

9. PROSTATE CANCER TREATMENT

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The core references for this chapter include the textbook *Cancer Treatment* (Haskell, 1995), CancerNet PDQ Information for Health Care Professionals (National Cancer Institute, 1996) on prostate cancer and recent review articles. Recent review articles were selected from a MEDLINE search identifying all English language review articles published on prostate cancer since 1992 (Garnick, 1993; Garnick and Fair, 1996a; Garnick and Fair, 1996b; Daneshgari and Crawford, 1993; Gibson, 1993; Perez et al., 1993). Where the core references cited studies to support individual indicators, these have been included in the references. Whenever possible, we have cited the results of randomized controlled trials. However, a dearth of such studies in the literature has necessitated that we rely heavily on case analyses and expert opinion to develop quality indicators.

IMPORTANCE

Prostate cancer (adenocarcinoma) is now the most common cancer in men. In men age 75 and older, prostate cancer and benign prostatic hypertrophy together account for about ten percent of office visits each year. In 1993, the annual incidence of prostate cancer was estimated to be 165,000. Since August 1994, when the FDA approved the use of prostate specific antigen (PSA) testing in association with digital rectal examination for early detection of prostate cancer, increasing numbers of tumors have been diagnosed and treated before they were palpable. As a result, it is estimated that 317,000 new cases will be diagnosed in the United States alone in 1996 (Parker et al., 1996).

The natural history of prostate cancer is highly variable. One-third of men older than 50 will have prostate cancer discovered incidentally at autopsy; however, clinically apparent prostate cancer develops in only ten percent of men during their lifetime (Epstein et al., 1986).

Because of the variability in its virulence, and the lack of controlled trials for its treatment, the management of prostate cancer remains confusing and controversial.

SCREENING

Screening for prostate cancer remains extremely controversial. Our rationale for not developing quality indicators for prostate cancer screening, including PSA and digital rectal exam, are discussed in Chapter 8.

However, in spite of a lack of consensus, screening for prostate cancer with PSA is rapidly increasing and is expected to dramatically increase the numbers of asymptomatic localized cancers diagnosed in the next few years.

DIAGNOSIS

Symptoms of urinary obstruction (urgency, nocturia, frequency of urination, and hesitancy) due to an enlarged prostate are the most common presenting symptoms of prostate cancer. These symptoms also occur with benign prostatic hypertrophy. Other less common presenting symptoms of prostate cancer are new onset impotence and less firm penile erections. If the physical exam in a man with symptoms of urinary obstruction is not suggestive of prostate cancer, often the diagnosis will be made incidentally upon pathological examination of tissue obtained during transurethral resection of the prostate (TURP) performed to relieve obstructive symptoms. The quality indicators for the evaluation of obstructive urinary symptoms is discussed in Volume III of this series (see Chapter 4: Benign Prostatic Hyperplasia).

Occasionally, patients present with complaints related to distant metastases, usually back pain from bony lesions, and rarely cord compression or acute urinary retention. When a work-up for back or other bone pain reveals metastatic lesions in a man, a diagnosis of prostate cancer should be pursued because it is the most treatable of the metastatic adenocarcinomas. Further evaluation should include a digital rectal examination of the prostate and PSA (Indicator 1) (Leonard and Nystrom, 1993).

Staging of a cancer refers to the process of determining the presence or absence of factors in a given patient in order to make predictions about the patient's prognosis and make recommendations for treatment. Factors considered useful for predicting prognosis in prostate cancer include the stage and histologic grade of the tumor, the level of the PSA, as well as the patient's age and comorbid conditions (Montie, 1996). Age and comorbidity are important in treatment decisions in prostate cancer because untreated localized prostate cancer has a prolonged course with ten year disease-

specific survival rates of approximately 85 percent and ten year overall survival rates of approximately 60 percent (Johansson et al., 1996; Whitmore, 1990; Adolffson, 1993). Therefore, no treatment may be indicated for patients who are not expected to live longer than ten years from the time of the diagnosis of their localized prostate cancer. For this reason we have limited the quality indicators for the treatment of localized prostate cancer with curative intent to men who are expected to live ten years or longer. We have done this by excluding men over 65, as well as men with known coronary artery disease or a second cancer, except for skin cancer (Indicator 5).

The main purpose for staging evaluations when a diagnosis of prostate cancer has been made is to determine if the disease is localized (and thus potentially curable), regionally advanced (and therefore not amenable to surgery with curative intent), or metastatic (not curable).

Two staging systems exist for prostate cancer: the "conventional" or Jewett system, and the American Joint Committee on Cancer/International Union Against Cancer TNM system (see Table 9.1). Below, we review the evidence for the various modalities that have been used to attempt to evaluate prostate cancer stage. Radical prostatectomy with pelvic lymphadenectomy is generally considered the gold standard against which other staging strategies are compared.

Experts recommend obtaining a serum PSA level as part of a staging evaluation for prostate cancer (Garnick and Fair, 1996; Montie, 1996; Oesterling et al., 1993). PSA correlates well with the pathological stage of the tumor: 70 to 80 percent of men with PSA less than 4 ng/ml have localized prostate cancer, and most men with PSA greater than 50 ng/ml have positive pelvic lymph nodes at surgery. However, 60 percent of men with localized prostate cancer have a PSA between 4 and 50 ng/ml so it is not specific enough to be used alone for staging but can be a useful adjunct to other staging evaluations (Partin and Oesterling, 1994; Oeesterling et al., 1993) (Indicator 2).

Digital rectal exam (DRE) is the primary means of determining if the cancer appears to be organ confined (Stage A or B) or has spread locally beyond the confines of the prostate gland (Stage C). However, the sensitivity of DRE for detecting disease that has spread beyond the prostate is only reported to be 10 to 30 percent (Hricak et al., 1987). While transrectal

ultrasound has a greater sensitivity for detecting cancer that has spread beyond the confines of the prostate than DRE (66 percent), its specificity is only 46 percent (Rifkin et al., 1990). CT Scan has been shown to have a comparable sensitivity of 67 percent with a specificity of 60 percent for detecting prostate cancer that has spread locally beyond the prostate (Platt et al., 1987). MRI is only slightly better than CT scan at identifying locally invasive prostate cancer, with a reported sensitivity of 75 percent and reported specificity ranging from 57 percent to 88 percent (Rifkin et al., 1993; Hricak et al., 1987).

Identifying patients who have prostate cancer that has already spread to pelvic lymph nodes (Stage IV/D) is even more problematic than identifying locally invasive prostate cancer (Stage III/C). Neither physical exam nor transrectal ultrasound are useful in evaluating pelvic lymph nodes. The sensitivity of CT scan for identifying pelvic lymph nodes involved with prostate cancer is zero percent (Platt, Bree, and Schwab, 1987). MRI has a sensitivity of only four percent for identifying positive lymph nodes in prostate cancer patients (Rifkin et al., 1990). Because of their poor performance in predicting patients with cancer that has spread beyond the prostate (Stage III/C and Stage IV/D), we do not recommend that DRE, transrectal ultrasonography, CT scan, or MRI be included in a quality indicator for the staging evaluation of prostate cancer.

A radionuclide bone scan is generally performed routinely to rule-out bone metastases (Stage IV/D) prior to initiating treatment in most patients with prostate cancer (Garnick, 1993; McGregor et al., 1978). A study evaluating the relationship of the PSA level to bone scan findings in 852 patients with prostate cancer found that no patients with a PSA less than 8.0 ng/ml had bone scan evidence of metastases. Furthermore, 0.5 percent of patients with a PSA less than 10 ng/ml had a positive bone scan, and 0.8 percent of patients with a PSA less than 20.0 ng/ml had a positive bone scan (Oesterling et al., 1993). In accordance with these data and expert opinion (Garnick and Fair 1996; Montie 1996; McGregor et al., 1978; Oesterling et al., 1993), we recommend two quality indicators for the staging of prostate cancer. First, all patients with a new diagnosis of prostate cancer should have a PSA checked within one month of diagnosis or prior to treatment, whichever comes first (Indicator 2). Second, patients with a new diagnosis of prostate cancer

and a PSA greater than 10 ng/ml should have a radionuclide bone scan within one month of diagnosis or prior to treatment (Indicator 3).

TREATMENT

Minimal Disease (Stage 0/A1)

No randomized controlled trials have been performed comparing treatment with no treatment in patients with Stage 0/A1 prostate cancer. In case series, rates of disease progression of 5 to 16 percent have been reported with a mean time to progression of six to nine years. However, the survival of men with Stage 0/A1 prostate cancer is comparable to the expected survival of men of similar ages in the general population (Epstein et al., 1986; Lowe and Listrom, 1988; Roy et al., 1990; Thompson and Zeidman, 1989; Zhang et al., 1991). Because the treatments for localized prostate cancer are associated with significant morbidity and survival does not appear to be affected in Stage 0/A1 disease, our proposed quality indicator requires that no treatment be offered to men age 60 and older with Stage 0/A1 disease (Catalona and Basler, 1993; Fowler et al., 1993)(Indicator 4). Since disease progression increases with time, some experts do recommend treating younger men (under age 60) with Stage 0/A1 disease (Catalona and Basler, 1993; Fowler et al., 1993; Epstein et al., 1986). However, because there is no consensus regarding the management of Stage 0/A1 disease in men younger than 60, we have limited our quality indicator to men 60 and older.

Localized Disease (Stage I & II / A2 & B)

Treatment of localized prostate cancer remains controversial. The greatest hope for curing prostate cancer is with radical prostatectomy or radiation therapy while it is still localized. The only randomized controlled trial of radical prostatectomy with no treatment failed to demonstrate a survival advantage with radical prostatectomy. However, the reliability of this result is often questioned because the sample size was only 142, and only 111 of 142 patients included in the trial were available for analysis (Graverson et al., 1990). Several non-randomized studies of expectant management ("watchful waiting") of patients with localized prostate cancer have demonstrated ten year disease-specific survival rates of approximately 85 percent and ten year overall survival rates of approximately 60 percent.

These results are comparable to those obtained with radical prostatectomy and radiation therapy (Perez et al., 1996; Bagshaw et al., 1993; Johansson et al., 1992; Whitmore, 1990; Adolffson, 1993). The only randomized controlled trial comparing radical prostatectomy with radiation therapy used time to first treatment failure as its primary endpoint and showed an advantage for radical prostatectomy (Paulson et al., 1982). But the study has been criticized because the patients treated with radiation were not surgically staged (Hanks, 1988). At the 1987 NIH Consensus Conference on Prostate Cancer, no consensus regarding treatment was reached, and none has been reached since. Still, most American experts recommend definitive treatment for localized prostate cancer for men with a life-expectancy greater than ten years (Gibbons 1993; Bagshaw et al., 1993; Paulson et al., 1982; Perex et al. 1993; Garnick 1993; National Cancer Institute, 1996).

Radical prostatectomy is usually performed via a retropubic approach and newer surgical techniques allow sparing of the neurovascular bundle in order to decrease the incidence of incontinence and impotence. Usually, a pelvic lymphadenectomy is performed prior to the prostatectomy, and the surgeon only proceeds if the lymph nodes are negative for metastatic disease on frozen section. Post-operative complications include incontinence, urethral stricture, rectal injury, impotence, and the morbidity and mortality associated with general anesthesia and a major surgical procedure (30-day mortality of two percent in one study of 10,600 radical prostatectomies). Reports in the literature of complication rates after radical prostatectomy are quite varied. In one large case study of men undergoing the nerve-sparing radical prostatectomy, significant incontinence occurred in six percent of men, while 35 to 60 percent of men who were sexually potent before surgery became impotent following the procedure (Catalona and Basler, 1993). However, in a national survey of Medicare patients who underwent radical prostatectomy in 1988-1990, over 30 percent of men reported the need for pads or clamps for incontinence, and about 60 percent reported having no erections since surgery, with 90 percent reporting no erections sufficient for intercourse during the month prior to the survey (Fowler et al., 1993).

While radioactive implants are used to treat prostate cancer, the most common technique currently in use today is external beam radiation (Garnick, 1993; Bagshaw et al., 1993; Perex et al., 1993). Using a linear accelerator,

67 to 70 Gy is delivered to the prostatic bed and periprostatic tissues over six to seven weeks, with the pelvic lymph nodes receiving approximately 50 Gy. If radiation therapy is chosen as definitive treatment, lymphadenectomy is usually not performed, resulting in those cases which are clinically Stage I or II/A or B but pathologically Stage III or IV/ C or D not being identified. This creates difficulties when trying to compare the outcomes of clinical trials of patients treated with radiation therapy with those treated with radical prostatectomy. The complications of radiation therapy, though infrequent, include diarrhea, proctitis, cystitis, hematuria, rectal bleeding, anal stricture, urethral stricture, rectal ulcer, bowel obstruction. These complications are usually reversible and rarely become chronic (Bagshaw et al., 1993; Garnick, 1993). Sexual potency is generally preserved in the short-term with radiation therapy, but may diminish over time.

Given the lack of clear evidence in favor of a particular treatment for localized prostate cancer, the variable complication rates after radical prostatectomy and radiation therapy, and the need for patients to have the option of a curative treatment when presenting with cancer at a curative stage, we propose a quality indicator specifying that men under age 65 with Stage II/A2&B should have been offered radical prostatectomy or radiation therapy (Indicator 5).

Locally Advanced Disease (Stage III/C)

The optimal treatment for patients with locally advanced prostate cancer is even less clear than that for localized disease. The results of radical prostatectomy in Stage III/C patients are greatly inferior to the results in localized disease (Gibbons, 1993). As surgical removal of the gland is often difficult in Stage III/C prostate cancer, radiation therapy is generally selected for patients with clinical Stage C prostate cancer. The ten year overall survival with both radical prostatectomy and radiation therapy for Stage III/C prostate cancer is about 35 percent. Neoadjuvant androgen ablation therapy has had some success in "downstaging" patients so that PSA levels become undetectable and the remaining cancer is organ confined in more patients at surgery (Labrie et al., 1994; Fair et al., 1993; Gleave et al., 1996). And while one randomized study of radiation therapy with and without androgen ablation showed an advantage in progression-free survival at five

years for the arm that received androgen ablation, to date, neoadjuvant androgen ablation has not been shown to provide an advantage in overall survival (Pilepich et al., 1995). Another treatment option for Stage III/C is early androgen ablation therapy (which will be discussed in the Advanced Disease section); but there is no evidence that it prolongs survival. Still another option is expectant management and treatment when necessary to relieve symptoms.

Given the poor ten year survival with locally advanced disease, many experts would recommend more aggressive treatment in younger men (less than age 60) (Haskell, 1995; National Cancer Institute, 1996; Garnick and Fair, 1996a; Gibbons, 1993; Bagshaw et al., 1993). If pathologic staging confirmed Stage III/C disease, many experts would recommend radical prostatectomy, if technically feasible, or radiation therapy with curative intent.

As there is little consensus on how to treat asymptomatic patients with Stage III/C prostate cancer, we do not recommend a quality indicator for the treatment of this group of patients.

Advanced Disease (Stage IV/D)

The most common symptoms of advanced prostate cancer originate from the urinary tract or from bone metastasis. Historically, more than 50 percent of patients present with bone metastases (prior to the advent of PSA screening) (Huggins and Hodges, 1941). Patients with bone pain, visceral involvement, impending cord compression, obstructive urinary symptoms or hydronephrosis should receive androgen ablation therapy for palliation. Experts also generally recommend treating patients with asymptomatic advanced prostate cancer with androgen ablation therapy; however, the data for this are not conclusive. In randomized controlled trials, androgen ablation therapy appears to slow disease progression in Stage IV/D prostate cancer, and may improve overall survival; however, it is not clear if starting androgen ablation therapy early, while patients are still asymptomatic, has an advantage over waiting until patients develop symptoms.

There are multiple approaches to androgen ablation therapy including orchiectomy alone, monotherapy with an luteinizing hormone-releasing hormone

(LHRH) analogue,¹ monotherapy with non-steroidal antiandrogen therapy,² or maximal androgen blockade (either orchiectomy or an LHRH analogue and antiandrogen therapy).

The major side-effects of all androgen ablation treatments include impotence (almost universally), breast tenderness, and hot flashes. In addition, with LHRH analogues, many patients experience a flare of bone pain and other symptoms after initiating treatment. Since 1941, orchiectomy has been considered the standard ablation treatment for advanced prostate cancer; however, it has not been compared to no treatment in a randomized trial, nor has it been shown to prolong survival (Huggins and Hodges, 1941). The only randomized placebo-controlled trial of androgen ablation compared DES with placebo. The VACURG study showed a slowing of disease progression in Stage IV/D patients treated with DES 5 mg/day compared with placebo, but overall survival was worse in the group treated with DES (diethylstilbestrol), largely due to an increase in cardiovascular mortality (Veterans Administration, 1967). As treatment with DES in this study was associated with an increase in cardiovascular complications and cardiac mortality, DES has been largely been replaced by the newer drugs (LHRH analogues and antiandrogens). Randomized controlled trials of bilateral orchiectomy, the LHRH analogue goserelin, and DES have shown them all to be equally effective in terms of slowing disease progression (Peeling, 1989; Vogelzang et al., 1995; Kaisary et al., 1991). However, none of these studies answer the specific question of whether immediate therapy has a survival advantage over deferred therapy with androgen blockade for advanced prostate cancer. A randomized trial is currently in progress to try to answer this question (EORTC protocol 30846, 1986).

¹ Chronic administration of LHRH analogues causes an inhibition of luteinizing hormone and follicle stimulating hormone release and subsequently a suppression of testicular testosterone secretion similar to that obtained by surgical castration. The commonly used LHRH analogues in the United States are:

- a. leuprolide (Lupron) 1 mg subcutaneous injection daily or 7.5 mg intramuscular injection monthly or 22.3 mg intramuscular injection every 3 months
- b. goserelin acetate (Zoladex) 3.6 mg depot injection monthly or 10.8 mg depot injection every 3 months.

²The antiandrogens block the effect of androgens at the receptor level in the prostatic tissue. The antiandrogens commonly used in the United States include:

- a. flutamide (Eulexin) 250 mg by mouth three times a day
- b. bicalutamide (Casodex) 50 mg by mouth daily
- c. nilutamide (Anandron) 300 mg by mouth daily for the first month of treatment followed by 150 mg by mouth daily thereafter.

Some experts advocate maximal androgen blockade therapy with the addition of an antiandrogen to either orchiectomy or an LHRH analogue alone (Labrie et al., 1993). Maximal androgen blockade is thought to be of benefit because, even in the face of medical or surgical castration, adrenal production of testosterone is able to maintain dihydrotestosterone levels in the testes of up to 40 percent of normal. The antiandrogens act on the prostate tissue to counter the effect of dihydrotestosterone at the receptor level. Several randomized controlled trials have shown increased progression free survival of three to six months and a survival benefit of approximately six months in patients treated with maximal androgen blockade as compared with monotherapy with an LHRH analogue or orchiectomy, though it only reached statistical significance in two of the studies (Crawford et al., 1989; Keuppens et al., 1990; Beland, 1990; Navaratil, 1987; Janknegt et al., 1993). A subgroup of patients with good performance status and minimal disease (lymph node involvement only) in the NCI randomized trial comparing leuprolide with and without flutamide had a pronounced survival advantage of 20 months (61 versus 41.5 months) when treated with maximal androgen blockade" (Labrie et al., 1993). However, overall the results overall are mixed, and two meta-analyses of monotherapy with LHRH analogues or castration compared with maximal androgen blockade showed no survival advantage for maximal androgen blockade (Bertagna et al., 1994; Prostate Cancer Trialists' Collaborative Group, 1995). Therefore, our quality indicator does not state a preference for maximal androgen blockade over other methods of androgen ablation.

Monotherapy with an antiandrogen is another approach that has been advocated by some experts because it is associated with fewer side-effects (Soloway and Matzkin, 1993). While breast tenderness often still occurs with the antiandrogens, along with occasional nausea and diarrhea, libido and potency, when present before therapy, are generally maintained. Randomized controlled trials comparing monotherapy with an antiandrogen to standard androgen blockade approaches are lacking. In several small randomized trials, flutamide and cyproterone acetate have produced objective responses equal to or greater than DES; yet, no studies have compared patients' survival with these agents (Pavone-Macaluso et al., 1986; Lund and Rasmussen, 1988). Given the absence of data, monotherapy with antiandrogens cannot be considered a standard therapeutic approach for advanced prostatic cancer; however,

individual patient preferences may make it the treatment of choice in specific circumstances.

In summary, since patients with Stage IV/D prostate cancer may have a benefit to both progression free survival and overall survival from treatment with androgen ablation, but the evidence in the literature does not clearly support one treatment over the others, we propose as a quality indicator that all men with Stage IV/D prostate cancer be offered at least one of the androgen ablative therapies -- orchiectomy, LHRH analogues, or antiandrogens (Indicator 6).

The advantages of orchiectomy over medical androgen ablation include better patient compliance and lower cost. The disadvantages are the surgical morbidity, the irreversibility of the hormone ablation (and therefore permanence of the associated side-effects), and the psychological effect on the patient of losing his testes. Because it is important for patients to have a choice of treatments, especially when one of them may be psychologically distressing to the patient and equally efficacious alternatives exist, we have developed a quality indicator to ensure that patients who undergo orchiectomy were given a choice. The proposed indicator requires documentation in the patient's chart that he was offered medical androgen ablation as an alternative therapy (Indicator 7).

Hormone Refractory Prostate Cancer

Prostate cancer that progresses while on androgen ablation therapy is termed hormone refractory prostate cancer. Once this occurs, treatment options are limited. A patient being treated with monotherapy when evidence of progression is noted (be it orchiectomy, LHRH analogues, antiandrogens, or DES), especially if symptoms are present, should be given a trial of the maximal androgen blockade. Even when patients progress on maximal androgen blockade, many physicians continue androgen ablation therapy because susceptible cancer cells may still be affected. Other treatment options that exist for hormone refractory prostate cancer include: stopping the antiandrogen (which occasionally produces disease remission), suppression of adrenal androgen production with high dose ketoconazole or aminoglutethamide, estramustine, suramin, or low dose steroids. If patients are asymptomatic and have hormone refractory prostate cancer, the aforementioned approaches can be

tried; however, there is no evidence that they delay progression or prolong survival. Thus, many physicians wait until patients have symptoms before instituting any further treatment. If patients have symptoms from prostate cancer that is hormone refractory, any of the above approaches may be used for palliation as well as for trying to slow disease progression. There is insufficient evidence for us to recommend a quality indicator for the treatment of hormone refractory prostate cancer.

Pain from Bone Metastases

Patients with prostate cancer that has metastasized to the bone often suffer from excruciating pain. A primary focus in the care of patients with metastatic prostate cancer is pain control. It is not uncommon for patients to require substantial narcotic analgesia. While narcotics generally provide pain relief, it is often at a cost to quality of life by inducing somnolence, dysphoria, or constipation. Pain may also be relieved, and narcotic requirements reduced, by treatment with androgen blockade or the other systemic therapies discussed in the hormone refractory prostate cancer section. Palliative radiation therapy directed at sites of bony metastases and strontium-89 have been shown to decrease pain and reduce narcotic analgesia requirements in approximately 80 percent of patients. Quality indicators related to pain management are covered in Chapter 11.

Cord Compression

Spinal cord compression develops in approximately seven percent of men with prostate cancer (Osborn et al., 1995). If a patient with prostate cancer develops new or worsening back pain, or neurologic symptoms, spinal cord compression by tumor should be considered. Back pain is the initial symptom in 75 to 100 percent of patients with cord compression. A normal neurologic exam in a patient with back pain does not rule out spinal cord compression. In a study of patients with known malignancy, back pain, and a normal neurologic exam, 36 percent had spinal epidural metastases on myelogram (Rodichok et al., 1981). Plain films of the spine have a sensitivity of 91 percent and a specificity of 86 percent for predicting epidural metastases (Grant et al., 1994). Bone scan has a sensitivity of 91 percent as well, but a specificity of only 53 percent. The positive predictive value of neurologic exam and plain films together varies between studies. False negative rates

for ruling-out cord compression with a normal neurologic exam and normal plain film range between zero and 17 percent (Rodichok et al., 1981). The gold standard for diagnosis of spinal cord compression is CT myelogram, and MRI scanning has been shown to have comparable sensitivity and specificity.

Experts recommend that any patient with underlying prostate cancer who develops new or worsening back pain and either has an abnormal neurological exam or abnormal plain films of the spine or an abnormal bone scan undergo either MRI or CT myelogram to rule-out cord compression (Rodichok et al., 1981). As patients with new or worsening back pain who have a normal neurologic exam with normal plain films or bone scan still may have up to a 17 percent risk of cord compression, experts recommend either proceeding on with a MRI and CT myelogram as well or, alternatively, applying a more sensitive test to rule-out metastatic bone disease, a CT scan of the spine (Rodichok et al., 1981). If the CT scan of the spine does not show bony metastases, then spinal cord compression is unlikely. However, if the CT scan of the spine demonstrates metastases, then MRI or CT myelogram are required to evaluate for cord compression.

We recommend that the quality indicator for the evaluation for spinal cord compression include documentation of a normal CT scan of the spine or performance of an MRI or CT myelogram (Indicator 8). No data exist in the literature regarding the time frame in which these tests should be obtained nor how long their results are still valid should new symptoms develop in the future. The evaluation of cord compression is generally considered an emergency, especially if neurologic deficits are present on exam, because the most significant prognostic variables for recovery of function are the severity of weakness at presentation and the duration of paraplegia before treatment is initiated. Therefore, we have selected 24 hours as a conservative maximum allowed time for obtaining an emergent diagnostic study to rule-out cord compression. Given that the median survival for men with hormone refractory prostate cancer is less than ten months (Garnick, 1993), and 57 to 82 percent of men with prostate cancer who develop cord compression are on hormone therapy (suggesting that they have become hormone refractory)(Lund and Rasmussen, 1988), we have allowed for diagnostic tests for cord compression that were obtained up to three months prior to the presenting complaint to satisfy the indicator requirements.

If the radiologic studies are consistent with cord compression, treatment with a minimum dose of dexamethasone (4 mg IV or PO every six hours) should be instituted immediately, followed by palliative radiation therapy or decompressive laminectomy (Lund and Rasmussen, 1988). Randomized controlled trials of higher doses of dexamethasone have not shown an improvement in neurologic recovery (Lund and Rasmussen, 1988). Experts recommend 72 hours of dexamethasone therapy and then a rapid taper (Lund and Rasmussen, 1988). Several retrospective studies comparing decompressive laminectomy alone with decompressive laminectomy followed by radiation therapy have demonstrated a benefit for the latter (Rodichok et al., 1981). When decompressive laminectomy was compared with radiation therapy alone, no differences in functional outcomes were observed; although, in a series of 22 patients with rapidly progressing neurologic signs, 54 percent of those treated with radiation therapy improved and none of those who underwent surgery improved (Lund and Rasmussen, 1988). In general, radiation therapy is considered first line therapy, though in selected cases, such as spinal instability, decompressive laminectomy may be indicated. The dose of radiation in the treatment of cord compression is not well established. Spinal cord toxicity can occur at doses greater than 4500 cGy. No dose-response relationship has been identified in the treatment of spinal cord compression secondary to prostate cancer, but 3000 to 4000 cGy fractionated over two to four weeks is commonly given. We propose that the quality indicator for the treatment of cord compression in prostate cancer include treatment with a minimum dose of 4 mg dexamethasone orally or intravenously every six hours for at least 72 hours, and either radiation therapy (total dose between 3000 cGy and 4500 cGy) or decompressive laminectomy within 24 hours (Indicator 9 and 10).

FOLLOW-UP

Some experts recommend follow-up with DRE and PSA testing for patients with Stage I to III prostate cancer every three months for one year, and every six months thereafter (Garnick, 1993). In addition, prostate biopsy has been recommended 18 to 24 months after completing radiation therapy or if the findings on DRE change (Garnick, 1993). For patients with Stage IV prostate cancer, experts recommend DRE and PSA testing every three months as well as a bone scan, if clinically indicated (Garnick, 1993). However, these

frequencies are based upon the follow-up of patients in clinical trials and may not be applicable in a clinical setting where the need to measure treatment outcome at regular intervals does not exist. To date, no studies have evaluated what constitutes necessary and appropriate follow-up of patients with prostate cancer. In addition, there are no data to suggest that diagnosing recurrence earlier leads to prolonged survival or better quality of life asymptomatic patients. As such, follow-up for prostate cancer should be tailored to a patient's symptoms and needs. Therefore, we do not recommend a quality indicator for the follow-up of patients with prostate cancer.

Table 9.1
Definition of Stages of Prostate Cancer

Stage	TNM	Definitions of Stage for Quality Indicators
Stage 0/A1	<u>T1a N0 M0 G1</u> - clinically inapparent tumor incidentally found in <u>5</u> percent of tissue resected by TURP and well-differentiated.	Patient without clinically evident prostate cancer, with prostate cancer found at TURP in <u>5</u> percent of tissue resected with a Gleason sum score <u>4</u> or described as well-differentiated.
Stage I/A2 & B0	<u>T1a N0 M0 G2-4</u> - clinically inapparent tumor incidentally found in <u>>5</u> percent of tissue resected by TURP and well-differentiated. <u>T1b N0 M0 any G</u> - clinically inapparent tumor incidentally found in <u>>5</u> percent of tissue resected by TURP. <u>T1c N0 M0 any G</u> - clinically inapparent tumor identified by biopsy (performed for evaluation of elevated PSA).	Patient without clinically evident prostate cancer localized to the prostate either: <ul style="list-style-type: none"> • found at TURP in <u>>5</u> percent of tissue; • found at TURP in <u>>5</u> percent of tissue with a Gleason sum score <u>>4</u> or described as moderately differentiated, poorly differentiated or undifferentiated; • identified by needle biopsy.
Stage II/B	<u>T2 N0 M0 any G</u> - tumor confined to the prostate.	Patient with prostate cancer confined to the prostate palpable on physical exam.
Stage III/C	<u>T3 N0 M0 any G</u> - tumor extends through the prostatic capsule.	Patient with prostate cancer that extends locally outside the prostate.
Stage IV/D	<u>T4 N0 M0 any G</u> - tumor invades or is fixed to adjacent structures other than seminal vesicles. <u>Any T N1-3 M0 any G</u> - tumor involved pelvic lymph nodes. <u>Any T any N M1 any G</u> - tumor has metastasized to sites beyond the pelvic lymph nodes.	Patient with prostate cancer that: <ul style="list-style-type: none"> • invades adjacent organs such as the anal sphincter, rectum or bladder or adjacent muscles; • involves pelvic lymph nodes; • involves any other part of the body including but not limited to the bones.

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Top 30 Diagnoses (ICD-9-CM Codes) for Men Ages 65-74 and Men Ages 75+.

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RECOMMENDED QUALITY INDICATORS FOR PROSTATE CANCER TREATMENT

The following criteria apply to men age 18 and older.

Indicator	Quality of Evidence	Literature	Benefits	Comments
Diagnosis				
<p>1. A patient <i>without</i> any previously known diagnosis of cancer who has an x-ray or radionuclide bone scan with blastic or lytic lesions, or with a notation that the findings are consistent with metastases, should be offered all of the following within the 12 months prior or the 3 weeks following the date of the x-ray or bone scan:</p> <ul style="list-style-type: none"> a. digital rectal exam; b. PSA. 	II-2, III	Leonard and Nystrom, 1993; Hainsworth and Greco, 1993; Huggins, 1941	Reduce prostate cancer morbidity and mortality.	50% of patients with prostate cancer present with bone metastases.
<p>2. Patients with a new diagnosis of prostate cancer, who have not had a serum PSA in the prior three months, should have serum PSA checked within one month after diagnosis or prior to any treatment, whichever comes first.</p>	II-2, III	Garnick, 1993; Montie, 1996; Partin and Oesterling, 1994; Oesterling, 1993	Reduce prostate cancer morbidity and mortality.	Provides prognostic information and if <10ng/ml, obviates need for bone scan. Only 0.5% of men with PSA less than 10ng/ml had a positive bone scan.
<p>3. Patients with a new diagnosis of prostate cancer who have a PSA > 10mg/ml should be offered a radionuclide bone scan within 1 month or prior to initiation of any treatment, whichever is first.</p>	II-2, III	Garnick, 1993; Montie, 1996; Partin and Oesterling, 1994; Oesterling, 1993	Reduce morbidity from unnecessary treatment. Target treatment to reduce metastatic prostate cancer morbidity.	Identify patients with metastatic disease. 50% of patients with prostate cancer present with bone metastases.

Indicator	Quality of Evidence	Literature	Benefits	Comments
Treatment				
<p>4. Men <i>over 60</i> with minimal prostate cancer (Stage O/A1) should not be offered any of the following treatments:</p> <ul style="list-style-type: none"> a. bilateral orchiectomy b. LHRH analogue;^{1, 2} c. antiandrogen;³ d. radical prostatectomy; e. radiation therapy. 	II-2, III	Epstein, 1986; Lowe, 1988; Roy , 1990; Thompson , 1989; Zhang, 1991	Reduce morbidity from procedure of unproven benefit.	Case series demonstrate survival comparable to general population.
<p>5. Men under 65, who do not have coronary artery disease⁴ or a second cancer,⁵ should be offered radical prostatectomy or radiation therapy for localized prostate cancer (Stage I & II/A2 & B) within 3 months of staging.</p>	I, II-2, III	Garnick, 1993; Gibbons, 1993; Perez, 1993; Bagshaw et al., 1992, Whitmore, 1990; Adolffson, 1993; Graverson et al., 1982	Improve survival in selected patients.	Case series suggest similar 10 year survival (85%) for radical prostatectomy, radiation therapy, and observation. While data from randomized controlled trials showing a definite survival benefit for radical prostatectomy or radiation therapy is lacking, most experts would recommend offering such treatment to men with a life expectancy greater than 10 years to provide an option for potential curative therapy.

Indicator	Quality of Evidence	Literature	Benefits	Comments
<p>6. Men with metastatic prostate cancer (Stage IV/D) should be offered at least one of the following androgen blockade treatments within three months of staging:</p> <ul style="list-style-type: none"> • bilateral orchiectomy; • LHRH analogue;¹ • Antiandrogen.² 	I,III	<p>Garnick, 1993; Daneshgari and Crawford, 1993; Huggins, 1941; VACURG, 1967; Peeling, 1989; Vogelzang , 1995; Kaisary et al. ,1991; EORTC Protocol, 1986; Kirk, 1984; Labrie, 1993; Crawford et al., 1989; Keuppens et al., 1990; Beland et al., 1990; Navaratil, 1987; Janknegt et al., 1993; Bertagna et al., 1994; Prostate Cancer Trialists' Collaborative Group, 1995; Soloway and Matzkin 1993; Pavone-Macaluso et al., 1986; Lund, 1988</p>	Reduce prostate cancer morbidity and mortality.	<p>Randomized controlled trials of bilateral orchiectomy and LHRH analogues have shown them to be equally effective at slowing disease progression. Results are mixed on whether "maximal androgen blockade" with an LHRH analogue and an antiandrogen has a survival benefit over treatment with an LHRH analogue alone. Data regarding monotherapy with antiadrogens is lacking; however, as they have fewer side-effects, they may be appropriate for palliation in some patients.</p>

Indicator	Quality of Evidence	Literature	Benefits	Comments
<p>7. Men who undergo orchiectomy for the treatment of prostate cancer should have documented that they were offered treatment with an LHRH analogue or antiandrogen within 12 months prior to surgery.²</p>	I, III	<p>Garnick, 1993; Daneshgari and Crawford, 1993; Huggins, 1941; VACURG, 1967; Peeling, 1989; Vogelzang et al., 1995; Kaisary et al., 1991; EORTC, 1986; Kirk, 1984; Labrie et al., 1993; Crawford et al., 1989; Keuppens et al., 1994; Beland et al., 1990; Navaratil, 1987; Janknegt et al., 1994; PCTCG, 1995; Soloway, 1993; Pavone-Macaluso et al., 1986; Lund, 1988</p>	Reduce prostate cancer morbidity.	Randomized controlled trials of bilateral orchiectomy and LHRH analogues have shown them to be equally effective at slowing disease progression.
<p>8. Prostate cancer patients who present with acute low back pain⁶ should have documentation within 24 hours of the complaint or in the preceding 3 months of one of the following:</p> <ul style="list-style-type: none"> • a CT scan of the spine <i>without</i> blastic or lytic lesions or compression fractures; • a CT myelogram; • an MRI of the spine. 	II-1, III	<p>Osborn et al., 1995; Rodichok et al., 1981; Grant et al., 1994</p>	Reduce prostate cancer morbidity.	Early diagnosis and treatment of cord compression improves functional outcome. 17% false negative rate for cord compression with a normal neurologic exam and normal plain films of the spine.

Indicator	Quality of Evidence	Literature	Benefits	Comments
<p>9. Prostate cancer patients with evidence of cord compression on MRI scan of the spine or CT myelogram should be offered one of the following within 24 hours of the radiologic study:</p> <ul style="list-style-type: none"> • radiation therapy to the spine at a total dose between 3000 cGy and 4500 cGy over 2-4 weeks; • decompressive laminectomy. 	I, II-2, III	Osborn et al., 1995; Rodichok et al., 1981; Grant R et al., 1994	Decrease back pain and improve functional outcome.	Case series show benefit for laminectomy followed by radiation therapy over laminectomy alone and no difference between laminectomy and radiation therapy alone.
<p>10. Prostate cancer patients with evidence of cord compression on MRI scan of the spine or CT myelogram should be offered at least 4 mg dexamethasone IV prior to the radiologic study or within 1 hour of its completion, followed by dexamethasone 4 mg IV or PO q six hours for at least 72 hours.</p>	I, II-2, III	Lund & Rasmussen, 1988; Osborn et al., 1995; Rodichok et al., 1981; Grant et al., 1994	Decrease back pain and improve functional outcome.	RCTs of higher doses of dexamethasone have not shown an improvement in neurologic recovery.

Definitions and Examples

¹ LHRH Analogue: The commonly used LHRH analogues in the United States are:

- a. leuprolide (Lupron) 1mg subcutaneous injection daily or 7.5 mg intramuscular injection monthly or 22.3 mg intramuscular injection every 3 months
- b. goserelin acetate (Zoladex) 3.6 mg depot injection monthly or 10.8 mg depot injection every 3 months

² Antiandrogen: The antiandrogens commonly used in the United States include

- a. flutamide (Eulexin) 250 mg by mouth three times a day
- b. bicalutamide (Casodex) 50 mg by mouth daily
- c. nilutamide (Anandron) 300 mg by mouth daily for the first month of treatment followed by 150 mg by mouth daily thereafter

³ Coronary Artery Disease: A person shall be considered to have coronary artery disease if he has any of the following documented in the chart in progress notes, problem lists, or as discharge diagnoses:

- a. coronary artery disease
- b. angina
- c. myocardial infarction
- d. coronary artery bypass graft surgery
- e. PTCA
- f. congestive heart failure
- g. a coronary angiogram with at least one vessel with an occlusion >70%

⁴ Second Cancer: A person shall be considered to have a second cancer if he has any of the following documented in the chart in progress notes, problem lists, or as discharge diagnoses:

- a. any cancer other than prostate cancer except for basal cell and squamous cell skin cancers
- b. treatment with chemotherapy

⁶ Acute low back pain: No record of chronic low back pain pre-dating the prostate cancer diagnosis.

Quality of Evidence Codes

I	RCT
II-1	Nonrandomized controlled trials
II-2	Cohort or case analysis
II-3	Multiple time series
III	Opinions or descriptive studies