Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

Morgan, et al.
EBRT is a standard definitive treatment for men with localized prostate cancer.

Hypofractionation may improve therapeutic ratio of EBRT due to differences in alpha-beta ratio of prostate cancer versus that of adjacent normal tissue.

There are recent large RCTs comparing conventional with moderate hypofractionation and population-based studies observing increasing use of ultrahypofractionated EBRT.

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

Studies concerning hypofractionated delivery of EBRT to the pelvic lymph nodes were beyond the scope of the guideline.
Guideline Development Methodology

The ASTRO/ASCO/AUA guideline process includes:

• a systematic literature review by ASTRO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• Modified Delphi process to determine consensus ratings
• final guideline approval by ASTRO, ASCO, and AUA

The full guideline methodology can be found at:
www.asco.org/genitourinary-cancer-guidelines
Key Questions

▪ Key Question 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 (e.g., prostate gland volume), and baseline urinary function?

▪ Key Question 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 (e.g. prostate gland volume), and baseline urinary function?
Key Questions

- **Key Question 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?

- **Key Question 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?

- **Key Question 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?
Key Questions

- **Key Question 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?

- **Key Question 7:** In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using IGRT compare to treatment not using IGRT in terms of prostate cancer control, toxicity, and quality of life?

- **Key Question 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-D CRT in terms of prostate cancer control, toxicity, and quality of life?
KEY QUESTION 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 (e.g., prostate gland volume), and baseline urinary function?

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%)
Summary of Recommendations

**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%)

**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 five years for most existing RCTs evaluating moderate hypofractionation. (Recommendation strength: Strong; Quality of evidence: High; Consensus: 94%)
Summary of Recommendations

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 (GU) and late GI toxicity compared to conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond five years for most existing RCTs evaluating moderate hypofractionation. (Recommendation strength: Strong; Quality of evidence: High; Consensus: 100%)
Summary of Recommendations

KEY QUESTION 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 (e.g. 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 since 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 impacted by patient age, comorbidity, anatomy, or urinary function. (Recommendation strength: Conditional; Quality of evidence: Moderate; Consensus: 100%)
Summary of Recommendations

KEY QUESTION 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. (Recommendation strength: 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. (Recommendation strength: 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. (Recommendation strength: Conditional; Quality of evidence: Low; Consensus: 94%)

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Summary of Recommendations

KEY QUESTION 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. (Recommendation strength: 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. (Recommendation strength: 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. (Recommendation strength: Conditional; Quality of evidence: Very Low; Consensus: 100%)
KEY QUESTION 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 two 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). (Recommendation strength: 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. (Recommendation strength: Strong; Quality of evidence: Low; Consensus: 100%)
KEY QUESTION 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. (Recommendation strength: Strong; Quality of evidence: Low; Consensus: 100%)
Summary of Recommendations

KEY QUESTION 7
In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using 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. (Recommendation strength: Strong; Quality of evidence: Moderate; Consensus: 100%)
Summary of Recommendations

KEY QUESTION 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
Non-modulated 3-D CRT techniques are not recommended when delivering moderately or ultrahypofractionated prostate EBRT. (Recommendation strength: Strong; Quality of evidence: Moderate; Consensus: 100%)
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/genitourinary-cancer-guidelines

Patient information is available at www.cancer.net
## Guideline Panel Members

<table>
<thead>
<tr>
<th>Name (and designation)</th>
<th>Affiliation/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard Sandler, MD, Co-Chair</td>
<td>Cedars-Sinai Medical Center, Los Angeles, CA, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Scott C. Morgan, MD, MSc, Co-Chair</td>
<td>The Ottawa Hospital and University of Ottawa, Ottawa, ON, Canada, Division of Radiation Oncology</td>
</tr>
<tr>
<td>Karen Hoffman, MD, MHSc, MPH</td>
<td>MD Anderson Cancer Center, Houston, TX, Department of Radiation Oncology</td>
</tr>
<tr>
<td>D. Andrew Loblaw, MD, MSc</td>
<td>Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Mark Buyyounouski, MD, MS</td>
<td>Stanford University, Stanford, CA and Palto Alto VA Health System, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Daniel Barocas, MD, MPH</td>
<td>Vanderbilt University Medical Center, Nashville, TN, Department of Urologic Surgery</td>
</tr>
<tr>
<td>Soren Bentzen, DSc, PhD</td>
<td>University of Maryland School of Medicine, Baltimore, MD, Division of Biostatistics and Bioinformatics</td>
</tr>
<tr>
<td>Michael Chang, MD</td>
<td>Hunter Holmes McGuire VA Medical Center and Virginia Commonwealth University, Richmond, VA, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Jason Efstathiou, MD, PhD</td>
<td>Massachusetts General Hospital, Boston MA, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Patrick Greany, PhD</td>
<td>Patient representative, Tallahassee, FL</td>
</tr>
<tr>
<td>Per Halvorsen, MS</td>
<td>Lahey Hospital and Medical Center, Burlington, MA, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Bridget Koontz, MS</td>
<td>Duke University Medical Center, Durham, NC, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Colleen Lawton, MD</td>
<td>Medical College of Wisconsin, Milwaukee, WI, Department of Radiation Oncology</td>
</tr>
<tr>
<td>C. Marc Leyrer, MD</td>
<td>Wake Forest University, Winston-Salem, NC, Department of Radiation Oncology</td>
</tr>
<tr>
<td>Daniel Lin, MD</td>
<td>University of Washington, Seattle, WA, Department of Urology</td>
</tr>
<tr>
<td>Michael Ray, MD, PhD</td>
<td>Radiology Associates of Appleton, ThedaCare Regional Cancer Center, Appleton, WI</td>
</tr>
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</table>

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