



# Different approaches in radiation therapy of craniopharyngioma

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Radiation therapy is a cornerstone in the therapeutic management of craniopharyngioma. The close proximity to neighboring eloquent structures pose a particular challenge to radiation therapy. Modern treatment technologies including fractionated 3-D conformal radiotherapy, intensity modulated radiation therapy, and recently proton therapy are able to precisely cover the target while preserving surrounding tissue. Tumor controls between 80 and in excess of 90% can be achieved. Alternative treatments consisting of radiosurgery, intracavitary application of isotopes, and brachytherapy also offer an acceptable tumor control and might be given in selected cases. More research is needed to establish the role of each treatment modality.

**Keywords:** craniopharyngioma, radiotherapy, post-operative

## INTRODUCTION

Surgery and radiotherapy are the cornerstones in therapeutic management of craniopharyngioma. Radical excision is associated with a risk of mortality or morbidity particularly as hypothalamic damage, visual deterioration, and endocrine complication between 45 and 90% of cases. By contrast, recurrent disease after partial excision alone is observed between in 50 and 91% (Becker et al., 1999). Today less radical surgery in combination with radiation therapy are favored achieving a progression-free survival between 70 and 90% (Fahlbusch et al., 1999; Chiou et al., 2001; Tomita and Bowman, 2005).

New technologies are currently under investigation to achieve a better balance between tumor control and the risk for hazardous effects for surrounding eloquent structures such as the pituitary gland, hypothalamus, optic apparatus, and arteries at the base of the skull.

## ROLE OF RADIOTHERAPY/CONVENTIONAL TECHNOLOGIES

External fractionated radiotherapy is presently standard of care to achieve an optimal progression-free survival after non-radical excision (Wen et al., 1989; Hetelekidis et al., 1993; Merchant et al., 2002; Stripp et al., 2004; Karavitaki et al., 2005; Lin et al., 2008). An excellent long-term outcome of conventional radiotherapy was found in many retrospective series reporting 10 and 20 years progression-free survival up to 95 and 54% (Table 1).

## MODERN TECHNOLOGIES IN RADIATION THERAPY

Advances in radiation therapy technologies have opened up new approaches in the radio-oncological management of craniopharyngioma. The selection of the adequate treatment technology is of ongoing debate.

## FRACTIONATED CONFORMAL RADIOTHERAPY/INTENSITY MODULATED RADIATION THERAPY

With the use of modern imaging technologies and treatment planning systems a precise coverage of the tumor area can be achieved by using stereotactic irradiation technologies. Stereotactic irradiation can be given in a single dose as stereotactic radiosurgery or in multiple doses as fractionated stereotactic radiotherapy. The modern systems permit an exact calculation of dose distribution within the tumor and provide a steeper dose gradient to surrounding normal tissue. If a cystic component is present, careful monitoring during radiotherapy is necessary (Winkfield et al., 2009). The results are shown in Table 2.

## PROTON THERAPY

The major advantage of proton therapy is the high degree of dose conformity to the target. Beltran et al. (2011) retrospectively evaluated proton treatment plans with IMRT plan. He concluded that compared with photon IMRT proton therapy has the potential to significantly reduce whole brain and body irradiation. Fitzek et al. treated 15 patients with craniopharyngioma with a mix of photon and protons. The tumor control rates at 5 and 10 years were 93 and 85%, respectively (Fitzek et al., 2006). Luu et al. (2006) treated 16 patients. Local control could be achieved in 14 of 15 patients (Luu et al., 2006).

## TIMING OF RADIATION THERAPY

Often immediate post-operative radiation therapy is favored in order to obviate early tumor progression leading to a functional deterioration caused by tumor growth or the necessity for repeat surgery. Others favor a watch-and-wait strategy fearing the long-term adverse effects of radiation therapy. The recent series of Stripp et al. (2004), Tomita and Bowman (2005), and Moon et al.

**Table 1 | Post-operative radiotherapy in craniopharyngioma/conventional techniques (tumor control and survival).**

Author	Patients	PFS (%)		OS (%)	
		5 years	10 years	5 years	10 years
Carmel et al. (1982)	14	78	78	90	80
Habrand et al. (1999)	32	78	56	91	65
Flickinger et al. (1990)	21	95	95	89	89
Rajan et al. (1993)	173	–	83	–	77
Hetelekidis et al. (1993)	46	–	86	–	91
Mark et al. (1995)	25	96	–	96	96
Varlotto et al. (2002)	24	89.1 (10 years)	54 (20 years)	100 (10 years)	92.3 (20 years)
Pemberton et al. (2005)	87	77 (10 years)	66 (20 years)	86 (10 years)	76 (20 years)

PFS, progression-free survival; OS, overall survival.

**Table 2 | Results after modern external fractionated radiotherapy techniques.**

Author	Patients	Technique	Dose	PFS	OS
Combs et al. (2007)	40	3-D conformal fractionated stereotactic radiotherapy	Median 52.2 Gy, range 50.4–56 Gy, 1.8–2 Gy single dose	100% local control at 5 and 10 years	5/10 years 79/89%
Minniti et al. (2007)	36	3-D conformal fractionated stereotactic radiotherapy	50 Gy in 30–33 fractions	3–5 years 97/92%	3/5 years 100%
Kanesaka et al., 2011 (adults)	16	3-D conformal fractionated stereotactic radiotherapy	30 Gy in 6 fractions	3 year local control 82.4%	3 year 94.1%
Hashizume et al. (2010)	10	FSRT Novalis IMRT	30–39 Gy in 10–15 fractions (median 33 Gy)	Control rate 100%	Not reported
Selch et al. (2002)	16	3-D conformal fractionated stereotactic radiotherapy	55 Gy fractionated	75% at 3 years	93% at 3 years

(2005) showed no differences between progression-free and overall survival between the different approaches (Table 3). However, in the recent series of Lin et al. (2008) early radiation therapy yielded a 100% local control rate at 10 years as compared with 32% when radiation therapy was performed at relapse.

## OTHER TECHNOLOGIES

### RADIOSURGERY

Stereotactic radiosurgery is an alternative to fractionated treatments in patients with craniopharyngioma harboring smaller lesions. The reported results of radiosurgery, however, suggest that tumor control is inferior to fractionated treatments and might carry the risk for optic neuropathies unless only smaller lesions are treated away from the optic apparatus (Tishler et al., 1993). Minniti et al. (2009) reviewed eight published series and found an average tumor control rate of 90% for solid tumors, 88% for cystic tumors, and 60% for mixed tumors (Table 4).

### CYBERKNIFE

CyberKnife includes a compact linear accelerator mounted on a robotic arm combined with the pair of diagnostic X-ray sources permitting an online reproducibility of the incident beams and a subsequent adjustment of the beam with a precision below 1 mm. Lee et al. reported results obtained in 16 patients treated

**Table 3 | Early versus delayed radiation therapy/impact on progression-free and overall survival.**

Author (year)	Patients	Early RT	RT at relapse
Sung et al. (1981)	10	–	70.9%, 10 years OS
Regine et al. (1993)	58	78%, 20 years OS	25%, 20 years OS
Stripp et al. (2004)	40	83%, 10 years OS	86%, 10 years OS
Tomita and Bowman (2005)	30	71%, 5 years PFS	90%, 5 years PFS
Moon et al. (2005)	50	91.3%, 10 years PFS	91.2%, 10 years PFS
Lin et al. (2008)	31	100%, 10 years LC	32%, 10 years LC

RT, radiotherapy; OS, overall survival; PFS, progression-free survival; LC, local tumor control.

for residual recurrent craniopharyngioma Tumor shrinkage was achieved in 7 of these 11 patients and tumor control in another 3 patients. The overall tumor control was achieved in 91% of patients without complications (Lee et al., 2008).

**INTERSTITIAL BRACHYTHERAPY**

There is one report from Barlas et al. (2000) in two patients in whom iodine<sup>125</sup>-seeds were implanted delivering a dose

of 67 and 60 Gy to tumor periphery. Response was partially observed in one and tumor completely resolved in the other patient 24 months after treatment. Radiation induced

**Table 4 | Outcome after stereotactic single dose radiosurgery in craniopharyngioma (Gamma Knife).**

Author	Patients	Dose	PFS	OS
Kobayashi et al. (2005)	98	Marginal dose 11 Gy	61 and 54% at 5 and 10 years	94.1 and 91% at 5 and 10 years
Ulfarsson et al. (2002)	21	3–25 Gy	34%	n.a.
Amendola et al. (2003)	14	14 Gy (11–20 Gy)	86%	All alive 6–86 months
Chiou et al. (2001)	10	Median 16.4 Gy	58%	n.a.
Yu et al. (2000)	46	Marginal dose 8–18 Gy	89.5%	n.a.
Chung et al. (2000)	31	9.5–16 Gy	87%	n.a.
Mokry (1999)	23	Marginal dose 8–9.7 Gy	74%	n.a.
Prasad et al. (1995)	9	13 Gy	62.5%	n.a.

*n.a., not analyzed.*

**Table 5 | Intracavitary instillation of radionuclides/impact on tumor control and visual function (modified according to Derrey et al., 2008).**

Author	Patients	Isotope	Complete remission	Reduction	No change	expansion	Tumor control	Visual impairment
Voges et al. (1997)	62 78 C	Y 90 Rhe 186 P 32	35/78	27/78	12/78	4/78	10 years OS Solid: 31% Cystic: 64%	4/62
Blackburn et al. (1999)	6 9 C	Y 90	0	6	1	2	n.a.	1/5
Hasegawa et al. (2004)	41 41 C	P 32	7	24	5	5	10 years: 70% Solid comp.: 32% increase	3/40 (RT induced)
Derrey et al. (2008)	39 44 C	Rhe 186	17	17	5	5	n.a.	3/39

*C, cysts; Y 90, Yttrium 90; Rhe 186, Rhenium 186; P 32, Phosphorus 32; OS, overall survival.*

**Table 6 | Advantages and disadvantages of modern treatment technologies in radiotherapy of craniopharyngioma.**

Technology	Advantages	Disadvantages
Conventional 2-D radiotherapy	Reliable clinical data and long follow-up indicating high efficacy of radiotherapy	Poor geometrical precision. No reliable protection of normal surrounding tissue
Fractionated conformal radiation therapy/IMRT	Excellent adjustment of treatment portals to tumor site. In 3-D. Sparing of normal tissue	Rigid head fixation (relocatable). Few patient numbers and not yet long follow-up
Fractionated proton therapy	Optimal coverage of tumor site. With maximal sparing of surrounding tissue	Few patient numbers. Limited access, high costs
Radiosurgery	Only one session. Excellent coverage of tumor. Almost no dose to non-target tissue	Limited clinical settings. Tumor control inferior to fractionated treatments? Low patient numbers. No long follow-up
Hypofractionated image guided radiosurgery (CyberKnife)	Only few session. The biological advantages of fractionation can be utilized. Excellent coverage of tumor. Almost no dose to non-target tissue	Very few experiences. Role still unclear. No reliable data for tumor control. No long-term follow-up. Only selected clinical settings
Intracavitary colloid isotope application	High tumor control rates for cystic components	Only cystic tumors. Underdosage in solid components. Leakage possible. Detrimental effects on visual function reported
Interstitial irradiation (Iodine seeds)	Excellent dose conformity. Optimal protection of normal tissue	Very few clinical data

toxicity or recurrence has not been reported 6 years after treatment.

### INTRACAVITARY APPLICATION OF ISOTOPES

Approximately 90% of craniopharyngioma display a cystic component often leading to a space occupying clinically relevant effect. There are different series reporting on the intracavitary application of different isotopes such as Rhenium<sup>186</sup>, Yttrium<sup>90</sup>, or Phosphorus<sup>32</sup>. The nuclides emit  $\beta$ -rays with a therapeutic range within only a few millimeters. Response rates and cyst controls can be achieved in more than 80% of case. Tumors with a solid component, however, are insufficiently controlled (Voges et al., 1997; Hasegawa et al., 2004). Deterioration of visual function due to ionizing irradiation of the nuclides can occur (Table 5).

### CONCLUSION

Standard treatments today consist of fractionated external irradiation therapy. The recent developments in modern treatment technologies permit an exact delineation of target and non-target surrounding normal tissue (Merchant et al., 2006). Tumor control and overall survival might be improved as compared with the excellent results obtained with conventional treatments at shorter follow-up periods. Longer follow-up periods, however, are warranted. Today the 5-year progression-free survival after modern fractionated irradiation is in the range between 80 and 100%. Good results are achieved with a combined approach (surgery + radiation therapy) using standard fractionation. The

recently introduced proton therapy opens up the possibility for a better sparing of normal surrounding tissue. Presently data are, however, limited and the expected improvement of functional outcome remains yet to be proven.

Post-operative radiation therapy is superior to surveillance after non-radical resection in terms of progression-free survival. The impact of different timing on functional outcome is still unknown. The current prospective German study Craniopharyngioma 2007 is addressing this issue in a randomized prospective study.

Radiosurgery as an option for circumscribed small lesions away from the optic apparatus is an attractive option because normal surrounding tissue is excellently spared. Single dose radiotherapy is, however, associated with an inferior tumor control according to retrospective data. CyberKnife as a new technological development utilizing image guided high precision stereotactic radiotherapy is able to use the radiobiologically advantageous fractionation concept. Interstitial treatments like the intracystic application of radioactive colloids might be used in selected cases in which only cystic tumors are present. It is, however, more a historical experience and should not be favored in the area of modern treatment technologies. Brachytherapy is of limited importance and the experiences so far obtained are very scarce. Minimizing the dose to non-target tissue will be the future step to reduce the risk for late effects. Reproducible data in prospective settings including neurocognitive function, quality of life, visual, and endocrinological function are still missing and require further research and evaluation. Table 6 gives an overview of the current technologies.

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