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DEFINITIVE EXTERNAL-BEAM IRRADIATION IN STAGE T1 AND T2 PROSTATE CANCER

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Summary of Literature Review

Introduction/Background

The outcome for patients with localized prostate cancer depends on the aggressiveness of their disease, their natural life expectancy, and the efficacy and toxicity of the chosen therapy. There is a paucity of prospective randomized studies comparing contemporary treatment options for patients with prostate cancer. Retrospective studies suggest that external-beam radiation therapy (EBRT) has a similar efficacy as surgery and brachytherapy for T1/T2 disease [1-4]. Prospective nonrandomized reports of toxicity after radical prostatectomy, EBRT, and brachytherapy indicate that each therapy carries a unique toxicity profile [5]. Recently published randomized controlled trials have suggested that definitive surgical or radiotherapeutic treatment results in improved outcomes when compared to watchful waiting [6-8] but it has not been tested whether it improves outcomes relative to active surveillance. There is increasing interest in the surveillance approach, particularly in men with a limited life expectancy and favorable-risk disease [9-11]. To help patients make an informed treatment decision, physicians need to thoroughly assess a patient's disease aggressiveness, comorbidity level and life expectancy, and the relative efficacy and toxicity of the multiple treatment options.

Risk Stratification

A commonly used risk grouping developed by D'Amico divides patients as follows: low risk (clinical stage T1c-T2a, prostate-specific antigen [PSA] ≤10 ng/mL, and Gleason score <7), intermediate risk (clinical stage T2b, PSA 10-20 ng/mL, or Gleason score =7), and high risk (clinical stage T2c, PSA >20, or Gleason score >7) [12]. The National Comprehensive Cancer Center Network (NCCN) guidelines have a similar system, however T2c is moved to intermediate risk, and clinical T3a is included in high risk [13]. Additionally, the percentage of positive prostate biopsies has been proposed as a prognostic indicator of biochemical PSA control. A significant difference in biochemical control in patients treated with EBRT or radical prostatectomy when stratified by <34% positive biopsies versus >50% positive biopsies has been demonstrated [14]. A PSA velocity >2 ng/mL in the year prior to diagnosis and the presence of tertiary Gleason score 5 disease have also been identified as adverse prognostic factors in patients with prostate cancer [15-17].

Evidence that Treatment Improves Outcome in T1-T2 Disease

A few randomized trials show how treatment can improve outcome in T1-T2 disease. The Swedish randomized trial of radical prostatectomy versus watchful waiting for mainly unscreened T1-T2 disease demonstrated a significant 6.6% absolute improvement in overall survival at 15 years (52.7% versus 46.1%) with prostatectomy [6]. However, the American PIVOT trial, consisting of mainly screened T1-T2 disease, did not demonstrate a difference in overall survival at 10 years with treatment except in men with PSA >10 in whom treatment

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improved survival by 13.2% (hazard ratio [HR] 0.67 (0.48–0.94), suggesting that treatment of screening-detected low-risk disease may not enhance survival [7]. Two randomized trials have proven that radiation improves survival when added to androgen deprivation therapy (ADT) alone, however both trials enrolled mainly patients with T3 disease [18,19]. For localized disease, Widmark et al [8] presented the results of a randomized trial of 214 unscreened men with T1b-T2N0M0 who were randomized to radiation or observation and found that at 15 years radiation improved metastasis-free survival (81% versus 65%, P<0.022) but not prostate-cancer specific or overall survival. It is noteworthy that none of these trials compared definitive treatment to active surveillance.

Optimal Use of External-Beam Radiation Therapy

Dose Escalation

EBRT is used as definitive therapy in patients with early and locally advanced disease. Increasing dose has been associated with improved outcomes. An update of the MD Anderson randomized controlled trial [20] of mainly intermediate- and high-risk patients demonstrated a statistically significant improvement in freedom from PSA failure (78% versus 59% at 5 years) in patients treated to a total dose of 78 Gy versus 70 Gy in 2 Gy per day fractions using conventional radiation therapy without hormonal therapy. Patients were stratified by PSA level, and a post-hoc analysis found that among men with PSA>10, the 10-year prostate cancer mortality was lower in the high-dose arm (15% versus 2%, P=0.03). Patients in the high-dose arm had higher grade 2 or greater gastrointestinal toxicity (26% versus 13%) but lower grade 2 or greater genitourinary toxicity (8% versus 13%).

Zietman et al [21,22] updated the combined Massachusetts General Hospital (MGH)/Loma Linda trial (PROG 95-09) on the use of proton boost combined with 3-D conformal photon radiation to the prostate, seminal vesicles, and periprostatic tissues. Patients with T1b-T2b disease and PSA <15 ng/mL were randomized to 50.4 Gy with photons plus a proton boost of either 19.8 or 28.8 Gy-equivalents (GyE), totaling 70.2 GyE (conventional dose) versus 79.2 GyE (high dose), all in 1.8 GyE per day fractions. With a median follow-up of 8.9 years, biochemical failure rates were 32.4% for the conventional-dose group and 16.7% for the high-dose group (P<0.0001) [21]. Two percent of patients in both arms experienced late grade 3 or higher genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade 3 or higher gastrointestinal toxicity. Of note, the doses in the MGH/Loma Linda trial were prescribed to a planning target volume (PTV), whereas the MD Anderson trial dose was prescribed to the isocenter. In current PTV terms, 78 Gy to the isocenter from the MD Anderson trial is similar to approximately 75.6 Gy to a PTV, and so radiation oncologists commonly employ doses in the range of 75.6–79.2 Gy to the PTV.

Pelvic Lymph Node Radiation

The role of radiation of the lymph nodes is controversial. The Radiation Therapy Oncology Group® (RTOG®) 9413 trial evaluated the use of whole pelvic versus prostate-only radiation in a randomized controlled trial in patients with positive pelvic lymph nodes, seminal vesicle involvement, or a >15% risk of having metastatic pelvic lymph nodes [23]. Approximately 30% of the patients had clinical stage T1-T2b disease, and 30% had a Gleason score <7. Radiation was 50.4 Gy in 1.8 Gy fractions in the first course followed by a cone down boost to a total of 70.2 Gy, all prescribed to the isocenter. Patients were additionally randomized to 4 months of neoadjuvant/concurrent or adjuvant ADT in the 2x2 factorial-design trial. Although the trial initially demonstrated a significant improvement in progression-free survival in patients treated with whole pelvis radiation therapy versus prostate-only radiation therapy, the difference was no longer significant when updated results of the trial were published in 2007. It is possible that an unexpected interaction between the 2 randomized arms limited the ability to detect a benefit to whole pelvis radiation therapy in the update [24]. Pommier et al [25] reported the results of the French GETUG-01 trial that included patients with T1c-T3 prostate cancer who were then randomized to irradiation of the whole pelvis or the prostate only. The data from this study showed no difference in progression-free survival or quality of life at 42-month follow-up. However, there were several concerns regarding this trial: many patients included were at low risk for lymph node involvement, the superior border of S1-S2 may have left some nodes out of the field, and hormones were used at the discretion of the treating physician, possibly making it more difficult to detect a potential benefit to whole pelvic radiation [26]. Further studies are needed to clearly define the role of pelvic node irradiation in this group of patients. The RTOG is currently conducting a randomized phase III trial (RTOG 0924, NCT01368588) with the endpoint of survival in which patients with high-risk or locally advanced prostate cancer receive hormonal therapy in conjunction with either prostate only or whole pelvic radiation.

If pelvic nodal irradiation is to be employed, radiation oncologists must determine whether to employ intensity-modulated radiation therapy (IMRT) or 3-D conformal radiation therapy (3-DCRT). Of note, both RTOG 9413

[23] and GETUG-01 [25] delivered pelvic radiotherapy using a 4-field approach; IMRT was not employed in either trial. Dosimetric data comparing 3-DCRT and IMRT suggest that IMRT reduces the dose to the bladder, rectum, and small bowel [27]. Other studies have also suggested that it may be easier to meet dose constraints using IMRT-based plans [28]. What remains unknown, however, is whether IMRT yields acceptable tumor control outcomes relative to 3-DCRT given that regions not delineated by the clinician are generally treated at lower doses by IMRT plans and because pelvic recurrences could potentially occur in regions further from the perivascular nodal regions commonly contoured as targets for IMRT plans (ie, areas that would have received the prescribed dose in 3-DCRT plans).

Brachytherapy Boost

Numerous single-arm studies that employ brachytherapy as a boost have been reported. Sylvester et al [29] reported the long-term results of a prospective trial in which 232 patients with clinically localized (T1-T3) prostate cancer (27%, 22%, and 51% were low, intermediate, and high risk by D'Amico criteria, respectively) were treated with EBRT to 45 Gy using a 4-field plan of varying size, followed by a I-125 (120 Gy) or Pd-103 (90 Gy) implant. ADT was not employed. Fifteen-year biochemical recurrence-free survival was 88%, 80%, and 53% in the low-, intermediate-, and high-risk cohorts, respectively). In a phase II prospective dose-escalation trial published by Lettmaier et al [30], 130 patients treated to 50.4 Gy with EBRT (a pelvic field was employed in high-risk patients) underwent an interstitial, pulsed-dose-rate brachytherapy boost of 25–35 Gy given in one session. Fifty-nine percent of patients underwent ADT. Approximately 56% and 44% of patients had intermediate-risk and high-risk disease, respectively. The 5-year biochemical recurrence-free survival was 86%. Hurwitz et al [31] reported the results of a prospective phase II trial in which 63 intermediate-risk patients were treated with EBRT (45 Gy) to the prostate and seminal vesicles followed up brachytherapy using I-125 (100 Gy) or Pd-103 (90 Gy) and 6 months of ADT. The 6-year biochemical disease-free survival (DFS) rate was 85%. Although preliminary results from these and other trials are encouraging, the difficulty in interpreting such single-armed trials is the lack of a comparison group treated with EBRT alone. To this end, Hoskin et al [32] reported preliminary results from a phase III randomized trial in which patients with T1-T3 prostate cancer were randomized to EBRT (55 Gy in 20 fractions) versus EBRT (35.75 Gy in 13 fractions) followed by high-dose-rate brachytherapy boost (17 Gy in 2 fractions). Approximately 76% of patients in each arm received ADT. With a median follow-up of 85 months, biochemical/clinical relapse-free survival was higher in the EBRT plus brachytherapy group (P=.04). Bowel/bladder toxicity was similar between the arms. Limiting the interpretation of this trial is a nonstandard fractionation schedule for the EBRT components of treatment. Sathya et al [33] compared EBRT alone (66 Gy in 33 fractions) to EBRT (40 Gy in 20 fractions) plus iridium implant (35 Gy over 48 hours) in patients with T2-T3 prostate cancer. Approximately 40% and 60% of patients in each arm were intermediate and high risk, respectively. The 5-year biochemical/clinical failure rate was 29% versus 61%, favoring the EBRT plus brachytherapy group (P=.002). Toxicity was similar in the 2 arms. Of note, by modern standards, the dose in the EBRT alone arm is lower than the current standard, and it is unknown whether brachytherapy plus EBRT would be superior to EBRT using present-day EBRT doses. Data to help address this issue are presented in a paper that retrospectively compared patients treated with ultra-high-dose IMRT to 86.4 Gy versus 50.4 Gy plus a high-dose-rate boost of 7 Gy x 3 found a significant improvement in biochemical relapse-free survival among patients who received the high-dose-rate boost, and this effect was particularly pronounced in intermediate-risk patients [34]. Also, approaching the question from the standpoint of whether or not supplemental EBRT needs to be added to brachytherapy, RTOG 02-32 enrolled men with either Gleason score of 7 or a PSA of 10–20 but not both and randomized them to low-dose-rate brachytherapy monotherapy versus low-dose-rate brachytherapy to a boost dose plus 45 Gy of supplemental EBRT. In summary, available data suggest that the addition of brachytherapy to EBRT may be reasonable in select patients, although it remains unclear from the randomized data if such an approach offers an advantage relative to EBRT alone when contemporary doses of radiation are employed [34].

Intensity-Modulated Radiation Therapy and Image-Guided Radiation Therapy

Although there are no randomized trials comparing IMRT with 3-DCRT, IMRT has become the current standard for definitive external radiation to the prostate. It has appeared in retrospective studies to reduce normal tissue toxicity while allowing an increase in radiation dose to the prostate. Zelefsky et al [35] have shown a decrease in rectal toxicity compared to 3-DCRT, with a reduction of grade 2–3 rectal bleeding from 15% to 3% with IMRT. In a 2002 report by Zelefsky et al [36] involving 772 patients, the 3-year actuarial rectal grade 2 toxicity was 4%, and the urinary grade 2 toxicity was 15%, comparing favorably to the results of 3-DCRT. Ninety percent of those

patients were treated to 81 Gy, and 10% to 86.4 Gy. The 3-year actuarial PSA biochemical control rates were 92% for favorable disease, 86% for intermediate disease, and 81% for unfavorable disease.

Spratt et al [37] recently updated the Memorial Sloan-Kettering experience on prostate cancer patients treated with 86.4 Gy. In this study of 1,002 patients, the 7-year prostate cancer-specific mortality rates were 0%, 3.3%, and 8.1% in the low-, intermediate-, and high-risk groups, respectively. Rates of Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 3 gastrointestinal and genitourinary toxicity were only 0.7% (mainly rectal bleeding) and 2.2% (mainly urethral strictures and hemorrhagic cystitis), respectively.

Michalski et al [38] recently published in abstract form a reanalysis of the RTOG 94-06 dose escalation studies in which patients were treated to 79.2 Gy using either 3-DCRT or IMRT (in a nonrandomized fashion) and found an association between the use of IMRT and reduced CTCAE grade 2 or higher acute genitourinary and gastrointestinal toxicity, although no significant difference in late toxicity was seen.

A study reported by Chung et al [39] also addressed the additional technical improvement of implanted fiducial markers, resulting in image-guided radiation therapy (IGRT). In this study prostate margins were reduced from 1 cm to 2–3 mm with the placement of fiducials, and this resulted in a decrease in grade 2 rectal toxicity (80% to 13%) and bladder toxicity (60% versus 13%). Zelefsky et al [40] also recently reported on a retrospective series in which men treated to the same dose with IGRT versus IMRT had significantly lower 3-year grade 2+ late urinary toxicity (10.4% versus 20.0%, P=0.03) although no difference in rectal toxicity was seen (P=0.81).

Proton Therapy

The potential dosimetric benefit of the Bragg peak has led to the investigation of proton therapy in treating prostate carcinoma, although its cost is currently substantially higher than IMRT [41]. However, there is some disagreement in the literature as to whether protons will produce a superior dose distribution to the prostate compared to IMRT. One planning study by Trofimov et al [42] used parallel-opposed beams for the protons and found that while the rectal V70 (volume receiving more than 70 Gy) was similar with each modality, the V70 of the bladder was actually 50% higher with proton therapy than with IMRT**,** although another planning study by Vargas et al [43] found that all rectal metrics from V10 to V80 were improved with protons compared to IMRT ($P<0.05$), and bladder wall V10 to V35 were also improved.

There is currently no published randomized data comparing protons to other treatments for prostate cancer. The previously mentioned PROG 95-09 randomized dose-escalation trial reported by Zietman et al included protons in both arms. A recent retrospective study by Coen et al [44] case-matched 141 brachytherapy-treated patients to 177 similar patients on the high-dose arm of the PROG 95-09 trial and found 8-year biochemical failure to be similar (16.1% versus 7.7%, P=0.42). In a recent SEER-Medicare based study comparing propensity score-matched patients treated with IMRT and proton therapy, IMRT patients were found to have lower rates of gastrointestinal toxicity although no differences in urinary toxicity or erectile dysfunction were seen [45]. A multicenter randomized trial comparing protons versus IMRT is currently open. (See Variant 1.)

Efficacy of Treatment and Comparison With Prostatectomy

There are no data directly comparing modern external radiation therapy and prostatectomy in a prospective randomized manner. One older randomized trial by the Uro-Oncology Research Group was published in 1982 and compared prostatectomy versus radiation in 97 men with T1-T2N0M0 disease and concluded that surgery had superior freedom from first failure at 5 years (85% versus 59%) [46]. However, this study has not been widely accepted due to issues with the randomization, allowing for possible selection bias, censoring of 2 surgical patients who developed local recurrence, and uncharacteristically poor results for T2 disease in the radiation arm [47]. In addition, radiation doses were lower than what would be used in contemporary series.

In a retrospective series, the outcome for patients treated with EBRT compares favorably with the outcomes for other treatment modalities. In an analysis of T1-T2 patients treated to a dose of 70 Gy or greater, the 7-year freedom-from-biochemical-failure rates were 77% for EBRT patients, 79% for radical prostatectomy patients, and 74% for patients treated with prostate brachytherapy. On multivariate analysis, only initial PSA and Gleason score were independent predictors of outcome [3] however treatment modality was not, and these findings have been confirmed in other reports [1,2]. A widely cited retrospective study from 1998 [12] examined 766 patients treated with external radiation, 218 treated with brachytherapy, and 888 treated with surgery, and found that external RT and surgery had similar biochemical DFS across all risk groups, but brachytherapy results were worse among intermediate- and high-risk patients, which dampened enthusiasm for brachytherapy except in low-risk disease.

However, some have pointed out that only 15 patients received brachytherapy monotherapy in the intermediate-risk group, and techniques of brachytherapy continued to improve during the 1990s and beyond. Additional reports were published showing that high-quality brachytherapy may be safely employed in patients with intermediate-risk disease. In a study by Taira et al [48] the 12-year biochemical progression-free survival rate for intermediate-risk patients treated with brachytherapy as monotherapy was 96.4%. Consequently, many experts as well as the 2012 American Brachytherapy Society guidelines acknowledge that modern brachytherapy yields excellent results when compared to other therapies for select patients with favorable intermediate-risk disease [49,50]. Interstitial brachytherapy is more fully discussed in the ACR Appropriateness Criteria® topic on "Permanent Source Brachytherapy for Prostate Cancer."

Other retrospective interspecialty comparisons have been reported. Vicini et al [4] reported on a pooled series involving 6,877 men treated at 7 different institutions with radiation therapy, surgery, or brachytherapy. Using uniform risk group stratification, no difference in 5-year biochemical outcomes was seen favoring any specific therapy. A study by Kupelian et al [51] from the Cleveland Clinic and Memorial Sloan Kettering compared almost 3,000 patients with prostate cancer who received EBRT, radical surgery, or brachytherapy. For all patients receiving modern therapy to a dose above 72 Gy, no differences were seen in cancer control rates using PSA-based endpoints. Another recent retrospective comparison from Aizer et al [52] examined the results of radical prostatectomy or radiation therapy with IMRT to a dose of ≥72 Gy with hormone therapy utilized when appropriate. They found no difference in biochemical DFS between radical prostatectomy and IMRT with the exception of patients with a poor pretreatment prognosis, in which case radiation therapy with hormone therapy was superior to radical prostatectomy (62.2% versus 38.4%). A limitation of all of these studies is that biochemical DFS is defined differently for different treatment. The study notes that prostate cancer-specific survival would be a more compelling endpoint across modalities. One recent retrospective study by Zelefsky et al [53] found that the 8-year metastasis-free survival with surgery was 97% compared to 93% for radiation, but on multivariable analysis, surgery was significantly associated with a shorter time to distant metastasis (HR=0.35; 95% CI, 0.19 to 0.65; P<.001) and prostate cancer death (HR=0.32; 95% CI, 0.13 to 0.80; P=.015). However, the findings may have been confounded by the fact that salvage ADT was initiated much sooner after biochemical failure in surgery versus patients who received radiation (13 months versus 69 months), which could have altered the time to distant metastasis. Also, most of the high-risk patients received short-course ADT, which may not have provided an adequate reduction in prostate cancer-specific mortality. Ultimately, prospective randomized studies are needed to definitively compare the efficacy of surgical and radiotherapeutic options for prostate cancer. To this end, the ProtecT trial undertaken in Britain will compare prostatectomy to radiotherapy to active surveillance. Preliminary results are expected in 2015.

Morbidity of External Irradiation

In studies of physician-reported toxicity, the overall incidence of significant urinary or rectosigmoid sequelae is approximately 3% for severe toxicity and 7%–10% for moderate toxicity [54-60]. Long-term urinary morbidity is rare, with a 0.3% urinary incontinence rate following external-beam prostate radiation reported in a multi-institutional review [60]. A higher incidence of urethral stricture (about 5% versus 3%) has been described in patients irradiated after a transurethral resection of the prostate [57]. Some degree of urinary incontinence, sometimes related to stress, is noted in about 2% of patients, more frequently after transurethral resection. The incidence of severe anal/rectal injury requiring colostomy is less than 1%. Older series in which patients were not treated with conformal techniques or image-guidance show low rates of severe toxicity for EBRT in the treatment of localized prostate cancer. In 1991, Lawton et al [56] reported on a review of RTOG multi-institutional randomized trials involving 1,020 patients, which demonstrated a 3.3% rate of long-term grade 3, 4, or 5 gastrointestinal toxicity, with 11 patients (1%) experiencing grade 4 and 5 rectal injuries with nonconformal techniques. Fatal complications in the treatment of localized carcinoma with external radiation are rare. In 1994, Perez et al [57] reported one rectovesical and one vesicosigmoid fistula in 738 patients (0.27%).The reported rate of 0.2% demonstrates the low risk of this therapy [56,57]. In 2010, Tucker et al [61] analyzed RTOG 94-06, a dose escalation protocol, which demonstrated a rate of grade 4 toxicity <0.2%.

Patient and spouse-reported toxicity following radical prostatectomy, EBRT, and brachytherapy was prospectively collected and reported descriptively by Sanda et al. In this study, 1,201 patients and 625 spouses reported on quality of life measures before and after treatment. After prostatectomy, urinary incontinence was observed, but urinary irradiation and obstruction improved, particularly in men with large prostates. No substantive bowel toxicity occurred in patients undergoing prostatectomy. Patients undergoing either EBRT or

brachytherapy experienced symptoms of urinary irradiation and obstruction, but these symptoms improved with time. Quality of life in patients receiving hormonal therapy along with radiation therapy appeared to be worse among multiple domains [5]. All 3 groups experienced quality of life impairment related to sexual dysfunction; it is important to note, however, that sexual function was rated as a "big problem" at 1 year by 26%, 16%, and 16% of patients undergoing prostatectomy, EBRT, and brachytherapy, respectively.

Chen et al [62] examined the impact of radical prostatectomy, EBRT, and brachytherapy on patient-reported urinary, bowel, and sexual symptoms after accounting for baseline function. Three-year outcomes in the 409 reviewed patients revealed that baseline function had a significant impact on toxicity. Specifically, those with normal baseline function experienced a greater increase in symptoms. Patients who had severe obstructive/irritative urinary symptoms at baseline experienced improvement in these symptoms with treatment, particularly prostatectomy.

Lu et al [63] correlated rectal morbidity with 3-DCRT to the rectal surface area irradiated instead of volume and noted that morbidity increased significantly when more than 20% of the area was irradiated to at least 65 Gy. Dale et al [64] reported a correlation of late rectal effects with higher doses delivered to small-volume fractions as shown on the dose-volume histogram, suggesting a more serial organization of the rectal tissue architecture than previously reported. Erectile dysfunction can be a significant treatment side effect affecting quality of life. Data from RTOG 9406, a dose-escalation trial, demonstrates that penile bulb dose plays an important role in potency rates. Patients with median penile bulb doses ≥52.5 Gy had higher impotency rates compared to those with doses below 52.5 Gy (P=0.039) [65]. The incidence of erectile dysfunction depends on a patient's potency prior to prostate radiation, along with the time point and method in which potency is measured. Several series reported impotency rates ranging from 30% to 45%, which increases with time in patient's potency prior to radiation therapy [66-68]. Alemozaffar et al [69] reported prospectively obtained erectile dysfunction outcomes after prostatectomy, EBRT, or brachytherapy. They showed that on multivariate analysis preservation of erectile function after EBRT appears to be associated with better pretreatment sexual function, avoidance of hormonal therapy, and a lower PSA level; brachytherapy patients were more likely to have preserved erectile function when they had better pretreatment sexual function, were younger, were African American, or when they had lower body-mass indices.

The use of oral erectogenic agents such as Sildenafil has shown a benefit, more so in radiation patients in comparison to patients undergoing radical prostatectomy [70,71]. Weber et al [71] demonstrated a 76% improvement in erectile function with the use of Sildenafil over a 5-week interval.

Leg, scrotal, or penile edema is extremely rare in patients treated with irradiation alone (less than 1%), but depending on the extent of lymph node dissection its incidence ranges from 10% to 30% in patients receiving "oral erectogenic agents." [58]. (See Variant 2 and Variant 3.)

Prostate-Specific Antigen in Post-treatment Evaluation

In 2005, an ASTRO consensus conference was held to establish an improved definition for biochemical failure following EBRT for prostate cancer. This conference was held in Phoenix, therefore the definition is referred to as the "Phoenix definition." The original ASTRO definition of 3 consecutive rises following a nadir was abandoned in favor of the panel recommendation that a rise of 2 ng/mL or more above the nadir PSA level should be considered biochemical failure following EBRT with or without ADT. The importance of adequate follow-up was also stressed in patients treated without hormonal therapy [72].

Presently, PSA failure has not been shown to be a surrogate for clinical progression or survival. Jhaveri et al [73] found similar overall survival rates in patients with biochemical failure compared to patients with biochemical control with 10-year follow-up. However, using Prentice's Criteria, one study suggested that a post-treatment PSA doubling time less than 3 months is a surrogate for prostate cancer mortality, with a median time to prostate cancer death of 6 years after the surrogate endpoint was reached [74]. Similarly, Freedland et al also found in the Johns Hopkins data that a PSA doubling time of less than 3 months was highly associated with prostate cancer death within 6 years [75]. Further studies are needed to validate this as a potential surrogate marker for death in clinical trials.

Positive Biopsy of the Prostate After Definitive Radiation Therapy

The use of prostate biopsy following radiation therapy is not commonly recommended due to the slow death rate of prostate adenocarcinoma following irradiation. Several authors have reported histologic evidence of viable

adenocarcinoma in the prostate at various times following completion of radiation therapy. Cox and Stoffel [76] noted that there was a decreasing incidence of positive biopsies as a function of time after irradiation (from 70% at 6 months to 20% after 24 months). Scardino [77] found that 32% of his patients with a positive biopsy at 12 months had a negative pathologic specimen at 24 months. Nevertheless, postirradiation biopsy findings do have some prognostic value in the experience of Freiha and Bagshaw [78] and Scardino [77], who reported 89% and 64% incidence, respectively, of positive biopsies in patients with suspected or definite clinical evidence of tumor regrowth, whereas the same authors reported 25% and 20% positivity, respectively, in patients with negative clinical examination of the prostate. In a publication by Scardino and Wheeler [79] the local recurrence rate was 52% at 5 years with a positive biopsy versus 12% with a negative specimen, and at 10 years the rates were 72% and 30%, respectively (P<0.001). Similarly, in a series including 498 Canadian men, Crook et al [80] found that 34% of patients had an either positive or indeterminate rebiopsy at last follow-up, and 18% overall developed a local failure. In that series, it was shown that, in addition to PSA nadir, the 24-month and 36-month biopsy status were independent predictors of ultimate outcome. (See Variant 4.)

Optimal Use of Androgen Deprivation Therapy

Three prospective randomized studies have demonstrated that 4–6 months of ADT improves overall survival when added to conventional-dose radiation in men with intermediate- and high-risk T1/T2 prostate cancer. Jones et al [81] (RTOG 94-08) tested 66.6 Gy prescribed to the isocenter with or without 4 months of ADT (consisting of flutamide plus goserelin or leuprolide) in 1,979 men with cT1b-T2b, PSA<20 disease and found that ADT improved overall survival at 10 years (62 versus 57%, P=0.03). On post-hoc analysis the benefit appeared to be limited to men with intermediate-risk disease, suggesting that ADT is not needed for low-risk disease, and 4 months may not be enough to improve survival in high-risk disease.

D'Amico et al [82] tested the addition of 6 months of ADT to 70 Gy of radiation prescribed to the isocenter in men with a PSA of 10–40 ng/mL or Gleason score ≥7. Low-risk patients were included if magnetic resonance imaging evidence of T3 disease was present. This study found an improvement in overall survival (74% versus 61% at 8 years). Finally, Denham et al [83] (TROG 96.01) randomized 818 men with T2b-T4 disease to radiotherapy alone (to 66 Gy) versus radiation plus 3 or 6 months of ADT (goserelin plus flutamide). Sixty-one percent of the patients had T2b or T2c disease. With a median follow-up of 10.6 years, the 6-month course, not the 3-month course, of ADT improved 10-year overall survival relative to radiotherapy alone (71% versus 58%, P=0.005).

Certain questions about the optimal use of ADT remain. First, it is unknown whether ADT is needed when modern high-dose radiation is used. Therefore, RTOG 08-15 is randomizing men with mainly intermediate-risk disease to high-dose radiation (EBRT to 79.2Gy or EBRT plus brachytherapy boost) plus or minus 6 months of ADT. The study aims to enroll 1,520 patients and is powered to test for the endpoint of overall survival.

A second question is whether high-risk men with T1/T2 disease would benefit from a longer duration of ADT. Bolla et al [84] randomized 970 men with mainly T2c-T4 disease to 70 Gy of radiation plus 6 months versus 36 months of ADT and found that overall survival was 3.8% better at 5 years with long-course ADT. However, fewer than 20% of patients on this trial had T2 disease. Similarly, Horwitz et al [85] published 10-year results of the RTOG 92-02 randomizing 1,554 men with T2c-T4 disease to 70 Gy radiation plus 4 versus 28 months of ADT and found that 28 months improved prostate-cancer specific survival (89% versus 84% at 10 years, P=0.0042) but not overall survival. In this trial, 45% of the patients had T2c disease, and in a post-hoc analysis the authors found that there appeared to be an overall survival benefit to longer course ADT in men with Gleason 8-10 disease (45.1% versus 31.9% at 10 years; P=0.0061). Although this postrandomization is considered hypothesis-generating only, many clinicians use this as a rationale to recommend long-term ADT for all men with Gleason 8-10 disease.

A final question is whether ADT should be avoided in men with certain comorbidities. A post-hoc reanalysis of the D'Amico trial found that men with no or minimal comorbidity on the ACE-27 scale experienced a very large overall survival benefit from the addition of 6 months of ADT to 70 Gy of radiation (90% versus 64% at 8 years, P<0.001), whereas those with moderate or severe comorbidity (mainly cardiac) experienced a near-significant *worsening* of survival with ADT (25% versus 54% at 8 years, P=0.08) [82]. A large retrospective study attempted to identify which specific comorbidities placed a man at highest risk of harm from ADT and found that ADT was associated with an increased risk of death only in men with a history of prior myocardial infarction or congestive heart failure [86]. However, these men accounted for only 5% of the total prostate cancer study population,

suggesting that the proportion of patients at risk for harm due to ADT may be small. In 2011, a meta-analysis of 4,141 men in 8 randomized trials of ADT versus no ADT in unfavorable-risk prostate cancer did not find any difference in the incidence of cardiovascular death in the 2 arms (11.0% versus 11.2%, respectively) but found that ADT significantly reduced prostate-cancer specific mortality (relative risk [RR] = 0.69, P<.001) and all-cause mortality (RR = 0.86, P<0.001) [87]. Because patients who enroll in randomized trials tend to be healthier than the general population this meta-analysis could not rule out the possibility that a small proportion of men are harmed by ADT.

Taken together, the data suggest that the majority of men with unfavorable-risk prostate cancer will benefit from the addition of ADT to radiation, but there may be a small subgroup of men with significant underlying cardiac comorbidity, particularly prior myocardial infarction or congestive heart failure, who can be harmed by ADT. It is necessary to weigh the potential risks and benefits with these men caution, including potentially referring these patients to a cardiologist for optimal medical management prior to ADT. Of note, the RTOG 08-15 trial discussed above is stratifying men by their ACE-27 comorbidity status and will be able to provide further information about how comorbidity impacts the benefits derived from ADT.

Hypofractionation and Stereotactic Body Radiotherapy

Unlike many cancers, it is believed that prostate cancer cells possess a low alpha/beta ratio, suggesting that they are more sensitive to hypofractionated radiation than an equivalent radiation dose given via a greater number of fractions [88-90]. In addition, radiation-sensitive surrounding normal tissues such as the rectum experience relative sparing using a hypofractionated approach, given their likely higher alpha/beta ratio [91]. Given the known benefit of dose escalation in patients with prostate cancer [20,21] as well as the limited tolerance of surrounding normal tissues such as the rectum, radiation oncologists have attempted to exploit the low alpha/beta ratio of prostate cancer to dose escalate using hypofractionation. It is important to note, however, that many studies attempting to characterize the alpha/beta ratio of prostate cancer were performed in the pre-IGRT era, and that patients undergoing low-dose-rate brachytherapy may not have received the dose used in the alpha/beta calculation. For these and other reasons, some investigators have asserted that the *low* alpha/beta ratio of prostate cancer should be considered an unconfirmed hypothesis [92].

Standard fractionation entails administration of 1.8–2.0 Gy/day to a typical dose of 74-80 Gy [20,21]; hypofractionated regimens may be as extreme as 36.25 Gy in 5 fractions [93]. Unfortunately, long-term follow-up from quality level one evidence comparing fractionation regimens is lacking. In addition, a multitude of different regimens are used in the United States.

Investigators from Italy reported preliminary results from a trial (n=168) comparing 80 Gy in 40 fractions (5 fractions per week) to 62 Gy in 20 fractions (4 fractions per week). With a median follow-up of 32 and 35 months, respectively, biochemical control rates at 3 years were 87% and 79% (P=.035) with no significant difference in late urinary or gastrointestinal toxicity [94]. Dearnaley et al [95] recently reported the results of a 3-armed randomized trial comparing 74 Gy in 37 fractions (n=153) to 60 Gy in 20 fractions (n=153) or 57 Gy in 19 fractions (n=151). With a median follow-up of 50.5 months, rates of late gastrointestinal and genitourinary toxicity were similar; tumor control outcomes were not highlighted in this publication. Investigators from Fox Chase Cancer Center compared 76 Gy in 38 fractions to 70.2 Gy in 26 fractions (2.7 Gy/fraction) in 303 patients. Slightly increased acute gastrointestinal toxicity was noted in the hypofractionated arm, but differences were mild [96]. Tumor control outcomes have been presented in abstract form; 5-year biochemical failure rates were 14.4% in the conventional fractionation arm and 13.9% in the hypofractionated arm. Rates of 5-year locoregional failure/distant metastases were about 1.0 and 1.3%, respectively, suggesting the equivalence of the 2 approaches (with limited follow-up) [97]. Investigators at MD Anderson Cancer Center compared 75.6 Gy in 42 fractions with 72 Gy in 30 fractions. Results are available in abstract form and show 5-year biochemical survival rates of 92% and 96%, respectively (P value not significant), although the hypofractionated arm displayed a trend toward higher gastrointestinal toxicity (P=.06) [98]. A Lithuanian group has compared 74 Gy in 37 fractions to 57 Gy in 17 fractions (13 fractions of 3 Gy plus 4 fractions of 4.5 Gy) in 91 patients [99]. The trial is currently ongoing, and data relating to survival metrics have not yet been published, although the PSA nadirs were similar in both cohorts [100].

Randomized reports of more extreme hypofractionation (ie, using fraction sizes of 6-10 Gy) are scant. However, early results of single-arm trials appear promising. As an example, King et al [101] reported outcomes in 67 patients (with a median follow-up of 2.7 years) treated with 36.25 Gy in 5 fractions. RTOG grade 3 bladder and

rectal toxicity were seen in 3% and 0% of patients, respectively. The 4-year biochemical DFS rate was 94%. McBride et al [102] reported on a multi-institutional cohort of 45 patients treated largely with 37.5 Gy in 5 fractions. The 3-year biochemical failure rate was 97.7%. Only 1 and 2 episodes of grade 3 genitourinary and gastrointestinal toxicity occurred, respectively, although unlike in the King et al study, there was a significant late decline in sexual scores and a small, late decline in bowel domain scores.

Despite the theoretical benefits of hypofractionation based on alpha/beta ratios and the obvious benefits with regard to patient convenience, caution should be exerted before recommending hypofractionated radiation in the absence of a clinical trial. As an example, a study of 936 patients with T1-T2 prostate cancer, which randomized patients to 66 Gy in 33 fractions or 52.5 Gy in 20 fractions, found an absolute difference of 7% in 5 year biochemical or clinical failure rates, which were worse in the hypofractionated arm (the confidence intervals for this difference did not include 0) [103]. Although the radiation doses used in this trial would be considered subtherapeutic by contemporary measures, these results do suggest inferior tumor control in the hypofractionated arm. However, another randomized trial using nearly the same treatment regimen (n=217), with patients randomized to 64 Gy in 32 fractions versus 55 Gy in 20 fractions, found improved biochemical control in the hypofractionated arm, with a median follow-up of 90 months [104]. Ultimately, additional randomized studies of contemporary radiation schema are required before definitive conclusions can be made regarding the appropriateness of hypofractionated therapy. At this point, although hypofractionated regimens are convenient for the patient, definitive evidence of the equality or superiority of hypofractionated radiation relative to standard fractionation requires longer term follow-up.

Fortunately, prospective, randomized comparisons involving hypofractionation are being conducted. A Canadian trial is comparing 78 Gy in 39 fractions with 60 Gy in 20 fractions in a cohort of approximately 1,200 men (ISRCTN 43853433), whereas a Dutch trial is comparing 78 Gy in 39 fractions to 64.6 Gy in 19 fractions in approximately 800 men (ISRCTN 85138529). With regard to extreme hypofractionation, a Scandinavian group is comparing 78 Gy in 39 fractions with 42.7 Gy in 7 fractions in approximately 600 men (ISRCTN 45905321) [95]. RTOG trial 09-38 is a randomized Phase II trial that has nearly completed enrollment of 174 patients comparing toxicity between 36.25 Gy in 7 fractions versus 51.6 Gy in 12 fractions. Therefore, within the following several years, additional data on the efficacy and safety of hypofractionated radiation regimens will be available.

Summary

- In retrospective series, definitive EBRT for the treatment of stage T1 and T2 prostate cancer appears to be as effective as other treatment modalities (eg, radical prostatectomy and brachytherapy).
- Dose escalation using IMRT has an improved therapeutic ratio with improved PSA relapse-free survival rates and reduced gastrointestinal and genitourinary toxicity.
- The role of pelvic lymph node irradiation for T1/T2 prostate cancer with a 15% or greater risk of having positive pelvic lymph nodes is controversial.
- ADT is generally not appropriate in low-risk prostate cancer (except possibly in cytoreduction of large prostates or in the presence of select adverse features such as >50% of positive biopsies) and improves survival in intermediate- and high-risk disease. Whether high-dose radiation will obviate the need for ADT in select intermediate-risk patients is being studied. A patient's comorbidity level may impact the benefit of ADT.
- The "Phoenix definition," a post-treatment rise of PSA ≥2 ng/mL above the nadir PSA, is considered biochemical failure following EBRT. This, however, can be confounded by a PSA bounce that can occur in up to 25% of men 12–24 months after treatment. Therefore, caution must be exercised in declaring failure following prostate irradiation.
- There are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment.
- There are growing data to suggest that hypofractionation at dose-per-fraction less the 3.0 Gy per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/SBRT studies at dose-per-fraction greater the 4.0 Gy appear promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed.

- The use of oral erectogenic medication is beneficial for some patients with erectile dysfunction after irradiation for prostate cancer.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition: **Definitive External-Beam Irradiation in Stage T1 and T2 Prostate Cancer**

Variant 1: **60-year-old man, asymptomatic in PSA screening program. PSA 5.2 ng/mL. Prostate within normal limits. No palpable lesions. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3+3=6. Metastatic workup negative.**

Treatment	Rating	Comments
External-beam radiation therapy alone (EBRT)	8	
EBRT with brachytherapy boost	3	This treatment might only be considered if highly adverse features are present, such as >50% of cores positive.
EBRT with short course (4–6 months) androgen ablation	3	This treatment might only be considered if highly adverse features are present, such as >50% of cores positive.
EBRT with long course (2–3 years) androgen ablation	1	
Inclusion of pelvic nodes (44–50.4Gy) in radiation field	2	
Addition of taxane-based chemotherapy	1	
Prostate Dose (conventional fractionation)		
>81 Gy	4	Perform this treatment only if standard dose constraints can be met.
78–81 Gy	8	
>75–<78 Gy	8	
>73–75 Gy	6	
70–73 Gy	3	This dose level is awaiting survival results from RTOG 0126.
Hypofractionated EBRT		
70 Gy in 2.5 or 2.7 Gy fractions	5	
Hypofractionation using 3.0–4.3 Gy per fraction	5	Ideally on trial.
SBRT (in the range of 6.7–7.25 Gy per fraction for 5 fractions)	4	Ideally on trial.
External-Beam Treatment Plan		See the ACR Appropriateness Criteria® topic on "External-Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer."
IMRT	8	
Proton therapy	7	
3-D-CT based plan	6	
2-D plan	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Definitive External-Beam Irradiation in Stage T1 and T2 Prostate Cancer**

Variant 2: **69-year-old generally healthy man. Screening PSA 15.2. Gleason score 4+3 in 3/6 cores on the right, 1/6 on the left. cT2a on examination.**

Treatment	Rating	Comments
External-beam radiation therapy alone (EBRT)	7	
EBRT with brachytherapy boost	8	The role of brachytherapy is discussed in the ACR Appropriateness Criteria® topic on "High Dose Rate Brachytherapy for Prostate Cancer."
EBRT with short course (4–6 months) androgen ablation	8	
EBRT with long course (2–3 years) androgen ablation	4	This treatment may be more appropriate if radiographic staging suggests higher risk disease.
Inclusion of pelvic nodes (44–50.4 Gy) in radiation field	4	
Addition of taxane-based chemotherapy	1	
Prostate Dose (conventional fractionation)		
>81 Gy	4	Perform this treatment only if standard dose constraints can be met.
78–81 Gy	8	
>75–<78 Gy	7	
>73–75 Gy	5	
70–73 Gy	3	
Hypofractionated EBRT		
70 Gy in 2.5 or 2.7 Gy fractions	5	
Hypofractionation using 3.0–4.3 Gy per fraction	5	Ideally on trial.
SBRT (in the range of 6.7–7.25 Gy per fraction for 5 fractions)	4	Ideally on trial.
External-Beam Treatment Plan		See the ACR Appropriateness Criteria® topic on "External-Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer."
IMRT	9	
Proton therapy	7	
3-D-CT based plan	6	
2-D plan	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Definitive External-Beam Irradiation in Stage T1 and T2 Prostate Cancer**

Variant 3: **69-year-old man with long-standing history of coronary disease and diabetes. Myocardial infarction 3 years ago required percutaneous stenting, but since then his cardiac status has been stable. Screening PSA 15.2. Gleason score 4+3 in 3/6 cores on the right, 1/6 on the left. cT2a on examination.**

Treatment	Rating	Comments
External-beam radiation therapy alone (EBRT)	7	
EBRT with brachytherapy boost	8	
EBRT with short course (4–6 months) androgen ablation	7	
EBRT with long course (2–3 years) androgen ablation	3	
Inclusion of pelvic nodes (44–50.4 Gy) in radiation field	4	
Addition of taxane-based chemotherapy	1	
Prostate Dose (conventional fractionation)		
>81 Gy	4	
78–81 Gy	8	
>75–<78 Gy	7	
>73–75 Gy	5	
70–73 Gy	3	
Hypofractionated EBRT		
70 Gy in 2.5 or 2.7 Gy fractions	5	
Hypofractionation using 3.0–4.3 Gy per fraction	5	Ideally on trial.
SBRT (in the range of 6.7–7.25 Gy per fraction for 5 fractions)	4	Ideally on trial.
External-Beam Treatment Plan		See the ACR Appropriateness Criteria® topic on "External-Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer."
IMRT	9	
Proton therapy	7	
3-D-CT based plan	6	
2-D plan	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Definitive External-Beam Irradiation in Stage T1 and T2 Prostate Cancer**

Variant 4: **70-year-old man who presented with a 3-year history of moderate dysuria, urinary frequency, and nocturia. Rectal examination shows prostate 1.5 normal size. PSA 36 ng/mL. 12 needle biopsy of prostate shows adenocarcinoma. Gleason score 4+4=8 in both right and left lobes, totaling 7 cores. Metastatic workup negative.**

Treatment	Rating	Comments
External-beam radiation therapy alone (EBRT)	2	
EBRT with brachytherapy boost alone	4	
EBRT with brachytherapy boost and androgen ablation	8	
EBRT with short course (4–6 months) androgen ablation	5	
EBRT with long course (2–3 years) androgen ablation	8	
Inclusion of pelvic nodes (44–50.4 Gy) in radiation field	6	
Addition of taxane-based chemotherapy	3	
Prostate Dose (conventional fractionation)		
>81 Gy	6	
78–81 Gy	8	
>75–<78 Gy	7	
>73–75 Gy	4	
70–73 Gy	3	
Hypofractionated EBRT		
70 Gy in 2.5 or 2.7 Gy fractions	5	
Hypofractionation using 3.0–4.3 Gy per fraction	4	Ideally on trial.
SBRT (in the range of 6.7–7.25 Gy per fraction for 5 fractions)	3	Ideally on trial.
External-Beam Treatment Plan		See the ACR Appropriateness Criteria® topic on "External-Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer."
IMRT	9	
Proton therapy	6	Perform this treatment only if seminal vesicles can be covered and constraints met.
3-D-CT based plan	5	
2-D plan	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**