Randomized Controlled Trial of Hypofractionated vs. Normo-Fractionated Accelerated Radiation Therapy with or without Cisplatin for Locally Advanced Head and Neck Squamous Cell Carcinoma (HYPNO)

Presented by:
Søren Bentzen, PhD, DMSc, FASTRO
University of Maryland
Disclosure & Study Team

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Full author list:

1Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD,
2International Atomic Energy Agency, Vienna, Austria,
3Department of Radiation Oncology, Tata Memorial Centre, Homi Bhабha National Institute, Mumbai, India,
4All India Institute of Medical Sciences, New Delhi, India,
5Barretos Cancer Hospital, Sao Paolo, Brazil,
6V.N. Cancer Centre, Coimbatore, India,
7Bahawalpur Inst. of Nuclear Medicine and Oncology, Bahawalpur, Pakistan,
8Fundación Escuela de Medicina Nuclear, Mendoza, Argentina,
9Siriraj Hospital, Mahidol University, Bangkok, Thailand,
10Instituto de Oncología y Radiobiología, Havana, Cuba,
11Centro Hospitalario Pereira Rossell, Montevideo, Uruguay,
12Epidemiology and Public Health, Univ. of Maryland, Baltimore, MD
Background

• Each year 10 million deaths worldwide are attributed to cancer. 7 million of these occur in low- and middle-income countries (LMIC).

• Head and neck cancer is the sixth most common cancer worldwide (4.5% of new cases) but affects low- and middle-income countries disproportionately. In India, for example, HNSCC constitutes 30% of incident cancers.

• Patients in LMIC generally have limited access to radiation therapy (and to surgery!).

• Reducing the number of radiation dose-fractions would allow more patients to be treated.
Fewer, larger fractions

We used mathematical models to analyze outcomes of published randomized controlled trials. Our modeling predicted, a 20-fraction, 4-week schedule could provide non-inferior outcomes for both tumor control and late adverse events compared with a ‘standard’ 35-fraction, 7-week schedule.

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
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<tr>
<td>Standard</td>
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<td>70 Gy, 2 Gy/F, 5 F/wk</td>
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<td>66 Gy, 2 Gy/F, 6 F/wk</td>
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<td>55 Gy, 2.75 Gy/F, 5 F/wk</td>
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12 days 9 days
Method

Stratified, randomized controlled open-label non-inferiority phase III trial

**STRATIFY:**
- Performance status
- Tumor sub-site
- Institution
- Chemotherapy

**RANDOMIZE**

- 66 Gy in 33F, 6F/week over 5.5 weeks ±weekly cisplatin
- 55 Gy in 20F, 5F/week over 4.0 weeks ±weekly cisplatin

Co-primary endpoints: loco-regional tumor control, Grade 3+ late adverse events

H0: Hypo-Fx non-inferior for BOTH primary endpoints, with non-inferiority margin: $\Delta=10\%$
The HYPNO trial – sponsor

- **792 patients** with locally advanced head and neck cancer randomized
- 12 centers, 10 low- and middle-income countries, 4 continents
Results: tumor effect & adverse events

<table>
<thead>
<tr>
<th>Strata</th>
<th>Hypo-Fx</th>
<th>Normo-Fx</th>
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<tbody>
<tr>
<td>Number at risk</td>
<td>395</td>
<td>227</td>
</tr>
<tr>
<td>397</td>
<td>232</td>
<td>186</td>
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</table>

- **LRC**
  - Hypo-Fx: 50.7±2.7%
  - Normo-Fx: 51.2±2.7%
  - P-value: 0.36

- **Late Grade 3+ AEs**
  - Hypo-Fx: 18.8±2.4%
  - Normo-Fx: 20.2±2.4%
  - P-value: 0.68
Results: Non-inferiority & Survival

Δ Loco-regional Control/Late Adverse Events (%)

LRC
G3+ LAE

Favors Normo-Fx  Favors Hypo-Fx

PRIMARY ANALYSIS

Non-inferiority tests:
Loco-regional control:  P=0.04
Grade ≥3 late adverse events:  P=0.004

Overall survival

p = 0.82

Number at risk

<table>
<thead>
<tr>
<th>Strata</th>
<th>394</th>
<th>279</th>
<th>202</th>
<th>150</th>
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<tr>
<td>Follow-up (years)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<th>Strata</th>
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<th>218</th>
<th>161</th>
<th>106</th>
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Conclusions

• Large RCT (N=792) testing a hypothesis derived from mathematical modeling of clinical trial data.

• Pragmatic randomized trial conducted in low- and middle-income countries with high incidence and mortality of HNSCC with the aim of informing health care in these populations.

• Resource-sparing Hypo-Fx ± weekly cisplatin is non-inferior to accelerated RT with 6/F per week with respect to BOTH adverse events and tumor control.