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2023 UPDATE ON THE SCREENING AND TREATMENT OF LOCALIZED PROSTATE CANCER

Introduction

Prostate cancer represents a major burden of disease in Canada. It represents the third leading cause of cancer mortality in men with more than 24,000 individuals diagnosed in 2021. The diagnosis and management of prostate cancer is a continuously evolving area, and the aim of this article is to provide current information on various aspects of prostate cancer care, as an aid for primary care physicians (PCPs) as they guide men through the prostate cancer journey.

Prostate Cancer Screening

The recommendations for prostate cancer screening with prostate specific antigen (PSA) testing have changed over the past decade. Recommendations for any type of screening are a balance between the benefit of early diagnosis (and improved oncologic outcomes) vs the harms associated with the screening and downstream tests.

The evidence supporting the benefit of PSA-based prostate cancer screening was based on two randomized clinical trials, with contradictory results. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that PSA-based screening in a largely unscreened population reduced prostate cancer-specific mortality.[1]

At a median follow-up of nine years, the relative risk reduction (RRR) of prostate cancer death was 20% by intention-to-treat (ITT) (i.e., how the patient was randomized) while the efficacy analysis (results according to whether or not patients were screened) was 27%. This translated to a number needed to screen (NNS) of 1410 and number needed to diagnose (NND) of 48 men to prevent one prostate cancer death. As the trial matured, the NNS and NND declined. At 13 years, the NNS and NND were 781 and 27 respectively, while at 21 years it was 246 and 14 respectively,[2] results similar or better than screening effectiveness for breast cancer (NNS 233-377) and cervical cancer (NNS 3497).[4]

The U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial confounded the screening guidelines as it showed no benefit in prostate cancer-specific mortality.[5] However, the data that was not noted by the U.S. Preventative Services Task Force (UPSTF) or the Canadian Task Force on Preventive Health Care (CTFPHC) committees is that 85% of the men randomized to screening were compliant, whereas 90% of the men in the control arm received opportunistic screening but were recorded as if they had received no screening.[6] The implication of this is that a greater number of men received screening in the "no-screening" control arm than the "screening" control arm, yet only ITT analyses were reported.[5]

More than one round of screening further reduces the risk of prostate cancer death (RRR 25% for one round vs 48% for more than one round of screening).[7] In addition, the initial PSA level can be used to guide decisions regarding further PSA testing (or the timing of the next screening). Specifically, in men age 55 to 69, a PSA level of <1.0 ng/mL resulted in a < 3% likelihood of being diagnosed with prostate cancer 16 years later.[8] If a second screening was conducted eight years after, the risk of prostate cancer death at 16 years was 0.03%.

Initial Work-up for Elevated PSA

There have been several changes in practice that have reduced the harm associated with screening. The first is to only refer men for work-up if they have a significant risk of having clinically significant prostate cancer (csPC: ISUP Grade Group 2 [i.e., Gleason 7] or higher disease). This can be calculated online (https://riskcalc.org/PCPTRC/); however, as a rule of thumb, for a 55-year-old Caucasian male with no family history, a normal digital rectal exam and no previous biopsy, the risk of csPC is equal to the PSA.

Generally, men with >5% risk of csPC should be investigated. Ideally, these men should be referred on to a multidisciplinary uro-oncology team. The establishment of multidisciplinary diagnostic programs, such as the Diagnostic Assessment Program (DAP) endorsed by Cancer Care Ontario, has enabled men with elevated PSA to have timely access to a multidisciplinary uro-oncology team for subsequent work-up (https://www.cancercareontario.ca/en/find-cancer-services/diagnostic-assessment-program-locations).

Multiparametric magnetic resonance imaging (mpMRI) is now a standard second screening test for men with elevated csPC risk (sometimes referred to as the "manogram"). It is primarily based on data from two Phase 3 randomized clinical trials.[9,10] In both trials, men with elevated PSA were randomized to standard systematic prostate biopsy, or upfront mpMRI followed by targeted biopsy of the MRI-detected prostate lesions (biopsy was not done if the MRI was negative). In the Canadian PRECISE study, the MRI-guided approach reduced the risk of requiring a biopsy by 30%, increased the likelihood of detecting csPC by 5%, and decreased the risk of detecting ISUP Grade Group 1 (i.e., Gleason 6) disease by 50%.[10] This is now the preferred approach endorsed by Cancer Care Ontario.[11]

Once a decision is made to proceed with prostate biopsy, it is most often performed using the transrectal (TR) approach, whereby under ultrasound guidance, the biopsy trocar is passed through the rectal wall

into the prostate. However, the transperineal (TP) approach, whereby the biopsy trocar passes through the transperineal skin (rather than the rectal wall), is recognized as being superior for various reasons.[12] TR biopsy is associated with increased risk of infection and urosepsis, despite the use of antibiotic prophylaxis. While there are no randomized trials comparing the TR and TP approaches in terms of infection rate, the differences in infection rates were shown to be stark with virtually zero risk of infection or urosepsis with TP,[13] even when prophylactic antibiotic was omitted.[14] In addition, there is some evidence suggesting that the TP approach provides superior detection of anterior tumour.[15] Currently, TP biopsy is available solely at Sunnybrook Hospital and North York General Hospital in Toronto.

Conservative Management: Active Surveillance vs Watchful Waiting

Screening tends to detect lower grade disease (77% in the PROTECT trial had ISUP Grade Group 1 disease)[16] and in the 2000's virtually all of these men with low grade disease (Gleason 3+3 or ISUP Grade 1) were treated with surgery or radiotherapy and experienced the attendant side effects.

However, clinical data has shown that not all men with newly diagnosed prostate cancer require upfront treatment. At least three randomized clinical trials have investigated active treatment with observation in men with localized prostate cancer.[16-18] With median follow-up of 15–20 years, all these studies have consistently shown no significant differences in prostate-cancer specific death with observation, especially in men with low-risk prostate cancer. This has prompted numerous guidelines to revise their recommendations to active surveillance (AS) for these men.[19,20] Population-based studies in Ontario show that more than 85% of men with low-risk prostate cancer are initially managed with AS (Cancer Care Ontario data). This reduces the harm associated with treatment[21] as more than 50% of men remain treatment-free 15 years following the initial diagnosis.[22]

The disease management objectives of men on AS is distinct from those of men managed with a *watchful waiting (WW)* program, where the care objective is not to delay curative-intent treatment, but to forgo curative-intent treatment and reserve palliative-intent treatment (including androgen deprivation therapy or palliative radiotherapy) for when symptomatic disease progression occurs. This approach is generally recommended for men with favourable prostate cancer with a life expectancy of fewer than 10 years. In these cases, PSA monitoring, tests or physical examinations should not be done; otherwise it represents a form of AS.

Curative-intent Treatment Options for Localized Prostate Cancer

Men who opt for curative-intent treatment have various treatment options, including surgery and radiotherapy, each with distinct side effect profiles.[23,24] The rapid advancement in both surgical and radiotherapy techniques over the years has improved outcomes post-treatment. Evidence suggests that robotic-assisted radical prostatectomy (RARP) might have better urinary continence and potency results vs those of open radical prostatectomy with equivalent tumour control.[25,26]

Advancements in radiotherapy technologies and an improved understanding of the radiobiology of prostate cancer have allowed us to deliver more precise and fewer doses of radiotherapy; this improves tumour control while reducing radiotherapy-related bowel and bladder toxicities. In addition, this has allowed us to shorten the course of prostate radiotherapy from 39 treatments over eight weeks to five treatments with stereotactic body radiotherapy (SBRT) over 1.5 weeks with favourable early toxicity and quality of life outcomes.[27] In the PACE-A randomized study of RARP vs SBRT, 0% vs 2% of men had significant bowel changes; 47% vs 5% of men reported incontinence pad use; and 40% vs 10% of men had loss of sexual function, respectively, at 2 years post-treatment.[28] These non-invasive, short-course treatments are extremely beneficial in terms of patient convenience and healthcare cost savings.

From a cancer outcome perspective, in the PROTECT trial, surgery and radiotherapy resulted in the same low risk of metastasis (5.4% at 15 years) and prostate cancer death (2.7% at 15 years) for men with intermediate-risk prostate cancer.[16] In a large, propensity matched study among U.S. Centres of Excellence comparing men with high-risk prostate cancer treated with surgery, external beam radiotherapy plus hormones, and external beam radiotherapy plus brachytherapy and hormones, both the risk of metastatic spread (32.7% vs 18.4% vs 10.7%) and prostate cancer death (13.3% vs 10.3% vs 9.3%) at 10 years were reduced.[29] There is no randomized clinical trial comparing surgery and radiotherapy in this population. Therefore, it is important that men considering curative-intent treatment be seen by both urologists and radiation oncologists prior to finalizing their treatment decision-making. However, currently in Ontario, fewer than 50% of men undergoing surgery are seen in consultation with a radiation oncologist.[30]

Conclusion

The diagnosis and management of localized prostate cancer is a continuously evolving area. PCPs play an important role in guiding men through their prostate cancer journey. It is important for PCPs to discuss the benefits and harm of PSA testing, ensure timely referral for further work-up in men with elevated PSA scores, and ensure that all men have the appropriate consultations within a multidisciplinary clinic prior to treatment decision-making.

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