Craniopharyngioma

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Our patient

7yo CF w/ hx HA and lethargy x 1mo

- Prior to initial presentation, sx increased over time in severity
- Outside imaging - sellar/suprasellar cystic mass
- Negative Endocrine Sx
- Prior to surgery, underwent ventriculostomy
- Two days later surgery for gross tumor resection
- Final path showed adamantinomatous CP
Epidemiology

• Incidence 0.13 cases per 100,000 person-years
• 2 to 5% of all primary neoplasms
  ▫ 5.6% to 15% of intracranial tumors in children
• Bimodal Presentation
  • Children 55%
    ▫ 5-14 years
  • Adults 45%
    ▫ 55 – 65 years
• No differences by gender
• No definite genetic relationships
  ▫ US incidence black > white
• Benign neoplasm that yields malignant chx from the mass effects of the tumor

Merchant et al. 2013
Anatomy and Physiology
Pathophysiology

- **Two Hypotheses:**
  - **Embryogenetic**
    - Transformation of embryonic squamous cell structures along the path of the craniopharyngeal duct
  - **Metaplastic**
    - Metaplasia of adenohypophyseal cells in pituitary stalk or gland  * Rathke’s pouch *

- **Defect in Wnt signaling pathway reactivation**
  - β-Catenin gene mutations effecting exon 3 suggesting nuclear β-Catenin accumulation

Wnt Signaling Pathway
Histology

- Two main histological subtypes:
  - **Adamantinomatous**
    - Predominantly children and adolescents
    - Cystic or solid components +/- calcifications
  - **Papillary**
    - Adults
    - Resembles oropharyngeal mucosa
    - Less infiltration of adjacent brain tissue

Clinical Presentation

• Symptoms manifest due to mass effects to various brain structures

  ▫ Neurologic
  ▫ Brain parenchyma
    • cognitive deficits
  ▫ Visual Optic pathways
    • Visual disturbances
  ▫ Ventricular system
    • Headaches, nausea/vomiting, hydrocephalus
  ▫ Hypothalopituitary (Endocrinological)
    • growth failure (children) hypogonadism (in adults)
Clinical Presentation

- Three major clinical syndromes based on location
  - Prechiasmal/chiasmal
    - Compression of optic apparatus
      - optic atrophy (e.g., progressive decline of visual acuity and constriction of visual fields) bitemporal vision loss
  - Retrochiasmal
    - 3rd ventricle obstruction
      - hydrocephalus, with signs of increased intracranial pressure (e.g., papilledema and horizontal double vision)
  - Intrasellar
    - Compression of pituitary stalk and hypothalamic region
      - Endocrinopathy and headache

More surgically accessible
Radiologic Findings

• General:
  ▫ Well encapsulated tumor, mixed cystic and solid component

• CT
  ▫ Detect calcifications
    • peds

• MRI
  ▫ Most important used to plan surgical approach
  ▫ Show relationship between tumor, vasculature, and optic apparatus

MRI -/+ Contrast
Differential Diagnosis

- Rathke Cleft Cyst
- Suprasellar Arachnoid Cyst
- Hypothalamic/Chiasmatic Astrocytoma
- Pituitary Adenoma
  - Can mimic CP when cystic and hemorrhagic
- Epi-Dermoid Tumors
- Thrombosed Aneursym
- Germinoma or Mixed Germ Cell Tumor with Cystic Components

Our patient
Prognostic Factors

- **Favorable:**
  - Lack of calcifications (esp in adults)
  - Extent of surgical resection
  - Caucasian race
  - # of weekly surveillance MR imaging evaluations

- **Unfavorable:**
  - Age younger than 5 years old
  - Size > 5 cm
  - Hydrocephalus
    - Need for CSF shunting

*Merchant et al., 2013*
Grading

• Based on degree of hypothalamic displacement:
  ▫ Grade 0 = None
  ▫ Grade 1 = Abutting/displacing
  ▫ Grade 2 = Involving/Infiltrating – marked by absence of hypothalamus on imaging

Puget et al.
Work-up

- Pretreatment evaluation
  - *Pre-contrast CT and MRI, occasional cerebral angiography*
  - Endocrinologic Eval
    - baseline serum electrolytes,
    - serum and urine osmolality, thyroid studies,
    - AM/PM cortisol levels
    - GH, LH and FSH levels in adolescent and adult ptx
  - Neuro-ophtalmologic
    - Important to establish pre-treatment baseline
  - Neuropsychological Assessment

Karavitaki and Wass, 2008
Treatment overview

- Surgical resection +/- EBRT
  - Mainstay Tx
- Intracystic RT
- Chemotherapy
  - Bleomycin – reduce tumor size
- Aspiration
  - Purely cyst mass with goal of delaying treatment
Intracystic RT and Chemotherapy

- **β** emitter 32 P, Yttrium-90
  - 200Gy to cyst wall
- Treat residual or recurrent cyst formation
  - Used in patients to delay definitive treatment
    - (ie. Surgery GTR or STR + EBRT) for young patients
- **Bleomycin** – limited success
  - Preoperative intralesional bleomycin may be effective at decreasing cyst size and fibrosing cyst wall
  - Associated with vasogenic edema
    - direct leakage of the drug to surrounding tissues during the installation procedure, diffusion though the cyst wall

Surgical

- Craniotomy
  - Pterional,
  - Bifrontal and interhemispheric
- Transsphenoidal route – 1990’s
  - Originally only dedicated to intrasellar masses due initial difficulty w/ CSF leaks, and difficulty visualizing w/ microscope

Stam 2010. Craniopharyngioma
Surgical

- Extended Transsphenoidal approach w/ endoscope
• 90% of intrasellar and parasellar tumors approached transphenoidally
• Use of *pterional* approach if above pituitary
• On previous MRI - Patient – suprasellar mass
  ▫ Rt - Lateral Pterional Craniotomy -> Gross-Total Resection
Surgical

• Complete resection
  ▫ Potentially curative
  ▫ Post-op imaging indicates residual calcifications or obvious tumor in 15-50% of “totally resected” cases
  ▫ Rate of recurrence after imaging confirmed total resection 15-30%

• Complications
  ▫ Given location of tumor many adverse effects and could increase morbidity of patient
  ▫ Extensive resection associated with DI in 90% and hypothalamic obesity in 50%
  ▫ Temporary DI seen in 25% of patients
    ▫ Our patient

Halperin
Surgical

- Partial resection/cyst aspiration
  - Rapid symptom relief
  - Progression in 70% within 3 years
  - Second surgery
    - less likelihood of complete resection
    - higher surgical morbidity and lower quality of life

- What role does radiation play in treating CP???
CRANIOPHARYNGIOMAS

TREATMENT BY COMBINED SURGERY AND RADIATION THERAPY

SIMON KRAMER, M.D.,* WYLIE McKISSOCK, F.R.C.S., and
JOSEPH P. CONCANNON, M.D.†

Royal Marsden Hospital, the National Hospital for Nervous Diseases, and
St. George's Hospital, London, England

(Received for publication May 28, 1960)

• 10 case reports of patients treated between 1952 and 1954
  • By 1986 reported total of 77 patients
• Median total dose of 56Gy w/ median dose of (1.5Gy/fx)
• PFS @ 5 years  83%    PFS @ 10 years 79%
Radiation

- Children’s hospital in Boston
- August 1976 - March 2003, n=79
- Median dose 54Gy
- LC at 10 years (no difference in OS)
  - Surgery alone: 52%
  - Surgery + planned RT: 84%
- 24 patients treated prior to conformal RT 1988
  - 63% recurred
  - after 1988 36% recurred

Winkfield et al. 2011.
Radiation

- St. Jude Children’s Research Hospital experience 1984-2001
  - Retrospective, n=30, f/u = 5 years
    - Surgery alone
    - Surgery + RT (55.8 Gy) 1.8Gy/fx
  - Surgery group had more endocrine, neurologic, ophthalmologic complications and IQ deficit
    - Surgery alone - lost ~ 9 IQ pts
    - Surgery + RT - lost ~ 1.25 IQ pts

Merchant et al.
Radiation

- St. Jude Children’s Research Hospital experience
- Prospective study, n=88, Median f/u = 5 yrs
  - Surgery + RT (55.8 Gy) 1.8Gy/fx
    - CTV Margins > 5mm  n=26
    - CTV Margins < 5mm  n=62
      - (88.1% 6.3% vs 96.2% 4.4% [P=.6386]) no difference
  - Outcome
    - CTV may be safely reduced w/o affecting rate of PFS
    - Reduced PTV for future treatments to 3mm

Merchant et al.
Treatment related morbidity and management of Craniopharyngioma

- 2012 Systematic Review
- 109 studies describing extent of resection for 531 patients
- Morbidity difference between extent of resection +/- radiation Therapy
  - Gross-total resection (GTR)
  - Sub-total resection (STR)
- Suggested reduced endocrine dysfunction

Clark et al. J Neurosurg 2012
TABLE 2: Association between extent of resection (biopsy +/- adjuvant therapy vs STR +/- RT vs GTR +/- RT) and outcomes irrespective of adjuvant therapy*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Biopsy</th>
<th>STR</th>
<th>GTR</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>postop endo dysfxn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>18 (21)</td>
<td>39 (55)</td>
<td>112 (59)</td>
<td>&lt;0.001</td>
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<tr>
<td>no</td>
<td>68 (79)</td>
<td>32 (45)</td>
<td>79 (41)</td>
<td></td>
</tr>
<tr>
<td>postop DI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>5 (6)</td>
<td>7 (10)</td>
<td>48 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no</td>
<td>81 (94)</td>
<td>64 (90)</td>
<td>143 (75)</td>
<td></td>
</tr>
<tr>
<td>postop obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>11 (6)</td>
<td>0.18</td>
</tr>
<tr>
<td>no</td>
<td>84 (98)</td>
<td>70 (99)</td>
<td>180 (94)</td>
<td></td>
</tr>
<tr>
<td>postop panhypopit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>2 (2)</td>
<td>10 (14)</td>
<td>30 (16)</td>
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<tr>
<td>no</td>
<td>84 (98)</td>
<td>61 (81)</td>
<td>161 (84)</td>
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<tr>
<td>postop visual dysfxn</td>
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<td></td>
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</tr>
<tr>
<td>yes</td>
<td>12 (14)</td>
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<td>11 (6)</td>
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<td>no</td>
<td>74 (86)</td>
<td>69 (96)</td>
<td>180 (94)</td>
<td></td>
</tr>
<tr>
<td>postop neuro dysfxn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1 (1)</td>
<td>5 (7)</td>
<td>20 (11)</td>
<td>0.02</td>
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<tr>
<td>no</td>
<td>85 (99)</td>
<td>66 (93)</td>
<td>171 (89)</td>
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</tbody>
</table>

* DI = diabetes insipidus; neuro = neurological; panhypopit = panhypopituitarism.
† Chi-square test.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>GTR</th>
<th>STR + RT</th>
<th>p Value</th>
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<tbody>
<tr>
<td>postop endo dysfxn</td>
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<tr>
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<td>108 (59)</td>
<td>11 (46)</td>
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<tr>
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<td>75 (41)</td>
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<tr>
<td>postop DI</td>
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<tr>
<td>yes</td>
<td>46 (25)</td>
<td>1 (4)</td>
<td>0.02</td>
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<tr>
<td>no</td>
<td>137 (75)</td>
<td>23 (96)</td>
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<tr>
<td>postop obesity</td>
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</tr>
<tr>
<td>yes</td>
<td>10 (6)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>no</td>
<td>173 (94)</td>
<td>23 (96)</td>
<td></td>
</tr>
<tr>
<td>postop panhypopit</td>
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<td></td>
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</tr>
<tr>
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<td>27 (15)</td>
<td>7 (29)</td>
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<td>no</td>
<td>156 (85)</td>
<td>17 (71)</td>
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<td>postop visual dysfxn</td>
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<td></td>
</tr>
<tr>
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<td>9 (5)</td>
<td>1 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>no</td>
<td>174 (95)</td>
<td>23 (96)</td>
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</tr>
<tr>
<td>postop neuro dysfxn</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>20 (11)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>no</td>
<td>163 (89)</td>
<td>24 (100)</td>
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Health Status in Long-Term Survivors of Pediatric Craniopharyngioma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (56.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (78.4)</td>
</tr>
<tr>
<td>Black</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>Age at diagnosis (years), median (min–max)</td>
<td>7.1 (1.2–17.6)</td>
</tr>
<tr>
<td>Years from diagnosis to long-term follow-up, median (min–max)</td>
<td>7.6 (5.0–21.3)</td>
</tr>
<tr>
<td>Treatment, n(%)</td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Surgery + radiation therapy only</td>
<td>44 (86.3)</td>
</tr>
<tr>
<td>Surgery + radiation therapy + chemotherapy</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>History of shunt placement, n (%)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>21 (41.2)</td>
</tr>
<tr>
<td>No</td>
<td>30 (58.8)</td>
</tr>
</tbody>
</table>

OS @ 20 years ~ 75%

Overall Survival
# Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Race</th>
<th>Age at diagnosis (years)</th>
<th>Date of diagnosis</th>
<th>Initially metastatic</th>
<th>Date of death</th>
<th>Survival (years)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/B</td>
<td>12.9</td>
<td>10/13/1986</td>
<td>No</td>
<td>12/8/2002</td>
<td>26.2</td>
<td>Diabetes, myocardial infarction</td>
</tr>
<tr>
<td>2</td>
<td>F/W</td>
<td>1.1</td>
<td>1/17/1994</td>
<td>No</td>
<td>7/19/2003</td>
<td>9.5</td>
<td>Metabolic complications, radionecrosis</td>
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<tr>
<td>3</td>
<td>F/B</td>
<td>13.8</td>
<td>9/15/1997</td>
<td>No</td>
<td>5/30/2003</td>
<td>5.7</td>
<td>Metabolic complications</td>
</tr>
<tr>
<td>4</td>
<td>M/B</td>
<td>6.0</td>
<td>3/07/2000</td>
<td>No</td>
<td>11/18/2007</td>
<td>5.7</td>
<td>Recurrent craniopharyngioma</td>
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</tbody>
</table>

### Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>20 (39.2)</td>
</tr>
<tr>
<td>History of seizures</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Abnormal cerebral vessel</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Oculomotor dysfunction</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Vision &lt; 20/100</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>18 (35.3)</td>
</tr>
</tbody>
</table>

### Variable

<table>
<thead>
<tr>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive delay</td>
</tr>
<tr>
<td>Individual educational plan for academic assistance</td>
</tr>
<tr>
<td>Educational attainment</td>
</tr>
<tr>
<td>Special education certificate of attendance</td>
</tr>
<tr>
<td>High school diploma</td>
</tr>
<tr>
<td>College graduate</td>
</tr>
<tr>
<td>Postgraduate degree</td>
</tr>
<tr>
<td>Psychological problems</td>
</tr>
<tr>
<td>Communication disorder</td>
</tr>
</tbody>
</table>
Outcomes

- Endocrine dysfunction most common morbidity
  - Cognitive delay 20% of patients (IQ <80)
- Outcomes suggested that better response rates of local tumor control does not correlate to long-term health.
  - Many patients burdened with significant medical complications post STR+RT

<table>
<thead>
<tr>
<th>Current Wechsler (WAIS-IV, WISC-IV, WPPSI-IV)</th>
<th>IQ Classification</th>
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</thead>
<tbody>
<tr>
<td>IQ Range (&quot;deviation IQ&quot;)</td>
<td></td>
</tr>
<tr>
<td>130 and above</td>
<td>Very Superior</td>
</tr>
<tr>
<td>120–129</td>
<td>Superior</td>
</tr>
<tr>
<td>110–119</td>
<td>High Average</td>
</tr>
<tr>
<td>90–109</td>
<td>Average</td>
</tr>
<tr>
<td>80–89</td>
<td>Low Average</td>
</tr>
<tr>
<td>70–79</td>
<td>Borderline</td>
</tr>
<tr>
<td>69 and below</td>
<td>Extremely Low</td>
</tr>
</tbody>
</table>
Our patient

- **GTR vs. STR and planned adjuvant RT**
  - Thermal dysregulation
  - Extreme somnolence
  - Impaired short term memory
  - Electrolyte disturbances
  - Visual Field deficits
    - R eye - superior and inferior temporal deficiencies
    - L eye - superior and inferior nasal deficiencies
      - New relative afferent pupillary defect (L)

- **Interval History**
  - Improved energy, but still lethargic, less visual field defects vs compensation, short-term memory deficits still remain
  - 3 month follow-up w/ MRI
Treatment overview

• Complete resection remains the goal of primary surgery
  ▫ High percentage of recurrences if tumor not radically removed

• Maximal safe resection
  ▫ If GTR – observe (LC 80-100%)
  ▫ If STR:
    ● adjuvant EBRT to 54 Gy at 1.8 Gy/ fx (LC 75-90%)
    ● Observation (LC 30%)
    ● Consider deferring RT for children < 3 yo, maybe 5 yo

Gunderson; Halperin
Complications

- 90% will have at least one hormone deficiency
  - Panhypopituitarism: hypogonadism, hypothyroidism, adrenal insufficiency, GH deficiency
  - Hypothalamic dysfunction: obesity, temperature regulation, sleep disorders, DI
- Post-treatment visual acuity highly dependent on pre-treatment status
  - Some patients might have improved vision
  - Majority will remain the same
- Secondary malignancies: glioma
- Vascular injury (1-2%): temporal cavernomas, aneurysms, moyamoya syndrome (before conformal)
- Cognitive dysfunction

Gunderson; Halperin
Treatment overview

**Craniopharyngioma suspected in imaging**

- **Tumor causing compressive signs or symptoms**
  - Predominantly cystic
    - Aspiration
    - Surgery
      - GTR
      - Recurrence
  - Mixed/solid
    - Surgery
      - Residual tissue in post-operative imaging
        - Adjuvant RT

- **Small tumor not causing compressive signs or symptoms**
  - Predominantly cystic
    - Biopsy/aspiration and RT
  - Mixed/solid
    - Biopsy and RT
      - Recurrence
        - Salvage surgery
          - Recurrence
Summary

• Surgical total resection does not necessarily guarantee cure.
  ▫ variable recurrence rates have been reported following what was considered a total resection of tumor the childhood craniopharyngioma.
• Because of the often unacceptably high complication rates and the lack of 100% prevention of recurrence following radical tumor resection, there has been a growing advocacy for less-invasive tumor resection with adjuvant therapy.
• RT response rates for craniopharyngiomas vary in the literature but have an overall good track record.

Clark et al. J Neurosurg 2012
Future Direction

- Reducing the limitations for comparison
  - There are no standard guidelines for approach to tumor
- The long-term side effects of RT upon the central nervous and neurovascular systems in their immature stage are still TBD
- Further determine optimal treatment for the 3 year-old child who presents with headaches and normal visual and hormonal functions.
- Examine epidemiological prognostic factors
References

- Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. Puget S et al.