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ASTRO Guideline

Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline

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Abstract

Purpose: The aim of this guideline is to present recommendations regarding moderately hypofractionated (240-340 cGy per fraction) and ultrahypofractionated (500 cGy or more per fraction) radiation therapy for localized prostate cancer.

Methods and Materials: The American Society for Radiation Oncology convened a task force to address 8 key questions on appropriate indications and dose-fractionation for moderately and ultrahypofractionated radiation therapy, as well as technical issues, including normal tissue dose constraints, treatment volumes, and use of image guided and intensity modulated radiation therapy. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and Society-approved tools for grading evidence quality and recommendation strength.

Results: Based on high-quality evidence, strong consensus was reached for offering moderate hypofractionation across risk groups to patients choosing external beam radiation therapy. The task force conditionally recommends ultrahypofractionated radiation may be offered for low- and intermediate-risk prostate cancer but strongly encourages treatment of intermediate-risk patients on a clinical trial or multi-institutional registry. For high-risk patients, the task force conditionally recommends against routine use of ultrahypofractionated external beam radiation therapy. With any hypofractionated approach, the task force strongly recommends image guided radiation therapy and avoidance of nonmodulated 3-dimensional conformal techniques.

Conclusions: Hypofractionated radiation therapy provides important potential advantages in cost and convenience for patients, and these recommendations are intended to provide guidance on moderate hypofractionation and ultrahypofractionation for localized prostate cancer. The limits in the current evidentiary base—especially for ultrahypofractionation—highlight the imperative to support large-scale randomized clinical trials and underscore the importance of shared decision making between clinicians and patients.

Introduction

External beam radiation therapy (EBRT) is a standard definitive treatment for men with localized prostate cancer.[1] The probability of cell survival after a dose of ionizing radiation is governed by the linear-quadratic model, in which curves of cell survival as a function of dose have an initial linear component followed by a steeper quadratic component. The relative weighting of each component, and thus the sensitivity of the irradiated

tissue to fractionation, is characterized by the alpha-beta ratio. The alpha-beta ratio of prostate adenocarcinoma is considered low compared with most neoplasms,[2] whereas that of adjacent dose-limiting normal structures has been estimated to be greater than that of prostate cancer.[3,4] An implication of this relationship is that hypofractionation, daily delivery with fraction sizes >200 cGy, may improve the therapeutic ratio of EBRT in localized prostate cancer.

In this guideline, hypofractionation is subdivided into moderate hypofractionation (fraction size 240-340 cGy) and ultrahypofractionation (fraction size ≥500 cGy). These are pragmatic definitions reflecting 2 distinct approaches to hypofractionation that have emerged in clinical practice. The fraction size gap created by these definitions (ie, >340 cGy but <500 cGy) represents a little-studied range that is outside of the scope of this document. Conventional fractionation is defined as a fraction size of 180 to 200 cGy.

These recommendations apply to men who require or prefer treatment instead of active surveillance and who have opted for EBRT instead of other treatment options.

This Executive Summary introduces the guideline and its recommendations. See the full-text guideline in the Supplementary Materials (available online at 10.1016/j.prro.2018.08.002) for discussion of the evidence underpinning the recommendations.

This guideline is endorsed by the Society of Urologic Oncology, the European Society for Radiotherapy & Oncology (ESTRO), and the Royal Australian and New Zealand College of Radiologists.

Methods and Materials

Process

The American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and American Urological Association proposed an evidence-based guideline on hypofractionated EBRT in localized prostate cancer, which was approved by the ASTRO Board of Directors in October 2016. A task force of radiation oncologists, medical physicists, and urologic surgeons/oncologists from academic settings, community practice, and the Veterans Affairs system was recruited. A radiation oncology resident and a patient representative were also included.

Through conference calls and emails, the task force and ASTRO staff refined the key questions (KQs), completed the literature review, and formulated recommendation statements and narratives. The draft was reviewed by 6 expert reviewers (see the Acknowledgments) and ASTRO legal counsel and was placed online for public comment in October and November 2017. The final guideline was approved by the 3 societies. The ASTRO Guidelines Subcommittee will monitor this guideline for updating because additional data have been published and presented since the end of the literature review, and an update in the near term is anticipated.

Literature review

The guideline was based on a systematic literature review in MEDLINE PubMed of English-language studies published between December 1, 2001 and March 31, 2017. Both Medical Subject Headings terms and text words were used, and hand searches supplemented the electronic searches. Included studies evaluated men with localized prostate cancer receiving hypofractionated EBRT to the prostate with or without the seminal vesicles. Outcomes of interest were prostate cancer control (biochemical and clinical recurrence-free survival, disease-specific survival, and overall survival), acute and late toxicity, and quality of life. Studies concerning radiation to the pelvic lymph nodes were outside the scope. For moderate hypofractionation, only randomized controlled trials (RCTs) or meta-analyses of RCTs were included. For ultrahypofractionation, RCTs, meta-analyses, and prospective observational studies with ≥50 patients were accepted. In total, 480 abstracts were screened; 419 were eliminated, and 61 were included and abstracted.

Abstracts from ASTRO, ASCO, ESTRO, and European Cancer Organisation meetings between January 2014 and January 2017 fulfilling the inclusion criteria were also identified. They could be discussed in the narrative but were not used to support recommendations.

Grading of evidence, recommendations, and consensus methodology

Recommendation statements were developed using a modified Grading of Recommendations Assessment, Development, and Evaluation method[5,6] and were based on high-quality data supplemented by expert opinion when necessary. Recommendations were classified as strong or conditional. A strong recommendation indicates the task force was confident the benefits of the intervention clearly outweighed the harms, or vice versa, and "all or almost all informed people would make the recommended choice." Conditional recommendations were made when risks and benefits were even or uncertain and "most informed people would choose the recommended course of action, but a substantial number would not," suggesting a strong role for shared decision-making.[5] The quality of evidence underlying each recommendation was categorized as follows:

- "High: We are very confident that the true effect lies close to that of the estimate of the effect,

- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different,
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect,
- Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate."[6]

Task force consensus on the recommendations was evaluated through a modified Delphi approach adapted from the ASCO process.[7] In an online survey, task force members rated their agreement with each recommendation on a 5-point Likert scale, ranging from strongly disagree to strongly agree. A prespecified threshold of $\geq$75% of raters selecting "agree" or "strongly agree" indicated consensus. If a recommendation did not meet this threshold, it was edited and resurveyed. Recommendations that achieved consensus that were modified after the first round were also resurveyed.

Results

KQ 1: In patients with localized prostate cancer who are candidates for EBRT, how does moderately hypofractionated EBRT (240-340 cGy per fraction) compare to conventionally fractionated EBRT (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life, based on

- **Prostate cancer risk stratification group?**
- **Patient age, comorbidity, anatomy (eg, prostate gland volume), and baseline urinary function?**

Prostate cancer control outcomes: Impact of risk stratification group

Statement KQ1A: In men with low-risk prostate cancer who decline active surveillance and receive EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 100%

Statement KQ1B: In men with intermediate-risk prostate cancer receiving EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 100%

Statement KQ1C: In men with high-risk prostate cancer receiving EBRT to the prostate, but not including pelvic lymph nodes, moderate hypofractionation should be offered.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

Four large, prospective, RCTs with over 6000 patients, as well as additional single-institution randomized trials, demonstrate that EBRT to the prostate using moderate hypofractionation provides prostate cancer control similar to that of EBRT delivered using conventional fractionation.

Prostate cancer control outcomes: Impact of patient age, comorbidity, anatomy, and urinary function

Statement KQ1D: In patients who are candidates for EBRT, moderate hypofractionation should be offered regardless of patient age, comorbidity, anatomy, or urinary function. However, physicians should discuss the limited follow-up beyond 5 years for most existing RCTs evaluating moderate hypofractionation.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

Toxicity and quality of life

Statement KQ1E: Men should be counseled about the small increased risk of acute gastrointestinal (GI) toxicity with moderate hypofractionation. Moderately hypofractionated EBRT has a similar risk of acute and late genitourinary and late GI toxicity compared with conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond 5 years for most existing RCTs evaluating moderate hypofractionation.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 100%

KQ 2: In patients with localized prostate cancer who are candidates for EBRT, how do moderately hypofractionated EBRT regimens used in clinical trials compare in terms of prostate cancer control, toxicity, and quality of life, and can particular regimens be recommended based on prostate cancer risk stratification group, age, comorbidity, anatomy (eg, prostate gland volume), and baseline urinary function?

Statement KQ2A: Regimens of 6000 cGy delivered in 20 fractions of 300 cGy and 7000 cGy delivered in 28 fractions of 250 cGy are suggested since they are supported by the largest evidentiary base. One optimal regimen cannot be determined because most of the multiple fractionation schemes evaluated in clinical trials have not been compared head to head.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Statement KQ2B: One moderately hypofractionated regimen is not suggested over another for cancer control for specific risk groups, and the efficacy of moderately hypofractionated EBRT regimens does not appear to be affected by patient age, comorbidity, anatomy, or urinary function.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Multiple moderately hypofractionated regimens have been evaluated in RCTs, including 6000 cGy in 20 fractions of 300 cGy and 7000 cGy in 28 fractions of 250 cGy. Significant differences in the populations enrolled in the trials, endpoint definitions, and use of concomitant androgen deprivation therapy preclude across-trial comparisons of the efficacy of the various regimens.

KQ 3: In patients with localized prostate cancer who are candidates for EBRT, how does ultrahypofractionated EBRT (≥500 cGy per fraction) compare to conventionally fractionated EBRT (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ3A: In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 88%

Statement KQ3B: In men with intermediate-risk prostate cancer receiving EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation. The task force strongly encourages that these patients be treated as part of a clinical trial or multi-institutional registry.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Statement KQ3C: In men with high-risk prostate cancer receiving EBRT, the task force does not suggest offering ultrahypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Several prospective, nonrandomized studies have documented the safe delivery of ultrahypofractionation for patients with localized prostate cancer. No prospective studies comparing ultrahypofractionated and conventionally fractionated EBRT in intermediate- and high-risk prostate cancer with published efficacy data were identified.

KQ 4: In patients with localized prostate cancer who are candidates for EBRT, how do ultrahypofractionated EBRT regimens used in clinical trials compare in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ4A: Ultrahypofractionated prostate EBRT of 3500 to 3625 cGy in 5 fractions of 700 to 725 cGy to the planning target volume may be offered to low- and intermediate-risk patients with prostate sizes less than 100 cm^3. The key dose constraints in KQ5B should be followed.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 88%

Statement KQ4B: Five-fraction prostate ultrahypofractionation at doses above 3625 cGy to the planning target volume is not suggested outside the setting of a clinical trial or multi-institutional registry due to risk of late toxicity.

- **Strength of recommendation**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Statement KQ4C: Five-fraction prostate ultrahypofractionation using consecutive daily treatments is not suggested due to potential increased risk of late urinary and rectal toxicity.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Very low
- **Consensus:** 100%

The evidentiary base is largest for regimens of 3500 cGy in 5 fractions of 700 cGy or 3625 cGy in 5 fractions of 725 cGy, and these regimens have been shown to be well tolerated with acceptable rates of biochemical control.

KQ 5: In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how do normal tissue constraints used in clinical trials compare in terms of toxicity and quality of life?

Statement KQ5A: At least 2 dose-volume constraint points for rectum and bladder should be used for moderately or ultrahypofractionated EBRT: one at the high-dose end (near the total dose prescribed) and one in the mid-dose range (near the midpoint of the total dose).

- **Strength of recommendation:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Statement KQ5B: Use of normal tissue constraints for moderately or ultrahypofractionated EBRT that differ from those of a published reference study is not recommended due to the risk of both acute and late toxicity.

- **Strength of recommendation:** Strong
- **Quality of evidence:** Low
- **Consensus:** 100%

KQ 6: In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how do treatment volumes used in clinical trials compare in terms of prostate cancer control and toxicity?

Statement KQ6A: Use of target volume and associated margin definitions for hypofractionated EBRT that deviate from those of a published reference study is not recommended, especially for ultrahypofractionated regimens.

- **Strength of recommendation:** Strong
- **Quality of evidence:** Low
- **Consensus:** 100%

Given substantial variation in target volume and margin definitions among reports of moderately hypofractionated or ultrahypofractionated EBRT, data are lacking to compare their impact on prostate cancer control and toxicity.

KQ 7: In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using image guided radiation therapy (IGRT) compare to treatment not using IGRT in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ7A: IGRT is universally recommended when delivering moderately or ultrahypofractionated EBRT.

- **Strength of recommendation**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

The vast majority of moderately hypofractionated and ultrahypofractionated EBRT reports have used IGRT, and it is considered central to the safe and effective delivery of hypofractionated regimens.

KQ 8: In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using IMRT compare to treatment with 3-dimensional conformal radiation therapy (3-D CRT) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ8A: Nonmodulated 3-D CRT techniques are not recommended when delivering moderately fractionated or ultrahypofractionated prostate EBRT.

- **Strength of recommendation:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Conclusion

This evidence-based guideline was developed to make recommendations on moderately and ultrahypofractionated EBRT for localized prostate cancer. Several large-scale RCTs demonstrate that moderate hypofractionation confers prostate cancer control outcomes and rates of late toxicity similar to those of conventional fractionation. Moderate hypofractionation holds important potential advantages for patient convenience and resource utilization. Based on this high-quality evidence, task force consensus was reached that moderately hypofractionated radiation therapy should be offered to patients who choose EBRT for treatment of prostate cancer. Although there is limited follow-up beyond 5 years in completed trials, the task force nonetheless concluded that the existing evidentiary base is sufficiently robust to justify routine use of moderate hypofractionation. Future updates to this guideline will discuss longer-term results from completed trials of moderate hypofractionation.

The task force reached a weaker consensus for ultrahypofractionated radiation therapy. To date, the evidentiary base consists largely of prospective, single-arm trials in low-risk and, to a lesser extent, intermediate-risk localized disease and with limited follow-up. No published efficacy data from RCTs are currently available. The recommendation for ultrahypofractionation in low-risk localized prostate cancer was graded as conditional, reflecting only moderate-quality evidence and the

remaining uncertainty in the balance between benefit and risk for this treatment strategy. The recommendation for ultrahypofractionated EBRT in intermediate-risk prostate cancer is also graded as conditional. However, because the evidentiary base is weaker than that in low-risk disease, support of clinical trials and multi-institutional registries in this population is strongly encouraged. The task force conditionally recommended against the routine use of ultrahypofractionated radiation in high-risk localized prostate cancer and escalation in dose beyond 3625 cGy with 5-fraction regimens outside of clinical trials.

When either moderately or ultrahypofractionated EBRT is undertaken, meticulous attention to the technical aspects of treatment planning and delivery are important, and the task force strongly recommends use of IGRT and avoidance of nonmodulated 3-D CRT techniques. The task force advocates the general principle that to confidently replicate the results of a published reference study, the approach used in that study should be followed to the extent possible.

The conditional recommendations regarding ultrahypofractionation underscore the importance of shared decision-making between clinicians and patients in this setting. The decision to use ultrahypofractionated radiation therapy should follow a detailed discussion of the uncertainties in the risk-benefit balance for this treatment approach and should be informed at all stages by the patient's values and preferences.

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Supplementary Materials

The full guideline is included as supplementary material (available online at https://doi.org/10.1016/j.prro.2018.08.002).

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