Impact of Real-time Tumor Tracking and Fraction Size on Treatment-related Morbidity in Prostate Cancer Patients Treated with Intensity-modulated Radiotherapy

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Introduction

- Radiation therapy relies on accurately delivering dose to tumor located inside of the body
- Tracking position of target (millimeter accuracy):
  - conventional targeting based on x-rays taken prior to each treatment and localizing Gold markers placed in tumor (because soft-tissue, e.g. prostate, is not visible)
  - Calypso® real-time tumor tracking technology which allows in-treatment tracking based on electromagnetic signal emitted by implanted beacons

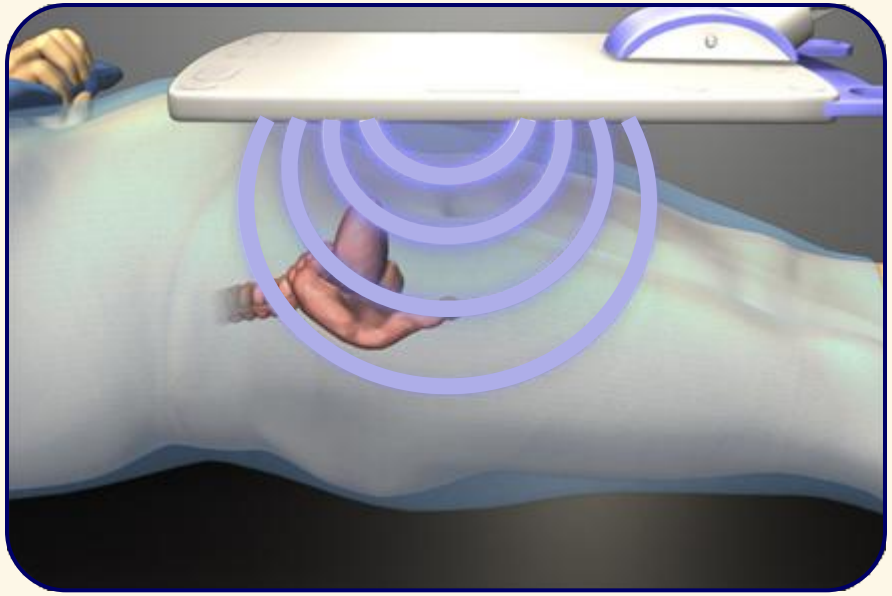
Implantable Golden Markers "Gold Seeds"

- 5 mm long
- Made of gold or other inert material
- 3 seeds are placed into the prostate

Implanted “Gold Seeds”

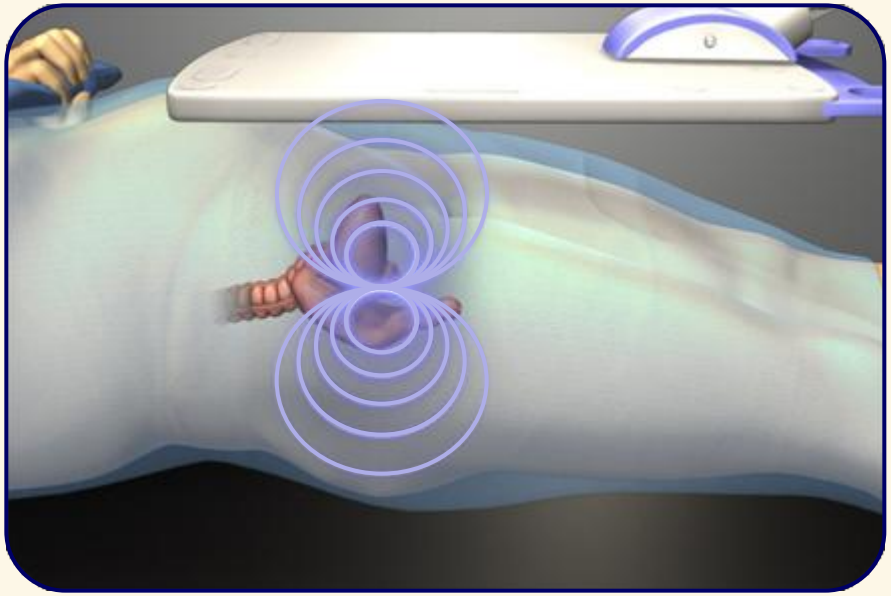
Calypso® Real-time Tumor Tracking

Electromagnetic array sends pulses of electromagnetic energy to beacons



Step 1

Beacons return electromagnetic signal to the array



Step 2

Electromagnetics Locate and Track Continuously

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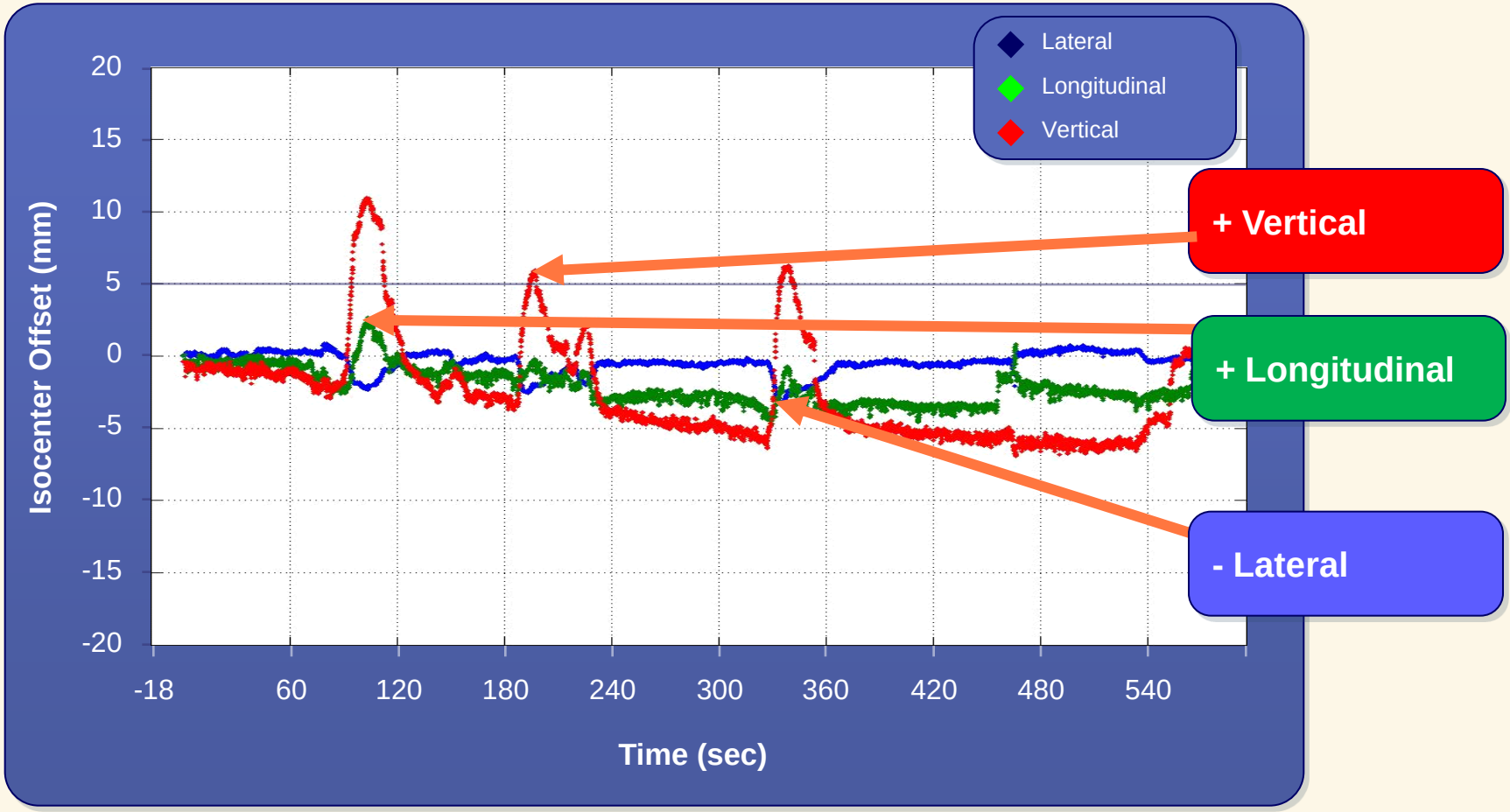
3D Intrafraction Motion



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Proposed Study

Specific Aim #1: Compare treatment-related urinary morbidity in patients treated with two different modalities of tumor tracking, Gold fiducials & Calypso systems.

Specific Aim #2: Similarly compare standard and hypofractionated regimens of radiotherapy where biological dose is the same:

- Standard fractionation is 39 treatments
- Hypofractionation is 28 treatments, larger dose per day

Hypothesis:

1. Real-time tumor tracking should enable reduced normal tissue toxicity by ensuring that target volume is always within radiation treatment field.
2. Hypofractionation will result in more acute urinary symptoms.

Study Design

- **Retrospective cohort study**
- **Inclusion criteria:**

  1) histologically confirmed cancer of the prostate gland
  2) underwent curative radiotherapy at OHSU between June, 2007 & April, 2011
  3) either Gold seeds or Calypso used for tumor tracking

- **Exclusion Criteria:**

  1) any surgical treatment for prostate cancer prior to or concurrent with radiotherapy

Study Design

- **Total 261 patients enrolled**
- **Gold seeds cohort: 87**
  Standard – 56
  Hypofractionated – 31
- **Calypso cohort: 174**
  Standard – 107
  Hypofractionated – 67
- **Median follow-up - 23 mo (range: 6-42 mo)**
- **Same physician & treatment planning team**

Measured Outcomes

- American Urological Association (AUA) BPH symptom score (primary outcome)
- Nocturia score
- Prevalence of urinary incontinence
- Use of alpha-blockers

AUA BPH Score Index

Measures frequency of 7 urinary symptoms:

- Incomplete emptying
- Frequency
- Intermittency
- Urgency
- Weak stream
- Straining
- Nocturia

➢ Total score 0-35: the higher the score - the more symptoms the patient experiences

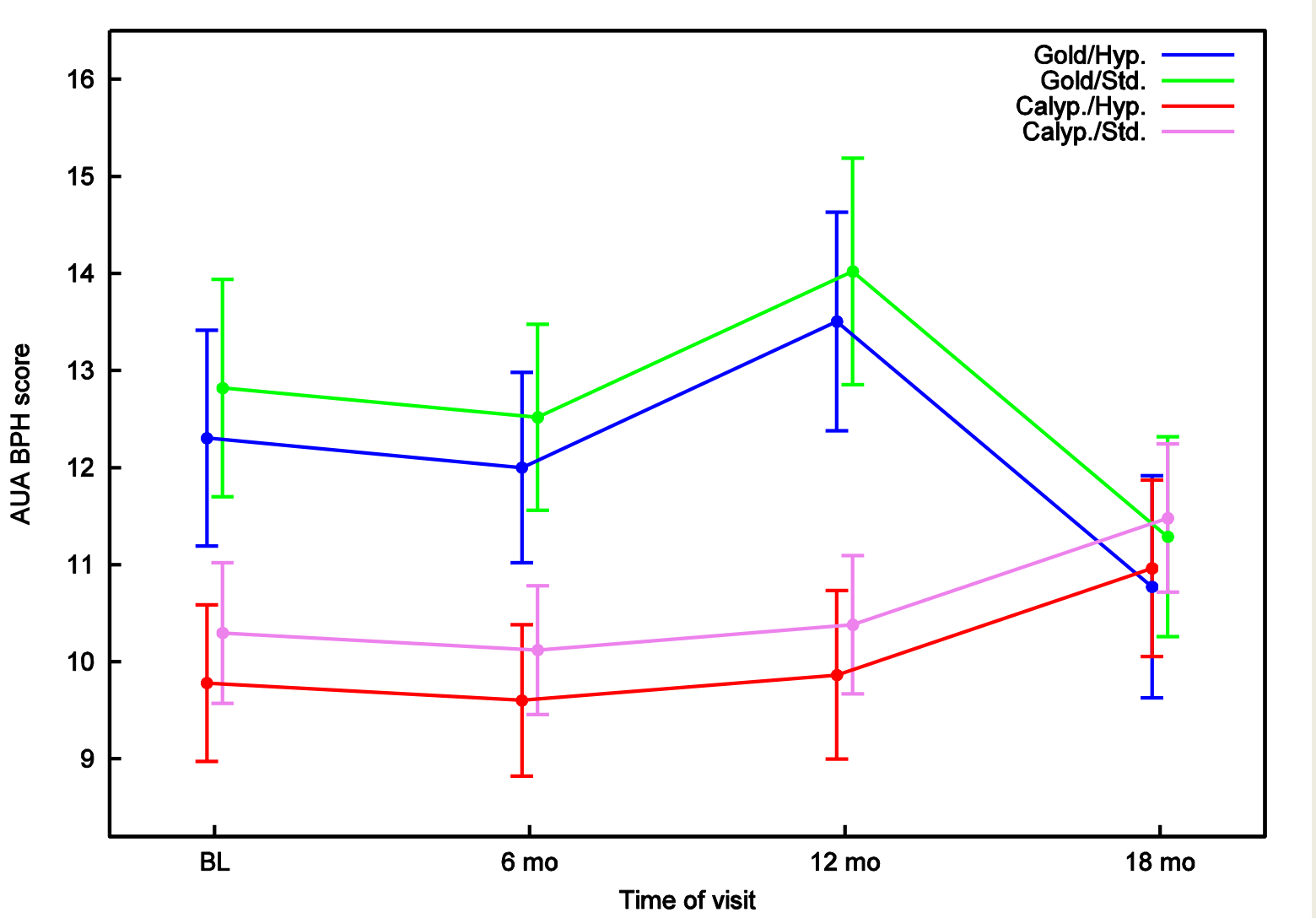
Statistical Analysis

- **Generalized estimating equation** models for continuous variables
  - accounts for repeated measures taken on the same subject over time
- **Chi-squared statistics & test of proportions** for binomial variables

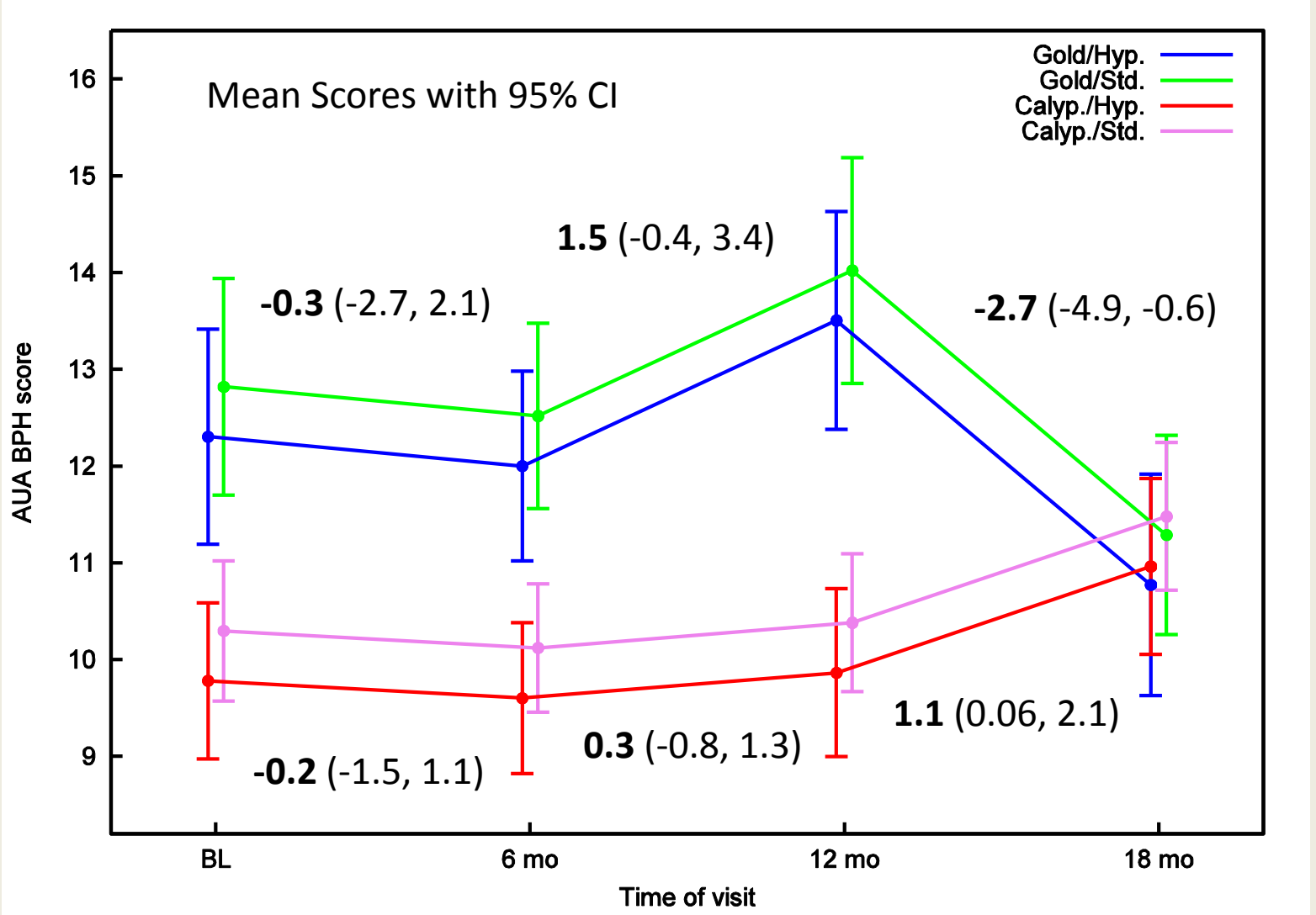
Results: AUA BPH Score

- Statistical model included adjustment for age (centered at 65 y.o.)
- Changes over time were influenced by tumor tracking modality ($p=0.014$) but not by treatment regimen ($p=0.36$)

Results: AUA BPH Score



Results: AUA BPH Score

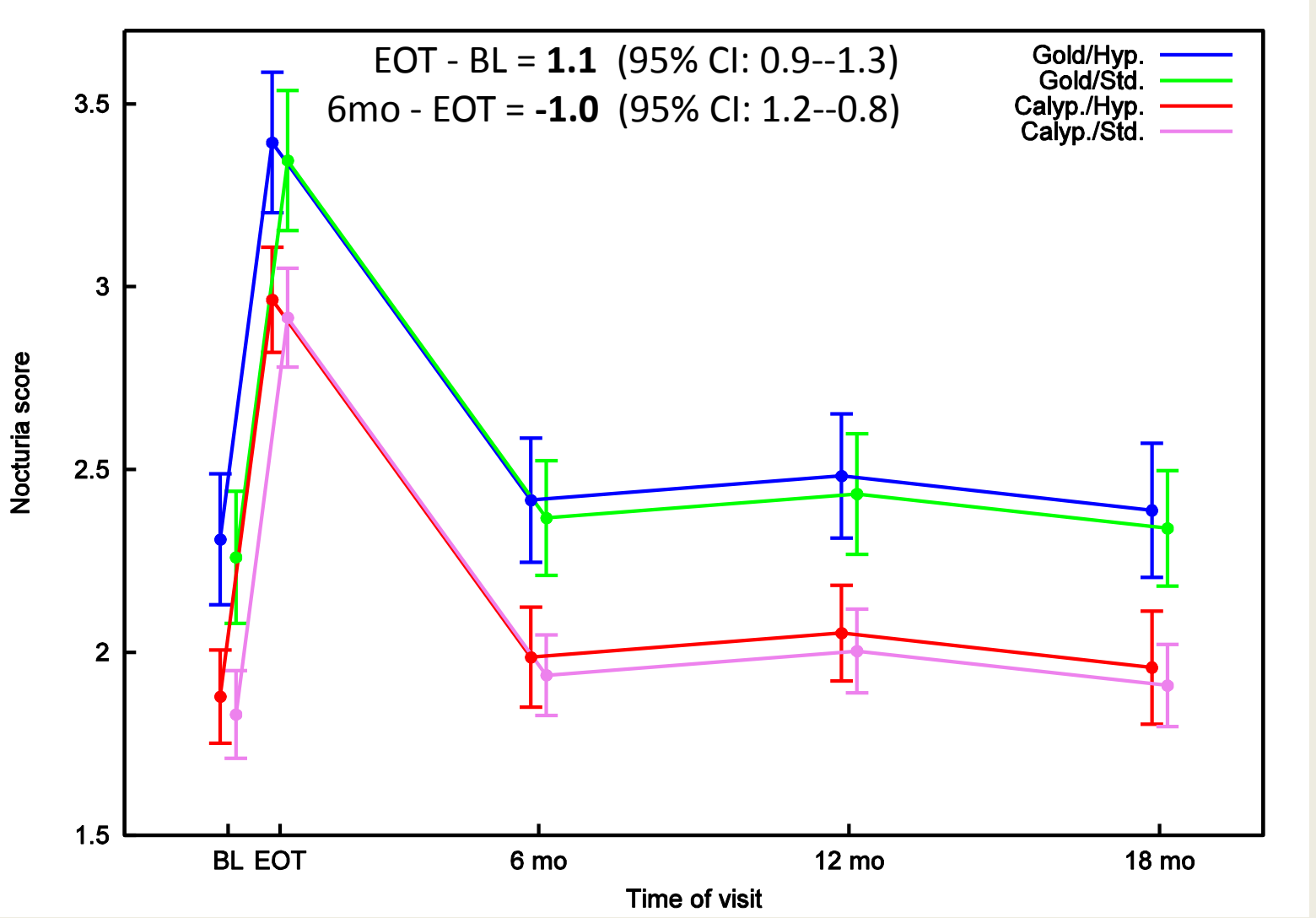


Results: AUA BPH Score

At 18 mo:

- neither modality showed any significant change relative to baseline (BL):
  - 1.2 unit increase in Calypso cohort, p=0.13
  - 1.5 unit decrease in Gold seeds cohort, p=0.28
- the net difference between the cohorts was not significant (2.7 points, p=0.09)

Results: Nocturia Score



Results: Alpha-Blocker Use

After adjustment for age,

- Odds of alpha-blocker use did not separate according to treatment regimen (p=0.84)
- However, odds of alpha-blocker use for Gold seeds patients were 34% (95% CI: 2--56%) greater than the odds for Calypso patients

Results: Urinary Incontinence

No difference in prevalence **at baseline**

Period prevalence **during follow-up:**

- 27 (95% CI: 12.9--41.3) percentage points greater in Gold seeds cohort compared to Calypso cohort among subjects treated with standard treatment regimen ($p<0.0001$)
- No difference between treatment regimens

Discussion

- No difference in urinary toxicity between standard and hypofractionated regimens
- The observed difference between Gold seeds and Calypso cohorts at 12 months is statistically significant but **clinically insignificant** (only 1 AUA BPH point)
- By 18 months, urinary morbidity returned to BL in both cohorts, and there was no difference between the cohorts

Discussion (continued)

- However, more patients in Gold seeds cohort, compared to Calypso cohort,
  - needed an alpha-blocker
    (odds were 34% higher for Gold seeds patients)
  - developed urinary incontinence
    (preval. was 27 pp higher in Gold seeds cohort)

Conclusions

Even though there was no clinically significant difference between treatment groups in changes of the AUA BPH and nocturia scores over time, a higher need for alpha-blockers and a higher period prevalence of urinary incontinence in Gold seeds cohort suggests a higher urinary toxicity of a tumor tracking method that utilizes golden fiducials, as compared to real-time tumor tracking.

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Questions ???