Should All Colorectal Cancer Patients Over Age 60 Be Screened for Prostate Cancer?

Not all patients with colorectal cancer are candidates for such screening, however, as a remaining life expectancy of at least 10 years is generally required in order for PSA screening to yield a significant mortality benefit.

**Recommendations for PSA-Based Screening for Prostate Cancer Among Patients With Colorectal Cancer**

Our results suggest that whether or not men over 60 years of age with colorectal cancer should be considered for prostate-specific antigen (PSA)-based screening depends on the presence and stage of the colorectal cancer, as well as patient age, comorbidities, race, and family history of prostate cancer. Men who are appropriate candidates for a discussion of the risks and benefits of PSA-based screening for prostate cancer include those with newly diagnosed stage I colorectal cancer who are healthy (with a life expectancy > 10 years), African-American, or who have a first-degree relative with prostate cancer. Men who may be appropriate candidates for such screening include those who have newly diagnosed stage II colorectal cancers, who are in good health (with a life expectancy > 10 years), and who are African-American or have a first-degree relative with prostate cancer.

Newly diagnosed stage III colorectal cancer patients are generally not appropriate candidates for screening for prostate cancer. However, if such patients attain a disease-free interval of 5 years after treatment of their colorectal cancer, they should be considered for PSA-based screening for prostate cancer if their remaining life expectancy is at least 10 years and they are either African-American or have a first-degree relative with prostate cancer.

The time to initiate PSA-based screening for prostate cancer would be at the time of diagnosis of stage I or II colorectal cancer and after a 5-year disease-free interval in men with stage III colorectal cancer, assuming that they have at least a 10-year remaining life expectancy and have been counseled about the potential risks and benefits of PSA-based screening. Patients with metastatic colon cancer are not appropriate candidates for PSA-based prostate cancer screening.

Once a patient has been appropriately educated by the primary care physician about the possible benefits and risks of PSA screening, then patient preference, as part of shared decision making regarding PSA screening, should be considered in all cases.

**Randomized trials and consensus statements relating to PSA-based screening for prostate cancer**

In 2012, the US Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer. In assigning such practice a grade D recommendation, the USPSTF indicated that they believed that there was moderate to high certainty that PSA-based screening had no benefit or that the harms outweighed the benefits. The recommendation applied to men in the general population, regardless of their age, remaining life expectancy, risk of developing an aggressive prostate cancer, and comorbidities.[1]

Several randomized trials have evaluated the role of PSA-based screening for prostate cancer. In the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial, conducted in the United States at 10 centers between 1993 and 2001, a total of 76,685 men aged 55 to 74 years were randomized to annual PSA screening for 6 years and an annual digital rectal exam for 10 years vs “usual care.”[2,3] With a follow-up of up to 13 years in the updated analysis,[3] a 12% relative increase in the incidence rate of prostate cancer was noted in the intervention arm (relative risk [RR] = 1.12; 95% confidence interval [CI], 1.07–1.17), although no differences were seen in prostate cancer–specific or all-cause mortality between the two arms. At 13 years, 158 and 145 deaths due to
prostate cancer had occurred in the intervention and control arms, respectively, a difference that was not statistically significant (RR = 1.09; 95% CI, 0.87–1.36). However, significant limitations of this trial—including the fact that 44% of patients had had at least one PSA test in the 3 years preceding randomization, and that in the control arm the rate of having had at least one PSA screening was estimated to be 85%[4]—hinder the ability to draw any firm conclusions about the value of PSA screening in this setting.

Between 1991 and 2003, the European Randomized Study of Screening for Prostate Cancer (ERSPC), which enrolled men from eight European countries, randomized 162,388 men in the “core age group” of 55 to 69 years to PSA-based screening (median screening interval, 4.02 years) vs no screening.[5,6] With a follow-up of 11 years, a total of 6,963 and 5,396 cases of prostate cancer were diagnosed in the screening and control groups, respectively (RR = 1.63; 95% CI, 1.57–1.69). There were 299 and 462 deaths from prostate cancer in the screening and control groups, respectively, corresponding to a 21% reduction of prostate cancer–specific mortality with screening (RR = 0.79; 95% CI, 0.68–0.91; \(P = .001\)). The number needed to screen to prevent one death from prostate cancer was 1,055; the corresponding number needed to treat was 37. Relative to the PLCO trial, the rate of PSA screening in the control group of the ERSPC trial was lower,[3] being 24% in the Rotterdam cohort of the ERSPC study[7] vs 85% in the PLCO study.[4] and the upper age of the core group analyzed in the ERSPC study was lower as well, increasing the likelihood that men would die of prostate cancer vs a comorbid condition; these differences potentially account for the variation in the outcomes of these two trials.

Starting in 1995, the Göteborg prostate cancer screening trial randomized 20,000 men aged 50 to 64 years and living in Göteborg, Sweden, to PSA-based screening every 2 years vs no screening.[8] The study was ongoing at the time of analysis in 2008. Men in the screening arm had PSA levels obtained until they reached (on average) 69 years of age. With a median follow-up of 14 years, prostate cancer was identified in 1,138 and 718 men in the screening and control arms of the study, respectively. At 14 years, the cumulative incidence of prostate cancer was 12.7% in the screening group and 8.2% in the control group (hazard ratio [HR] = 1.64; 95% CI, 1.50–1.80; \(P < .0001\)). In the intervention and control groups, 44 and 78 men, respectively, died of prostate cancer. The relative risk of PSA-screened men dying of prostate cancer was 0.56 (95% CI, 0.39–0.82; \(P = .002\)). The number needed to screen to prevent one death from prostate cancer was 293; the corresponding number needed to treat was 14.[8] Given the sometimes indolent nature of prostate cancer, and that the rate of death due to prostate cancer increases 15 to 20 years after the diagnosis,[9] the number needed to screen and treat in order to save one life will likely decrease with further follow-up.

Assuming overdiagnosis and screening efficacy consistent with results of the ERSPC, investigators have estimated that the number needed to screen and treat to avoid one prostate cancer death at 25 years will be 262 and 9, respectively.[10] There are a number of possible reasons that the Göteborg study yielded a larger survival benefit with PSA screening than the ERSPC study and the PLCO study (the latter of which did not identify such a benefit). Notably, the median age of 56 years for men in the Göteborg study was lower than the median ages of men in the PLCO and ERSPC studies (with the median in both studies being greater than 60 years), increasing the likelihood that men would die from prostate cancer rather than from the effects of a competing risk factor. The threshold for biopsy (PSA > 2.5–3.0 ng/mL) was also lower in the Göteborg study than in the PLCO study (PSA > 4 ng/mL) and the ERSPC study (PSA generally > 3 ng/mL).[8] Moreover, a higher percentage of patients with a positive screening result underwent a prostate biopsy in the Göteborg trial relative to the PLCO study (93% vs 30% to 40%[8,11]). In addition, only 3% of patients in the Göteborg study had PSA level measured before the start of the study (while up to 45% of patients in the PLCO study had PSA level assessed in the 3 years before study initiation). Last, the Göteborg study possesses the longest follow-up period of any of the randomized studies for prostate cancer screening. For these reasons, the Göteborg study is likely the most rigorously conducted PSA-screening trial to date and most accurately reflects the magnitude of the prostate cancer–specific mortality benefit seen with PSA screening.

It is important to note that in addition to improving prostate cancer–specific survival, PSA-based screening for prostate cancer reduces the likelihood of metastatic disease. In the ERSPC study, 0.67% and 0.86% of men in the screening and control arms, respectively, developed metastatic disease by 12 years; the HR for the association between screening and development of distant metastases was 0.70 (95% CI, 0.60–0.82; \(P = .001\).[12] Low-risk patients managed with radical prostatectomy[13] or radiation therapy[14] display lower rates of distant metastatic disease than those managed expectantly. The physical and psychological suffering that follows a diagnosis of metastatic prostate cancer can have a significant impact on quality of life. Also, the management of
patients with metastatic disease results in significant cost to the US healthcare system.[15] Therefore, as other authors have suggested, survival may not be the only pertinent metric when evaluating the utility of PSA-based screening for prostate cancer.[16] The Prostate Cancer Intervention Versus Observation (PIVOT) trial, published in 2012, did not identify differences in prostate cancer-specific mortality between low-risk patients managed conservatively vs definitively.[13] However, the PIVOT trial was designed to accrue 2,000 men, but only 731 men enrolled in the study before it was closed. In addition, approximately 20% of patients in the observation arm received definitive therapy. Together these factors render the study markedly underpowered to measure a difference in death from prostate cancer in the men randomized to treatment vs observation, although this comparison did approach statistical significance (P = .09). Moreover, 4-year all-cause mortality estimates in patients managed with curative vs non-curative intent in the PIVOT trial were 9.6% and 14.2%, respectively; these rates are significantly higher than estimates among the general population (mortality of 4.33% and 9.27% for men managed with curative vs non-curative approaches, respectively), suggesting that men in the PIVOT study represent a less healthy cohort compared with the general population. Therefore, the results may not be generalizable to the US population at large.[17] For these reasons, and because another randomized trial did demonstrate a survival benefit to prostatectomy vs observation,[18] it is still not clear whether definitive treatment improves survival for all patients or only for select patients with favorable-risk prostate cancer.

Many expert consensus groups do not concur with the recommendations of the USPSTF. The American Urological Association (AUA) states that “shared decision-making is recommended for men age 55 to 69 years [who] are considering PSA-based screening,” stating that this population is “a target age group for whom benefits may outweigh harms.” Based on the available evidence, routine PSA-based screening could not be recommended by the AUA for patients 40 to 54 years old and those over 69 years of age.[19] The European Association of Urology guidelines recommend a baseline PSA test at age 40 to 45 years, with follow-up testing starting at age 45 for all men with a life expectancy greater than 10 years.[20]

**Prognosis in men 60 years or older with colorectal cancer**

A reduction in death from prostate cancer due to PSA-based screening was not seen in the ERSPC study and in the Göteborg study until approximately 7 years of follow-up, reflecting the time it takes for men to be diagnosed with and treated for prostate cancer, experience metastasis, and then die from their disease.[6] Therefore, accurate estimation of life expectancy for patients considering screening for prostate cancer is vital, as average-risk patients with a life expectancy of less than 7 years would not be expected to benefit from PSA screening. To estimate the prognosis of patients with colorectal cancer, we used the Surveillance, Epidemiology and End Results (SEER) program[21] to identify 12,354 patients diagnosed with colorectal cancer between 1998 and 2000. Sponsored by the National Cancer Institute, the SEER program collects and publishes cancer incidence, treatment, and survival data from population-based cancer registries; the program captures approximately 97% of incident cancers, and the tumor registries currently include approximately 28% of the US population.[21] The Figure shows Kaplan-Meier estimates of overall survival (OS) in men 60 to 75 years of age with colorectal cancer, as stratified by stage at diagnosis. Median survival, 5-year OS, and 10-year OS for men 60 to 75 years of age with colorectal cancer, stratified by stage at diagnosis, are presented in the Table. The estimates in the Figure and Table provide generalizable prognostic information for patients with colorectal cancer, and the use of SEER data allowed us to focus on the men in the target age range of 60 to 75 years. Of note, given that we needed to calculate 10-year survival estimates, and given that SEER data are not available beyond 2011, our cohort extends back to 1998-2000. Other important limitations of such an approach include the fact that advances in the management of colorectal cancer (since the year 2000) are not reflected in these figures. Also, survival estimates in the more modern era of colorectal cancer management are likely greater than those provided here. However, our results are comparable to those seen in clinical trials,[22,23] although selection criteria (age, comorbidity, performance status, etc) in clinical trials could account for the mildly decreased survival metrics observed in the SEER cohort. We set 75 years as the upper age limit of inclusion for our cohort, given that the median remaining life expectancy for American males decreases to 10.0 years beginning at the age of 76, according to the 2007 Social Security Life Tables.[24] Therefore, PSA-based screening for prostate cancer may not be appropriate for the average man over 75 years of age. However, men older than 75 years who have no or minimal comorbidity and risk factors for development of prostate cancer may still benefit from screening, especially given that advancing age is a risk factor for development.
of aggressive (ie, high-grade) prostate cancer.\[17,25\]

Last, it is notable that the third edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual was used to stage prostate cancer patients, as shown in the Table; however, changes between the third and seventh editions of the manual have not been dramatic, so the information is still relevant.\[26\]

Given that a prostate cancer–specific survival benefit can likely be attributed to PSA screening, and that patients with colorectal cancer have a significant competing risk that may preclude death from prostate cancer, a critical question is, which of these colorectal cancer patients over age 60 should be screened for prostate cancer? To answer this question, one must be able to estimate the median survival of patients with colorectal cancer of a specific stage. In addition, a validated metric for measuring remaining life expectancy (one that accounts for age and comorbidity in patients with cancer) should be utilized. Risk factors for presenting with more advanced prostate cancer, and therefore poor outcomes following treatment with the available therapies, should also be considered. Last, the patient and his primary care physician should engage in a shared decision-making process regarding whether or not PSA-based screening should be employed, after consideration of the known risks and benefits of PSA screening for that individual patient.

Who can we exclude from PSA-based screening for prostate cancer?

As shown in the Table, patients with metastatic (stage IV) colorectal cancer have a poor prognosis, with a median survival of approximately 1 year. PSA screening is not warranted in such patients. Similarly, many patients with stage III colorectal cancer do not warrant prostate cancer screening, given their relatively short median survival of 5.4 years. However, approximately 35% of patients with stage III colorectal cancer survive at least 10 years, and many of these patients will have been cured of their disease. Consequently, after a clinically significant recurrence-free interval (ie, 5 years), PSA-based screening for prostate cancer can be considered in men with stage III disease, assuming that they have no other competing risks that would likely confer a remaining life expectancy of less than 10 years. For patients with stage I–II prostate cancer, additional information relating to age, race, comorbidity, and remaining life expectancy is warranted before the appropriateness of PSA-based screening for prostate cancer can be determined.

Impact of patient comorbidity and age

Recently presented data suggest that comorbidity should be a driving factor in determining whether definitive management is warranted for patients with low-risk prostate cancer and a prior cancer diagnosis.\[27\] Multiple methodologies exist for assessing the impact of comorbid conditions on prognosis. The Charlson Comorbidity Index and its variant indices have commonly been employed to quantify the severity of numerous comorbid conditions, although the score is not specific to patients with cancer.\[28,29\] The Adult Comorbidity Evaluation–27 (ACE-27) is a 27-item, validated method of comorbidity classification specifically in patients with cancer.\[30\] The ACE-27 yields four tiers of comorbidity, and it has been validated and shown to be useful in assessing the severity of comorbidity in patients with cancer. The impact of age on survival can be evaluated by several metrics. The Social Security Life Tables estimate expected survival by age and gender among patients in the general population. As previously noted, according to the Social Security Life Table from 2007, men 76 years of age and older have a remaining life expectancy of 10.0 years.\[24\]

Individual practitioners use a variety of tools to determine life expectancy for a given patient; the National Comprehensive Cancer Network recommends adjusting the age-predicted survival by the degree of comorbidity, where the expected survival of patients in the upper and lower quartiles of comorbidity scores is increased and decreased by 50%, respectively.\[31\] Such an approach has been validated by population-level data.\[32\] Therefore, men in the general population over age 75 who are in the most favorable quartile of comorbidity burden may still benefit from prostate cancer screening, given that their life expectancy exceeds 10 years. Among those with colorectal cancer, men with stage I–II disease and either advancing age or significant comorbidity leading to remaining life expectancies less than 10 years are not good candidates for PSA-based screening for prostate cancer. In contrast, younger, healthier patients with stage I–II colorectal cancer and remaining life expectancies exceeding 10 years remain good candidates for such screening.

Impact of African-American race and family history of prostate cancer

Patients at risk for development of aggressive prostate cancers may be more likely to benefit from
PSA-based screening for prostate cancer. Sundi et al recently demonstrated that African-American patients who have very-low-risk prostate cancer at diagnosis are significantly more likely to harbor cancers that are not confined to the prostate and cancers of higher than anticipated Gleason score,[33] after adjustment for known predictors of upstaging and upgrading. Other investigators have shown that African-Americans diagnosed with prostate cancer have poorer survival.[34] In addition, studies show that a positive family history of prostate cancer confers a higher risk of a prostate cancer diagnosis.[25] Therefore, patients with a family history of prostate cancer who are in good health and who are likely cured of their colorectal cancer should benefit from PSA-based screening.[35] These data suggest that PSA screening may be more appropriate for otherwise healthy patients with stage I–II colorectal cancer at diagnosis (or stage III colorectal cancer after a 5-year disease-free interval) who are either African-American or who possess a family history of prostate cancer.

Are patients diagnosed with colorectal cancer at increased risk for developing prostate cancer?

Investigators have demonstrated that chromosomal aberrations, such as variants of chromosome 8q24, can predispose patients to development of both colorectal cancer and prostate cancer.[36] In addition, heritable conditions (such as BRCA) exist that predispose some men to development of both prostate and colorectal cancers.[37] However, it is unclear whether these genetic associations yield clinically significant increases in prostate cancer diagnosis after a new diagnosis of colorectal cancer. Hoffman et al showed that, among 27,692 men diagnosed with colorectal cancer (and not treated with radiation), 1,690 (6.1%) developed prostate cancer (at a median interval of 3.5 to 4.0 years).[38] External beam radiation treatment for rectal cancer is associated with a decrease in subsequent prostate cancer diagnosis. Of these prostate tumors, 22% were well differentiated, 58% to 60% were moderately differentiated, and 21% to 28% were poorly differentiated (Gleason score not available). No comparison in patients without colorectal cancer is available, so it is unclear how these results compare to those seen in the general population. However, at a median follow-up of 11.5 years, in the screened arm of the PLCO trial there were 2,820 prostate cancers (among a total of 38,343 men, for a rate of 7.4%).[2] Given that more men in the screening arm of the PLCO trial were screened for prostate cancer (compared with the SEER cohort evaluated by Hoffman et al), it is possible that the rate of prostate cancer in the colon cancer population exceeds that of the general population.

Of note, in the study by Hoffman et al, patients who received radiation therapy for rectal cancer displayed lower incidences of prostate cancer, possibly as a result of sterilization of subclinical disease by the radiation. Cancers that develop after rectal irradiation, however, may be of higher grade.[38] Huo et al found that patients who develop a colon cancer before the age of 50 years, or between ages 50 and 59, or between ages 60 and 69, have an increased risk of developing prostate cancer, with standardized incidence ratios of 1.38, 1.14, and 1.06, respectively (all statistically significant values). Patients diagnosed with colon cancer after age 70, however, do not show an increased risk of prostate cancer, possibly because of mortality resulting from competing risks.[39] The authors conclude that the increased prostate cancer risk in a patient under 50 years of age with newly diagnosed colon cancer may justify screening for prostate cancer. Although the literature on the topic is limited, it does appear that a diagnosis of colorectal cancer, particularly in a younger man (< 70 years of age), may increase the likelihood of development of prostate cancer, but not necessarily prostate cancer of a higher grade; therefore, the risk is similar to that incurred by a family history of prostate cancer. This may be a rationale to screen (for prostate cancer) select patients with colorectal cancer. Specifically, one could consider screening men at the time of diagnosis of stage I or II colorectal cancer who have at least a 10-year life expectancy. In addition, PSA screening could be initiated in men with stage III colorectal cancer who have at least a 10-year life expectancy and have remained disease-free for at least 5 years following the colorectal cancer diagnosis.

Conclusions

Two randomized clinical trials have demonstrated a prostate cancer–specific survival benefit associated with PSA-based screening for prostate cancer. Not all patients with colorectal cancer are candidates for such screening, however, as a remaining life expectancy of at least 10 years is generally required in order for PSA screening to yield a significant mortality benefit. The usual risk factors for prostate cancer include patient age, race, comorbidity level (assessed by validated metrics such as the Charlson Comorbidity Index or ACE-27 index) and resulting life expectancy, and
family history of prostate cancer. In addition to these factors, among males over age 60, the presence and stage of colorectal cancer, as well as the disease-free interval, determine the appropriateness of PSA-based screening for prostate cancer.

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The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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