TREATMENT OPTIONS IN CRANIOPHARYNGIOMAS: BRACHYTHERAPY AND RADIOTHERAPY

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CRANIOPHARYNGIOMAS

• « Craniopharyngiomas are the most challenging intracranial neoplasms... »
  H. Cushing (1932)

• « Very few neurosurgical entities have been as controversial as the management of craniopharyngioma »
  F. J. Epstein (1993)

• « There is perhaps no other primary brain tumour that evoques more passion, emotion and as a result, controversy than does craniopharyngioma »
  J.T. Ruthka (2002)
CRANIOPHARYNGIOMAS: Treatment Options

• SURGICAL EXCISION WITH OR WITHOUT ADJUVANT RADIOTHERAPY
  CONVENTIONAL EXTERNAL BEAM IRRADIATION AS PRIMARY THERAPY /
  TREATMENT OF RECURRENT DISEASE

• STEREOTACTIC RADIOSURGERY
• STEREOTACTIC RADIOTHERAPY
• INTRACYSTIC IRRADIATION (BRACHYTHERAPY)

• INTRACYSTIC BLEOMYCIN
• INTRACYSTIC INTERFERON Alpha
• SYSTEMIC CHEMOTHERAPY (INTERFERON Alpha)
PRIMARY THERAPY
SURGICAL EXCISION WITH OR WITHOUT ADJUVANT RADIOTHERAPY

- **Aggressive (Complete/ Radical) surgery** can be associated with significant Morbidity and Mortality due to adherences to vital neurovascular structures:
  - Visual apparatus, hypothalamic–pituitary axis, secondary diabetes insipidus,
    - poor functional outcomes, reduced quality of life,
  - Hypothalamic damage leads to: morbid obesity, sleep and temperature dysregulation, electrolytes disturbances, cognitive and behavioural abnormalities.
SURGICAL EXCISION

• Reasons for incomplete removal:
  - firm adherance to hypothalamus (26.8%), obstructed view (21.4%),
  - major calcification (14.3%), adherances to perforating vessels (10.7%),
  - severe bradycardia during dissection (5.4%), blood loss (1.8%),
  - impression of complete removal (7.1%)
  
  Residual Tumor, Disease progression, Recurrence
  

• Recent microsurgical series Mortality rate ranges between 0-5.4%
• Meta-analysis including 2955 patients :
  
  Early mortality 2.6% after transsphenoidal
  3.1% after transcranial surgery

CONSERVATIVE (LIMITED) SURGICAL APPROACH FOLLOWED BY RADIOTHERAPY

Is adopted after reports of excellent local control and significant reduction in the incidence of complications.
SURGICAL EXCISION WITH ADJUVANT RADIOTHERAPY

- A. IANNALFI and all. (2013), Clinical Oncology (25) pp 654-667: Meta-analysis (1990-2012), 43 Studies including 2292 patients, 1710 cases with clinical reported outcomes

**Limited Surgery + Radiotherapy:**

- 10-year local control rates ranged between 77-100%,
- 20-year overall survival 66-92%
- Long term toxicity less than that with Radical Surgery

- Rajan(1993): **Limited surgery followed by Fractioned external beam radiotherapy** provided excellent tumor control with a recurrence rate of 17% compared with 73% after subtotal resection only
The superiority of conservative resection and adjuvant radiation for craniopharyngiomas

Adam Schoenfeld,
Department of Radiation Oncology, University of California, San Francisco (UCSF), 1600 Divisadero St. Suite H1031, San Francisco, CA 94143-1708, USA

- 122 patients 1980 -2009,
- Age m :30 y, range 11-52 y, 47 children < 18 years

- 30 (24%) : treated with only GTR, 3 (2.8%): GTR + RT
- 41 (33.6%) : treated with STR only, 48 ( 39.3% ) : STR+RT
- Median follow-up : 56.4 months
- 66 patients without progression, 56 patients progressed
- STR associated with significantly shortened OS compared to STR+RT or GTR,
- GTR was associated with significantly greater risk of DI and Panhypopituitarism when compared with STR+RT

STR +RT provides superior clinical outcome, achieving better disease control than Surgery alone ( GTR or STR), and limit side effects associated with aggressive surgical resection.
CONVENTIONAL RADIOTHERAPY

- Carpenter R.C. and all. (1937) first described benefit effects of Radiotherapy following aspiration of cyst contents in 4 cases.

- Kramer S. (1961) reports favourable outcome of the combination of minimal surgery and high-dose super voltage irradiation in a series of 10 patients.
Conventional Radiotherapy

- **Fractioned external beam radiotherapy** is considered an optimal post operative management strategy for craniopharyngioma as these tumors are radiosensitives (*Flickinger, 1990*)

- Visual deterioration is twice as common in surgical removal (13-54%) than in radiotherapy (6-24%) (*N, Karavitaki. Endocrine. Reviews. 2006, 27,4, pp371-397*)

- Dose achieving long term control + minimising adverse sequelae is **50-54 Gy delivered with conventional fractionation.**

- The visual risk increases with dose > 50-54 Gy (*De Vile, 1996 J.Neurosurg. 85 pp73-81*)

- The potential risk of delayed hypothalamo-pituitary disturbance is greater after conventional radiotherapy, late neuropsychological sequelae to the developing brain and risk of tumor induction in young children treated by conventional radiotherapy.

- **Modern Stereotactic Radiotherapy (FSRT) and Radiosurgery (Gamma-Knife) achieving long term tumor control and minimise adverse sequelae** (*RE. Elliott, 2011*)
CRANIOPHARYNGIOMAS: Treatment Options

- Surgical excision with or without adjuvant radiotherapy conventional external beam irradiation as primary Therapy / Treatment of recurrent disease

- **Stereotactic radiosurgery**
- Stereotactic radiotherapy
- Intracystic Irradiation

- Intracystic Bleomycin
- Intracystic interferon α
- Systemic Chemotherapy (Interferon α)
STEREOTACTIC RADIOSURGERY

- Delivers single fraction of high dose ionizing radiation on precisely mapped targets (Gamma Knife)

- Minimal exposure of adjacent structures and reducing the late radiation induced adverse sequelae

- Particularly useful for well defined residual disease, following surgery or the treatment of small solid recurrent tumor,

- Tumor volume and close attachment to critical structures are limiting factors: 10-15 Gy is the maximum tolerated doses to the optic apparatus,
• 10 patients, 9 - 54 y (median 14.5y) treated between 1988-1998
• Radiosurgery done to control solid component of the tumor
  Median margin dose 16.4 Gy
  Dose to the optic nerve less than 8 Gy
  – Follow-up: median 63 months
  – 7/12 tumors became smaller or vanished within median of 8.5 months
  – Prior visual defect improved in 6 children

Fig. 2. (A) A contrast-enhanced CT scan showing a residual suprasellar craniopharyngioma and (B) a contrast-enhanced axial MRI for comparison.
STEREOTACTIC RADIOSURGERY

• 7 series: Small residual or recurrent tumor treated by stereotactic radiosurgery

Niranjan A. (2010): 78 cases

• 5 y. Progression Free Survival : 61-68%
• Visual deterioration 3%
• Endocrine morbidity 2%
• Neurological complications 2%
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STEREOTACTIC RADIOTHERAPY

• Combining the accurate focal dose delivery of stereotactic radiosurgery with the radiobiological advantages of fractionation (LINAC)

• Combs S.E. (2007): 40 patients, most for tumor progression after surgery
  Median follow-up 98 months
  Median Target Dose 52.2 Gy

Local control 100% at both 5 and 10 years
Overall survival rates at 5 and 10 years 97 and 89%
Impaired pituitary function 16.6%
No deterioration of vision nor radionecrosis
• 55 patients (1989-2012)
  – 8 children(< 18y) Median age 37y (6-70y)
• Radiotherapy for tm progression/recurrence after surgery
• Median dose 52.2 Gy (50-57.6 Gy)
• Follow-up: median 128 months
  – Local control
    • 95.3% after 5 y, 92.1% 10 y, 88.1% 20 y
  – Overall survival
    • 10 y : 83.3% 20 y : 67.8%
• Well tolerated treatment
• Side effects
  – 1/55 anosmia
  – 1/55 impaired vision
  – 4/55 endocrinologic dysfunction
  – No secondary malignancies

Figure 4 Comparison of representative sagittal, coronal and transversal images from pre- and posttherapeutic MR scans of a 56 year-old female patient before (a) and six months after radiotherapy (b): a substantial decrease of the solid-cystic tumor can be detected leaving only small residues.
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- STEREOTACTIC RADIOSURGERY
- STEREOTACTIC RADIOTHERAPY
- INTRACYSTIC IRRADIATION

- INTRACYSTIC BLEOMYCIN
- INTRACYSTIC INTERFERON α
- SYSTEMIC CHEMOTHERAPY (INTERFERON α)
INTRACYSTIC IRRADIATION

• First reported by Leksell and Liden (1952),

• Intracavitary irradiation (brachytherapy) stereotactically guided instillation of β emitting isotopes into cystic craniopharyngioma,

• Delivers higher radiation doses to the cyst lining compared with the one offered external beam Radiotherapy,

• β emitting isotopes: ¹² Phosphore, ⁹⁰ Yttrium, ¹⁸⁶ Rhenium ¹⁹⁸ Gold...
  but none of them has the ideal physical and biological profile: pure β emitter, short half life, tissue penetration limited to cover only the cyst wall,

→ No concensus on which is the most suitable therapeutic agent
INTRACYSTIC IRRADIATION


  - Mean follow-up ranging: 3.1-11.9 years
  - $^{90}$ Yttrium or $^{32}$ Phosphorus, providing 200-270 Gy
  - **Complete or partial cyst resolution 71-88%**
  - Stabilisation 3-19 %, Increase 5-10%
  - New cyst formation or increase of solid component 6.5-20%
  - Delayed visual deterioration 10-58%
20 patients with predominantly cystic Craniopharyngioma.
11 as primary treatment, 9 as adjuvant treatment after tumour resection
Irradiation dose: 400 – 500 Gy
   – 6 patients once/week
   – 5 twice/week
   – 5 three times/week
   – 4 four times/week
All patients achieved tm shrinkage or stabilisation
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INTRACYSTIC BLEOMYCIN

- First described by Takahashi (1985),

- Bleomycin (antineoplastic agent) administrated through an Ommaya reservoir connected to a catheter placed in the cyst stereotactically or through craniotomy.

- Small number of published series, limited number of cases, variable total doses, time intervals suggest that intracystic bleomycin may be an effective therapy for some cystic tumor.

- Direct leakage of the drug to surrounding tissues, diffusion through the cyst wall high drug dose, reported toxicity: hypothalamic damage, blindness, hearing loss, ischemic attacks, peritumoral edema...
• **Takahashi (1965)**: 4 children, cystic tumors, treated initially with aspiration/biopsy followed by Bleo, no recurrence in 4 cases, median follow-up 5.5 y.

• **Hader W.J. (2000)**: 7 newly diagnosed cystic cranio. treated with Bleo, 6 cases 50% decrease in tm. size, mean period observation 3 y., 4 remained stables, 2 underwent surg.

• **Franck F.**: 6 patients treated with Bleo., all cysts regrew within 1 y. and 5 of them requiring surgery
Huge Craniopharyngioma cysts appearing after STR. Ommaya reservoir and intracavitary cathether for Bleomycine injection.

In our experience: 2000-2014
31 patients, 3-39 years, 25 < 18 years
6 patients underwent intracystic bleomycine
4 remain stables, 2 cyst recurrence with new cysts
CRANIOPHARYNGIOMAS: Treatment Options

- Surgical excision with or without adjuvant radiotherapy conventional external beam irradiation as primary Therapy / Treatment of recurrent disease
- Stereotactic radiosurgery
- Stereotactic radiotherapy
- Intracystic Irradiation
- Intracystic Bleomycin
- Intracystic interferon $\alpha$
- **Systemic Chemotherapy** (Interferon $\alpha$)
SYSTEMIC CHEMOTHERAPY / INTERFERON ALPHA

- **Very limited number of cases**,

- **Lippens (1998)**: 4 children with very rapid or multiple recurrences
  5 courses of Doxorubicin+ Lomustin
  Local control 75%, after 3-12 years follow-up

- **Jakacki (2000)**: 12 patients (inf. 21 years) with progressive or recurrent tum.
  Interferon Alpha Tumor reduction 25% in 3 patients,
  and in 67% patients completing 1 year of therapy
  Cytotoxicity: hepatic, neurologic, cutaneous..

- **Yeung (2012)**: 5 children with recurrent tumor after surgery
  pegylated interferon -a -2b
  sustained response
  delaying or avoiding Radiotherapy
TREATMENT ALGORITHM FOR CRANIOPHARYNGIOMAS
Fig. 10. Treatment algorithm for craniopharyngiomas.
CONCLUSION

• Optimal management of craniopharyngioma remains controversial,

• Primary treatment includes surgery for decompression and pathology diagnosis,

• Post-op. MRI: GTR : clinical control
  STR: conventional radiotherapy.

• Tumor progression or recurrence:
  cystic → intracystic irradiation or intracystic Bleomycine
  solid → Radiosurgery or FSRT.

• Recurrence: tailored individual treatment option...
THANK YOU
The reported control rates combined with its low surgical morbidity render Brachytherapy an attractive option for predominantly cystic tumors and particularly the monocystic ones,

Intracavitary irradiation seems to offer a good prospect for the reduction or stabilisation of the cystic cranio.
Craniopharyngioma surgery

Fig. 6 Treatment algorithm in craniopharyngiomas

Major Surgery

- Gross Total Resection
  - Observation
  - MRI every year
  - Recurrence
    - Chance of (sub)total Resection
      - Re-Operation
        - Total Resection
          - MRI every year
        - Less than Total Resection
          - High Precision Fract. RT
          - Intraocular Irradiation
            - Cystic
  - No chance of (sub)total Resection
    - Intracavitary Bleomycin
      - Cystic (<3 years of age)
    - Intracavitary Irradiation
      - Small Lesion; Distant to optic nerves/chiasm

- Subtotal Resection
  - Observation
  - MRI every 6 months

- Partial Resection
  - High Precision Fract. RT
  - Radiosurgery
    - Small Lesion; Distant to optic nerves/chiasm

- Short-term Observation
  - <3 years of age