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Overview of Randomized Controlled Treatment Trials for Clinically Localized Prostate Cancer: Implications for Active Surveillance and the United States Preventative Task Force Report on Screening?

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Prostate cancer and its management have been intensely debated for years. Recommendations range from ardent support for active screening and immediate treatment to resolute avoidance of screening and active surveillance. There is a growing body of level I evidence establishing a clear survival advantage for treatment of subsets of patients with clinically localized prostate cancer. This chapter presents a review of these randomized controlled trials. We argue that an understanding of this literature is relevant not only to those considering active surveillance but also to those evaluating the merits of screening. In addition, a number of important evidence-based conclusions concerning what should and should not be done can be gleaned from these trials.

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The argument for active surveillance (AS) in men with localized prostate cancer is critically dependent on whether a delay in the initiation of treatment adversely affects outcome *and* the degree to which treatment is proven to be safe and effective at prolonging survival. If treatment is not effective, then delays may be irrelevant. If on the other extreme, treatments are successful regardless of the extent of disease, then delays in treatment may also be irrelevant. Unfortunately, although moderately effective, the available treatments are frequently not curative in patients with advanced disease, and thus delays may have an adverse impact on outcome. This review concisely summarizes the data from the randomized treatment trials for localized prostate cancer. When appropriate and possible, we also comment on the number needed to treat (NNT) to render benefit (1). Our summaries focus on the degree to which various types of treatments are effective as well as on the subsets of patients who benefit. We not only demonstrate that there is a large and growing body of level I evidence, supporting the notion that there are populations of men with prostate cancer who clearly benefit from specific treatments, but also that certain treatments are ineffective and should be avoided. The modest impact of treatment on survival shown in some of these trials may provide support for the rationale of AS (particularly in the subsets for whom no benefit is shown). This conclusion can be explained by the fact that competing causes of death tend to attenuate benefits of treatment in patients with moderate- to high-risk disease and may overwhelm the potential beneficial impact of treatment in patients with very low-risk disease.

Using the outcome data from all of the randomized control trials (RCTs) (primarily phase III) published at the time of writing of this article that address clinically localized prostate cancer, we argue that this evidence may have relevance not only to the issue of AS but also to screening. Our rationale for including all of these trials comes from the third question posed by the United States Preventive Services Task Force (USPSTF), which asks, "What are the benefits of treatment of early-stage or screening-detected prostate cancer?" On the surface, this question seems simple enough; however, on deeper inspection, many uncertainties arise. First, the question does not define "early-stage" prostate cancer (ie, localized vs low-risk vs high-risk), how much of an improvement in survival might be expected, and when these benefits should be expected. Second, the question does not address whether some subsets of screened patients may benefit from treatment. To answer this question, the USPSTF chose to include only two RCTs for evaluating the impact of treatment on localized disease. For a more comprehensive review, we choose to include 50 trials (2) in our analysis. We argue that the body of literature included in this review may provide important information as to who, when, and how much patients can be expected to benefit from various types of treatment and early detection. Although many of the trials summarized below included patients who are not relevant to the issue of screening and AS, we argue that these studies may provide useful insight into this issue nonetheless.

The Data

Table 1 summarizes trials involving radical prostatectomy (RP) with or without the addition of androgen deprivation therapy (ADT) or RP compared with "watchful waiting" (WW). Although some say that WW is not to be compared with AS, there is no clear consensus as to what constitutes WW and AS; thus, useful information may still be gleaned from their collective evaluation. The only major trial comparing WW with RP showed that with a median of 12.8 years, 166 men in the RP group and 201 in the WW group died of any cause ($P = .007$) (3). Of note, 55 and 81 of

Table 1. Randomized trials using radical prostatectomy (RP) to "watchful waiting" or RP with or without androgen deprivation therapy (ADT) for clinically localized prostate cancer*

First author, year (reference)	Design	Conclusions	Comments
Bill-Axelson, 2011 (3)	RP vs "watchful waiting"	RP associated with better survival	Most benefits for men < age 65 y; 12.8/10/15†;NNT range: 5.78–39.47, (95% CI)‡
Studer, 2006 (4)	RP+/– adjuvant ADT	Small improvement in overall survival	No improvement in cause-specific survival or quality of life
Klotz, 1999 (5)	RP vs ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Aus, 1998 (6)	RP vs ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Soloway, 2002 (7)	RP vs ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Schulman, 2000 (8)	RP vs ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Homma, 1997 (9)	RP vs ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
van Poppel, 1995 (10)	RP vs estramustine + RP	Similar rate of PSA failure and no survival advantage	Does not support the estramustine with RP
Messing, 1999 (11)	RP +/– ADT in node+ patients	Improvement in overall survival	Node+ patients benefit from early ADT; 7.1/5/–†; NNT range: 2.7–26.33 (95% CI)‡

* CI = confidence interval; NNT = number needed to treat; PSA = prostate-specific antigen.

† Median follow-up (years)/NNT/time to survival advantage (years).

‡ NNT ranges calculated from the upper and lower limits of relative risk reduction CI (1).

Table 2. Postoperative external beam radiotherapy (EBRT) after radical prostatectomy (RP) for clinically localized prostate cancer*

First author, year (reference)	Design	Conclusions	Comments
Thompson, 2009 (12)	pT3 +/– adjuvant EBRT	Improved PSA control, clinical failure, and overall survival	Longest follow-up of post op trials, 10.6/9.1/12.6†; NNT range: 4.89–63.18 (with 95% CI)‡
Wiegel, 2009 (13)	pT3 +/– adjuvant EBRT	Improved PSA control	Follow-up too short to address survival?
Bolla, 2005 (14)	pT3 or + margins +/– adjuvant EBRT	Improved PSA control, clinical failure, metastasis-free survival	Follow-up too short to address survival?

* CI = confidence interval; NNT = number needed to treat; PSA = prostate-specific antigen.

† Median follow-up (years)/NNT/time to survival advantage (years).

‡ NNT ranges calculated from the upper and lower limits of relative risk reduction CI (1).

the deaths were attributed to prostate cancer to the RP and WW groups, respectively. The survival benefit observed appeared to be confined to men younger than age 65 years. The number needed to treat to avert one death was 15 overall and 7 for men younger than age 65 years. The remaining studies demonstrated that there is no advantage to adding ADT except as an adjuvant therapy in men with positive lymph nodes (11).

Table 2 summarizes the three major trials addressing adjuvant postoperative radiotherapy (RT). The relevance of these studies to screening and AS may seem questionable because, for example, only 302 of the 431 patients on the Thompson trial had a preoperative prostate-specific antigen (PSA) and approximately 50% of these men had a PSA < 10 ng/mL. However, despite screening, 25%–30% of men undergoing a radical prostatectomy will still have evidence of extracapsular extension or positive margins and thus will be candidates for adjuvant RT (15). The data from the Thompson trial provide information regarding both the sample size and timeline required to document a survival benefit with adjuvant therapy. It took more than 10 years to show the benefits of postoperative RT; thus, it is likely that it would take an even longer follow-up period to demonstrate the impact of treatment in the remaining men with organ-confined disease. Furthermore, nonscreened men who are diagnosed with more advanced disease might be expected to have a prolonged survival due to early aggressive postoperative interventions further complicating the short-term analysis of men offered deferred management.

Table 3 addresses the role of primary external beam radiotherapy (EBRT) compared with other modalities (eg, radical prostatectomy or cryoablation with higher doses). Because of their small size and short follow-up at first review, it may appear that these studies would be of little relevance to the screening or AS controversies. However, their shortcomings tell us "what *not* to do" and explain why we have not resolved the uncertainty concerning the relative effectiveness of these treatment options. The point here is that we

Table 3. Radical prostatectomy (RP) vs external beam radiation therapy (EBRT) and EBRT vs Cryosurgery (CRYO)*

First author, year (reference)	Design	Conclusions	Comments
Paulson, 1982 (16)	RP vs EBRT (n = 97)	More clinical failures in EBRT group but pattern quite unusual	No survival data; study underpowered study pre-PSA era, low-dose radiation, no ADT
Akakura, 2006 (17)	RP + ADT vs EBRT + ADT (n = 95)	No statistically significant difference in OS, PSA, or clinical progression-free rates	Low-dose radiation, no ADT, no image guidance
Chin, 2008 (18)	Cryoablation vs EBRT (n = 64)	Improved PSA control with EBRT compared to CRYO, clinical failure, metastasis-free survival	Underpowered to address survival, RT doses too low, no ADT
Donnelly, 2009 (19)	NHT + CRYO or EBRT (n = 244)	No significant difference in OS, PSA but higher positive biopsy rates after EBRT	Radiation doses too low, no ADT, definition of progression problematic

*ADT = androgen deprivation therapy; NHT = neoajuvant hormonal therapy; OS = overall survival; PSA = prostate-specific antigen.

should avoid conducting underpowered studies when assessing interventions that are likely to have relatively small differences in effectiveness.

Table 4 addresses the impact of different types and doses of radiation used in the treatment of prostate cancer. Several studies did not provide sufficient details to allow an accurate assessment of the number of low-risk patients included (23, 24, 29, 32). Some studies specifically excluded low-risk patients (26, 28, 30, 31, 34). In several studies, approximately 20% of the patients could be considered low-risk patients (20–22). In other studies, up to 40%–50% or more would generally be considered low-risk patients (25, 27, 33). Ultimately, although the Table 4 studies consistently show a reduction in the PSA detected recurrence rates with higher doses of radiation, there was no evidence that survival was improved. These findings should discourage investigators from expecting to detect improvements in survival between patients with early prostate cancer who were treated with relatively modest doses of radiation.

Table 5 summarizes phase III trials performed by the Radiation Therapy Oncology Group (RTOG) using radiation with or without ADT, and Table 6 lists major non-RTOG phase III prostate cancer radiation trials with or without ADT. These studies when taken together provide a large body of level I evidence for the addition of ADT to EBRT in selected patients with intermediate- to high-risk prostate cancer. Their relevance to early-stage screening is that they provide data from which relative risk estimates, sample size estimates, and timelines can be made.

Table 7 addresses the role of primary ADT with or without EBRT. Again, although the relevance of these data to AS or screening is not immediately obvious, there are lessons learned from these trials. The first two and the last two trials included only patients with locally advanced disease. The third trial listed included a subset of 1627 men with early-localized disease, who were randomized to placebo or 150 mg of bicalutamide. When taken together, these studies demonstrated that treatment with ADT was beneficial in men with locally advanced disease, but such treatment resulted in a *lower* survival in men on WW (54). This study highlights that even though an intervention is beneficial to men with locally advanced disease, it does not necessarily mean that it will be beneficial in men with early disease. In addition, these data reinforce the notion that PSA alone is not an adequate endpoint and that it is important that studies be adequately powered.

Based on these data, the following conclusions concerning the impact of various treatments on the survival of men with clinically localized disease can be drawn:

1. RP prolongs survival compared with WW [Table 1, Bill-Axelson et al. (3)].
2. Primary ADT appears to be more effective than observation in some subsets of patients, but there is no role for neoadjuvant ADT prior to RP. There may be a small impact on outcome in the adjuvant setting and a survival advantage with the use of early ADT in men with pathologically proven lymph node positive disease [Table 1, Studer et al. (4) and Messing et al. (11)].
3. Postoperative EBRT delays the time to biochemical recurrences and may improve survival [Table 2, Thompson et al. (12), Wiegel et al. (13), and Bolla et al. (14)]. The addition of an oral antiandrogen therapy appears to further delay the time to clinical failure [Table 5, Shipley et al. (35)].
4. The relative effectiveness of RP compared with EBRT and the effectiveness of cryoablation compared with EBRT also remain unresolved (Table 3). In general, all of these studies were underpowered for assessing a survival endpoint.
5. Higher dose EBRT improves PSA control, but to date it provides no overall survival advantage (Table 4). Hypofractionation (large doses over a reduced number of days) has generated conflicting results and remains unproven as a strategy for improving outcomes (Table 4).
6. Neutron-based EBRT may improve local control compared with low-dose photons but with a trend for increased complications. The effectiveness of mixed neutrons and photons on PSA control rates may be sequence dependent (Table 4).
7. EBRT plus ADT is better than EBRT alone for intermediate- and high-risk patients (Tables 5 and 6). High-risk patients benefit from long-term ADT (2+ years), whereas those with intermediate-risk disease appear to require only 4–6 months (Tables 5 and 6).
8. ADT plus EBRT is better than ADT alone for men with locally advanced disease. Adjuvant antiandrogen therapy may also improve survival in men with high-risk disease (Tables 7).
9. NNT is a common statistical tool (measured as the inverse of the absolute risk reduction), and with the ranges from the positive trials (shown in these tables) it supports the value of treatment

Table 4. Radiation: dose escalation, protons, hypofractionation, neutrons, and brachytherapy*

First author, year, (reference)	Design	Conclusions	Comments
Kuban, 2011 (20)	70 vs 78 Gy EBRT	Patients with PSA >10 ng/mL or high-risk benefit from 78 Gy	20% low-risk; 78 Gy improved PSA, clinical failure, and prostate cancer deaths (post hoc)
Peeters, 2006 (21)	68 vs 78 Gy EBRT	PSA control was better in the 78-Gy arm	18% low-risk; no impact on survival yet
Dearnaley, 2007 (22)	64 Gy vs 74 EBRT (ADT on each arm)	74 Gy improved PSA control	24% low-risk; no impact on survival yet
Beckendorf, 2011 (23)	70 vs 80 Gy EBRT	Improve 5-y PSA failure with 80-Gy benefit most if PSA >15	88% <T3 and 63% <GS 7 and 38% PSA<10 ng/mL; no impact on survival yet
Sathya, 2005 (24)	66 Gy EBRT vs 40 Gy + 35 Gy Ir-192 implant	Improved PSA control with additional higher doses with implant	Intermediate- and high-risk 40% and 60%, respectively; no impact on survival yet
Zietman, 2010 (25)	70.2 EBRT vs 79.2 Gy with protons	Better 5-y PSA control improved with 79.2 Gy	58% low-risk; no impact on survival yet
Shipley, 1995 (26)	75.6 cGE (via proton boost) vs 67.2Gy (x-rays)	Improved local control for poorly differentiated tumors (post hoc analysis)	T3-4 N0-2; increased complications with protons
Lukka, 2005 (27)	66 Gy in 33 fractions or 52.5 Gy in 20 fractions ("hypofractionated")	Chosen hypofractionated radiation regimen may be inferior to the standard regimen	49% GS <7 and PSA <15 ng/mL; doses on both arms considered too low by today's standards
Arcangeli, 2010 (28)	9 mo ADT + 62 Gy/20 fractions or conventional EBRT (80 Gy/40 fractions/8 weeks)	3-y PSA control favored the hypofractionation 87% vs 79% with conventional (P = .035).	60 < T2c and 24% < GS = 7 and 37% < 20 ng/mL; no impact on survival yet
Pollack, 2011 (29)	76 Gy in 2-Gy fractions vs 70.2 Gy in 2.7-Gy fractions	Despite a higher biologic dose (84 Gy) for hypofractionated arm; no difference in PSA failure and higher complications	Risk groups not available; suggests that larger radiation fractions used with hypofractionation may not be as helpful as expected
Laramore, 1985 (30)	Mixed beams (neutrons + photons) vs photons only	Improved local/regional and survival with mixed beams with patients not treated per protocol are included	High risk; statistical significance lost when the patients treated per protocol guidelines are considered
Russell, 1994 (31)	Neutrons vs 70-Gy photons	Improved local-regional and PSA control but increased complications and no improved survival	High risk; small study (n = 178) trend for better outcomes with neutrons
Forman, 2002 (32)	Randomize sequences: neutrons then photons vs photons followed by neutrons	Neutrons followed by photons more effective than photons followed by neutrons	Most intermediate to high risk; Sequence-dependent biologic interactions
Wallner, 2003 (33)	Radioactive seed implantation with (125)I (144 Gy) vs (103) Pd (125 Gy)	No differences in cancer control–related outcomes by isotope	All low-risk (n = 115); type of radioactive isotopes does not matter if the dose distribution is good
Wallner, 2005 (34)	44 Gy vs 20-Gy preimplant EBRT followed by Pd-103, 90 vs 115-Gy, see implants	3-year PSA control rates not statistically different 84% vs 94% (20 vs 44-Gy EBRT (P = .16).	All intermediate- to high-risk (n = 159); trend for a higher control rates with EBRT cause for concern

*ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; GS = Gleason score; PSA = prostate-specific antigen.

for localized disease. For the RCTs that offer a survival advantage, NNT can be used as a tool to compare different treatment outcomes. With the assumption that relative risk reduction is constant for all levels of risk, NNT may be extrapolated to different patients with a baseline risk (1).

Remaining Questions and Important Gaps in Scientific or Medical Knowledge

Despite the considerable progress made due to the trials summarized above, there are still many unanswered questions. A partial list of completed, ongoing, or closed trials addressing some of the remaining questions among men treated for clinically localized disease is provided below:

1. Which is the preferred treatment (RP vs EBRT or brachytherapy) for men who require treatment, with respect to quality of life and cancer outcomes (55)?
2. Among men who experience local recurrences after EBRT, can "salvage" PPI be used safely and effectively (eg, RTOG 0526) (56)?

Table 5. Phase III Radiation Therapy Oncology Group (RTOG) prostate cancer trials: radiation (RT) with or without androgen deprivation therapy (ADT), treatment volume effects*

First author, year (reference)	Design	Conclusions	Comments
Shipley, 2011 (35)	RTOG 9601: RT vs RT + bicalutamide 150 mg for increasing PSA after prostatectomy	Improved PSA control, reduced metastasis rate	Pending assessment of primary endpoint due to short follow-up
Jones, 2011 (36)	RTOG 9408: +/– NHT 2 mo prior and during RT (66 Gy)	Overall and cause-specific survival advantage	Benefit of ADT greatest for intermediate risk; 9.1/19.8/10†; NNT range: 10.67–136.93 (with 95% CI)‡
Roach, 2008 (37)	RTOG 8610: RT +/– ADT 2 mo prior to and during WPRT	Cause-specific survival advantage	High-risk patients require longer-term ADT
Pilepich, 2005 (38)	RTOG 8531: RT +/– long-term adjuvant ADT	Overall survival advantage	Essentially all subsets with high risk benefitted; 7.6/10/10†; NNT range: 6.15–27.36 (with 95% CI)‡
Hanks, 2003 (39)	RTOG 9202: RT + 4 or 28 mo ADT	Survival advantage GS = 8–10	High-risk patients require longer-term ADT; 5.8/9.8/5†; NNT range: 5.2–86.12 (with 95% CI)‡
Roach, 2003 (40)	RTOG 9413: RT + 4 mo ADT started either before or after RT and +/– WPRT	Improved progression-free survival with WPRT and ADT started before RT	Trial to confirm value of WPRT (RTOG 0924) underway
Pilepich, 1987 (41)	RTOG 7506: prostate and WPRT +/– paraortic radiation in high-risk patients	No evidence of benefit to extended field RT	Pre-PSA era, low doses, no image guidance, and no ADT
Asbell, 1988 (42)	RTOG 7706: prostate only vs prostate and WPRT in low-risk patients	No evidence of benefit to WPRT	Pre-PSA era, low doses, and no image guidance

* GS = Gleason score; NHT = neoajuvant hormonal therapy; NNT = number needed to treat; PSA = prostate-specific antigen; WPRT = whole pelvic lymph node radiation therapy.

† Median follow-up, years/NNT/time to survival advantage, years.

‡ NNT ranges calculated from the upper and lower limits of relative risk reduction CI (1).

Table 6. Non-Radiation Therapy Oncology Group (RTOG) phase III prostate cancer trials radiation with or without androgen deprivation therapy (ADT)*

First author, year (reference)	Design	Conclusions	Comments
Armstrong, 2011 (43)	70 Gy + 4 vs 8 mo neoadjuvant ADT	No advantage	Included mostly high-risk patients
Denham, 2011 (44)	66 Gy to prostate +/– 3 or 6 mo ADT	ADT for 6 mo improves overall survival	Need at least 6 mo of ADT?; 10.6/7.1/10†; NNT range: 4.51–16.39 (with 95% CI)‡
Bolla, 2009 (45)	70 Gy (50 Gy WP); 6 mo vs 3 y ADT	Improved survival with 3 y	Long term > short term; 6.4/13.9/5†; NNT range: 7.97–53.48 (with 95% CI)‡
D'Amico, 2004 (46)	70 Gy +/– 6 mo ADT	Improved survival	Need at least 6 mo of ADT?; 4.5/9.7/5†; NNT range: 4.88–463.9 (with 95% CI)‡
Crook, 2009 (47)	66–67 Gy + 3 mo vs 8 mo ADT	Overall no advantage in DFS	Improved DFS in subset of high risk, on 8-mo arm
Bolla (2002) (48)	70 Gy +/– 3 y ADT	Improved survival for very high-risk patients	5.5/6.4/5†; NNT range: 4.07–14.57 (with 95% CI)‡

* CI = confidence interval; DFS = disease-free survival; NNT = number needed to treat; WP = whole pelvis.

† Median follow-up (years)/NNT/time to survival advantage (years).

‡ NNT ranges calculated from the upper and lower limits of relative risk reduction CI (1).

Table 7. Randomized prostate cancer trials: androgen deprivation therapy (ADT) vs deferred or radical prostatectomy (RP) and ADT with or without radiation therapy (RT)*

First author, year (reference)	Design	Conclusions	Comments
Medical Research Council, 1997 (49)	938 patients with MO or asymptomatic metastatic disease randomized either to immediate or delayed ADT	Among the MO patients, with 119 and 81 deaths from prostate cancer, died after deferred compared with immediate treatment, respectively ($P < .001$ two-tailed).	Supports immediate treatment in MO patients
Fellows, 1992 (50)	EBRT alone (n = 88), orchiectomy alone (n = 90), and combined therapy (n = 99)	Orchiectomy (+/– EBRT) produced a delay in detection of mets compared with EBRT alone. There were no statistically significant differences in local control or overall survival.	Grossly unpowered study
McLeod, 2006 (51)	Bicalutamide as an adjuvant to RP, or EBRT or compared to placebo with "watchful waiting"	With a total >8000 patients (analyzed by combining three trials), no overall improved outcome but a trend to a decreased survival for patients with "watchful waiting"	A trend for an improved survival in patients treated with EBRT and those with high-risk disease
Widmark, 2009 (52)	ADT +/– RT for locally advanced disease	Better survival with addition of RT	Used primarily antiandrogens; 7.6/10.2/10†; NNT range: 6.22–28.13 (with 95% CI)‡
Warde (2011) (53)	ADT +/– RT for locally advanced disease	Better survival with addition of RT	Used LHRH drug; 6/19.9/10†; NNT range: 10.0–2272.39 (with 95% CI)‡

* CI = confidence interval; EBRT = external beam radiation therapy; LHRH = luteinizing hormone-releasing hormone; MO = locally advanced; NNT = number needed to treat.

† Median follow-up (years)/NNT/time to survival advantage (years).

‡ NNT ranges calculated from the upper and lower limits of relative risk reduction CI (1).

3. Among men with adverse pathologic features noted after RP, should radiotherapy be administered immediately or held and administered at the time the PSA becomes detectable (eg, Radiotherapy and Androgen Deprivation in Combination After Local Surgery [RADICALS], GETUG-17, and Trans-Tasman Radiation Oncology Group Radiotherapy-Adjuvant Versus Early Salvage [TROG RAVES] trials).
4. Can overall treatment time be reduced, by increasing EBRT dose fraction sizes improving outcomes and reducing cost without increasing morbidity (eg, RTOG 0415, 0938) (28)?
5. Among men undergoing EBRT for recurrent disease after a RP, should ADT and or prophylactic whole pelvic lymph node radiotherapy (WPRT) be added to improve outcomes (eg, RTOG 0534) (57).
6. Can prophylactic WPRT prolong overall survival in men with unfavorable intermediate- or favorable high-risk prostate cancer when combined with ADT without increasing morbidity (RTOG 0924) (58)?
7. Can drugs active in the setting of castration-resistant prostate cancer be added earlier in the course of the disease and prolong survival longer compared with long-term ADT and EBRT (eg, RTOG 0521)?
8. Can the prophylactic adjuvant use of pharmacologic agents reduce the risk of radiation-induced erectile dysfunction (eg, RTOG 0831)?

Discussion

Although many of the studies included in the review contain participants who would not have been candidates for AS, there still appear to be lessons that can be learned from these trials. In order to understand the risk associated with AS, it is important to understand the potential benefits of treatment. In order to understand the benefits of treatment, it is critical to understand the magnitude and timeline in which benefits of treatment might be expected for men with low-risk disease. There are, however, very limited data available on which to make such estimates. In addition, some men who appear to have limited disease when AS is initiated will, in fact, have higher-risk disease later, which will require treatment. Neither the trials reviewed nor the cohort studies chosen by the USPSTF are robust enough to provide such data. For example, in the manuscript published by the USPSTF, they also included eight cohort studies including as few as 316 men with or without prostatectomy and five cohort studies including as few as 334 men treated with or without RT, with follow-up as short as 4 years (2). From these cohort studies, there appeared to be a decrease in all-cause mortality with both treatment approaches compared with WW. However, the RCTs (which they did not include) suggest that the magnitude of the benefits for treatment might have been greater had postoperative RT been routinely added to patients with adverse pathological features prostatectomy (National Cancer Institute National Clinical Trial Network's SWOG) and ADT been

added to RT in subsets of patients with T1-2 disease diagnosed in the PSA-era (eg, RTOG 9408). These sorts of details might have helped inform the discussion concerning Question #3 from their report asking, "What are the benefits of treatment of early-stage or screening-detected prostate cancer?"

This perspective is not meant as a criticism of the USPSTF's position on prostate cancer screening nor is it meant to argue against the potential value of AS, but rather to set realistic expectations using existing data from phase III treatment trials. Our premise is that understanding data provided by the numerous randomized clinical trials that have demonstrated the benefits of therapy in men with localized prostate cancer, we can rationally find support for determining in which patients AS might likely be safest. Similarly, the treatment data can help us model the distribution of advanced disease in the population that would need to be exceeded in order to maximize the benefits of treatment after screening. Some might argue that we already know that we need huge sample sizes and very long timelines to assess the benefits of screening and AS and that we already know that AS entails some risk of missing the "window of curability." We argue that the data from the randomized control treatment trials can actually allow us to answer these questions concerning which subsets of patients are actually likely to benefit the most from which type of treatment and who might be best served by AS. For example, it is well known that roughly 10%–15% of men with newly diagnosed prostate cancer have high-grade disease (Gleason scores of 8–10), and they represent the patients for whom the benefits of treatment have most consistently been shown in a number of randomized trials (eg, RTOG 8531, RTOG 9202, EORTC) (summarized in Tables 5 and 6). Given this fact, such patients should probably be excluded from studies assessing the merits of AS. Thus, we provide a cautionary point to the USPSTF that by limiting the assessment of the benefits of treatment to only two trials, they limit their ability to accurately address the complicated issues related to the timeline of treatment delivery and thus the ability to assess the merits of delayed treatment and screening.

Gaps and Challenges

Despite the studies completed and pending completion, it is also clear that important gaps in our scientific and medical knowledge will remain for years to come. Perhaps the two most promising areas involve advances in imaging that will help us assess the true extent and distribution of disease and the identification of biomarkers that hold promise for helping select the most appropriate level of therapy for an individual patient (59,60).

Unfortunately, because of our reimbursement structure and nature of the criteria required to secure Food and Drug Administration clearance, the prospects for imaging advances appear dire. Despite a large body of literature published in Europe and elsewhere demonstrating the value of positron emission tomography using agents such as acetate and choline as well as the promising results with magnetic resonance imaging using dextran-coated nanoparticles, neither of these agents/modalities are currently available for routine reimbursement in the United States (61–70).

Although the prospects for the development of prognostic biomarkers appear to be somewhat less challenging than the development of imaging agents, the results to date have been less promising. Despite many studies completed to date, none appear "ready for prime-time" (60). If these biomarkers could be proven to predict disease outcome and guide treatment, they would hold great promise for selecting how, when, and if patients may best be treated. Acquiring this understanding could consequently lower the cost and morbidity of treatment for clinically localized prostate cancer.

Conclusions

The data found in these prospective randomized trials provide clear evidence that certain types of patients benefit from certain types of treatment. The data also suggest that the follow-up time *and* the sample size required to show the benefits from treatment are inversely proportional to the risk group. In other words, low-risk patients require very long follow-up, whereas high-risk patients require a shorter follow-up and smaller sample size. Based on this body of treatment literature, we should expect to be able to better identify those subsets of patients for whom less might be more.

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