
Systematic Reviews			
Patel et al, 2011 [74]	• Reviewed 35 studies	• RArP	• Assessed complications after RArP • Measured pentafecta outcomes – attainment of continence, attainment of potency, no evidence of BC recurrence, complications, positive surgical margins • Weighted means (range) for continence were 87.8% (54.0 – 97.1%) at 6MPO and 91.8% (70.0 – 97.0%) at 12MPO
Hsiao et al, 2007 [19]	• Reviewed 14 studies	• Any treatment for localized PCa	• Assessed symptom distress at diagnosis, during treatment and post-treatment • Defined symptom distress as the perception of physiological or psychological discomfort resulting from a particular symptom experienced • Three most common treatment-related symptoms after therapy: bowel dysfunction, sexual dysfunction and urinary incontinence
Cohort Studies			
Crook et al, 2011 [31]	• n = 168	• rP or BT	• Health-related QoL collected from the phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT), which closed after two years due to poor accrual • After initial lack of accrual, the men already enrolled in the study were invited to an educational session on rP and EBRT • Of the 263 men who attended, 190 consented to still participate, with 34 consenting to random assignment, 62 choosing rP and 94 choosing BT

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• QoL was then evaluated five years later with EPIC and both the physical component scale and the mental component scale of the Short Form 12 questionnaire • Of the 190 men who were sent the questionnaires, 168 responded • Men treated with BT scored better in the urinary domain (p=0.02) • Within the urinary domain, compared with rP, men treated with BT showed more favourable results for how often urine leakage occurred (p<0.001), urinary control (p<0.001), degree of problem with dripping or leaking urine (p<0.001) • There were no differences between treatments for irritative and obstructive symptoms
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years follow-up • QoL assessment included elements from both the SF36 and the UCLA-PCI at baseline and then every six months • Function decreased in men immediately after rP, BT and BT+EBRT • rP resulted in worst function but also best recovery • Bother increased in year 1 for men after rP or any form of RT with recovery by year 2 of follow-up • For ADT, gradual decrease in urinary function and bother over four years
Pettersson et al, 2013 [26]	• n = 863 cases and 242 controls	• Primary treatment with EBRT, prostatectomy followed by salvage EBRT, or EBRT+BT	• Urethral pain compared between long-term survivors of PCa and population-based controls • 11% of men who received primary treatment with EBRT, 10% of men who received salvage EBRT, 23% of men who received EBRT+BT and 9% of controls experienced urethral pain • Subgroup analysis demonstrated that when followed for at least three years, 19% of men treated with EBRT+BT reported pain, compared with 10% of men treated with EBRT as primary salvage treatment
Stensvold et al, 2013 [22]	• n = 462	• RArP, RT, or RT+ADT	• Study assessed bowel, urinary and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completing of treatment • Bowel, urinary and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the SF-12, and neuroticism was assessed with the appropriate section of the EPQ • By two years post-treatment, 60% of men who received RArP had regained baseline urinary bother scores • By two years post-treatment, 79% of men who received RT had regained baseline urinary bother scores • By two years post-treatment, 75% of men who received RT+ADT had regained baseline urinary bother scores

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Prabhu et al, 2014 [23]	• n = 1788	• rP	• Evaluated incidences of urinary incontinence with UCLA-PCI-UFI at baseline, followed by at three, six, 12, 24, 96 and 120 months post-rP • Continence rates declined from baseline to 3MPO ($p<0.001$), then returned to baseline levels by two years post-rP • By 10 years post-rP, continence rates were lower than at baseline ($p=0.024$) • Age stratified analysis demonstrated that for men over the age of 60, continence rates declined between two and 10 years post-treatment ($p=0.047$), while rate remained stable for men under the age of 60 ($p=0.364$)
Chen et al, 2014 [24]	• n = 204	SBRT	• Urinary incontinence evolution assessed for three years following treatment with SBRT • Urinary incontinence was assessed with the EPIC questionnaire before treatment and then one month after completion of SBRT, every three months for one year and every six months for two more years • Urinary incontinence bother was significantly higher at one month post-SBRT compared with baseline ($p<0.0001$) • Bother returned to baseline levels by three months post-SBRT • At three years post-SBRT, urinary incontinence bother had increased again beyond baseline levels ($p<0.0001$)
King et al, 2012 [25]	• n = 67	• SBRT delivered by CyberKnife	• Study compared bladder and rectal toxicities before and after treatment • Men followed for a median time of 2.7 years • PSA level and validated QoL questionnaires for urinary and bowel function were obtained at baseline, then every three months post-treatment the first two years, then at six month intervals thereafter • Patient-reported toxicity was scored on the RTOG urinary and rectal toxicity scale at last follow-up • Before treatment 92% of enrolled men reported no urinary issues and 8% reported minor issues (Grade 0-1) • During follow-up, 68.5% men reported no urinary issues (Grade 0), while 23% had Grade 1 issues, 5% experienced Grade 2 and 3.5% experienced Grade 3 urinary issues

Abbreviations: ADT, androgen deprivation therapy; BC, biochemical; BNSRrP, bilateral nerve-sparing radical retropubic prostatectomy; BT, brachytherapy; EBRT, external beam radiotherapy; ED, erectile dysfunction; EFR, erectile function recovery; EPIC, Expanded Prostate Index Composite; EPQ, Eysenck Personality Questionnaire; IIEF, International Index of Erectile Function; LrP, laparoscopic radical prostatectomy; MPI, months post-treatment initiation; MCS, mental component summary; MPO, months post-operation; OET, other early treatment; OrP, open radical prostatectomy; PCa, prostate cancer; PCS, physical component summary; PDE5-I, phosphodiesterase 5 inhibitor; PSA, prostate-specific antigen; QoL, quality of life; RArP, robot-assisted radical prostatectomy; rP, radical prostatectomy; RR, relative risk; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy; SF, short form; UCLA PCI, The University of California, Los Angeles Prostate Cancer Index; UFI, urinary function index; WW, watchful waiting.

Table 4. Interventions for management of late side-effects from surgery and radiation therapy.

Study	Sample Size	Intervention	Effects of Intervention
Health-related QoL			
Cohort Studies			
Badger et al, 2011 [38]	• n = 71 survivors and 70 partners	• Telephone-based psychosocial intervention	• Enrolled survivors and their partners to compare two telephone-based interventions for maintenance of QoL domains of psychological, physical, social and spiritual well-being • 1) Interpersonal counselling intervention (TIP-C) ○ Eight week program of standard interpersonal psychotherapy plus cancer education over the telephone ○ Addressed mood and management, emotional expression, interpersonal communication and relationships, social support and cancer information ○ Survivor's partner also received separate session every other week • 2) Health education attention condition (HEAC) ○ Eight week program with no counselling, but instead written materials from the National Cancer Institute and weekly telephone calls to review the materials ○ Materials covered PCa diagnosis and treatment, and health-related topics such as nutrition, exercise and smoking cessation ○ Survivor's partners received calls every other week • Improvements higher for survivors in HEAC group compared with TIP-C group for depression ($p<0.001$), negative affect ($p<0.001$), perceived stress ($p<0.001$), fatigue ($p<0.01$) and spiritual well-being ($p<0.01$) • Partners in HEAC group had greater improvement than partners in TIP-C group for depression ($p<0.05$), fatigue ($p<0.01$), social support from family members ($p<0.05$), social well-being ($p<0.01$) and spiritual well-being ($p<0.01$)
Physical Function			
Systematic Review			
Keogh and MacLeod, 2012 [36]	• Reviewed 12 studies	• Any exercise intervention	• Summarized effects of exercise on symptoms and QoL • Studies enrolled both men receiving and not receiving ADT • Strong evidence suggests exercise may improve muscle mass, muscle strength, functional performance, and social and physical domain of QoL tools • Group-based interventions appear to provide more benefit than home-based programs, especially when resistance training is included
RCT			
Park et al, 2012 [35]	• n = 66	• Combined exercise intervention – resistance,	• Compared combined exercise intervention to only Kegel exercises in PCa survivors that were at least 65 years old

Study	Sample Size	Intervention	Effects of Intervention
		flexibility, Kegel exercises	• Exercise intervention consisted of a combined exercise intervention with resistance, flexibility and Kegel exercises twice a week for 12 weeks, while the control group performed only Kegel exercises for the 12 week period • The primary outcome of the RCT was physical function and the secondary outcomes were continence status and QoL after exercise • Of the 66 men originally enrolled, only 49 completed the 12 week study • After 12 weeks, compared with the Kegel only group, exercise group had better physical function for all evaluated domains of functional physical fitness, flexibility, and balance ($p<0.05$), except for grip strength exercise intervention group had better physical function ($p<0.05$) • Exercise intervention group showed faster improvements for 24-hour pad test (12.2g vs. 46.2g) and continence rate (at 12 weeks: 73.1% vs. 43.5%) • Compared with baseline, only men in the exercise intervention group showed improvement in QoL scores after 12 weeks
Gynecomastia			
Systematic Review with meta-analysis			
Viani et al, 2012 [65]	• Pooled 6 RCTs	• Prophylactic RT or tamoxifen (TMX)	• Assessed if prophylactic RT or TMX reduces gynecomastia and breast pain • Prophylactic RT and incidence of gynecomastia: ○ Compared to observation, reduced incidence (OR, 0.21; 95%CI, 0.21-0.37; $p<0.001$) ○ Absolute risk reduction (ARR): 29.4% ○ Number needed to treat to avoid one case (NNT): 3.4 • Prophylactic RT and incidence of breast pain: ○ Compared with observation, reduced incidence (OR, 0.34; 95%CI, 0.20-0.57; $p<0.0001$) ○ ARR: 19.9%; NNT: 5 • TMX and incidence of gynecomastia ○ Compared with observation, reduced incidence (OR, 0.07; 95%CI, 0.0-0.14; $p<0.0001$) ○ ARR: 64.1%; NNT: 1.56 • TMX and incidence of breast pain: ○ Compared with observation, reduced incidence (OR, 0.04; 95%CI, 0.02-0.08; $p<0.0001$) ○ ARR: 47.6%; NNT: 2.1 • Adverse effects: ○ Absolute risk increase to harm: 1.6% for RT and 9.8% for TMX ○ Number needed to treat to cause harm: 62.5 for RT and 10 for TMX
Psychosocial/Emotional Problems			
RCT			

Study	Sample Size	Intervention	Effects of Intervention
Schover et al, 2012 [69]	• n = 186 couples	• Internet-based sexual counselling compared with traditional	• Couples randomized to one of three interventions or to a three month waitlist control group ○ 1) three sessions of face-to-face counselling over 12 weeks (FF) ○ 2) original internet-based format (WEB1) ○ 3) second internet-based added later (WEB2) • After 3 months on waitlist, control couples were re-randomized to either WEB1 or WEB2 • At baseline, post-waitlist, post-treatment, six months into follow-up and 12 months into follow-up, participants completed the IIEF, the FSFI, the Brief Symptom Inventor-18 to measure emotional distress and the abbreviated Dyadic Adjustment Scale • 34% of couples dropped out across all groups • Improvements in outcomes were not different across intervention groups indicating internet-based was not inferior to face-to-face counselling • When all participants were pooled: ○ IIEF scores at 12 months were improved compared with baseline (36.2 ± 22.4 vs. 29.7 ± 17.9; p<0.001) ○ Female Sexual Function Index scores also improved at 12 months compared with baseline (18.2 ± 10.7 vs. 15.4 ± 8.5; p=0.034)
Sexual Dysfunction			
Systematic Review			
Chisholm et al, 2012 [37]	• Reviewed 16 RCTs	• Any psychosocial intervention	• Evaluated RCTs looking at effectiveness of psychosocial intervention for sexual and relationship functioning • Strategies that positively affected sexual functions: ○ Face-to-face delivery, sexual function as a focus of the intervention, strategies that targeted sexuality in men and relationships ○ Explicit use of sex therapy techniques – taking a sexual history, teaching sensate focus, challenging the negative thoughts related to sexuality and masculinity ○ Focus on communication skills around sexual problems and intimacy concerns • Interventions for sexual bother were more effective when delivered face-to-face compared with telephone-based • Studies focused on interventions for relationship functioning for PCa survivors or sexual and relationship function of partners provided inconclusive results
Urinary Dysfunction			
Systematic Review			
Welk and Herschorn, 2012 [40]	• Reviewed 20 studies	• Male slings	• Evaluated studies focused on outcomes and adverse events associated with the bone-anchored sling (BA), retrourethral transobturator sling (RTS) and adjustable retropubic sling (ARS) • BA sling: ○ Success rate: 40-88% with four years of follow-up

Study	Sample Size	Intervention	Effects of Intervention
			○ Sling explantation: required with mesh infection, rate of 2-12% • RTS sling: ○ Success rate: 76-91% with 12-27 month follow-up ○ Sling explantation: reported low rate • ARS: ○ Success rate: 72-79% with 26-45 months of follow-up ○ Sling explantation: required with erosion (rate, 3-13%) and infection (3-11%) • Most studies defined success as either 'dry' or 'improved', while true cure rates were not reported
RCTs and Comparative Cohort Study			
Overgard et al, 2008 [41]	• n = 85	• Pelvic floor training	• All enrolled men were instructed in correct pelvic floor muscle contractions after rP and were encouraged to train • Men then randomized to either physiotherapist-guided group, with additional training instruction, or control group, with no additional training • Continence (0 pads) status and perceived urinary function problems were assessed at 6 weeks post-operation, 3 months post-operation (MPO), 6MPO and 12 MPO • 3MPO: ○ No significant difference in continence status between groups (46% vs. 43%; p=0.73) ○ 97% of men in physiotherapist-guided group compared with 78% in the control group (p=0.01) reported no or mild problems with urinary function • 6MPO: ○ 79% of physiotherapist-guided group and 58% of control group (p=0.061) experienced continence • 12MPO: ○ 92% of physiotherapist-guided compared with 72% of control group (p=0.028) experienced continence
Nilssen et al, 2012 [75]	• n = 85	• Pelvic floor training	• Companion study to Overgard et al RCT [41] • Evaluated effects of the training intervention on QoL • QoL was assessed using the PCS and MCS of the 12-item Short Form (SF-12), plus the urinary, sexual, and bowel function and bother of the UCLA-PCI at six weeks, 3MPO, 6MPO and 12MPO • No differences in QoL domains when physiotherapist-guided group was compared to control group
Rajkowska-Labon et al, 2014 [42]	• n = 81	• Physiotherapy	• Study assessed efficacy of physiotherapy intervention for urinary incontinence after rP • Men were divided into either a physiotherapy intervention group or a control group • Men in the control group had reported persistent urinary incontinence following rP, but had not entered therapy for personal reasons

Study	Sample Size	Intervention	Effects of Intervention
			• Physiotherapy intervention involved pelvic floor muscle training under guidance from a physiotherapist plus a home-based exercise program • Continence was assessed at baseline and then on completion of therapy with the one-hour and 24-hour pad test • Men who underwent the intervention experienced superior continence compared to the control group (89% vs. 11%; p=0.0001), with a reduction in urine loss (p<0.001) and pad usage (p<0.001) compared with baseline

Abbreviations: ADT, androgen deprivation therapy; ARR, absolute risk reduction; CI, confidence interval; FSFI, Female Sexual Function Index; HEAC, health education attention condition; IIEF, International Index of Erectile Function; MCS, mental component summary; MPO, months post-operation; NNT, number needed to treat; OR, odds ratio; PCa, prostate cancer; PCS, physical component summary; QoL, quality of life; RCT, randomized controlled trial; rP, radical prostatectomy; RT, radiation therapy; SF, short form; TIP-C, interpersonal counselling intervention; TMX, tamoxifen; UCLA PCI, The University of California, Los Angeles Prostate Cancer Index.

Late Side-Effects of Androgen Deprivation Therapy

Anemia

Rates of Late Treatment Effects (Table 5)

An identified systematic review discussed the hematological consequences of ADT and the effects of androgen and androgen withdrawal on the red blood cell lineage [43]. Some evidence included in the review suggests that ADT-associated anemia may contribute to fatigue and reduced QoL; however, there are no data evaluating whether treatment of ADT-associated anemia alters clinically important outcomes or mortality.

Body Composition Alterations

Rates of Late Treatment Effects (Table 5)

A meta-analysis reviewed longitudinal studies that examined the association between ADT treatment and changes in body composition [44]. Analyses indicated that ADT results in an increase in body fat, body weight and body mass index (BMI), and a decrease in lean body mass [44]. A systematic review of the primary literature identified three additional cohort studies published after the meta-analysis. A case-control designed to compare men initiating continuous ADT, prostate cancer controls not on ADT and healthy controls, found that the proportion of men that gained weight during was higher among the men treated with ADT than both the control groups at multiple intervals over the 36 months study period [45]. A second case-control study, which sought to determine whether ADT contributes to geriatric frailty, demonstrated that compared with a control group, more men undergoing ADT showed signs of being pre-frail and obese frailty [46]. A third cohort study assessed body composition alterations in men on intermittent ADT and found that lean mass decreased while fat mass increased, following treatment [47].

Bowel Dysfunction

Rates of Late Treatment Effects (Table 5)

Both the previously mentioned Huang et al [21] and Stensvold et al [22] cohort studies also assessed bowel dysfunction in men who had received ADT. The Huang et al [21] cohort study found that men who received ADT experienced a gradual decrease in bowel function and bother from treatment completion to two years post-treatment and then no further change. Conversely, the Stensvold et al [22] cohort study indicated that by two years post-RT+ADT treatment, 59% of men had regained baseline bowel bother rates.

Cognitive Side-Effects

Rates of Late Treatment Effects (Table 5)

A systematic review with meta-analysis sought to assess the effects of ADT on cognitive domains, including attention/working memory, executive functioning, language, verbal memory, visual memory, visuomotor ability and visuospatial ability [48]. Analysis indicated that men treated with ADT demonstrated significantly worse functioning in the visuomotor ability domain.

Depression

Rates of Late Treatment Effects (Table 5)

A case-control study examined whether ADT leads to worsened depression compared with depression often reported after treatment for prostate cancer [63]. The study compared three cohorts of men, including a cohort initiating continuous ADT, a prostate cancer patient control cohort and a healthy control cohort. ADT was not a significant predictor of depression symptoms in men who were depressed at baseline, nor in men not depressed at baseline [63].

A comparative cohort study examined whether ADT after RT resulted in an increase in depression and if the increase is caused by the ADT itself, or by the poor prognosis associated with having (neo)adjuvant hormonal therapy [64]. Men receiving ADT in two clinics were assessed to superficially compare the effects of ADT alone with the effects of poor prognosis. The study found that depression was significantly increased in men receiving ADT, irrespective of study setting [64]. A final cohort study, which was described under the depression heading for surgery and RT treatments, assessed anxiety and depression in men receiving ADT compared with men who chose WW [33]. Men who received ADT reported higher depression and anxiety scores 12 months post-treatment [33].

Health-related QoL

Rates of Late Treatment Effects (Table 5)

The Postoperative Adjuvant Androgen Deprivation (PADD) controlled before-and-after study assessed testosterone and hemoglobin kinetics in correlation with QoL after radical retropubic prostatectomy (RRP) and found that ADT did not result in any decline in general QoL compared with a control group [66]. Married men who were previously enrolled in the PADD study [66] were invited to participate in a companion study with their spouses to investigate spousal QoL [67]. Spouses experienced mental health functioning improvement over the course of the study, while physical health was directly associated with the degree of symptoms experienced by the patient.

Hot Flushes

Rates of Late Treatment Effects (Table 5)

One before-and-after comparison sought to examine the relationship between ADT-related hot flushes and distress during the first three months of ADT treatment [49]. By six week after ADT initiation 53% of men reported experiencing hot flushes, but there was no reported significant change in distress levels compared with baseline [49].

Management Strategies (Table 6)

An identified systematic review evaluated treatments for hot flushes in men with prostate cancer [53]. Included studies indicated that diethylstilbestrol, megestrol acetate and cyproterone acetate have the strongest effect, giving a 75% decrease in the number of hot flushes experienced by enrolled men. The review also indicated that venlafaxine and medroxyprogesterone may reduce the incidence of hot flushes, but the results have not been verified in any large randomized controlled trial (RCT) as of yet. Unfortunately, many of the included studies did not include side-effect profiles for the men receiving the treatments, but the few that did noted side-effects that included gynecomastia, weight gain, muscle spasms, insomnia, depression, headache, flu-like symptoms and elevated blood pressure.

Physical Function

Rates of Late Treatment Effects (Table 5)

An identified case-control study evaluated the effects of ADT on physical function by comparing men on continuous ADT with prostate cancer controls and healthy controls [50]. Both control groups showed an increase in physical function scores and six minute walk test scores, while men undergoing ADT showed declines in both these domains. Men on ADT also demonstrated upper extremity decline over the study period.

Management Strategies (Table 6)

In addition to the Keogh et al systematic review [36], which evaluated exercise interventions for men both receiving and not receiving ADT and was discussed previously, a

second systematic review, which only evaluated studies enrolling men on ADT [51], was identified. Both systematic reviews have been included in this evidentiary base as the one conducted by Garner et al [51] is newer than the Keogh et al review [36] and has included additional ADT studies, while the Keogh et al review [36] covers all prostate cancer survivors. The Keogh et al [36] systematic review indicated that exercise may improve muscle mass, muscle strength, functional performance, and social and physical domains of QoL questionnaires. The systematic review by Gardner et al [51] included studies that assessed the effects of aerobic and/or resistance training on treatment-related adverse effects in men receiving ADT and found that exercise training may improve muscle strength, cardiorespiratory fitness, functional task performance, lean body mass and fatigue. One RCT [52] conducted after the search date of the Gardner et al [51] systematic review was identified. The RCT randomized men to either an exercise group or a printed material control group. Men in the exercise group demonstrated significant improvements over the control group in term of cardiorespiratory fitness, lower-body physical function, and improved leg and chest muscle strength, while there were no differences found between groups for total body fat mass, trunk fat mass, percent body fat, estimated visceral adipose tissue, total body weight or waist circumference [52].

Sexual Dysfunction

Rates of Late Treatment Effects (Table 5)

Both the Huang et al [21] and the Stensvold et al [22] cohort studies, which have been discussed previously, assessed sexual dysfunction in men undergoing ADT. The Huang et al [21] cohort study found that all men experienced a worsened sexual function and bother immediately after treatment and little or no recovery over the four year study period. Conversely, the Stensvold et al [22] cohort study reported that men experienced sexual bother immediately after ADT, but that 47% of men who received RT plus ADT regained their baseline sexual bother rates by two years post-treatment.

Urinary Dysfunction

Rates of Late Treatment Effects (Table 5)

Both the Huang et al [21] and the Stensvold et al [22] cohort studies assessed urinary dysfunction in men undergoing ADT. The Huang et al [21] study reported a gradual urinary function decrease and bother increase over the four-year study period for men on ADT, while the Stensvold et al [22] study reported that men on ADT experienced an initial increase in urinary bother, but that for 75% of enrolled men, baseline scores were regained by two years post-treatment.

Table 5. Rate of late side-effects for androgen deprivation therapy.

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Anemia			
Systematic Review			
Grossmann and Zajac, 2012 [43]	• Not specified	• ADT	• Reviewed studies on effects of androgens on red blood cell lineage • ADT-associated anemia may contribute to fatigue and reduced QoL • No data evaluating treatment of ADT-associated anemia on clinical outcomes
Body Composition Alterations			
Systematic Review with meta-analysis			
Haseen et al, 2010 [44]	• Pooled 16 studies	• ADT	• Reviewed longitudinal studies that examined the association between ADT treatment and changes in body composition, including increased fat and reduced lean mass • There was high heterogeneity (I^2) among the pooled studies • Body fat increased 7.7% (95%CI, 4.3-11.2; p<0.0001; I^2, 99%) after treatment with ADT • ADT decreased lean body mass by 2.8% (95%CI, (-)3.6-(-)2.0; p<0.001; I^2,73%) • ADT increased body weight by 2.1% (95%CI, 1.4-2.9; p<0.0001; I^2, 55%) • ADT increased BMI by 2.2% (95%CI, 1.2-3.1; p<0.0001; I^2, 63%)
Cohort Studies			
Timilshina et al, 2012 [45]	• n = 85 ADT cases, 86 PCa controls, 86 healthy controls	• CADT, PCa control not on ADT, healthy controls	• Case-control study examined long-term weight gain for men on ADT over 36 months • Weight was assessed before treatment, then every 6 months during the 36 month study period • At baseline, cohorts were similar in age, education, BMI, weight and comorbidity • Treatment with ADT resulted in weight gain above baseline at 6 months post-initiation (MPI; p=0.006), 12MPI (p=0.015), 18MPI (p=0.028), 24MPI (p=0.003), 30MPI (p=0.014), 36MPI (p=0.0004) • Proportion of men that gained weight over study was higher for ADT group than both control groups at 3MPI (p=0.08), 6MPI (p=0.024), 24MPI (p=0.026) and 36MPI (p=0.002) • Among men on ADT, patients less than 65 years of age had a greater weight gain over time compared with men over 65 years of age (4.7kg vs. 1.4kg; p=0.005)
Bylow et al, 2011 [46]	• 63 cases and 71 controls	• ADT after BC relapse	• Case-control study compared older men (older than 60 years of age) on ADT due to BC relapse with PCa survivors without BC relapse to assess whether ADT contributes to geriatric frailty • 8.7% of men on ADT showed obese frailty compared with 2.9% controls (p=0.02) • 56.5% of men on ADT were pre-frail compared with 48.8% on controls (p=0.02)
Spry et al, 2013 [47]	• n = 72	• IADT	• Analyzed FM, whole body, and regional LM alterations over 33 months • Following the treatment phase, LM decreased by 1.3kg (p<0.001) while FM increased by 2.3kg (p<0.001). Levels did not further change nor return to baseline during the follow-up phase

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• Men who failed to recover testosterone levels by month 33 experienced significant increase in FM compared with those who recovered to eugonadal levels (p=0.019) • Changes in testosterone were correlated to changes in percent FM (r, -0.314; p=0.028) and LM (r, 0.3.00; p=0.036) during follow-up phase
Bowel Dysfunction			
Cohort Study			
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years of follow-up • QoL assessment included elements from both the SF-36 and the UCLA-PCI at baseline and then every six months • Bowel function and bother: o ADT group experienced gradual decrease in function and bother through year 2, then no change
Stensvold et al, 2013 [22]	• n = 462	• RArP, RT, or RT+ADT	• Study assessed bowel, urinary and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completing of treatment • Bowel, urinary and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the SF-12, and neuroticism was assessed with the appropriate section of the EPQ • By two years post-treatment, 59% of men who received RT+ADT had regained baseline bowel bother rates
Cognitive Side-Effects			
Systematic Review with meta-analysis			
McGinty et al, 2014 [48]	• Pooled 14 studies	• ADT	• Examined the effects of ADT on seven cognitive domains: attention/working memory, executive functioning, language, verbal memory, visual memory, visuomotor ability and visuospatial ability • Men treated with ADT demonstrated worse functioning in visuomotor ability domain (p=0.008) • Magnitude of deficit larger in studies where a shorter follow-up time after ADT treatment (p=0.04) • No detrimental effects were found for attention/working memory, executive functioning, language, verbal memory, visual memory or visuospatial ability
Depression and Psychological Impact			
Case-control and Cohort Studies			

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Timilshina et al, 2012 [63]	• n = 85 ADT cases, 86 PCa controls, 86 healthy controls	• CADT, PCa control, healthy control	• Case-control study compared depression rates for men on continuous ADT to PCa survivors who did not receive ADT and healthy controls • 8.9% of men on ADT compared with 1.4%% of PCa controls and 5.0% of health controls developed incidences of depression over the 12-month study (p>0.05) • Among men not depressed at baseline, ADT was not a significant predictor of depression symptoms at 3MPI (p=0.42), 6MPI (p=0.25) or 12MPI (p=0.19) • Among men who were depressed at baseline, ADT was not a significant predictor of depression symptoms at 3MPI (p=0.11), 6MPI (p=0.74) or 12MPI (p=0.12)
van Tol-Geerdink et al, 2011 [64]	• n = 287	ADT after RT	• Compared ADT use at two clinics to determine whether ADT resulted in increased depression and if the depression is due to ADT itself or poor prognosis associated with its use • At clinic 1 (n=198) almost all patients receive ADT, representing effects of ADT, while at clinic 2 (n=89) ADT only given to high-risk patients, representing effects of poor prognosis • During ADT treatment, depression was significantly increased for men in both clinic 1 (p<0.001) and clinic 2 (p<0.01)
Couper et al, 2009 [33]	• n = 211	• rP, ADT or other early treatment (OET; included EBRT and BT)	• Compared psychological domains for men receiving treatment for localized PCa to men who chose watchful waiting (WW) • Depression and anxiety were assessed by the Brief Symptom Index, while physical and psychosocial aspects of QoL were assessed by the Short-Form Health Survey, both at treatment initiation (T1) and 12 months post-treatment (T2) • At T1: o Men scheduled to receive ADT reported poorer vitality levels than WW controls (p<0.001) o ADT patients reported higher depression scores than WW (p<0.05) • At T2: o Men in ADT group reported higher depression (p<0.05) and anxiety scores (p<0.05) than WW controls o ADT men also reported worse QoL domains including physical function (p<0.001), role-physical (p<0.01) and vitality (p<0.01) compared with controls
Health-related QoL			
Cohort Studies			
Black et al, 2007 [66]	• n = 43	• RRP + ADT	• Men randomized to ADT (n=21)or observation (n=22) after RRP • Study assessed testosterone and hemoglobin kinetics in correlation with QoL over 24 months • Serum testosterone levels were castrate in 90% of men at 3MPI and 100% of men at 6MPI

Study	Sample Size	Primary Treatment	Rate or Level of Distress
			• General QoL showed no decline with ADT • Sexual functioning declined during ADT treatment compared with controls, but returned to baseline levels by 24MPI
Sterba et al, 2011 [67]	• n = 43 spouses	• Not applicable	• Companion study to Black et al cohort study [66] • QoL for spouses was assessed every six months over two year study period by telephone interview • Spouses experienced mental health functioning improvements over study period ($p<0.05$) • Spouses with husbands in the observation control group has worse mental disturbance ($p=0.01$) and worse mental health ($p=0.02$) scores than women with husbands in ADT group • Physical health in spouses was directly associated with degree of symptoms experienced by her husband ($p=0.02$) • There was no change in sexual bother for all women, but women reported worse sexual function at 18 and 24 months compared with baseline ($p=0.02$)
Hot Flushes			
Cohort Study			
Ulloa et al, 2009 [49]	• n = 68	• ADT	• Examined relationship between ADT-related hot flushes and distress during first three months of ADT treatment • Hot flush frequency and severity was assessed before treatment with ADT, at six weeks and at three months post treatment initiation • Men were asked if they had experienced a hot flush in the previous two weeks and if they had, they were asked to estimate the number experienced and the severity using a four-point scale • Total hot flush score was calculated by multiplying hot flush frequency by hot flush severity • Men also completed the Hot Flash-Related Daily Interference Scale (HFRDIS) to assess the degree to which hot flushes interfere with daily activities at the six week and three month time points • Cancer-related distress was assessed by the Impact Even Scale (IES) at baseline and three months post-ADT • At six weeks post-ADT initiation, 53% of men reported experiencing hot flushes • No change in distress within the cohort over the three month study • Men who did not experience hot flushes showed a reduction in cancer-related distress compared with baseline ($p=0.01$)
Physical Function			

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Cohort Study			
Alibhai et al, 2010 [50]	• n = 87 cases of men on ADT, 86 PCa controls, 86 healthy controls	• CADT, PCa controls, healthy controls	• Evaluated the effects of ADT on physical function over 12 months • Physical function was assessed by the six minute walk test (6MWT), grip strength, and timed-up-and-go (TUG) test at baseline, three, six and 12 months • QoL assessed at the same intervals using the SF-36 questionnaire • For men on ADT, distance traveled in a 6MWT did not change over the 12 months (p=0.96), while both controls groups showed improvement (p<0.05) • ADT men showed upper extremity decline according to the grip strength test (p=0.04), while PCa control group showed no change over 12 months (p=0.31) and healthy control group showed improvement (p-0.008) • Lower extremity strength, measured by a timed-up-and-go tests did not change over time or across groups • QoL questionnaires indicated that men on ADT experienced a decline in physical function summary scores (p<0.001) over the 12 months, while both control groups showed an increase (p<0.001)
Sexual Dysfunction			
Cohort Study			
Stensvold et al, 2013 [22]	• n = 462	• RArP, RT, or RT+ADT	• Study assessed bowel, urinary and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completion of treatment • Bowel, urinary and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the SF-12, and neuroticism was assessed with the appropriate section of the EPQ • By two years post-treatment, 47% of men who received RT+ADT had regained baseline sexual bother rates
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years follow-up • QoL assessment included elements from both the SF36 and the UCLA-PCI at baseline and then every six months • Sexual function and bother: o All men experienced worsened sexual function and bother immediately after treatment o Men experienced little or no recovery after decline for both function and bother domains
Urinary Dysfunction			
Cohort Study			

Study	Sample Size	Primary Treatment	Rate or Level of Distress
Stensvold et al, 2013 [22]	• n = 462	• RArP, RT, or RT+ADT	• Study assessed bowel, urinary, and sexual bother evolution from pre-treatment to two years post-treatment • Men were assessed with multiple questionnaires pre-treatment (baseline), then at three, six, 12 and 24 months after completion of treatment • Bowel, urinary, and sexual bother was scored with a Norwegian translated version of the UCLA-PCI, physical and mental QoL with the SF-12, and neuroticism was assessed with the appropriate section of the EPQ • By two years post-treatment, 75% of men who received RT+ADT had regained baseline urinary bother scores
Huang et al, 2010 [21]	• n = 1269 from CaPSURE registry	• rP, EBRT, BT, BT+EBRT, or ADT	• QoL evolution from diagnosis through four years of follow-up • QoL assessment included elements from both the SF-36 and the UCLA-PCI at baseline and then every six months • Urinary function (incontinence) and bother (irritative and obstructive voiding): o For ADT, gradual decrease in urinary function and bother over four years

Note: For studies that appear in both Table 3 and Table 5, only ADT-specific data are included in Table 5.
Abbreviations: ADT, androgen deprivation therapy; BC, biochemical; BMI, body mass index; BT, brachytherapy; CADT, continuous course ADT; EBRT, external beam radiotherapy; EPQ, FM, fat mass; IADT, intermittent course ADT; LM, lean mass; MPI, months post-initiation; PCa, prostate cancer; QoL, quality of life; RArP, robot-assisted radical prostatectomy; rP, radical prostatectomy; RRP, radical retropubic prostatectomy; RT, radiation therapy; SBRT, stereotactic body radiotherapy; SF, Short Form.

Table 6. Interventions for management of late side-effects from androgen deprivation therapy.

Study	Sample Size	Intervention	Effects of Intervention
Physical Function			
Systematic Review			
Keogh and MacLeod, 2012 [36]	• Reviewed 12 studies	• Any exercise intervention	• Summarized effects of exercise on symptoms and QoL • Studies enrolled both men receiving and not receiving ADT • Strong evidence suggests exercise may improve muscle mass, muscle strength, functional performance, and social and physical domain of QoL tools • Group-based interventions appear to provide more benefit than home-based program, especially when resistance training is included
Gardner et al, 2014 [51]	• Reviewed 10 studies	• Aerobic and/or resistance training	• Assessed the effects of aerobic and/or resistance training on treatment-related adverse effects in men receiving ADT • The review authors found it difficult to compare the effects of exercise intervention as there was substantial variability among the exercise regimens employed in the studies

Study	Sample Size	Intervention	Effects of Intervention
			• Exercise training improved muscle strength, cardiorespiratory fitness, functional task performance, lean body mass and fatigue • Impact of exercise on adiposity, QoL, cardiometabolic risk markers and bone health remain controversial
RCT			
Galvao et al, 2014 [52]	• n = 100	• Combined progressive resistance and aerobic training	• RCT randomized men to either the exercise group or the printed material control group • Men in the exercise group attended supervised resistance and aerobic training twice a week plus two exercise session a week for six months, followed by six months of home-based exercise • The control group received an educational booklet and recommendation to perform 150 minutes of moderate activity every week for 12 months • Compared with the control group, men in the exercise group demonstrated improvements in cardiorespiratory fitness at six ($p=0.029$) and 12 months ($p=0.028$), lower-body physical function at six ($p=0.006$) and 12 months ($p=0.001$), improved leg muscle strength at six ($p<0.001$) and 12 months ($p=0.011$) and improved chest muscle strength at six ($p=0.004$) and 12 months ($p=0.015$) • Exercise intervention resulted in improved QoL domains, including physical functioning at six ($p=0.006$) and 12 months ($p=0.002$), role physical at six months ($p=0.021$), social functioning at six months ($p<0.001$), role emotional at 12 months ($p=0.025$), and the mental health component summary score at six months ($p=0.025$)
Hot Flushes			
Systematic Review			
Frisk, 2010 [53]	• Reviewed 5 RCTs	• Treatments for hot flushes	• Evaluated treatments for hot flushes • Treatments with positive affects resulted in 75% decrease in number of hot flushes experienced by enrolled men and included: ○ Diethylstilbestrol ○ Megestrol acetate ○ Cyproterone acetate • Small cohort studies indicated venlafaxine and medroxyprogesterone may reduce the incidence of hot flushes, but not yet verified by RCTs • Few of the identified studies noted side-effects of the treatments, but noted side-effects included: ○ Gynecomastia, weight gain, muscle spasms, insomnia, depression, headache, flu-like symptoms, elevated blood pressure • None of the studies evaluated long-term effects • No RCTs evaluated effects of selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, intravenous nutrient therapy or acupuncture

Abbreviations: ADT, androgen deprivation therapy; QoL, quality of life; RCT, randomized controlled trial.

Ongoing Studies

Ongoing studies were searched through https://clinicaltrial.gov with three studies identified. PROMOTE exercise trial that has an unknown status and hasn't been updated since August 2011 (NTC01410656). PROCAN RCT, which is a sexual and urological intervention not yet recruiting (NTC02103088). Finally, an erectile dysfunction intervention study following RT or 'basic' prostatectomy that is recruiting (NTC01996852). The literature search also identified one RCT that is still recruiting [78] which will randomize men starting ADT to either 12 month individualized home exercise program or control and will measure bone health, physical function, and QoL.

Question 4: Is there a relationship between the model of follow-up care in terms of care provider, setting, availability of patient navigator or mentor, and the effective detection and management of progression or metastatic disease?

The search for existing systematic reviews identified two systematic reviews to inform this research question, while the current systematic review of the primary literature identified three RCTs and one controlled before-and-after study. Two systematic reviews [39,54] and one study [55] summarized studies assessing the holistic needs of survivors. Two additional studies evaluated models of follow-up care, with one focusing on nurse-coordinated care [56] and the other on a shared model [57]. A final study evaluated the association between satisfaction with care and survivor QoL [76].

Models of Care incorporating Holistic Needs of Survivors

A systematic review examined studies that evaluated interventions aimed at improving psychological adjustment and QoL in men with prostate cancer and their partners [39]. The review included 21 RCTs that were published from 1999 through 2009 and were all deemed to be of low quality. Weak evidence indicated that group cognitive-behavioural and psycho-education interventions promoted better psychological adjustment and improved QoL. Weak evidence also indicated that coping skills training for couples improved QoL for both prostate cancer patients and their partners. Research in this area is lacking, especially for minority groups and men with advanced disease.

A second systematic review summarized literature focused on the effects of diet and dietary supplements of prostate cancer progression, recurrence and survival [54]. The review included 32 studies published from 1996 through 2007, nine of which were RCTs with a PSA as an end point and were reviewed in more detail than the non-RCT studies. Very weak evidence identified by this review indicated that diet and dietary supplement interventions slows disease progression with varying results. In three studies a significant decrease in PSA was observed with low-fat vegan diets, soy beverages, or lycopene supplementation. Another study found that lycopene supplementation resulted in significantly increased PSA doubling time. The review points to a lack of well-designed trials in this area.

An RCT published after the search dates of the included systematic reviews compared a holistic intervention with control for prostate cancer survivors with rising PSA levels [55]. Survivors were randomized to either an intensive diet, physical activity, and meditation intervention, or a control group. The intervention was a six-month cycle with 'homework' assignments that consisted of cooking the recommended diet, physical activity, and stress reduction activities. Men in the intervention group experienced a 39% decrease ($p<0.0001$) in saturated fatty acids and a 12% decrease ($p<0.05$) in total calorie intake; however, this did not result in any change in PSA level.

Nurse-led Follow-up Care

An RCT that compared on-demand contact with a specialist nurse versus traditional follow-up by an urologist (specialist) for prostate cancer patients with newly diagnosed or previously known disease at any stage was conducted in Sweden [56]. The study compared outcomes in safety, patient satisfaction and resource utilization. In the nurse follow-up group, the men were contacted by the nurse every six months by telephone for three years, or the patient could initiate contact if they had concerns. As well, the specialist nurse could consult directly with an urologist or other specialists if a patient had signs and symptoms of progressive disease. The study demonstrated that there was no difference between groups when looking at lag time between diagnosed symptoms and intervention and amount of hospital care (545 days specialist-led versus 403 days nurse-led), indicating equivalent safety and resource utilization. There were also no significant differences in depression and anxiety between the groups, using the Hospital Anxiety and Depression Scale. Finally, the study found that patients were equally satisfied with both forms of follow-up care.

Shared Care Model

An RCT compared a multidisciplinary rehabilitation intervention to usual care for follow-up care of prostate cancer survivors [57]. The study randomized 161 prostate cancer patients to either intervention or control after completion of RT and ADT. Men in usual care (control group) received one visit with an oncologist four weeks after RT, plus muscle strength tests at four weeks and 20 weeks post-RT. In addition to the follow-up provided to men in the control group, men in the intervention group also received two visits with a physical therapist (at four weeks and eight weeks post-RT) and two visits with an oncology nurse (at eight weeks and 20 weeks post-RT). The physical therapist provided guidance on functional home training, pelvic floor exercises, and an individualized training plan, while the oncology nurse identified patient needs in relation to lifestyle, psychological support and sexual problems. Men in the intervention group were also invited to bring their spouses to all counselling and instruction sessions to increase understanding. The primary outcome of the RCT was the urinary irritative sum-score, based on the Expanded Prostate Index Composite (EPIC-26). Secondary outcomes included QoL, based on the SF-12, as well as urinary incontinence, bowel, sexual and hormonal sum-scores, assessed by the EPIC-26. Compared with usual care, men in the multidisciplinary intervention demonstrated improved urinary irritative sum-scores (p=0.011), urinary sum-scores (p=0.023), hormonal sum-scores (p=0.018), and physical component domains of QoL (p=0.002). Pelvic floor muscle strength declined in both groups compared with pre-treatment (p=0.0001), with no difference between intervention and control. There were no significant changes demonstrated for incontinence, bowel or sexual sum-scores, as measured by the EPIC-26.

Patient Satisfaction with Care

A controlled before-and-after study followed newly diagnosed prostate cancer patients for two years and analyzed the association between patient-reported satisfaction with care and QoL [76]. The study enrolled 590 men who were to receive curative treatment with rP or EBRT. The men completed the Client Satisfaction Questionnaire (CSQ-8) to assess satisfaction with care and both the SF-36 and The University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) to assess QoL before treatment, then at three, six, 12 and 24 months post-treatment. Men treated with rP reported higher satisfaction with care scores than those treated with EBRT (odds ratio [OR], 7.9; p=0.043), which was associated with improved QoL scores.

Ongoing Studies

Upon searching the http://clinicaltrials.gov database for ongoing studies, one study was identified. This study is investigating family physician led follow-up for men after RT treatment and is currently suspended for data review (NTC00823771).

Study Summary

This research question focused on the holistic needs of prostate cancer survivors, as well as the follow-up care models. An identified systematic review evaluated the literature that focused on effects of diet and found very weak evidence for a decrease in PSA with low fat vegan diets, soy beverages and lycopene supplementation [54]. An RCT, which assessed a holistic intervention of intensive diet, exercise and meditation, found that the intervention results in decreased saturated fatty acids and total caloric intake, but no change on PSA level [55]. Two RCTs evaluated follow-up care models, with one comparing nurse-led care with traditional urologist-led care [56], and the other comparing a shared care model with usual care [57]. The nurse-led follow-up study indicated that nurse-led care was not inferior to urologist-led care when lag time, amount of hospital care time, depression, anxiety and satisfaction with care outcomes were compared [56]. The shared care model randomized men to follow-up visits with the treatment oncologists, plus a physical therapist and an oncology nurse and resulted in improved urinary scores and physical component domains of QoL, but no change in incontinence, bowel, or sexual scores compared with the usual care group [57]. The final identified cohort studies found that satisfaction with treatment care was associated with improved QoL scores [76].

DISCUSSION

Question 1: What is the appropriate timing for PSA testing?

In order to adequately inform this research question, the Working Group originally planned to only include RCTs that compared PSA testing schedules. It was believed that evidence-based guidance could only be obtained from randomized comparative data. Unfortunately, both the search for existing systematic reviews and the systematic review of the primary literature did not identify any evidence. This lack of evidence is of great concern as without it, health care providers and guideline development groups must depend on knowledge of PSA kinetics to base timing decisions. It is well established that after rP, PSA usually drops to an undetectable level (<0.03ng/mL) within two months, while after any form of RT, PSA falls slowly and reaches its lowest level, or nadir, after at least six months. Any detectable PSA level following surgery or a PSA level above the PSA nadir indicates the possibility of BC recurrence. Due to the lack of evidence, the Working Group used a consensus approach to make a recommendation on a PSA testing schedule. The Working Group considered other clinical practice guidelines [1,2,61,79], the primary therapy received, PSA kinetics following that therapy, and their clinical experience. For men who have received curative-intent treatment with surgery, PSA testing should occur every three months in year 1, followed by every six months until end of year 2 and then annually until end of life. For men who received curative-intent treatment with non-surgical primary therapy, including any form of RT, cryotherapy, or HIFU, PSA testing should occur six months after treatment completion, followed by every six months until the end of year 5 and then annually until end of life. Although the Working Group feels confident in recommending annual screening until end of life, health care professionals should use their own discretion in determining the applicability of annual PSA testing in men who are unlikely to benefit from treatment if BC recurrence is detected.

Question 2: After biochemical recurrence, what diagnostic tests are effective at detecting progression or occurrence of metastasis? What are the common symptoms of symptomatic recurrence?

Very limited evidence was identified for appropriate diagnostic imaging after BC recurrence. The studies that were identified focused on bone scan, CT, MRI and PET/CT. An identified meta-analysis indicated that MRI had high diagnostic performance and was able to accurately detect local recurrence with a sensitivity of 82% (95% confidence interval [CI], 78-86%) and a specificity of 87% (95%CI, 81-92%) after rP, and sensitivity of 82% (95%CI, 75-88%) and specificity of 74% (95%CI, 64-93%) after EBRT [9]. Primary studies conducted after the meta-analysis also indicated that MRI can localize local recurrence after rP [12] and may be promising for biopsy guidance after HIFU [11]. An additional meta-analysis found that MRI has low sensitivity (39%; 95%CI, 22-56%) for detection of lymph node metastases from prostate cancer [13].

A second meta-analysis, which evaluated PET/CT, found that choline PET and PET/CT showed high sensitivity (all sites: 85.6%; 95%CI, 82.9-88.1%) and specificity (all sites: 92.6%; 95%CI, 90.1-94.6%) for detection of locoregional recurrence and distant metastatic disease in men with BC recurrence [6]. A prospective cohort study conducted after the meta-analysis indicated that NaF PET/CT may be a useful diagnostic tool for detection of occult disease with a positive predictive value of 64% and a negative predictive value of 73% [7]. A second prospective cohort study correlated the sensitivity of FCH PET/CT to PSA level and found sensitivity was only 33% for men with a PSA level of less than 0.3ng/mL and 77% for men with a PSA level greater than 0.3ng/mL (p=0.001) [8].

A large prospective cohort study, which was limited by a small sample size of men with PSA levels above 5ng/mL, sought to determine the PSA level at which bone scans are positive for men with BC recurrence [5]. The study found that bone scans are very rarely positive at PSA levels below 5ng/mL [5]. The other two identified studies that assessed bone scan, the gold standard for bone metastases detection, compared bone scan to a newer diagnostic imaging modality. One study found that WBMRI demonstrated an increased sensitivity for detection of bone metastases compared with bone scan plus targeted X-ray [3], while the other found that imaging with FECH PET/CT did not significantly increase sensitivity beyond a bone scan [4].

According to the postoperative radiotherapy guideline jointly published by the American Urological Association and the American Society of Radiation Oncology, patients with adverse pathologic features, such as seminal vesicle invasion, extracapsular spread or positive margins and those with BC recurrence and no evidence of distant metastatic disease, should be offered postoperative RT [14]. In the guideline, BC recurrence was defined as a detectable or rising PSA value after surgery of >0.2ng/mL and a second confirmatory level >0.2ng/mL. Given that the vast majority of men with recurrent disease after prostatectomy will have a PSA of less than 5ng/mL and the fact that salvage RT control rates are poor when PSA is greater than 2ng/mL [15], routine restaging investigations are not warranted.

Local salvage therapies, including prostatectomy and BT have been shown to have reasonable biochemical salvage rates of 54-61% [16,17], but generally worse genitourinary and gastrointestinal late side-effects compared with primary therapies, while salvage cryotherapy and HIFU appear to have inferior control rates [17,18]. Therefore, salvage prostatectomy or BT are reasonable options for selected, motivated, and informed men. Appropriate men will include those with biopsy proven local recurrence and an absence of distant metastases, as results seem to be better when relapse PSA is less than 10ng/mL [16,17].

Due to the limited available evidence identified by the systematic review, plus the known data on available salvage therapies, the Working Group decided to summarize the

identified diagnostic tests according to their appropriateness for use. The Working Group is concerned about the overuse of diagnostic tests that do not affect patient management. For example, if the treating oncologist suspects BC recurrence after treatment with rP and plans to treat with salvage RT, it is not clear whether an MRI-based diagnosis of local recurrence would affect this decision. Thus, for each diagnostic test, the Working Group weighed the ability of the test to inform the next stage of treatment against the over-use of the test. Diagnostic tests that may be considered upon BC recurrence are summarized in Table 7 and defined as usually appropriate, sometimes appropriate, or not usually appropriate in a clinical setting, based on the available evidence and its quality, as well as the clinical experience of the Working Group members.

Table 7. Appropriateness of diagnostic imaging upon biochemical recurrence.

Diagnostic Test	Appropriateness	Notes
When local salvage therapy is planned after radiotherapy:		
Bone scan	Usually appropriate	• Appropriate for all men being considered for local salvage therapy
CT	Usually appropriate	• Appropriate for thorax, abdomen and pelvis imaging
Multiparametric MRI	Sometimes appropriate	• Appropriate when used for targeted biopsy
FDG, NaF, or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental
When salvage radiotherapy is planned after radical prostatectomy:		
Bone scan	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
CT	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
Multiparametric MRI	Not usually appropriate	• If performed before initiating salvage RT, would not change treatment decision
FDG or NaF or choline PET	Not usually appropriate	• Use of NaF and choline PET should be considered experimental

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NaF, sodium fluoride; PET, positron emission tomography; PSA, prostate specific antigen; RT, radiation therapy.

Published data indicate that 30% to 50% of men will develop BC recurrence within 5 years following treatment with surgery or RT [61]. For men who are going to experience recurrence, scheduled PSA testing greatly increases the chance that BC recurrence detection occurs before clinical recurrence with associated symptoms. However, if men are not regularly followed with PSA testing, they may present with clinical recurrence symptoms that require evaluation. Unfortunately, the literature search designed to identify the symptoms of clinical recurrence did not return any systematic reviews or studies. Due to this lack of evidence, the Working Group decided to use a consensus process to list the symptoms of clinical recurrence in their expert opinion. During the project planning stage of the guideline, the clinical experts provided the methodologist with a list of symptoms to use when designing the literature search. The methodologist created a draft list of symptoms, which the clinical experts then voted on including. The final list of symptoms agreed upon by the Working Group is included in Table 8. These symptoms warrant further evaluation based on the symptoms. Additionally, PSA testing should be performed on these men.

Table 8. Symptoms of clinical recurrence.

• Severe and progressive axioskeletal bone pain

- Unexplained weight loss
- Hematuria
- New urinary symptoms
    - Significant incontinence requiring changing of undergarments, pads, or diapers
    - Urgency
    - Obstructive symptoms
    - Voiding discomfort
    - Nocturia
- Swelling of legs
- New bowel symptoms
    - Rectal bleeding
    - Rectal pain
    - Urgency
    - Change in bowel movement
- Fatigue
    - Tiredness unrelated to sleep disturbance
    - Lack of energy
    - Weakness or lack of muscle strength
    - Physical, emotional and/or cognitive exhaustion

Question 3: What are the rates and level of distress for common late side-effects of prostate cancer treatment? What interventions are available to manage late treatment effects?

Following curative-intent treatment, men experience very specific and oftentimes long lasting effects from their treatment. For men undergoing ADT, the subset of treatment side-effects is even larger. It has been well established that all primary treatments cause sexual side effects, while RT results in increased incidences of bowel and urinary dysfunctions, and ADT leads to more negative physical effects. The Working Group decided *a priori* that only RCTs and systematic reviews of RCTS would be used to inform intervention evidence for this research question, while prospective cohort studies would be added for reporting of side-effect bother rates. Unfortunately, since all non-randomized studies carry an unclear risk of bias and many of the studies relied on the use of self-reported QoL tools, which inherently introduce recall bias, it was believed that the studies informing this evidence were of moderate to low quality. The literature was divided into treatment side-effects caused by surgery or any form of RT, and those caused by ADT. Since men on ADT may still experience some of the same common side-effects as men who received surgery or RT, Table 9 is organized according to side-effect. Additionally, Table 9 indicates which primary treatment can cause the side effect, but prevalence rates are not included. For these studies, data are difficult to compare and summarize because different studies recruited different populations, used different instruments to assess the side-effects, and in many instances, defined the outcomes differently. Thus, all of the included side-effects may occur after the primary therapy indicated in Table 9. For management strategies, where no RCTs existed, the clinical standard, in accordance with other guidelines, best available evidence, and expert clinical opinion, have been included in Table 9.

When evaluating curative-intent therapy with surgery or any form of RT, an identified systematic review [19], as well as several more current cohort studies [20-26], found that the three most common treatment-related side-effects are bowel, urinary, and sexual dysfunction. Erectile dysfunction is also common, with an identified meta-analysis indicating that 58% of men report erectile function recovery after surgery [27]. Additional cohort studies found that

that men recovered orgasmic function within 24 months of bilateral nerve-sparing radical retropubic prostatectomy [28], while multiple domains of the International Index of Erectile Function (IIEF) and EPIC QoL questionnaires remain reduced through 24 to 36 months of follow-up after treatment with BT [29,30]. Conversely, a failed-to-accrue phase III trial that collected QoL data reported that men treated with brachytherapy experienced more favourable sexual erectile dysfunction recovery than men treated with rP [31]. The identified literature also indicated that after primary therapy, prostate cancer survivors have increased fatigue [32], report worse QoL domains [33], and almost 20% are depressed [34]. Intervention strategies that include exercise aided men experiencing fatigue and declining QoL domains [35,36]. Exercise interventions for survivors are becoming more popular; as such, the Working Group expected to identify more studies looking at the effects of exercise on prostate cancer survivors. Unfortunately, most of the identified exercise intervention studies focused on a mixed cancer survivor population and mixed populations were excluded from this review a priori. The PEBC is currently developing a guideline on exercise interventions for all cancer survivors (GL#19-5) and will address further benefits of exercise, as well as guidance on safety and appropriate types of exercise. Psychosocial counselling interventions also proved beneficial for prostate cancer survivors and resulted in improved psychological well-being [38] and erectile dysfunction [37]. An identified meta-analysis demonstrated that both prophylactic RT and tamoxifen reduce gynecomastia and breast pain in survivors, with RT having a lower rate of adverse effects [65]. Finally, for urinary dysfunction, cohort studies indicated that men treated with both rP and BT experience urinary incontinence and irritation [30,31], with brachytherapy treatment demonstrating more favourable recovery [31]. A meta-analysis assessed male slings and found that most report similar efficacy for improvement and may be a valid option [40], while cohort studies found that pelvic floor muscle training resulted in increased continence rates [41,42].

When studies that focused exclusively on men undergoing ADT were analyzed, it was determined that these men deal with additional treatment-related side-effects, such as anemia [43], body composition alterations [44-47], cognitive side-effects [48], hot flushes [49], and decline in physical function [50]. Exercise interventions with this specific subset of patients improved muscle strength [36,51,52] and mass [36], cardiovascular fitness [51,52], lean body mass [51] and fatigue levels [51], as well as social domains of QoL tools [36,52]. A final systematic review evaluated treatment for hot flushes and found that treatment with Diethylstilbestrol, Megestrol acetate, and Cyproterone acetate resulted in 75% decrease in the number of hot flushes; however, none of the identified literature evaluated long-term effects of the treatments [53].

Risk of osteoporosis is an additional relevant side-effect that threatens men on ADT. The PEBC is currently developing a guideline focusing on bone health (GL#3-14), which will address the need for guidance in this area. Thus, the Working Group opted to not include osteoporosis as an outcome of interest in this guideline.

Table 9. Common late side-effects of localized prostate cancer treatment.

Side-Effect	Primary Treatment	Management Options
Sexual Dysfunction *A guideline focusing on the sexual health of cancer patients is under development (PEBC Guideline 19-6) and will provide more in depth recommendations for sexual dysfunction outcomes.*		
Erectile dysfunction	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors as first line treatment* • Men who do not respond to PDE5 inhibitors will need more advanced treatments and should be referred to a urologist*

Side-Effect	Primary Treatment	Management Options
		• Men may be referred to penile rehabilitation programs, which include PDE5 inhibitors, vacuum constriction devices, intracorporal or intraurethral therapy, or placement of penile prostheses*
Loss of libido	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling • Testosterone therapy can be considered in men with signs and symptoms of testosterone deficiency and documented low serum testosterone levels provided their cancer is treated and without evidence of persistent or recurrent disease, and if prescribed by the treating oncologist after extensive review of the potential risks*
Anorgasmia	Surgery, RT, and ADT	• Men and their partners should be referred to a healthcare professional with training in sexual health counselling*
Dry ejaculate	Surgery, RT, and ADT	• Men should be educated on dry ejaculate*
Climaturia	Surgery, RT, and ADT	• Men should be provided education on self-management strategies, such as emptying the bladder before sexual relations, use of a condom, use of a penile constriction band, and Kegel exercises*
Penile shortening or curvature	Surgery, RT, and ADT	• Men may be prescribed PDE5 inhibitors, intraurethral and intracorporal prostaglandins, vacuum erection device, or penile prostheses*
Infertility	Surgery, RT, and ADT	• Men and their partner should be informed that men treated with rP will become infertile • Men and their partners should be informed that some men treated with RT may remain fertile, even when experiencing sexual dysfunction symptoms*
Urinary Dysfunction		
Obstructive symptoms	Surgery and RT	• Men should be referred to a urologist to determine whether bladder neck dilatation, transurethral resection, or clean intermittent catheterization may be necessary* • Selective alpha antagonists (not in men who underwent rP) may be prescribed*
Urgency symptoms	Surgery and RT	• If the man is able to completely empty his bladder, anticholinergic medications may be appropriate* • All refractory symptoms should result in a referral to a urologist for evaluation and escalation of therapy if appropriate*
Hematuria	RT	• Men with hematuria should be referred to a urologist for evaluation*
Incontinence requiring urinary pads	Surgery and RT	• Men with persisted leakage impacting QoL should be referred to a urologist to evaluate the cause of incontinence (stress, overflow, etc)* • Exercise intervention including resistance, flexibility, and Kegel exercises may improve continence. Specialized physiotherapists may help patients with stress incontinence following rP • In men with post-prostatectomy incontinence who are unable to perform pelvic floor training, urethral slings or artificial urinary sphincters can be considered
Bowel Dysfunction		
Rectal bleeding	RT	• All men with rectal bleeding should be referred to a gastroenterologist for colonoscopy if not done within five years* • For men with rectal bleeding post-RT, referral to a gastroenterologist who has experience in managing RT proctitis is recommended. The anterior rectum should only be biopsied when absolutely necessary as this can cause a fistula of the rectum*

Side-Effect	Primary Treatment	Management Options
		• For men with bleeding secondary to RT proctitis, the following strategies may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (Salofalk suppositories, topical formalin or argon plasma laser treatments) ○ Refractory RT proctitis should be considered for hyperbaric oxygen
Urgency and frequency symptoms	RT	• For men with urgency and frequency symptoms, the following options may be considered: * ○ Dietary changes to bulk stool ○ Hydration education ○ Medical treatments (antidiarrheals, anticholinergics) ○ Pelvic floor muscle therapy
Other Physical Side-Effects		
Anemia	ADT	• Investigation for common sources of anemia should be considered*
Body composition alterations	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Fatigue	Surgery, RT, and ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Gynecomastia/ Mastodynia	ADT	• In severe cases, surgical excision can be considered and patients should be referred to the appropriate specialist*
Hot flushes	ADT	• Treatment with diethylstilbestrol, megestrol acetate, venlafaxine, cyproterone acetate, and medroxyprogesterone have been shown to decrease number of hot flushes, but should be used with caution because treatment with these medications have been associated with side-effects (e.g., gynecomastia, depression, weight gain, muscle spasms, insomnia, nausea, elevated blood pressure)
Physical activity/ function	ADT	• Men should be encouraged to participate in an exercise program ○ Strategies thoroughly described in PEBC Guideline 19-5 (in development)
Bone health	ADT	• This outcome described in PEBC Guideline 3-14v2 (in development)
QoL and Psychosocial Side-Effects		
Cognitive side-effects	ADT	• Healthcare provider may consider neurocognitive assessment*
Psychological distress (depression and anxiety)	Surgery, RT, and ADT	• In-office psychological therapy and pharmacotherapy as appropriate • Recommendations for depression of cancer survivors are described in PEBC Guideline 19-4v2.
General QoL and Psychosocial sequelae	Surgery, RT, and ADT	• During scheduled follow-up clinical visits, the psychosocial status of men should be assessed and distress should result in referral to specialized psychosocial care* • Patients should be encouraged to participate in an exercise program ○ Strategies more thoroughly described in PEBC Guideline 19-5 (in development) • Referral to applicable support groups for coping training for couples, as well as social and emotional QoL well-being, may be considered

Abbreviations: ADT, androgen deprivation therapy; PDE5, phosphodiesterase 5; PEBC, Program in Evidence-Based Care; QoL, quality of life; rP, radical prostatectomy; RT, radiation therapy.

Question 4: Is there a relationship between the model of follow-up care in terms of care provider, setting, availability of patient navigator or mentor, and the effective detection and management of progression or metastatic disease?

This research question was designed to inform multiple aspects of follow-up care. The Working Group sought to identify the most appropriate model of care in relation to the health care providers involved and the best setting. Additionally, the literature was searched for studies that assessed the availability of psychosocial care, as well as the holistic needs of men, including exercise, nutrition, and returning to work. Unfortunately, very little data were identified to inform this question.

For the holistic needs of men following primary treatment for prostate cancer, the literature search returned one systematic review on diet and one RCT using a holistic intervention. The systematic review evaluated the literature that focused on effects of diet and found very weak evidence for a decrease in PSA with low fat vegan diets, soy beverages and lycopene supplementation [54]. An RCT, which assessed a holistic intervention of intensive diet, exercise and meditation, found that the intervention resulted in decreased saturated fatty acids and total caloric intake, but no change on PSA level [55]. Based on this evidence, the Working Group was unable to provide a recommendation for a specific holistic intervention for prostate cancer survivors. Although exercise is recommended for prostate cancer survivors, the outcome of interest was PSA reduction, which was valued more highly than healthy dietary intake. There is currently no association between exercise, diet or food supplement and a reduction in PSA level.

The remaining two studies identified for this research question focused on the most appropriate provider for follow-up care. One RCTs compared nurse-led care with traditional urologist-led care [56], and another RCT compared a shared care model with usual care [57]. The nurse-led follow-up study indicated that nurse-led care was not inferior to urologist-led care when lag time, amount of hospital care time, depression, anxiety and satisfaction with care outcomes were compared [56]. This study was of high methodological quality; however, the study was conducted more than 10 years ago and PSA testing was not mandatory in either arm. Thus, there was no possibility of detecting symptom-free or BC recurrence, leading to a difference in patient management compared with today and potential generalizability issues. The shared care model study was of high quality and randomized men to usual follow-up with the treating oncologist, or follow-up visits with the treatment oncologist plus a physical therapist and an oncology nurse, resulting in improved urinary scores and physical component domains of QoL, but no change in incontinence, bowel, or sexual scores compared with the usual care group [57]. The Working Group considered the lack of evidence, as well as the limitations of the nurse-led study and accepts these studies as the best available evidence. Additionally, for this research question, QoL and satisfaction with care are highly valued. Although the identified literature only evaluated hospital-based nurse-led care and shared care within the hospital setting, expert opinion supports family physicians being involved in all survivorship care models. Thus, the Working Group believes that transition from specialist-led to family physician or hospital-based nurses may be a reasonable option for prostate cancer survivors. Although the identified literature only evaluated hospital-based nurse-led care and shared care within the hospital setting, expert opinion supports family physicians being involved in all survivorship care models. Additionally, there is a recent clinical trend towards multidisciplinary care that is focused on treating the patient and not just the tumour. Although the shared care model identified by the literature did not include a psychosocial intervention focus, in order to address the holistic needs of prostate cancer survivors, expert opinion supports multiple disciplines being involved in shared care models.

CONCLUSIONS

Based on the available evidence and expert opinion, the Working Group makes the following recommendations for adult men who have completely primary treatment for prostate cancer and who are without evidence of disease:

Timing of PSA testing:

1. Following curative-intent treatment with surgery, prostate cancer survivors should receive PSA testing. If PSA remains undetectable, PSA testing should occur every three months in year 1, every six months in year 2, then annually thereafter. If PSA levels become detectable, a more frequent PSA surveillance schedule may be appropriate.
    a. Even though PSA follow-up is recommended annually until end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in men who are unlikely to benefit from treatment.
2. Following curative-intent treatment with non-surgery primary therapy, including any form of RT, cryotherapy, or HIFU, prostate cancer survivors should receive PSA testing six months after treatment completion, followed by every six months until end of year 5, then annually thereafter.
    a. Even though PSA follow-up is recommended annually until end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in men who are unlikely to benefit from treatment.

Diagnostic tests upon biochemical recurrence:

3. Diagnostic imaging should only be ordered if that test will result in management decisions and the follow-up healthcare provider should consider the appropriateness of the test (Table 7), coupled with available salvage options. Additionally, salvage therapies following RT or ablation therapies is something that needs to be performed at specialized centres, with imaging decisions dependent on the local evaluation process.

Symptoms of clinical recurrence or metastasis:

4. In the expert opinion of the Working Group, if men are being followed as outlined in Recommendations 1 through 3, detection of BC recurrence should occur before clinical recurrence with associated symptoms. However, if men are not regularly followed, they may present with clinical recurrence symptoms that require evaluation, as outlined in Table 8.

Treatment-related side-effects:

5. Following curative-intent treatment, men experience very specific and oftentimes long lasting effects from their treatment. Table 9 summarizes the primary therapies that may cause these side-effects and management strategies for survivors and their follow-up care provider.

Holistic interventions for prostate cancer survivors:

6. The Working Group was unable to provide a recommendation for a specific holistic intervention for prostate cancer survivors. For this research question, PSA reduction was valued more highly than healthy dietary intake and there is currently no association between exercise, diet or food supplement and an improvement in cancer outcomes.

Most responsible care provider and care location:

7. For prostate cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by the treating oncologists or urologist. Surveillance may also be provided by a family physician, nurse practitioner or hospital-based nurses with training in PSA kinetics following prostate cancer treatment with surgery and any form of RT.
    a. Although the identified literature only evaluated hospital-based nurse-led care and shared care within the hospital setting, expert opinion supports family physicians being involved in all survivorship care models. Additionally, with the greater emphasis on a person-centered approach to care, a multidisciplinary approach to survivorship, which includes a psychosocial focus to recovery, is recommended. Although the shared care model identified by the literature did not include a psychosocial intervention focus, in order to provide person-centered care, expert opinion supports multiple disciplines being involved in shared care models.

Guideline 26-4: Section 5

Follow-up Care and Psychosocial Needs of Survivors of Prostate Cancer: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 10 members of the GDG Expert Panel, nine members cast votes and one abstained, for a total of 90% response in February, 2015. Of those that cast votes, nine approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 1.

Table 1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Instead of 'patient' or 'survivor' change to 'men'.	We have changed instances of 'patient' and 'survivor' to 'men' or 'man' wherever possible.
2. I would like the group to consider the use of Patient Reported Outcomes. PROs are important for the clinicians to understand the impact that the treatments have had on the man.	We have added a statement before the table within Recommendation 5 that discusses men respond differently to treatment and that individual outcomes should be measured.
3. There is no recommendation on the role of routine digital rectal examination in follow-up after radical radiotherapy. This is a significant omission as guidance in the role for DRE would be useful to clinicians.	We have added a statement before the symptoms listed in Recommendation 5 that indicates scheduled clinical visits should include a medical history, clinical examination, PSA level testing and a DRE where indicated.
4. The group should consider defining salvage within the recommendation.	We have added a note below the table in Recommendation 3 that defines salvage therapy.
5. I would have appreciated a recommended schedule of proactive follow-up psychosocial care as quality of life aspects were more of a daily impact for me than the potential of cancer coming back.	There is no evidence to support scheduled psychosocial evaluations; however, the Working Group believes that the psychosocial status of men should be assessed during scheduled clinical visits. We have added such a statement to the management option for general QoL within Recommendation 5.
6. For management options that include referral to sexual health counselling, please change to include men and their partners.	We had added 'partner' to any management options that suggests referral to sexual health counselling.
7. Based on the recommendation for gynecomastia management, I am concerned by the potential for pervasive use of breast radiotherapy in this setting and specifically by the potential for late radiation-induced lung cancers, breast cancers or sarcomas in the treated field. The use of ionizing radiation for the management of a benign	We have removed this management option for gynecomastia.

disease such as gynecomastia has to be approached with great caution	
8. No guidance is given as to the "select patients" for whom testosterone supplementation is warranted in Recommendation 5. I am unaware of high-quality evidence for particular clinical scenarios in which testosterone supplementation has been shown to be safe over the long term and none appears to be quoted in the guideline. I would favour a more cautious approach and would recommend removing or at least revising this recommendation.	We have revised this management option to emphasize that the treating oncologist, who may prescribe testosterone supplement, needs to extensively review the potential harms and risks of the treatment.
9. Persistent or marked distress from any symptoms should trigger referral to specialized psychosocial care, consistent with distress screening guidelines. Also, any of the sexual symptoms including erectile dysfunction could trigger referral for sexual health counselling	Within Recommendation 5, we have added to the general QoL management option that men experiencing distress should be referred to specialized psychosocial care.
10. There is no doubt that nurse practitioners, hospital nurses, and family physicians can be trained to expertly interpret PSA kinetics following radiotherapy (and indeed, such follow-up models already exist in many centres), but this is not a part of the usual training of either nurses or family physicians. If the Working Group is recommending – in the absence of any published evidence – family physician-led or nurse-led follow-up care after radical radiotherapy, then in my view it must also recommend that family physicians and nurses receive appropriate formal training in the interpretation of PSA kinetics after radiotherapy as this is not a part of the usual training of these clinicians.	We have added a Qualifying Statement to Recommendation 7 which states that all healthcare practitioners that provide PSA surveillance must have training in PSA kinetics following primary therapy for prostate cancer.
11. There should be more info to indicate what is meant by 'fatigue' in Recommendation 4 given that other symptoms are broken down into components.	We have further defined fatigue within Recommendation 4 based on domains of various fatigue assessment scales.

Report Approval Panel Review and Approval

Three RAP members, including the Program in Evidence-Based Care (PEBC) Director, reviewed this document in January and February 2015. The RAP approved the document on March 4, 2015. The main comments from the RAP and the Working Group's responses are summarized in Table 2.

Table 2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. It is not stated a priori how recommendations will be crafted when evidence is limited. A consensus approach is	Within Section 2 we have clarified when a consensus process has been used and have justified the reasons behind this decision. Since drafting of the

mentioned for Question 1 but guideline formulation methods are less clear for Question 2	recommendations is not part of the systematic review methods, but is instead part of the guideline development methods, it was believed that adding this information to the systematic review methods (Section 4) would be inappropriate.
2. For "hot flushes" from ADT, the implication is that it is safe to prescribe DES, megestrol or cyproterone based on meta-analyses showing benefit. As RCTs of DES and meta-analyses of the addition of non-steroidal antiandrogens to monotherapy ADT have shown these increase mortality, this should be approached with some caution.	We have modified the management option for hot flushes within Recommendation 5. We have added that these medications should be used with caution as they have all been associated with side-effects.
3. Question 3 addresses rates and level of distress but these are not addressed in the recommendations. Could this be included in the Table recommendation 5, as it is in the results section?	The Working Group initially planned to include the rates and levels of distress within Recommendation 5, but due to the large variability within the identified studies, the ranges for these values were thought too broad to actually provide any benefit for readers.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Eight targeted peer reviewers from Ontario and Alberta who are considered to be clinical experts on the topic were identified by the Working Group. Four agreed to be the reviewers and three provided feedback (Appendix 1). Results of the feedback survey are summarized in Table 3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 4.

Table 3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			2		1
2. Rate the guideline presentation.				2	1
3. Rate the guideline recommendations.			1		2
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. Rate the overall quality of the guideline report.			1	1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	1
8. I would recommend this guideline for use in practice.			1	1	1

9. What are the barriers or enablers to the implementation of this guideline report?	Barriers – getting busy practitioners to take the time to review the guideline

Table 4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. For many of the recommendations there is a good evidence base. However for most recommendations they are based on the expert opinion of the panel members. As excellent as the panel members are there might have been more effort to seek validation from a large group. Furthermore, with respect to the literature review it doesn't appear that much if any weight was given to papers written based on expert opinion.	As part of the guideline development process, the draft recommendations were developed by the 10 Working Group members and approved by a further 13 internal reviewers. The GDG did rely on their expert opinion when evidence was not sufficient to inform an evidence-based recommendation. The GDG believes that the consensus approach used for expert opinion-based recommendations allowed for a dialogue about the issues among the experts and minimized bias that may have been introduced by a smaller group.
2. There appears to have been very limited involvement of psychosocial experts as part of the Working Group, given that the guideline purports to address "psychosocial needs" – even if it is the secondary aim of the guideline, the title leads the reader to believe it is a significant focus. Yes, it is perhaps understood by some readers that "psychosocial" includes the entire range of "non-medical" needs including sexual dysfunction, fatigue, nutrition, etc. – but the emotional effects still remain under-represented.	The GDG sought to address all psychosocial needs reported by prostate cancer survivors both in the literature and in the medical and psychological clinics run by the GDG panel members. The GDG believes that the guideline did address QoL issues, as well as depression and levels of distress. To help highlight these issues, headings within Recommendation 5 have been altered.
3. There are good papers with treatment guidelines that I think are in a more clinically helpful form. Perhaps references for some of these papers could be provided for further reading. Here is couple of examples of the kinds of papers I'm thinking of: Elliott, S., Latini, D., Walker, L., Wassersug, R., Robinson, J. and the ADT Survivorship Working Group. (2010) Androgen deprivation therapy for prostate cancer: Recommendations to improve patient and partner quality of life Journal of Sexual Medicine Impact Factor=4.884 Sep;7(9):2996-3010 Walker LM, Wassersug RJ, Robinson JW. Psychosocial perspectives on sexual recovery after prostate cancer treatment. Nat Rev Urol. 2015 Mar;12(3):167-176. doi: 10.1038/nrurol.2015.29. Epub 2015 Mar 10.	Unfortunately the provided papers were narrative reviews and as such were excluded from the evidentiary base of this guideline a priori.
4. Under the subtitle QoL and Psychosocial Side-Effects, the description of management options for depression uses the word counselling. Counselling is, unfortunately, a generic term that is difficult to interpret. Based on current evidence for management of depression in cancer patients, and in	The GDG agrees that 'counselling' undervalues the practitioner providing this psychological therapy. When referring to therapy for depression, all uses of 'counselling' have been changed to 'psychological therapy'

Comments	Responses
order to be consistent with the forthcoming guideline on management of depression, the more appropriate term is psychological therapy	

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All members of the PEBC database who had indicated interest in survivorship, systemic therapy and prostate cancer, radiation and prostate cancer, surgery and prostate cancer, primary care and prostate cancer, imaging and prostate cancer, nursing and prostate cancer, or post-treatment follow-up and prostate cancer were contacted by email to inform them of the survey. Notification of the survey was sent to 129 professionals, 107 who practice in Ontario and 22 who practice outside of Ontario. Thirty-two (24.8%) responses were received. Fourteen professionals stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 18 people are summarized in Table 5. The main comments from the consultation and the Working Group's responses are summarized in Table 6.

Table 5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				9 (50%)	9 (50%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (5.6%)	10 (55.5%)	7 (38.9%)
3. I would recommend this guideline for use in practice.			1 (5.6%)	4 (22.2%)	13 (72.2%)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers – time constraint, lack of training for healthcare providers, lack of access to specialists for side-effect management, Enablers – a pocket-sized version for reference/training				

Table 6. Responses to comments from professional consultants.

Comments	Responses
1. Page 5: Bone Health: there should be at minimum the option to counsel patients starting ADT in taking appropriate doses of vitamin D and calcium (diet and supplement) and have a baseline bone density test.	At inception of this project it was known that the PEBC was also developing a bone health guideline, so no literature in relation to bone health was included in the evidentiary base for this guideline. Without having reviewed the evidence, the GDG is not comfortable providing any guidance on bone health
2. Recommendation 6: although there is no evidence for diet or food supplements improving outcome, obese men or men gaining weight after cancer treatment	The GDG believes this comment is off scope for this guideline. Recommendation 6 sought to establish a link between diet and cancer outcomes and thus weight control is out of scope. It is hoped that

Comments	Responses
should have the option to be referred to a dietician.	healthcare providers would counsel patients on all risky lifestyle behaviours, irrespective of cancer status
3. There appears to be a typographical error on page 4. under the list of side effects the statement Infertility is not a side-effect seems to be a reviewers comment rather than a heading.	This text was originally in italics to denote that infertility may not be a side effect of some primary therapy. Italics have been removed and the wording of the management option has been altered to reduce confusion.
4. Target population: This seems well defined. However, to avoid any possibility of confusion, would a statement 'excluding patients in active surveillance' be warranted and refer the reader to EBS 17-9?	An additional sentence that refers clinicians to PEBC guideline 17-9 for patients on active surveillance has been added to the Target Population section.
5. In the Qualifying Statement for Recommendation 7, I am uncertain what is meant exactly by 'training in PSA kinetics'. It is probably worth fleshing this out a bit.	For the sake of clarity this Qualifying Statement has been edited to indicate healthcare providers that are providing PSA surveillance should follow the CCO Prostate Cancer Pathway to ensure men are introduced back into active therapy at the appropriate thresholds.
6. Recommendation 7, for management of hot flushes, I see that a member brought up the potential for increased mortality with the use of progestational agents. Although there aren't good data, I think that there should be mention somewhere about the risk associated with using these drugs in particular in men with a history of cardiovascular disease.	The GDG believes that Recommendation 5 sufficiently cautions the use of these treatments and outlines the associated adverse side-effects.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

Appendix 1. Members of the Prostate Cancer Follow-up Guideline Development Group.

Working Group Members

Name and Expertise	Affiliation	Conflict of Interest
Andrew Matthew, PhD, C.Psych Psychologist	Dept. of Surgical Oncology Princess Margaret Cancer Centre 610 University Ave. Toronto, ON M5G 2M9	Has published multiple studies and opinion pieces on prostate cancer follow-up care
Lesley H Souter, PhD Health Research Methodologist	Dept. of Oncology, McMaster University, Juravinski Hospital Site 711 Concession St. Hamilton, ON L8V 1C3	None
Rodney H Breau, MSc, MD, FRCSC Urologist	Ottawa Hospital Cancer Centre 501 Smyth Rd. Ottawa, ON K1H 8L6	None
Christina Canil, MD FRCPC Medical Oncologist	Ottawa Hospital Cancer Centre 501 Smyth Rd. Ottawa, ON K1H 8L6	None
Masoom Haider, MD Radiologist	Sunnybrook Health Sciences Centre 2075 Bayview Ave. Toronto, ON M4N 3M5	An increase in MRI utilization could result in an increased income for MH
Leah Jamnicky, BScN Registered Nurse	University Health Network 200 Elizabeth St. Toronto, ON M5G 2C4	None
Robin Morash, RN, MHS Advanced Practice Nurse	Ottawa Hospital Cancer Centre 501 Smyth Rd. Ottawa, ON K1H 8L6	Manages a trust account for Champlain Cancer Surgery Communities of Practice with donations from Sanofi-Aventis, with no personal benefit
Dan Smith, MD Family Physician	Family Practice office 224-1929 Rusell Rd. Ottawa, ON K1G 4G3	None
Mark Surchin Patient Representative	N/A*	None
Andrew Loblaw, MSc, MD FRCPC Radiation Oncologist	Odette Cancer Centre 2075 Bayview Ave. Toronto, ON M4N 3M5	None

*The PEBC respects the privacy of our patient representative and will not supply contact information for this individual.

Report Approval Panel Members

Name	Affiliation	Conflict of Interest
Melissa Brouwers, PhD Director, Program in Evidence-based Care	Dept. of Oncology, McMaster University, Juravinski Hospital Site 711 Concession St. Hamilton, ON L8V 1C3	None
Eric Winquist Medical Oncologist	Dept. of Oncology, Western University, London Health Sciences Centre, 790 Commissioners Rd E. London, ON N6A 4L6	None

Donna Maziak Surgical Oncologist	Ottawa Hospital 501 Smyth Rd. Ottawa, ON K1H 8L6	None

Expert Panel Members

Name	Affiliation	Conflict of Interest
Lee Donohue Family Physician	Ottawa Hospital, Ottawa, ON	None
Shauna Duigenan Radiologist	Ottawa Hospital, Ottawa, ON	None
Andrew Fiefer Urologist	Credit Valley Hospital, Mississauga, ON	Has consulted for a pharmaceutical company with financial compensation
Margaret Fitch Nurse Researcher	Odette Cancer Centre, Toronto, ON	None
Esther Green Provincial Head, Nursing and Psychosocial Oncology	Cancer Care Ontario, Toronto, ON	None
Gurpreet Grewal Registered Nurse	Mississauga Halton/Central West Regional Cancer Program Mississauga, ON	None
Michael Lock Radiation Oncologist	London Regional Cancer Program, London, ON	Has received a grant from a pharmaceutical company to complete a study on circulating tumour cells in colorectal patients
Scott Morgan Radiation Oncologist	Ottawa Hospital Cancer Centre Ottawa, ON	Recommended scheduled follow-up frequency could affect professional income
Don Park Patient Representative	N/A*	None
Gary Rodin Psychiatrist	University Health Network, Toronto, ON	None

*The PEBC respects the privacy of our patient representative and will not supply contact information for this individual.

Targeted Peer Reviewers

Name	Affiliation	Conflict of Interest
Nelson Byrne Psychologist	Mississauga Halton/Central West Regional Cancer Program Mississauga, ON	Partner is a private practice that provides psychological assessment and intervention
Ilias Cagiannos Urologist	Ottawa Hospital, Ottawa, ON	None
John Robinson Psychologist	Tom Baker Cancer Centre Calgary, AB	None

Appendix 2: Literature Search Strategies.

Q1&Q2 Tests MEDLINE

1. Exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp.
3. 1 or 2
4. care.mp.
5. continuity.mp.
6. follow up.mp.
7. shared care.mp.
8. (after care or aftercare).mp.
9. surveillance.mp.
10. survivo$.mp.
11. or/4-10
12. recurrence/
13. neoplasm recurrence, local/
14. recurren$.mp.
15. metastas$.mp.
16. Or/12-15
17. 11 or 16
18. exp "sensitivity and specificity"/
19. (sensitivity or specificity).tw.
20. exp Diagnostic Errors/
21. predictive value$.tw.
22. predictive value$ of test$.tw.
23. (false adj (negative or positive)).tw.
24. accuracy.tw.
25. reference value$.tw.
26. likelihood ratio$.tw.
27. ((pre-test or pretest) adj probability).tw.
28. post-test probability.tw.
29. Diagnosis, differential/
30. Diagnostic tests, routine/
31. reproducibil$.tw.
32. Or/18-31
33. (CT adj scan$).mp.
34. prostate-specific antigen/
35. Psa.mp
36. prostate specific antigen.mp.
37. prostate-specific antigen.mp.
38. (elevated adj serum adj psa).mp.
39. (elevated adj serum adj prostat$).mp.
40. (elevated adj (psa or prostat$)).mp.
41. (CBC or FBC or full blood count).mp.
42. exp blood cell count/
43. blood sedimentation/
44. erythrocyte sedimentation rate.mp.
45. Urine/cy [Cytology]
46. urine cytology.mp.
47. urinalysis/
48. urine microscopy.mp.
49. tomography, X-Ray Computed/
50. Ct.mp
51. exp ultrasonography/
52. ultrasound.mp.
53. urography/
54. intravenous urogram$.mp.
55. intravenous pyelogram$.mp.
56. ((per rect$ or pr) adj exam$).mp.
57. digital rectal examination/
58. DRE.mp.
59. bone scan.mp.
60. (bone adj densit$).mp.
61. (prostat$ adj biopsy).mp.
62. mri.mp.
63. magnetic resonance imaging/
64. (testosterone adj level$).mp.
65. (vitamin adj D).mp.
66. secondary primary tumor$.mp.
67. secondary primary tumour$.mp.
68. Second primary tumor$.mp
69. Second primary tumour$.mp
70. Or/33-69
71. 32 or 70
72. 3 and 17 and 71
73. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
74. 72 not 73
75. limit 74 to English
76. Animal/
77. Human/
78. 76 not 77
79. 75 not 78
80. limit 79 to yr="2000-2013"

Q1&Q2 Tests EMBASE

1. exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp.
3. 1 or 2
4. care.mp.
5. continuity.mp.
6. (follow-up or follow up).mp.
7. exp follow up/
8. shared care.mp.
9. after care/
10. long term care/
11. (after care or aftercare).mp.

12. surveillance$.mp.
13. survivor$.mp.
14. or/4-13
15. exp recurrent cancer/ or exp recurrent disease/
16. recurren$.mp.
17. neoplasm recurrence, local/
18. metastas$.mp.
19. Second$ primary tumor$.mp
20. Second$ primary tumour$.mp
21. Second primary cancer$.mp
22. Or/15-21
23. 14 or 22
24. "sensitivity and specificity"/
25. sensitivity.tw.
26. specificity.tw.
27. exp "prediction and forecasting"/
28. predictive value$.tw.
29. predictive value$ of test$.tw.
30. exp diagnostic error/
31. (false adj (positive or negative)).tw.
32. diagnostic accuracy/
33. accuracy.tw.
34. reference value/
35. reference value$.tw.
36. likelihood ratio$.tw.
37. ((pre-test or pretest) adj probability).tw.
38. post-test probability.tw.
39. differential diagnosis/
40. reproducibil$.mp.
41. Or/24-40
42. (CT adj scan$).mp.
43. Prostate-Specific Antigen/
44. psa.mp.
45. (elevated adj serum adj psa).mp.
46. prostate specific antigen.mp.
47. (elevated adj (psa or prostat$)).mp.
48. (elevated adj serum adj prostat$).mp.
49. exp blood cell count/
50. (CBC or FBC or full blood count).mp.
51. c-reactive protein.mp.
52. C Reactive Protein/
53. erythrocyte sedimentation rate/
54. erythrocyte sedimentation rate.mp.
55. Urine Cytology/
56. urine cytology.mp.
57. exp urinalysis/
58. urine microscopy.mp.
59. cancer cytodiagnosis/
60. Computer Assisted Tomography/
61. ct.mp.
62. ultrasound/
63. ultrasound.mp.
64. intravenous urography/ or intravenous pyelography/
65. (intravenous adj (urogra$ or pyelogra$)).mp.
66. ((per rect$ or pr) adj exam$).mp.
67. Digital rectal examination/
68. dre.mp.
69. bone scan.mp.
70. (prostat$ adj biopsy).mp.
71. (bone adj densit$).mp.
72. mri.mp.
73. magnetic resonance imaging/
74. (testosterone adj level$).mp.
75. vitamin D/
76. Or/42-75
77. 41 and 76
78. 3 and 23 and 77
79. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
80. 78 not 79
81. Limit 80 to English
82. Animal/
83. Human/
84. 82 not 83
85. 81 not 84
86. Limit 85 to yr="2000-2013"

Q2 symptoms and Q3 MEDLINE

1. Exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp.
3. 1 or 2
4. care.mp.
5. continuity.mp.
6. follow up.mp.
7. shared care.mp.
8. (after care or aftercare).mp.
9. surveillance.mp.
10. survivo$.mp.
11. or/4-10
12. Recurrence/
13. neoplasm recurrence, local/
14. recurren$.mp.
15. metastas$.mp.
16. second$ primary tumor$.mp.
17. second$ primary tumour$.mp.
18. or/12-17
19. 11 or 18
20. prostate-specific antigen/
21. Psa.mp
22. prostate specific antigen.mp.
23. prostate-specific antigen.mp.
24. (elevated adj serum adj psa).mp.
25. (elevated adj serum adj prostat$).mp.

26. (elevated adj (psa or prostat$)).mp.
27. (bone$ adj pain).mp.
28. (axioskeletal adj pain).mp.
29. (weight adj loss).mp.
30. (weight adj1 (loss or gain or change$)).tw.
31. fatigue.mp.
32. (swell$ adj leg$).mp.
33. or/20-32
34. incontinence/
35. incontinence.mp.
36. urinary incontinence, urge/
37. urge incontinence.mp.
38. (rectal adj (bleeding or blood)).mp.
39. (rectal adj pain).mp
40. (bowel movement$ adj change$).mp.
41. (bowel adj2 urgen$).mp.
42. obstructive urinary syndrome$.mp.
43. (bladder adj2 urgen$).mp.
44. (voiding adj discomfort).mp.
45. voiding symptom$.mp.
46. dysuria.mp.
47. (hematuria or haematuria).mp.
48. nocturia.mp.
49. dysorgasmia.mp.
50. (dry adj ejaculate).mp.
51. Impotence.mp
52. impotence/
53. erectile dysfunction$.mp.
54. (lack adj2 libido).mp.
55. (loss adj2 libido).mp.
56. (decreas$ adj2 libido).mp.
57. ((lack or loss or decreas$) adj2 sexual desire).mp.
58. well-being.mp.
59. well being.mp.
60. quality of life/
61. quality of life.mp.
62. qol.mp.
63. depression.mp.
64. anxiety.mp.
65. (psychosocial adj distress).mp.
66. psychosocial.mp.
67. (sexual adj health).mp.
68. (psychosocial adj care).mp.
69. (social adj relation$).mp.
70. (relation$ adj (spouse$ or famil$ or partner$)).mp.
71. or/34-70
72. 33 or 71
73. 3 and 19 and 72
74. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
75. 73 not 74
76. Limit 75 to English
77. Animal/
78. Human/
79. 77 not 78
80. 76 not 79
81. Limit 80 to yr-"2000-2013"

Q2 symptoms and Q3 EMBASE

1. exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp.
3. 1 or 2
4. care.mp.
5. continuity.mp.
6. (follow-up or follow up).mp.
7. exp follow up/
8. shared care.mp.
9. after care/
10. long term care/
11. (after care or aftercare).mp.
12. surveillance$.mp.
13. survivor$.mp.
14. or/4-13
15. exp recurrent cancer/ or exp recurrent disease/
16. recurren$.mp.
17. neoplasm recurrence, local/
18. metastas$.mp.
19. Second$ primary tumor$.mp
20. Second$ primary tumour$.mp
21. Second primary cancer$.mp
22. Second$ primary cancer$.mp
23. Or/15-11
24. 14 or 23
25. prostate-specific antigen/
26. Psa.mp
27. prostate specific antigen.mp.
28. prostate-specific antigen.mp.
29. (elevated adj serum adj psa).mp.
30. (elevated adj serum adj prostat$).mp.
31. (elevated adj (psa or prostat$)).mp.
32. (bone$ adj pain).mp.
33. (axioskeletal adj pain).mp.
34. (weight adj loss).mp.
35. (weight adj1 (loss or gain or change$)).tw.
36. fatigue.mp.
37. (swell$ adj leg$).mp.
38. or/25-37
39. incontinence/
40. Incontinence.mp
41. urinary incontinence, urge/
42. urge incontinence.mp.

43. (rectal adj (bleeding or blood)).mp.
44. (rectal adj pain).mp
45. (bowel movement$ adj change$).mp.
46. (bowel adj2 urgen$).mp.
47. Obstructive urinary symdrome$.mp
48. (bladder adj2 urgen$).mp.
49. (voiding adj discomfort).mp.
50. voiding symptom$.mp.
51. dysuria.mp.
52. (hematuria or haematuria).mp.
53. nocturia.mp.
54. dysorgasmia.mp.
55. (dry adj ejaculate).mp.
56. Impotence.mp
57. impotence/
58. erectile dysfunction$.mp.
59. (lack adj2 libido).mp.
60. (loss adj2 libido).mp.
61. (decreas$ adj2 libido).mp.
62. ((lack or loss or decreas$) adj2 sexual desire).mp.
63. well-being.mp.
64. well being.mp.
65. quality of life/
66. quality of life.mp.
67. qol.mp.
68. depression.mp.
69. anxiety.mp.
70. (psychosocial adj distress).mp.
71. Pschosocial.mp
72. (sexual adj health).mp.
73. (psychosocial adj care).mp.
74. (social adj relation$).mp.
75. (relation$ adj (spouse$ or famil$ or partner$)).mp.
76. or/39-75
77. 38 or 76
78. 3 and 24 and 77
79. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
80. 78 not 79
81. Limit 80 to English
82. Animal/
83. Human/
84. 82 not 83
85. 81 not 84
86. Limit 85 to yr-"2000-2013"

Q4 MEDLINE

1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. Or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. Review.py
14. 12 and 13
15. 7 or 8 or 9 or 14
16. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
17. 15 not 16
18. exp prostate cancer/
19. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp
20. 18 or 19
21. Care.mp
22. continuity.mp.
23. follow up.mp.
24. shared care.mp.
25. (after care or aftercare).mp
26. surveillance.mp.
27. survivo$.mp.
28. or/21-27
29. recurrence/
30. neoplasm recurrence, local/
31. recurren$.mp.
32. metastas$.mp.
33. or/29-32
34. 28 or 33
35. exp primary health care/
36. general practitioner/
37. ((family or general) adj practitioner$).mp.
38. gp.mp.

39. family physician/
40. Family physician$.mp
41. Family doctor$.mp
42. General practice/
43. ((family or general) adj practice$).mp
44. Primary care.mp
45. Primary health care.mp
46. Tertiary cae.mp
47. Tertiary health care.mp
48. Specialist/
49. Medical oncologist$.mp
50. Specialist.mp
51. Radiation oncologist$.mp
52. Oncologist$.mp
53. Radiologist$.mp
54. Surgeon$.mp
55. Nurse$.mp
56. Registered nurse$.mp
57. Nurse/
58. Rn.mp
59. Apn.mp
60. Advanced practice nurse.mp
61. Advanced practice registered nurse.mp
62. Nurse practitioner.mp
63. (community adj care).mp
64. (hospital adj care).mp
65. (institution$ adj care).mp
66. Cancer centre.mp
67. Out-patient clinic.mp
68. Outpatient clinic.mp
69. Clinic.mp
70. Or/35-69
71. 17 and 20 and 34 and 70
72. Limit 71 to English
73. Animal/
74. Human/
75. 73 not 74
76. 72 not 75
77. Limit 76 to yr="2000-2013"

Q4 EMBASE

1. Exp meta analysis/ or exp "systematic review"/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. Exp "Review"/ or review.pt
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. Or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. 9 or 10 or 11
13. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
14. 12 not 13
15. exp prostate cancer/
16. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp
17. 15 or 16
18. care.mp.
19. continuity.mp.
20. (follow-up or follow up).mp.
21. exp follow up/
22. shared care.mp.
23. after care/
24. long term care/
25. (after care or aftercare).mp.
26. surveillance$.mp.
27. survivor$.mp.
28. or/18-27
29. Recurrence/
30. exp recurrent cancer/ or exp recurrent disease/
31. recurren$.mp.
32. neoplasm recurrence, local/
33. metastas$.mp.
34. Or/29-33
35. 28 or 34
36. exp primary health care/
37. general practitioner/
38. ((family or general) adj practitioner$).mp.
39. gp.mp.
40. family physician/
41. Family physician$.mp
42. Family doctor$.mp
43. General practice/
44. ((family or general) adj practice$).mp
45. Primary care.mp
46. Primary health care.mp
47. Tertiary cae.mp
48. Tertiary health care.mp
49. Specialist/

50. Medical oncologist$.mp
51. Specialist.mp
52. Radiation oncologist$.mp
53. Oncologist$.mp
54. Radiologist$.mp
55. Surgeon$.mp
56. Nurse$.mp
57. Registered nurse$.mp
58. Nurse/
59. Rn.mp
60. Apn.mp
61. Advance$ practice nurse.mp
62. Advance$ practice registered nurse.mp
63. Nurse practitioner.mp
64. (community adj care).mp
65. (hospital adj care).mp
66. (institution$ adj care).mp
67. Cancer centre.mp
68. Out-patient clinic.mp
69. Outpatient clinic.mp
70. Clinic.mp
71. Or/36-70
72. 14 and 17 and 35 and 71
73. Limit 72 to English
74. Anima/
75. Human/
76. 74 not 75
77. 73 not 76
78. Limit 77 to yr="2000-2013"

Q5 MEDLINE

1. Exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp
3. 1 or 2
4. Care.mp
5. Continuity.mp
6. Follow up.mp
7. Shared care.mp
8. (after care or aftercare).mp
9. Surveillance.mp
10. Survivo$.mp
11. Or/4-10
12. ADT.mp
13. Androgen deprivation therapy.mp
14. (hormone adj therapy).mp
15. (androgen adj therapy).mp
16. Hormone therapy.mp
17. Or/12-16
18. 11 and 17
19. Prostate-specific antigen/
20. Psa.mp
21. Prostate specific antigen.mp
22. Prostate-specific antigen.mp
23. (elevated adj serum adj psa).mp
24. (elevated adj serum adj prostat$).mp
25. (elevated adj (psa or prostat$)).mp
26. osteopenia.mp.
27. Osteoporosis.mp
28. (bone density adj loss).mp
29. (weight adj gain).mp
30. (weight adj1 (loss or gain or change$)).tw
31. Fatigue.mp
32. Hot flash$.mp
33. Night sweat$.mp
34. (increase$ adj3 bofy fat).mp
35. (loss adj3 body hair).mp
36. (decreas$ adj3 body hair).mp
37. (increase$ adj3 fat).mp
38. (decreas$ adj3 muscle).mp
39. (loss adj3 muscle).mp.
40. (dry adj ejaculate).mp.
41. Anemia.mp
42. Impotence.mp
43. Impotence/
44. Erectile dusfunction$.mp
45. (lack adj2 libido).mp.
46. (loss adj2 libido).mp.
47. (decreas$ adj2 libido).mp.
48. (sexual desire adj2 (loss or lack)).mp.
49. (intimacy adj2 impact$).mp.
50. genital$ shrinkage.mp.
51. gynecomastia/
52. gynecomastia.mp.
53. (androgen adj level).mp.
54. (testosterone adj level).mp.
55. Vitamin D/
56. Vitamin D.mp
57. Well-being.mp
58. Well being.mp
59. Quality of life/
60. Quality of life.mp
61. Qol.mp
62. Depression.mp
63. Anxiety.mp
64. (psychosocial adj distress).mp
65. Psychosocial.mp
66. (sexual adj health).mp
67. (psychosocial adj care).mp
68. (social adj relation$).mp
69. (relation$ adj (spouse$ or famil$ or partner$)).mp
70. Or/19-69
71. 3 and 18 and 70
72. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education

handout or case report or historical article).pt
73. 71 not 72
74. Limit 73 to English
75. Animal/
76. Human/
77. 75 not 76
78. 74 to 77
79. Limit 78 to yr="2000-2013"

Q5 EMBASE
1. exp prostate cancer/
2. (prostat$ adj2 (neoplasm$ or cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp
3. 1 or 2
4. care.mp.
5. continuity.mp.
6. (follow-up or follow up).mp.
7. exp follow up/
8. shared care.mp.
9. after care/
10. long term care/
11. (after care or aftercare).mp.
12. surveillance$.mp.
13. survivor$.mp.
14. or/4-13
15. ADT.mp
16. Androgen deprivation therapy.mp
17. (hormone adj therapy).mp
18. (androgen adj therapy).mp
19. Hormone therapy.mp
20. Or/15-19
21. 14 and 20
22. Prostate-specific antigen/
23. Psa.mp
24. Prostate specific antigen.mp
25. Prostate-specific antigen.mp
26. (elevated adj serum adj psa).mp
27. (elevated adj serum adj prostat$).mp
28. (elevated adj (psa or prostat$)).mp
29. osteopenia.mp.
30. Osteoporosis.mp
31. (bone density adj loss).mp
32. (weight adj gain).mp
33. (weight adj1 (loss or gain or change$)).tw
34. Fatigue.mp
35. Hot flash$.mp
36. Night sweat$.mp
37. (increase$ adj3 bofy fat).mp
38. (loss adj3 body hair).mp
39. (decreas$ adj3 body hair).mp
40. (increase$ adj3 fat).mp
41. (decreas$ adj3 muscle).mp
42. (loss adj3 muscle).mp.
43. (dry adj ejaculate).mp.
44. Anemia.mp
45. Impotence.mp
46. Impotence/
47. Erectile dusfunction$.mp
48. (lack adj2 libido).mp.
49. (loss adj2 libido).mp.
50. (decreas$ adj2 libido).mp.
51. (sexual desire adj2 (loss or lack)).mp.
52. (intimacy adj2 impact$).mp.
53. genital$ shrinkage.mp.
54. gynecomastia/
55. gynecomastia.mp.
56. (androgen adj level).mp.
57. (testosterone adj level).mp.
58. Vitamin D/
59. Vitamin D.mp
60. Well-being.mp
61. Well being.mp
62. Quality of life/
63. Quality of life.mp
64. Qol.mp
65. Depression.mp
66. Anxiety.mp
67. (psychosocial adj distress).mp
68. Psychosocial.mp
69. (sexual adj health).mp
70. (psychosocial adj care).mp
71. (social adj relation$).mp
72. (relation$ adj (spouse$ or famil$ or partner$)).mp
73. Or/22-72
74. 3 and 21 and 73
75. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
76. 74 not 75
77. Limit 76 to English
78. Animal/
79. Human/
80. 78 not 79
81. 77 to 80
82. Limit 81 to yr="2000-2013"

Appendix 3: Details of inclusion criteria according to study design for each research outcome.

Research Question	Outcome	Study Design Inclusion Criteria
Q1. Appropriate timing for PSA testing	PSA testing frequency and timing	• Randomized controlled trials (RCTs) ○ Only RCTs comparing PSA testing frequencies
Q2. Diagnostic tests after biochemical recurrence and symptoms of recurrence	Imaging tests if PSA rise	• Diagnostic cohort studies ○ Diagnostic test most appropriate for assessing detection of recurrence
	Symptoms of clinical recurrence	○ RCTs ○ Prospective cohort studies ○ Expect no RCTs to address this outcome
Q3. Late treatment effects – rate, level of bother and management	Anemia	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Body composition alteration	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Bowel or gastrointestinal dysfunction	• RCTs ○ All management strategies must be assessed by a RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Cardiovascular side effects	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Cognitive side effects	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Depression	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Fatigue and exercise	• RCTs ○ All management strategies must be assessed by a RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies

Research Question	Outcome	Study Design Inclusion Criteria
	General ADT long-term effects	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Gynecomastia	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Health-related QoL	• RCTs • Prospective cohort studies ○ Expect few RCTs to include health-related QoL as an outcome
	Hot flushes	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Osteoporosis	• This outcome is thoroughly covered in EBS 3-14
	Physical function	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Psychosocial or emotional problems	• RCTs • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Sexual dysfunction	• RCTs ○ All management strategies must be assessed by a RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Prolonged low testosterone level	• RCTs ○ Any study looking at management must be an RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
	Treatment specific side effects	• RCTs ○ Only RCTs comparing two treatment options that analyze late effects
	Urinary dysfunction	• RCTs ○ All management strategies must be assessed by a RCT • Prospective cohort studies ○ Rate and level of distress will most likely be self-reported and an outcome of cohort studies
Q4. Models of follow-up care	Available psychosocial care	• RCTs ○ Care models must be assessed by a RCT

Research Question	Outcome	Study Design Inclusion Criteria
	Holistic needs (exercise, nutrition, return to work)	• RCTs ○ All interventions must be assessed by a RCT
	Nurse intervention	• RCTs ○ All nurse interventions must be compared to usual care and assessed by a RCT
	Patient care satisfaction	• RCTs • Prospective cohort studies ○ Satisfaction with care will most likely be self-reported and an outcome of cohort studies

Abbreviations: ADT, androgen deprivation therapy; QoL, quality of lifer; PSA, prostate specific antigen; RCT, randomized controlled trial.

Appendix 4: AMSTAR Quality Assessment of Included Systematic Reviews

AMSTAR Tool:	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Chisholm et al, 2012 [37]	yes	no	yes	no	yes	yes	yes	yes	yes	no	yes
Chambers et al, 2011 [39]	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	No
Evangelista et al, 2013 [6]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Frisk, 2010 [53]	yes	no	yes	no	yes	yes	yes	no	yes	no	yes
Gardner et al, 2014 [51]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Grossmann and Zajac, 2012 [43]	yes	no	yes	no	no	no	no	no	yes	no	yes
Haseen et al, 2010 [44]	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no
Hovels et al, 2008 [13]	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no
Hsiao et al, 2007 [19]	yes	no	yes	no	yes	yes	yes	no	yes	no	no
Keogh and MacLeod, 2012 [36]	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes
Patel et al, 2011 [74]	yes	no	yes	no	no	yes	no	no	yes	no	yes
Tal et al, 2009 [27]	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes
McGinty et al, 2014 [48]	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes
Van Patten et al, 2008 [54]	yes	no	yes	no	yes	yes	yes	yes	yes	no	no
Viani et al, 2012 [65]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes
Watts et al, 2014 [34]	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes
Welk and Herschorn, 2012 [40]	yes	no	yes	yes	no	yes	yes	yes	yes	no	yes
Wittmann et al, 2009 [68]	yes	no	yes	no	no	yes	no	no	yes	no	yes
Wu et al, 2013 [9]	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no

Note: The AMSTAR questions are as follows:

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of the publication used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Appendix 5: Quality Assessment of Included Studies

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
Randomized Controlled Trials							
Dieperink et al, 2013 [57]	RCT, n=161	RT+ADT	Shared care follow-up	Between groups	Urinary irritative sum-score and specific QoL domains	Denmark	Odense University Hospital Research Foundation, University of Southern Denmark, Danish Cancer Society, CIRRO – the Lundbeck Foundation Center for Interventional Research in Radiation Oncology, Mette Hede Nielsen Foundation, Danish Nurses Organization Research Foundation, Propa Vita Foundation
Helgesen et al, 2000 [56]	RCT, n=400	Any primary	On-demand nurse follow-up	Between groups	Safety, patient satisfaction, and resources	Sweden	Dagmar-50 project of the Swedish government, Orebro Medical Centre Research Foundation, Orebro Council Research Committee
Hebert et al, 2012 [55]	RCT, n=47	rP, RT, or rP+RT	Diet, exercise, meditation program	Between groups	Dietary intake and PSA level	USA	US Department of Defense Army Award, National Cancer Institute
Galvao et al, 2014 [52]	RCT, n=100	RT+ADT	Exercise program	Between groups and across time within groups	Body composition alterations and specific QoL domains	Australia and New Zealand	Prostate Cancer Foundation of Australia's Research Program
Nilssen et al, 2012 [75]	RCT, n=85	rP	Pelvic muscle floor contractions	Between groups and across time within groups	Specific QOL domains	Norway	Norwegian Fund for Postgraduate Training in Physiotherapy, Norwegian Cancer Society

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
Overgard et al, 2008 [41]	RCT, n=85	rP	Pelvic muscle floor contractions	Between groups and across time within groups	Urinary continence	Norway	Norwegian Fund for Postgraduate Training in Physiotherapy, Norwegian Cancer Society
Park et al, 2012 [35]	RCT, n=66	Laparoscopic rP	Exercise program	Between groups	Physical function and continence	Korea	Medical Research Institute of Pusan National University Hospital
Schover et al, 2012 [69]	RCT, n=186 couples	rP or RT	Internet-based sexual counselling	Between groups	Erectile and sexual function	USA	American Cancer Society
Warren et al, 2006 [5]	RCT, n=8,113	rP, RT or watchful waiting	Bone scan	Patients received all interventions	Diagnostic accuracy	North America, Europe and Scandinavia	Not specified
Non-Randomized Prospective Cohort Studies							
Alibhai et al, 2010 [50]	Case-control, n=87 controls, 172 controls	ADT	Treatment modality	Between cases and 2 types of controls plus across time	Physical function	Canada	Canadian Cancer Society and American Society of Clinical Oncology
Aoki et al, 2009 [20]	Comparative cohort, n=296	BT or BT+EBRT	Treatment modality	Between groups	Rate of rectal bleeding	Japan	Not specified
Badger et al, 2011 [38]	Controlled before-and-after, n=71 couples	Any	Telephone-based psychosocial counselling	Between groups and across time within groups	Specific QoL domains	USA	National Cancer Institute
Bellizzi et al, 2008 [72]	Before-and-after comparison, n=730	rP, BT, or EBRT	Primary treatment	Within cohort across time	Association between fear of recurrence and QoL	USA	CaPSURE Scholars Grant from University of California, San Francisco
Black et al, 2007 [66]	Controlled before-and-after, n=43	ADT	Treatment modality	Between groups and across time within groups	Hemoglobin levels, testosterone	USA	AUA Foundation, NIH, NCI

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
					levels, general QoL		
Bylow et al, 2011 [46]	Case-control, n=63 cases and 71 controls	ADT	Treatment modality	Between cases and controls	Body composition alterations	USA	American Society for Clinical Oncology
Chen et al, 2014 [24]	Before-and-after, n=204	SBRT	Treatment modality	Within cohort across time	Urinary incontinence	USA	James and Theodore Pedas Family Foundation, NIH
Couper et al, 2006 [70]	Controlled before-and-after, n=103 couples	Any	Disease stage	Localized vs. metastatic disease	Depression, anxiety, psychological distress, and marital status	Australia	National Health and Medical Research Council and Bethlehem Griffiths Research Foundation
Couper et al, 2009 [33]	Controlled before-and-after, n=211	rP, ADT, EBRT, or BT	Treatment modality	Between groups and across time within groups	Depression, anxiety, specific QoL domains	Australia	National Health and Medical Research Council and Bethlehem Griffiths Research Foundation
Crook et al, 2011 [31]	Comparative cohort, n=168	rP or BT	Treatment modality	Between groups	Specific QoL domains	Canada	Not specified
Ezer et al, 2012 [71]	Before-and-after comparison, n=81	Surgery or RT	Disease diagnosis	Within cohort across time	Specific QoL domains	Canada	Montreal General Hospital Research Foundation, Social Science Health Research Council at McGill University and Research Institute of McGill University Health Centre
Fransson, 2010 [32]	Before-and-after comparison, n=407	EBRT	Treatment modality	Within cohort across time	Fatigue	Sweden	Swedish Cancer Society
Hart et al, 2008 [73]	Before-and-after	rP	Treatment modality	Within cohort across time	Treatment satisfaction, fear	USA	CaPSURE and National Institutes of Health/National Cancer

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
	comparison, n=333				of recurrence, QoL		Institute University of California
Huang et al, 2010 [21]	Before-and-after comparison, n=1,269	rP, EBRT, BT, EBRT+BT, or ADT	Treatment modality	Between groups and across time within groups	QoL evolution	USA	National Institutes of Health
Jayadevappa et al, 2010 [76]	Controlled before-and-after, n=590	rP or EBRT	Treatment modality	Between groups and across time within groups	Satisfaction with care and general QoL	USA	Department of Defense Prostate Cancer Research Program
King et al, 2012 [25]	Before-and-after comparison, n=67	SBRT	Treatment modality	Within cohort across time	Rate of bladder and rectal toxicities	USA	Not specified
Lecouvet et al, 2012 [3]	Comparative cohort, n=100	Local therapy or ADT	WBMRI	WBMRI vs. bone scan plus CT	Diagnostic accuracy	Belgium	Fondation Saint Luc
Matsushima et al, 2013 [29]	Before-and-after comparison, n=119	BT	Treatment modality	Within cohort across time	Erectile function	Japan	Not specified
Pettersson et al, 2013 [26]	Case-control, n=863 cases and 242 controls	EBRT, rP+EBRT, or EBRT+BT	Treatment modality	Between cases and controls plus between treatment groups	Urethral pain	Sweden	Not specified
Prabhu et al, 2014 [23]	Before-and-after comparison, n=1,788	rP	Treatment modality	Within cohort across time	Urinary incontinence	USA	National Center for the Advancement of Translational Science
Rajkowska-Labon et al, 2014 [42]	Comparative cohort, n=81	rP	Physiotherapy intervention	Between groups and across time within group	Urinary incontinence	Poland	Not specified

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
Salonia et al, 2010 [28]	Before-and-after comparison, n=334	BNSRrP	Treatment modality	Within cohort across time	Erectile and orgasmic function	Italy	Not specified
Sanda et al, 2008 [30]	Comparative cohort, n=1201 patients and 625 spouses	rP, BT, EBRT, or ADT	Treatment modality	Between groups	Specific QoL domains	USA	National Institutes of Health
Spry et al, 2013 [47]	Before-and-after comparison, n=72	Intermittent ADT	Treatment modality	Within cohort across time	Body composition alterations	Australia	Movember New Directions Development Award
Stensvold et al, 2013 [22]	Before-and-after comparison, n=462	RARP, RT, or RT+ADT	Treatment modality	Between groups and across time within groups	Rate of bowel, urinary, and sexual bother	Norway	Not specified
Sterba et al, 2011 [67]	Controlled before-and-after, n=43 couples	ADT	Treatment modality	Between groups	Specific QoL domains for spouse	USA	TAP Pharmaceutical, AstraZenecam Schering Plough, NCI, NIH
Takesh et al, 2012 [4]	Comparative cohort, n=37	rP, RT, or ADT	FECH PET/CT	FECH PET/CT vs. bone scan	Diagnostic accuracy	Germany	Not specified
Timilshina et al, 2012 [45]	Case-control, n=85 cases, 172 controls	ADT	Treatment modality	Between case and controls plus across time	Long-term weight gain	Canada	Not specified
Timilshina et al, 2012 [63]	Case-control, n=85 cases, 172 controls	ADT	Treatment modality	Between cases and controls plus across time	Depression	Canada	Canadian Cancer Society
Ulloa et al, 2009 [49]	Before-and-after, n=68	ADT	Treatment modality	Within cohort across time	Hot flushes and distress	USA	Not grant funded

Study	Study Design and Sample Size	Primary Treatment	Intervention	Comparison or Comparison Type	Outcome(s)	Country	Funding Body
van Tol-Geerdink et al, 2011 [64]	Comparative cohort, n=289	ADT	Treatment modality	Between groups	Depression	The Netherlands	Dutch Cancer Society
Diagnostic Cohort Studies							
Beheshti et al, 2013 [8]	Fully paired diagnostic cohort study, n=250	rP, RT or ADT	FCH PET/CT	Patients received all interventions	Diagnostic accuracy	Austria	Not specified
Jadvar et al, 2012 [7]	Fully paired diagnostic cohort study, n=37	Surgery or RT	NaF PET/CT and FDG PET/CT	Patients received all interventions	Diagnostic accuracy	USA	NIH and National Cancer Institute
Liauw et al, 2013 [12]	Fully paired diagnostic cohort study, n=88	rP	Endorectal MRI – T2W, DWI and DCE	Patients received all interventions	Diagnostic accuracy	USA	Not specified
Rouviere et al, 2010 [11]	Fully paired diagnostic cohort study, n=59	HIFU (primary or recurrence after EBRT primary)	T2W and DCE MRI	Patients received all interventions	Diagnostic accuracy	France	

Note: Studies are grouped by study design in descending order according to the study quality as a consequence of the design. Non-randomized studies were further defined using the Cochrane Collaboration schema (Handbook Table 13.2a) as controlled before-and-after studies (provided comparisons between groups), case-control studies (comparison between case and controls) and before-and-after comparison (used longitudinal data collection within the group). All included non-randomized studies used prospective data collection and a form of comparison; however, because the comparison is within the group for before-and-after comparisons, this study designs carries the highest risk of bias. All RCT and non-randomized studies with QoL as an outcome relied on the use of QoL tools that survivors filled out at home, resulting in potential recall bias. The Working Group does recognize however that for QoL studies, this is the best available evidence. Although not of a lower quality than the non-randomized studies, diagnostic cohort studies are included at the end of the table. All diagnostic cohort studies used a fully paired model so that all patients received all interventions, thus reducing selection bias.

Abbreviations: ADT, androgen deprivation therapy; BNSRrP, bilateral nerve-sparing radical retropubic prostatectomy; BT, brachytherapy; CT, computed tomography; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted; EBRT, external beam radiotherapy; FCH, fluoromethylcholine; FDG, fluorodeoxyglucose; FECH, fluoroethylcholine; HIFU, high-intensity focused ultrasound; NaF, sodium fluoride; PET, positron emission

tomography; PSA, prostate-specific antigen; RArP, robot-assisted radical prostatectomy; rP, radical prostatectomy; RT, radiation therapy; SBRT, stereotactic body radiotherapy; T2W, T2-weighted; WBMRI, whole-body magnetic resonance imaging.

Appendix 6: List of Abbreviations.

ADT	Androgen deprivation therapy
AGREE II	Appraisal of Guideline for Research and Evaluation version 2
AMSTAR	A Measurement Tool to Assess Systematic Reviews
BC	Biochemical
BNSRrP	Bilateral nerve-sparing radical retropubic prostatectomy
BS	Bone scan
BT	Brachytherapy
BVC	Best valuable comparator
CI	Confidence interval
CT	Computed tomography
DCE	Dynamic contrast-enhanced
DWI	Diffusion weighted
EBRT	External beam radiotherapy
EBS	Evidence-based series
EFR	Erectile function recovery
EP	Expert Panel
EPIC	Expanded Prostate Cancer Index Composite
EPQ	Eysenck Personality Questionnaire
FCH	Fluoromethylcholine
FDG	Fluorodeoxyglucose
FECH	Fluoroethylcholine
FQ	Fatigue questionnaire
GDG	Guideline Development Group
HADS	Hospital Anxiety and Depression Scale
HIFU	High-intensity focused ultrasound
HR	Hazard ratio
IIEF	International Index of Erectile Function
MPO	Months post-operation
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopic imaging
NaF	Sodium fluoride
OR	Odds ratio
OS	Overall survival
PEBC	Program in Evidence-based Care
PET	Positron emission tomography
PSA	Prostate-specific antigen
QLI	Quality of Life Index
QoL	Quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
rP	Radical prostatectomy
RR	Relative risk
RRP	Radical retropubic prostatectomy
RT	Radiation therapy
SBRT	Stereotactic body radiotherapy
SR	Systematic review
T2W	T2-weighted imaging
TRUS	Transrectal sonography
TXR	Targeted x-ray
WBMRI	Whole body MRI
WG	Working Group

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