NWT Clinical Practice Information Notice

UPON RECEIPT: (1) PLEASE FOLLOW THE DIRECTIONS BELOW
(2) FILE THIS NOTICE IN SECTION C, CLINICAL PRACTICE INFORMATION BINDER FOR FUTURE REFERENCE

The following clinical practice has been approved for use in the Northwest Territories Health and Social Services system, and has been distributed to:

- [x] Hospitals
- [x] Community Health Centers
- [x] Public Health Units
- [x] Doctors' Offices
- [ ] Social Services Offices
- [x] Other: CDC Manuals

The information contained in this document is a Departmental:

- [ ] Policy
- [ ] Standard
- [ ] Protocol
- [ ] Procedure
- [x] Guidelines

Title: Clinical Practice Guidelines for the Use of Free PSA Ratio and Total PSA in the Screening for Prostate Cancer

Effective Date: April 19, 2002

Statement of approved clinical practice:
The attached Clinical Practice Guidelines for the Use of Free PSA Ratio and Total PSA in the Screening for Prostate Cancer, dated March 2002 are recommended by the NWT Laboratory Advisory Committee.

Please file the attached Clinical Practice Guidelines in the ***Laboratory Manual*** in use within your facility/region.

Those who do not have a laboratory manual should retain the attached information for reference in their own filing system.

Attachment:

- Clinical Practice Guidelines for the Use of Free PSA Ratio and Total PSA in the Screening for Prostate Cancer

This clinical practice is approved. _____

(signature)

Assistant Deputy Minister [ ] **Chief Medical Officer of Health** [x] **Director, Child & Family Services** [ ] **Director, Adoptions** [ ]

Clinical Practice Guidelines
Use of Free PSA Ratio and Total PSA in the Screening for Prostate Cancer
(Developed by the NWT Laboratory Advisory Committee)

Goals

- To provide guidance about appropriate use of prostate specific antigen (PSA) and free PSA testing
- To help physicians and their patients make informed decisions regarding screening for prostate cancer in asymptomatic men of age

Recommendations

1. The appropriate use of free PSA/PSA testing includes:
   - evaluation of a patient with an abnormal digital rectal examination (DRE) (free PSA)
   - evaluation of a patient with symptoms of prostatism (Free PSA)
   - follow-up of a patient with prostate cancer (PSA)

2. Free PSA/PSA testing should be discussed with the following patient groups (see text):
   - those at a higher risk for the development of prostate cancer
   - those who express a concern about the development of prostate cancer

3. Free PSA/PSA testing is inappropriate in patients with a reduced life expectancy

4. Free PSA/PSA testing detects prostate cancer at an earlier stage. However, this benefit is unproven as a routine screening test in asymptomatic, low risk males. Thus:
   - given the widespread use of Free PSA/PSA men should be advised of its availability, reliability, and the potential risks and benefits of treatment
   - if proceeding with screening then both a DRE and a free PSA should be performed

5. The measurement of the ratio of free-to-total PSA can improve specificity for distinguishing between benign prostatic hyperplasia (BPH) and prostatic carcinoma.

The above recommendations are systematically developed statements to assist the practitioner and patient decisions regarding appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision-making.

Overview of the Evidence

BACKGROUND

According to the National Cancer Institute of Canada (1996), prostate cancer is the most frequent cancer and the second leading cause of death from cancer in men, exceeded only by lung cancer.[1] Prostate cancer accounts for 27% of all male cancers and 13% of male cancer-related deaths. While the incidence has increased significantly over the past 35 years, the mortality rate has only increased slightly. The lifetime risk developing prostate cancer is 12%.

Risk factors for prostate cancer include: age, race, diet, and family history. The risk of getting prostate cancer increases rapidly after age 50. The incidence of prostate cancer in men 75 years of age is thirty times greater than that of men 50 years of age.[1] A high intake of dietary fat also seems to be associated with a higher risk for developing cancer.[2] African-American men have a 30% greater incidence of prostate cancer compared with white men. There is an increased risk for the development of prostate cancer in men who have first-degree relatives with the disease.

The reason for the dilemma in prostate cancer screening relates to the following two confirming factors:

1. Not all prostate cancers are serious or clinically important. Most men will die with, rather than from the disease. Autopsy studies report that more than 30% of all men over the age of 50 have histologic evidence of prostate cancer, but only 3% will die from it. How we identify those requiring potentially curative therapy from those, who can be safely followed without treatment remains to be elucidated.

2. Locally advanced or metastatic prostate cancer is very serious. It can cause premature death and painful suffering. Ten year survival rates are as follows:

   - 75% when confined to the prostate,
   - 55% with regional extension, and
   - 15% with distant metastases.

USE OF FREE PSA AND PSA TESTING

PSA is a protein produced by both normal and cancerous prostate tissue. It is found in three molecular forms: free PSA, PSA complexed with *u* 1-antichymotrypsin and PSA complexed with a *u* 2-macroglobulin. Elevated serum levels of PSA may identify the presence of cancerous and noncancerous abnormalities of the prostate gland.
60 - 75% of men with prostate cancer will have elevated levels.[3] Mild elevations of PSA are commonly associated with benign prostatic disease. For a given individual there may be variations in PSA levels independent of disease.

Free PSA

Recent studies have shown the measurement of the ratio of free-to-total PSA can improve specificity for distinguishing between benign prostatic hyperplasia (BPH) and prostatic carcinoma. Published studies have reported various cutoffs related to the specificity of free-to-total PSA in detecting prostatic cancer. The message that emerges from these studies is that patients with higher ratios of free PSA are more likely to have benign findings and patients with lower ratios are more likely to have prostatic carcinoma. Free PSA can be helpful in establishing patient-specific risk for prostatic carcinoma, but no free PSA value can conclusively rule out or rule in a malignant diagnosis. It is also clear that free-to-total PSA ratio will have the its greatest benefit for men with early, potentially curable disease and total PSA values between 4 and 10 *u*g/L. The ratio may be useful in patients with total PSA values up to 20 *u*g/L.

Interpretation of Free PSA Values

Following are guidelines for the interpretation of free PSA values in establishing patient specific risk for prostatic carcinoma:

- ⇨ Free-to-total PSA ratios of greater than 0.20 are more likely to be benign. As the ratio increases, the likelihood of BPH increases.

- ⇨ Free-to-total PSA ratios of less than 0.10 are more likely to be prostatic carcinoma. As the ratio decreases, the likelihood of carcinoma increases.

- ⇨ Free-to-total PSA ratios between 0.10 and 0.20 show substantial overlap of clinical findings with both malignant and benign diagnosis.

- ⇨ There is some overlap of clinical findings throughout the range of free PSA ratios. No free PSA ratio will conclusively rule out or rule in prostatic carcinoma.

- ⇨ The free-to-total PSA ratio is most useful in patients with total PSA values between 4 and 10 *u*g/L. The ratio may be useful in patients with total PSA values up to 20 *u*g/L.

Evaluation of Symptomatic Patients

Benign prostatic hyperplasia (BPH) and prostate cancer are both common diseases in men as they age. Prostatism, a symptom of both conditions, warrants further investigation based on the number of factors which may include age, and life expectancy of the patient. It remains unclear at this time whether BPH is associated with increased risk for prostate cancer. However, symptoms of BPH associated with urinary tract obstruction are similar to those of prostate cancer.

Various methods have been proposed to detect and diagnose cancer in men with BPH. It should be remembered that some men with BPH will have mildly elevated PSA levels. The most appropriate way to detect prostate cancer in these men is a combination of DRE and PSA. The free-to-total PSA ratio will be of benefit in helping with the diagnosis of BPH. Trans rectal ultrasound (TRUS) of the prostate is not useful as a screening test for prostate

cancer. TRUS does provide an excellent means of guiding trans rectal biopsies of the prostate.

Evaluation of a Patient with an Abnormal Digital rectal examination (DRE)
Digital rectal examination (DRE) is easy to perform and is the traditional test to detect changes in the prostate gland. DRE is useful in detecting other colorectal disease. Suspicion arises when irregularities are found in the prostate gland. However, DRE has a limited sensitivity and specificity in the detection of prostate cancer.[5] A suspicious DRE is an indication for serum PSA testing.

Evaluation of a Patient with Risk Factors for Prostate Cancer
African-American men and men with first degree relatives diagnosed before the age of 70 have a higher risk than general population. However there is no evidence to suggest that early detection efforts will provide more benefit to such individuals than to normal risk patients. One study revealed, however, that when presented with information about PSA testing, patients with risk factors show a greater interest in pursuing PSA screening than those with no risk factors.[6]

Investigation and follow-up of a patient with prostate cancer
In patients with prostate cancer, serum total PSA levels are often proportional to the clinical stage of the disease and the volume of prostate cancer found in the gland. Thus, PSA may help predict the likelihood discovering lymph node or seminal vesicle involvement.

Increasing PSA values after definitive radiotherapy or radical prostatectomy for localized prostate cancer can predict residual localized cancer or the development of metastases. Following the initiation of hormone therapy in metastatic disease, PSA values are useful in predicting response to therapy. The Alberta Uro-oncology group[4] has produced recommendations of the use of PSA for follow-up of patients with prostate cancer.

BENEFITS AND RISKS ASSOCIATED WITH SCREENING FOR PROSTATE CANCER

Unfortunately, prostate cancer does not lend itself well to screening for the following reasons:

- ⇨ The natural history of the disease is poorly understood as it is not possible to predict reliably the biological potential of a given tumor in any single individual to progress to significant morbidity and mortality.

- ⇨ There has been little or no impact of improvements on detection and treatment of prostate cancer on overall mortality of the disease. Mortality from prostate cancer has not significantly increased over the last 30 years.

- ⇨ Screening tests with high sensitivity and specificity do not exist

- ⇨ It is not clear that the benefits outweigh the risks of screening for prostate cancer.

There is little evidence to suggest that patients who are screened have better outcomes than those who are not screened. Some researchers suggest that early detection increases survival because men who are diagnosed with localized tumors and receive treatment have a greater chance of being cured than those with more advanced disease.[7, 8] Others argue that some men with early stage prostate cancer have good outcomes with delayed or conservative treatment.[9] No controlled studies have ever addressed the question of health benefits associated with screening for prostate cancer. Trials are underway in Canada, United States and Europe, but the results will not be available for more than a decade.

In assessing the potential benefits of any screening tests the problems of false positive results, the potential harm of testing and the risks of treatment must also be evaluated. For example, in men over 50, the positive predictive value of a PSA > 4.0 *ug*/L is only 31%. Two out three men with abnormal results on routine screening will not have cancer. Before cancer is ruled out, must undergo additional testing such as repeat PSA testing, ultrasonography and biopsy. Anxiety and its consequent health problems may become a significant issue for patients with positive PSA and negative work up.

Risks associated with radical prostatectomy and/or radiotherapy include incontinence, urethral stricture, bowel damage, erectile dysfunction and complications arising from anaesthesia and major surgery, including death.[8] The treatment of patients with clinically insignificant cancer would lead to unnecessary morbidity.

Notwithstanding these issues, however, definitive treatment of prostate cancer is potentially curative if the disease is confined to the prostate gland when diagnosed. Although evidence is not conclusive, there is data that suggest a greater proportion of cancers being detected by screening are organ confined and that the majority of these tumors may be clinically significant. Whether or not this will result in an improvement in the survival rates in prostate cancer remains to be seen.[10]

ADVICE TO PATIENTS

The NWT Laboratory Advisory Committee supports the right of the patient to make an informed decision about his health care options. Patient decisions will vary as a result of individual fear of cancer (which may be associated with family history), the potential impact of iatrogenic complications on the quality of life, and individual interpretation of the evidence relative to health benefits. Patient education is paramount in decisions surrounding prostate cancer. It is important for asymptomatic men to be aware of the consequences of their decisions to be screened or not screened.

Before deciding on testing, the patient should consider procedures that would necessarily follow an abnormal result and whether or not he would want to be treated if cancer were diagnosed.

"In particular, men with a life expectancy of less than 10 years should be advised that screening is unlikely to be helpful and may worsen the quality of their lives." [8]

If a patient wishes to proceed with screening after discussion of the risks and benefits associated with diagnosis and treatment of prostate cancer, then DRE combined with PSA is indicated. The positive predictive value of these two tests is better than each alone.[11, 12]

DEFINITIONS

Sensitivity: the proportion of men with prostate cancer who have a positive test result

Specificity: the proportion of men without prostate cancer who have a negative test result

Positive Predictive Value: the proportion of men with a positive prostate test result who have prostate cancer

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