

## Supplementary Online Content

Jalali R, Gupta T, Goda JS, et al. Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain tumors: a randomized clinical trial. *JAMA Oncol*. Published online June 1, 2017. doi:10.1001/jamaoncol.2017.0997

**eTable 1.** Neuropsychological evaluation tools

**eTable 2.** Neuroendocrine evaluation tools (clinical & biochemical)

**eTable 3.** Comparison of other neurocognitive function scores (anxiety scales and depression scales) between SCRT and conv RT arm at baseline and 5 years using Analysis of co-variance (ANCOVA) test

**eFigure 1A.** Isodose distribution in axial, coronal and sagittal planes of a representative patient of craniopharyngioma planned with Stereotactic Conformal Radiotherapy (upper panel) and re-planned with conventional radiotherapy (lower panel) for illustrative purpose

**eFigure 1B.** Dose Volume Histogram (DVH) of the same patient (efigure 3a) using Stereotactic Conformal Radiotherapy (upper panel) and re-planned with conventional radiotherapy (lower panel)

**eFigure 2.** Isodose distribution (axial, coronal, and sagittal planes) and dose-volume histogram in a patient of craniopharyngioma planned and treated with conventional radiotherapy technique

**eFigure 3.** Longitudinal change in the mean FSIQ scores over five years compared between SCRT and Conventional RT based on clinical and tumor factors

**eFigure 4.** Cumulative percentage risk of new endocrine dysfunctions in tumors according on their proximity to the hypothalamic-pituitary axis, treated with SCRT or Conventional RT

This supplementary material has been provided by the authors to give readers additional information about their work.

## Supplement 2

### eTable 1: Neuropsychological evaluation tools

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Assessment of Intelligence in Children between 6-16 years of age

- Verbal Intelligence Quotient\*
  - General information
  - General comprehension
  - Arithmetic
  - Similarities
  - Vocabulary
- Performance quotient\*
  - Picture completion
  - Picture arrangement
  - Block design
  - Object assembly
  - Coding
- Assessment of Intelligence in Children above 16 years of age
  - Memory Intelligence Quotient<sup>¶</sup>
    - Personal & current information
    - Orientation
    - Mental Control
    - Memory
    - Visual reproduction
    - Associate learning
  - Performance Quotient (Bhatia's IQ tests)
    - Kohs block design test
    - Passalong test
- Vithoba Paknikar Performance Tests for Blind (Maximum score 118)
  - Circle formation
  - Sorting out similar forms
  - Roughness discrimination
  - Weight discrimination
  - Constructive ability test

Anxiety-depression assessment

Lowenstein cognitive assessment

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\*Using Wechsler Intelligence Scale Chart (WISC III). WISC-III is a collection of 13 distinct subtest divided into two scales- a Verbal and Performance Scale. Five of the subtest in each scale produce scale specific IQS, and the 10 subtest scores produce a Full Scale IQ. Standardized norms are available for Indian population.

<sup>¶</sup>Using Wechsler Memory scale (WMS)

The Wechsler Memory Scale - 3rd Edition (WMS-III) is an individually administered measure of memory for verbal and figural stimuli, memory for meaningful and abstract material, and delayed and immediate recall. Primary index scores scale scores produce memory score.

**eTable 2:** Neuroendocrine evaluation tools (clinical & biochemical)

<b>Axis</b>	<b>Clinical</b>	<b>Biochemical</b>	<b>Normal levels</b>
Growth	Anthropometry Height velocity	ITT Peak GH IGF-1 (at 13 years)	>10ng/ml Female: 126-637ng/ml Male: 103-603ng/ml
Puberty	SMR	FSH LH	2.5-10mIU/ml 2.5-10mIU/ml
Thyroid	Clinical evaluation for hypothyroidism	T4	5-12.5mcg/dl
steroid	Clinical evaluation of hypocortisolism	Basal Cortisol ITT	>10mcg/dl >18 mcg/dl

ITT: Insulin Tolerance Test, FSH: Follicular Stimulating Hormone, LH: Luteinizing Hormone, SMR : sexual maturity rating (Tanner Staging) in adolescents, GH: Growth Hormone, T4: Thyroxine.

Definition of endocrine dysfunction was defined as dysfunction in atleast one axis compared to baseline evaluation or previous evaluation. The neuroendocrine evaluation tools consisted of both clinical & biochemical tests as assessed for all the endocrine axes in the present randomized study.

**eTable 3:** Comparison of other neurocognitive function scores (anxiety scales and depression scales) between SCRT and conv RT arm at baseline and 5 years using Analysis of co-variance (ANCOVA) test  
 SCRT: Stereotactic conformal radiotherapy, ConvRT: Conventional radiotherapy, HARS:

Scales	SCRT arm		ConvRT arm		p-value
	Baseline	5 years	Baseline	5 years	
<b>Neurocognitive &amp; Neuropsychological outcomes</b>					
<b>Trait Anxiety (C1)</b>	36.2 ± 13.7	26.4 ± 4.0	29.9 ± 12.4	21.5 ± 11.4	0.319
<b>State Anxiety (C2)</b>	29.2 ± 11.3	23.8 ± 4.4	22.5 ± 9.5	21.5 ± 12.5	0.789
<b>HARS</b>	18.2 ± 9.8	10.4 ± 7.1	12 ± 8.4	4.7 ± 5.4	0.098
<b>HDRS</b>	16.2 ± 14.6	5.8 ± 4.3	9.2 ± 7.1	2.1 ± 1.5	0.296

Hamilton Anxiety reporting Scale, HDRS: Hamilton Depression reporting scale.

**The State-Trait Anxiety Inventory** self-report measure indicates the intensity of feelings of anxiety; it distinguishes between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening). Total scores for state and trait (STAI) are calculated, ranging from 20 - 80. Higher scores indicate greater anxiety.

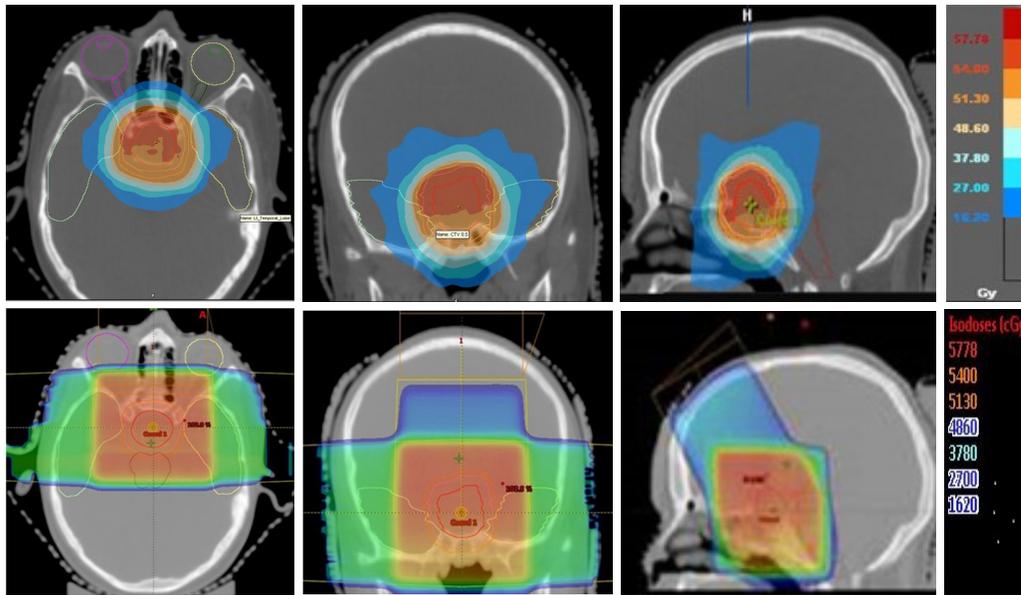
Hamilton Depression Rating Scale is a Clinician-administered depression assessment scale.

- Scores below 7 generally represent the absence or remission of depression.
- Scores between 7-17 represent mild depression
- Scores between 18-24 represent moderate depression
- Scores 25 and above represent severe depression

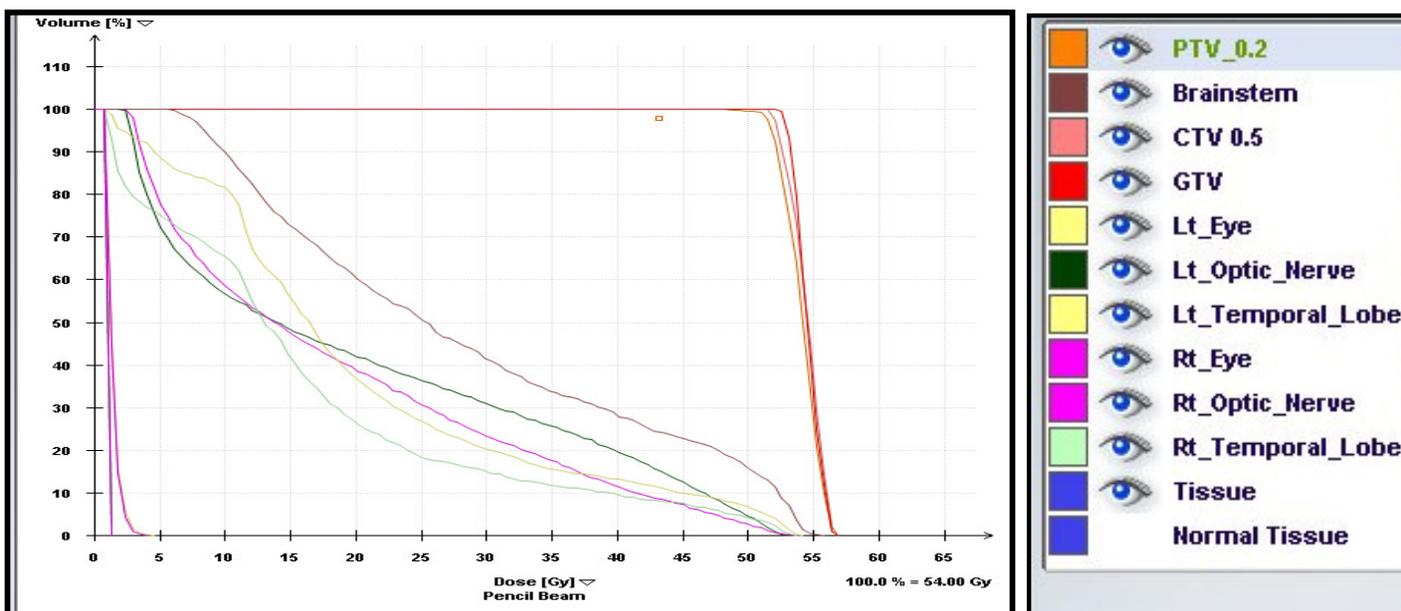
Hamilton Anxiety Rating Scale – is a clinician-administered anxiety assessment scale

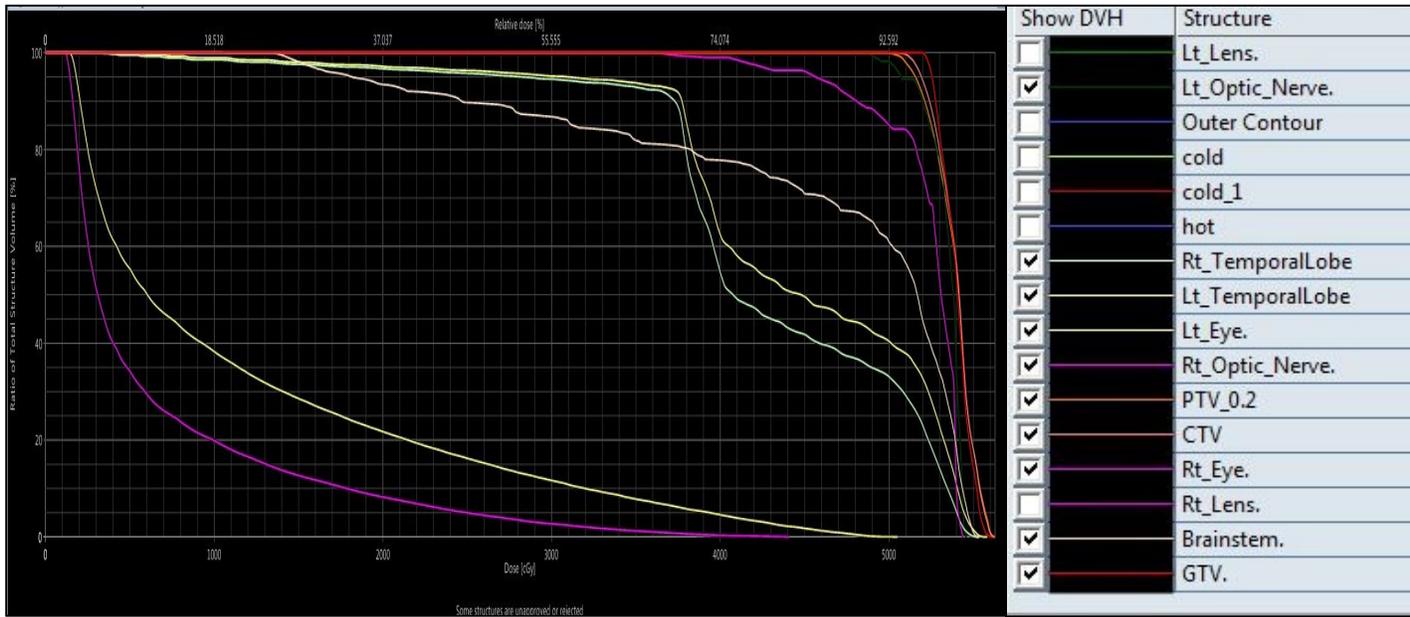
- 14-17 = Mild Anxiety
- 18-24 = Moderate Anxiety
- 25-30 = Severe Anxiety

**eFigure 1A: Isodose distribution in axial, coronal and sagittal planes of a representative patient of craniopharyngioma planned with Stereotactic Conformal Radiotherapy (upper panel) and re-planned with conventional radiotherapy (lower panel) for illustrative purpose. Note the high and medium dose conformity of stereotactic plan compared to conventionally planned open fields.**

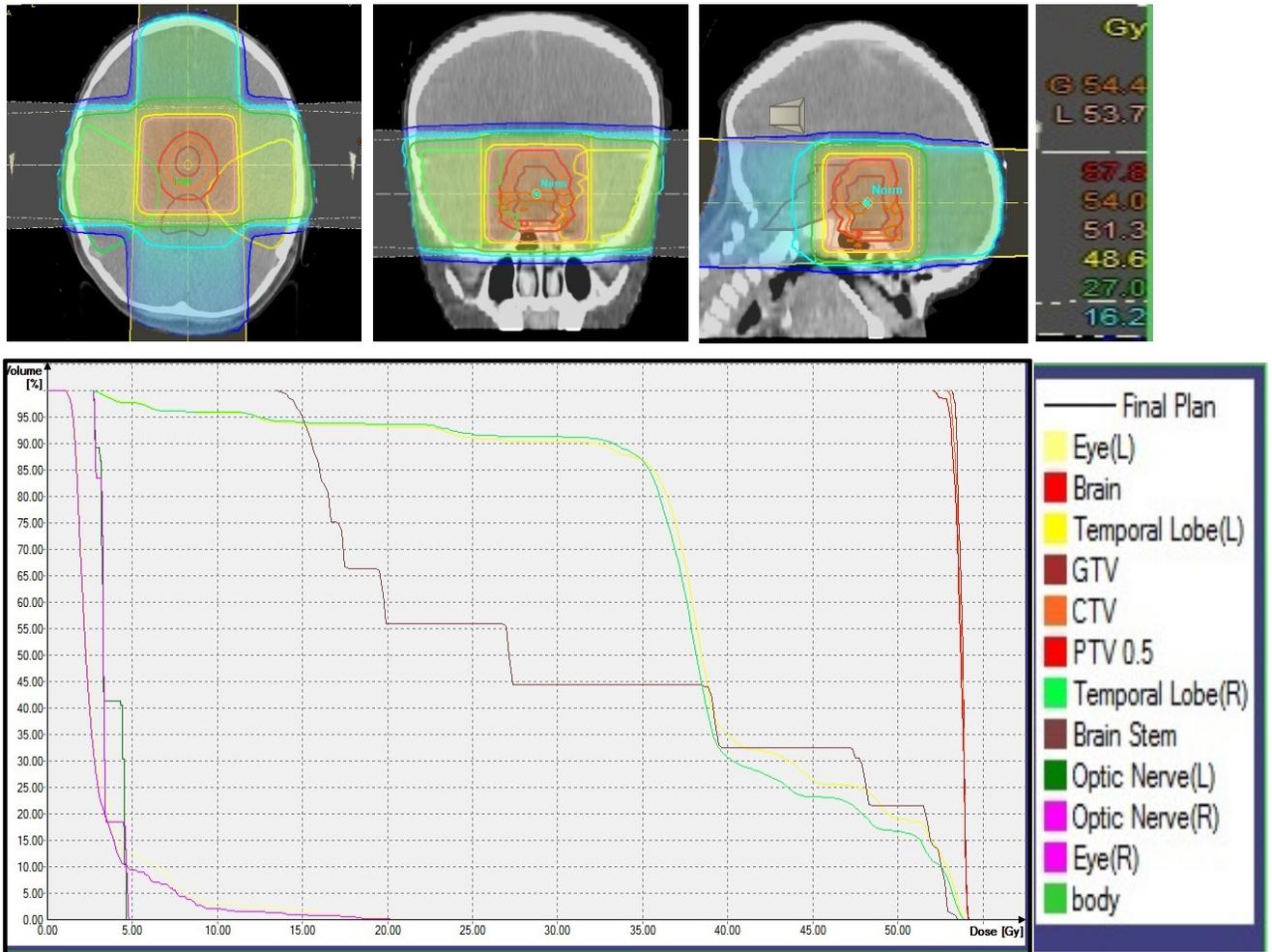


**eFigure 1B: Dose Volume Histogram (DVH) of the same patient (efigure 3a) using Stereotactic Conformal Radiotherapy (upper panel) and re-planned with conventional radiotherapy (lower panel). Note similar coverage of the planning target volume with both techniques but significantly increased doses to non-target tissues and organs-at-risk with conventional technique.**



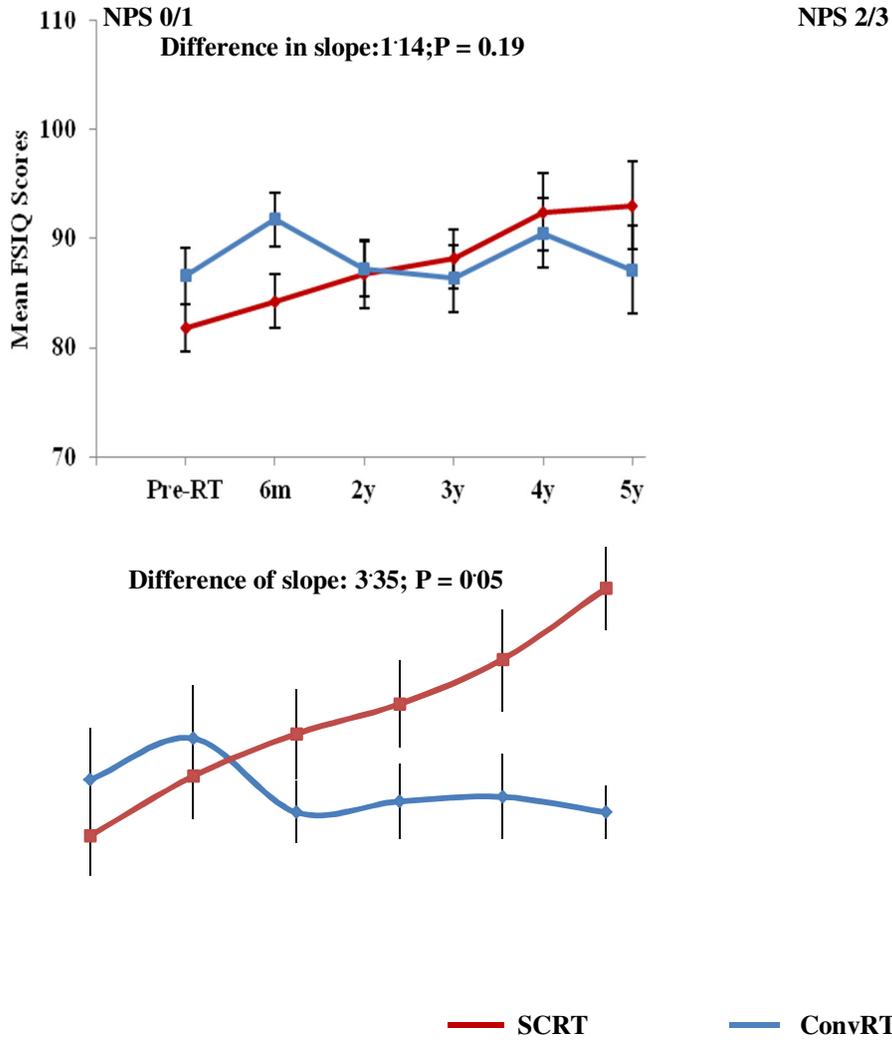


**efigure 2: Isodose distribution (axial, coronal and sagittal planes) and dose-volume histogram in a patient of craniopharyngioma planned and treated with conventional radiotherapy technique**



**eFigure 3 Longitudinal change in the mean FSIQ scores over five years compared between SCRT and Conventional RT based on clinical and tumor factors**

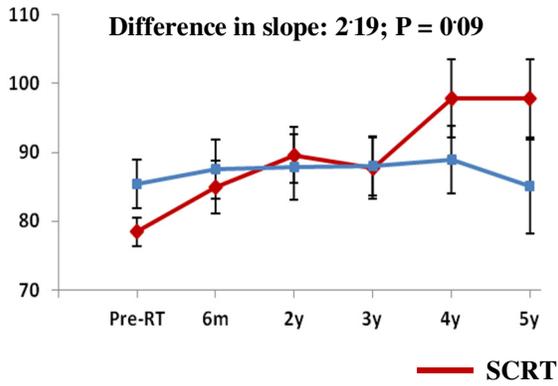
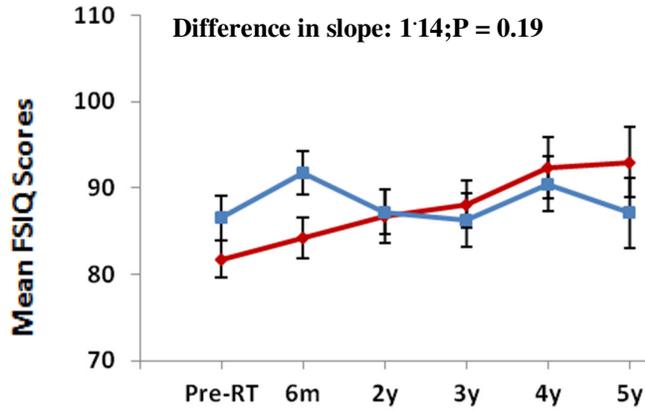
**A**



**B**

**No/Mild hydrocephalus**

**Moderate/Severe hydrocephalus**



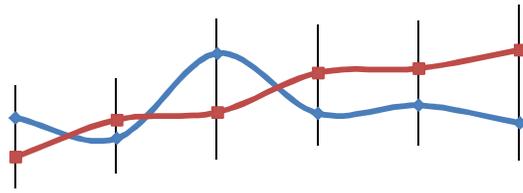
**C**

**Infratentorial Tumors**

**Supratentorial Tumors**

Mean FSIQ Scores

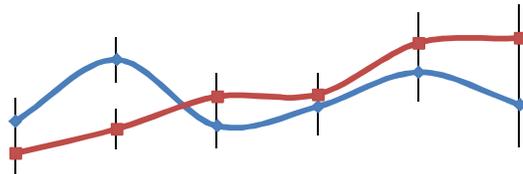
Difference in slope: 1.07; P= 0.31



— SCRT

— ConvRT

Difference in slope: 1.76; P= 0.05

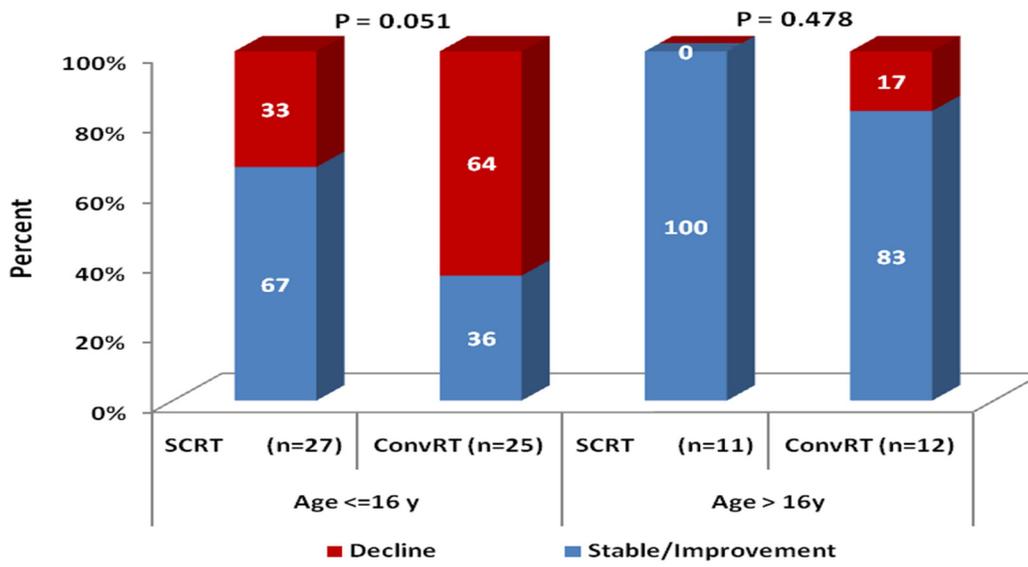


Shown are the trends and the difference in slopes of the full scale IQ scores in various subgroups based on based on clinical and tumor factors in patients treated on SCRT arm and Conv RT arm and longitudinally followed up for atleast 5 years. The difference in slopes between the SCRT arm and the ConvRT arm were compared by linear mixed model.

**D Analysis of the distribution of FSIQ scores in the SCRT arm and ConvRT differentiated by age groups ( ≤16 years and > 16 years).**

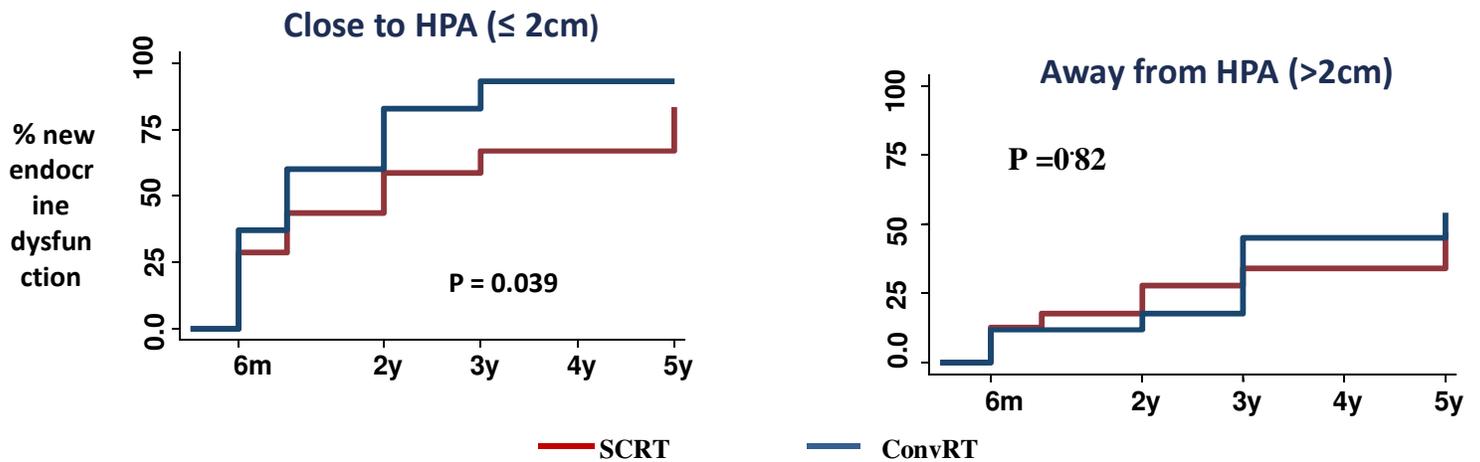
**P= 0.05**

**P= 0.48**



The difference in FSIQ scores between baseline and 5 years were represented as stable (difference between -5 & +5 points) or improved (> 5 point increase from baseline) and decline (>5 point decrease from baseline). At 5 years, the proportion of patients in the age group  $\leq 16$  years having stable or improved FSIQ scores was higher in the SCRT arm(67%) than the ConvRT arm(36%) and was statistically significant (P=0.05). However, in patients >16 years, although 100% patients in the SCRT arm had either stable or improved FSIQ scores as opposed to patients in the Conv RT arm (83%),this was not statistically significant (P=0.47)

**eFigure 4 Cumulative percentage risk of new endocrine dysfunctions in tumors according on their proximity to the hypothalamic-pituitary axis, treated with SCRT or Conventional RT.**



Kaplan–Meier curves representing the cumulative percentage risk of developing new endocrine dysfunction developing over time in patients with tumours located close to the hypothalamic-pituitary axis ( $<2\text{cm}$ ) and away from the hypothalamo-pituitary axis ( $>2\text{cm}$ ) treated by SCRT and ConvRT. The slope estimates of the two groups thus obtained were compared using log rank test