Rep Pract Oncol Radiother, 2005; 10(3): 131-134

Original Paper

Received: 2005.01.06
Accepted: 2005.04.06
Published: 2005.07.15

500 kHz hyperthermia assisted HDR brachytherapy in the treatment of recurrent cervical and endometrial cancer in previously irradiated fields

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The proceedings from the 3rd Congress of the Polish Society of Radiation Oncology. Technical, Biological, and Clinical Advances in Radiotherapy, 13–16 October 2004, Bydgoszcz.

Summary

Background The biological effectiveness of elevated temperature (hyperthermia) on cancer cells is a well documented issue. Nevertheless, it is still not widely used in clinical practice, mainly due to technical difficulties. The main limiting factor is the protection of healthy tissue during the hyperthermia procedure. Hyperthermia, used as an adjuvant treatment with brachytherapy, provides the possibility of lowering total radiation doses, without reducing biological effects.

Aim The aim of this work was to present the advantages of using 500 kHz hyperthermia in HDR brachytherapy of cervical & endometrial cancer.

Materials/Methods Hyperthermia procedures were performed in 8 endometrial cancer patients and 2 cervical cancer patients with early recurrent local disease in previously irradiated areas. One or two interstitial hyperthermia procedures were performed using rigid metal needles, both for brachytherapy and temperature elevation. The total radiation dose was 30 Gy, delivered in 3 or 6 Gy per fraction. In the case of 3 Gy per fraction, a scheme of two fractions per day, separated by at least 8 hours, was used. The total treatment time ranged from 5 to 14 days. Hyperthermia was performed concurrently with brachytherapy.

Results During the treatment, no acute reactions were observed. In each case, tumour regression over 50% was noted. During the 3 to 14 month follow-up period, complete vaginal tumour regression was seen in 8 of 10 cases.

Conclusions 500 kHz hyperthermia assisted interstitial brachytherapy can be regarded as effective and safe procedure, especially when applied as secondary (salvage) treatment. More cases and longer observation time are needed to make definite conclusions.

Key words **cervical cancer • endometrial cancer • brachytherapy • secondary radiotherapy**

Full-text PDF: http:/www.rpor.pl/pdf.php?MAN=7581

Word count: 1719
Tables: –
Figures: –
References: 14

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Background

Despite diagnostic and therapeutic progress, cervical cancer still has one of the worst epidemiological indices in Poland. Data analysis for the year 2000, has shown a morbidity level of 6.8% and a mortality level 5.4% for all malignancies. During the same period, 3597 new cases of cervical cancer were diagnosed and 1987 deaths were recorded as being caused by this disease [1]. In quite a large proportion of patients, because of the advanced clinical stage of the disease (IIB-IIIB according to FIGO), the treatment of choice is radiotherapy or radio-chemotherapy with intent to-treat. To reach the optimum dose distribution, the accepted standard is to supplement the dose delivered during external beam radiotherapy, with intracavitary brachytherapy [2]. The epidemiological indices for endometrial cancer, during the same year were 3276 (6.2% of all malignancies), and are not so pessimistic. During the year 2000, a total of 808 deaths caused by endometrial cancer were noted, which accounts for 2.2% of all deaths caused by these malignancies. Better results of therapy in this case are mainly owing to less advanced disease which gives the possibility for radical surgical treatment (and eventual adjuvant external beam or brachytherapy) [3]. In either of the above mentioned tumour sites, there may be some problems with patients suffering from relapse in a previously irradiated field. Co-exisitng conditions and the impossibility of injury avoidance, often exclude surgical treatment, while the tolerance dose of critical organs makes secondary irradiation impossible. Improved biological effectiveness from elevated temperatures (hyperthermia) on cancer cells and the potential of its association with radiotherapy is a well known issue. Nevertheless it is not used widely enough in oncological practice. The main limiting factors are technical difficulties regarding hyperthermia procedures. The problems are connected with limited capabilities in obtaining therapeutic temperatures (>42.5°C) inside the tumour while maintaining healthy tissue protection. Hyperthermia, used as a complementary treatment to radiotherapy provides the possibility to deliver lower doses with the same biological effects. Interstitial brachytherapy may enhance this phenomenon by reducing the irradiated volume and makes it possible to deliver simultaneous hyperthermia to the irradiated tissues via the same applicators. A unique therapeutic HT-2 set, used in the Centre of Oncology, allows the practical use of hyperthermia in the treatment of cervical and endometrial cancer [4].

Materials

Hyperthermia procedures were performed in 10 patients: 8 endometrial cancer cases and 2 cervical cancer patients with early recurrence in a previously irradiated field. Hyperthermia was combined with interstitial HDR brachytherapy. Patients were aged between 46 and 75 years (average 65). All the patients underwent, prior to recurrence detection, primary post-operative, external beam irradiation (box technique, 46Gy/23fr) with the addition of vaginal cuff HDR brachytherapy (2–3 × 7,5Gy/fr/0,5cm from the applicator surface).

Methods

An HT-2 set with a 500 kHz frequency generator [4] was used. One or two interstitial hyperthermia procedures were performed, using rigid metal needles for an HDR Ir-192 source (Gammamed 12i) and for energy transmission. The total dose was 30 Gy, dose per fraction 3 or 6 Gy, and total treatment time was from 5 to 14 days. In the case of 3 Gy per fraction, irradiation was performed twice daily with an interval of at least 8 hours. Dose distribution calculations were based on x-ray needle localizations using the Abacus computer planning system. The dose was specified as 0.5–0.7 mm from the needle surface. The irradiated volume ranged from 25 to 50 cm^3 (average 30 cm^3). For this group of patients, thanks to the mobility and the compact size of the HT-2 set, unique application of brachytherapy during the hyperthermia procedure was possible (after the therapeutic values of the temperatures were obtained, brachytherapy was started, without interruption of the hyperthermia procedure). In each case, in order to avoid the thermoresistance effect, the hyperthermia procedure was performed at 48 hours intervals. The total treatment time was 45–60 minutes and included at least 45 minutes with temperatures at up to 46–49°C.

Results

Early sequelae, which may have caused interruptions in treatment, were not observed. In every case, irradiation reactions appeared as erythema with superficial subsidence of the epithelium and intensified mucous secretion. Rectal and bladder reactions were observed in 6 patients but were limited to grade I, according to the EORTC/RTOG scale, and were cured spontaneously. Follow-ups were performed one month after treatment and every 3 months thereafter. Post-irradiation reaction

symptoms disappeared 2–3 months after conservative treatment (local steroids, vessel wall protectant / oxerutin / anti-infamatory agents / diclofenac). No late side-effects were observed. During the follow-up period of 3 to 14 months, complete vaginal tumour regression was confirmed by clinical examination in 8/10 cases. In two cases no regression was seen. In one case of cervical cancer, a tumour of 4 cm was observed in CT scans before treatment. Complete regression of the tumour was seen after treatment. This effect lasted for 10 months. This patient died as a result of sigmoid perforation, followed by peritonitis. From the surgical point of view, the observed lesions were located outside the re-irradiated volume. The perforation was owing to sigmoid occlusion caused by adhesions. In a second case, after 5 months follow-up with complete regression, vaginal recurrence (outside the re-irradiated field) and pulmonary metastases were detected. In this case, chemotherapy according to the PAC scheme (cis-platin, adriamycine, cyclophosphamide) was performed. Tumour stabilization was observed.

Discussion

The treatment of early recurrence in previously irradiated fields is not an easy task. The possibilities for surgical treatment are often limited because of the impossibility of obtaining optimal margins without serious injury to the patient (often colpectomy or ureterotomy). Further irradiation is often impossible owing to risks in exceeding the tolerance doses for healthy tissues. The only alternative method is chemotherapy, which cannot be regarded as radical treatment. It seems that the most interesting possibility for this group of patients is the application of hyperthermia as a method for strengthening the effects of radiation therapy [5]. Several recently published papers show a higher index of clinical effectivness after incorporating hyperthermia into radiotherapy. Among the most relevant of these are the results of the "Dutch Deep Hyperthermia Group". This was a prospective, randomised, multi-centre study based on the treatment results of 358 patients with cervical, rectal or bladder cancers. In this group, the 114 patients with cervical cancer were divided into two subgroups – 58 patients received radiotherapy and hyperthermia and 56 patients received radiotherapy alone. Local control rates were 61% and 41% with 3-year survival times being 51% and 27% respectively and being statistically significant. In the subgroup of patients with rectal cancer (143 patients) no statistically relevant difference was observed. Again, the local control rates were respectively 16% and 8% with 3-year survival times of 22% and 13% respectively. For the 101 patients with bladder cancer respective values were 42% versus 33% and 28% versus 22%[6]. It is very important to note that these results were obtained using "external heating" which is not so effective as intracavitary heating due to treatment intolerance and a lower range of temperatures.

In a randomised trial by Harima et al, assessing the concentration of Bax and Bcl-2 proteins in irradiated cervical carcinoma cells, significantly different protein concentrations were found when treatment by hyperthermia and radiotherapy was compared with radiotherapy alone. This was positively correlated with the percentage of complete tumour regression (83.3% in the hyperthermia combined group vs. 52.6% in the radiotherapy alone group). A negative correlation was observed with lack of response (5.6% vs. 21.1% respectively) [7].

Vasanthan et al. found no benefits from the addition of hyperthermia to radiotherapy in cervical cancer patients. It should be pointed out that the temperatures achieved in this study were in many cases significantly lower than needed minimum of 42.5°C [8]. Being multi-centered, this study included a very limited number of patients from each institution (1–27) and irradiation was performed in a non-uniform manner. The hyperthermia procedure was performed using different machines and using different protocols. Temperature measurements were not performed in more than 50% of the hyperthermia sessions. With respect to the increasing efficiency of radiotherapy, limitation of the total dose and avoidance of late sequelae are possible. An interesting observation was made by Van der Zee et al. [9] while evaluating post-irradiation injuries in post mastectomy breast cancer patients, treated for scar recurrence. Two adjacent regions of the thoracic wall were irradiated with the same dose. The difference between these areas was the addition of simultaneous hyperthermia to irradiation therapy in one field. As a result, significantly fewer signs of telangiectasia were observed in hyperthermia treated fields. Authors associate this with faster sub-lethal injury repairs to intraepithelial cells damaged during irradiation. In their study, Li et al. [10], treating breast cancer patients with recurrence, confirmed a higher percentage of complete remissions in previously irradiated fields when hyperthermia was added. Even significantly lower doses (43 Gy in radiotherapy + hyperthermia

group vs. 59.5 Gy in radiotherapy alone group), were more effective when hyperthermia was applied. In a recently published paper, Kouloulias et al. showed a higher sphincter preservation rate (95.8% radiotherapy + hyperthermia vs. 68.0% radiotherapy alone) when hyperthermia was added to the standard radio-chemotherapy of anal cancer patients [11].

With respect to the necessarily high radiation doses used in gynaecological malignancies, hyperthermia provides a means to limit radiation induced injuries. This fact is crucial in the case of re-irradiation. Studies with practical hyperthermia application, performed over several years at Centre of Oncology in Warsaw [4,12], confirmed its biological effect and proves its practical usefulness. In particular, simultaneous interstitial brachytherapy and hyperthermia allows us to take maximum advantage of the combination of both methods [13,14]. To date, however, the results presented above refer to a small group of patients with relatively short follow-up. Nevertheless, on this basis we may take advantage of the therapeutic potential of simultaneous hyperthermia and radiotherapy.

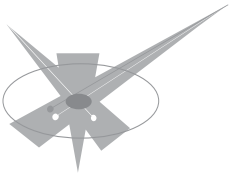
Conclusions

A 500 kHz hyperthermia assisted interstitial brachytherapy can be regarded as effective and safe procedure, specially when applied as secondary (salvage) treatment. More cases and longer observation time are needed to make definite conclusions.

References:

1. Didkowska J, Wojciechowska U, Tarkowski W, Zatoński W: Nowotwory złośliwe w Polsce w 2000 roku. Centrum Onkologii – Instytut im. M. Skłodowskiej-Curie Warszawa, 2003
2. Perez C: A Uterine Cervix w: Principles and practice of radiation oncology. red. Perez CA, Brady LW, Lippincott-Raven, 1998, 1733–84
3. Glassburn JR, Brady LW, Grigsby PW: Endometrium w: Principles and practice of radiation oncology red. Perez CA, Brady LW, Lippincott-Raven, 1998, 1835–52
4. Piotrkowicz N, Zieliński J, Łyczek J, Dębicki P: 500kHz intracavitary hyperthermia in the treatment of patients with cervical and endometrial cancer – preliminary results and treatment description. Nowotwory, 2002; 5: 403–6
5. Overgaard J. The current and potential role of hyperthermia in radiotherapy. Int J Radiat Oncol Biol Phys, 1989; 16: 535–49
6. van der Zee J, Gonzales Gonzales D, van Rhoon G: Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective, randomised, multicentre trial. Lancet, 2000; 355: 1119–25
7. Harima Y, Nagata K, Harima K et al: Bax and Bcl-2 protein expression following radiation therapy versus radiation plus thermoradiotherapy in stage IIIb cervical carcinoma. Cancer, 2000; 1: 132–38
8. Vasanthan A, Mitsumori M, Park J et al: Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency Int J Radiat Oncol Biol Phys, 2005; 1: 145–53
9. van der Zee J, Wijnmaalen AJ, Haveman J et al: Hyperthermia may decrease the development of teleangiectasia after radiotherapy. Int J Hyperthermia, 1998; 1: 57–64
10. Li G, Mitsumori M, Ogura M et al: Local hyperthermia combined with external irradiation for regional recurrent breast carcinoma. Int J Clin Oncol, 2004; 3: 179–83
11. Kouloulias V, Plataniotis G, Kouvaris J et al: Chemoradiotherapy combined with intracavitary hyperthermia for anal cancer: feasibility and long – term results from a fase II randomised trial. Am J Clin Oncol, 2005; 1: 91–99
12. Piotrkowicz N, Zieliński J, Roszkowska K et al: Wstępne wyniki zastosowania śródjamowej hipertermii 500 kHz u chorych na raka szyjki i trzonu macicy – ocena kliniczna i patologiczna. Gin Pol, 2003; 9: 824–29
13. Arcangeli G, Nervi C, Cividalli A: Problem of sequence and fractionation in the clinical application of combined heat and radiation. Cancer Res, 1984; 44(Suppl): 4857–63
14. Valdagni R, Liu FF, Kapp DS: Important prognostic factors influencing outcome of combined radiation and hyperthermia. Int J Radiat Oncol Biol Phys, 1988; 15: 959–72

Rep Pract Oncol Radiother, 2005; 10(3): 135-140



Original Paper

Received: 2004.12.20
Accepted: 2005.06.06
Published: 2005.07.15

Conformal radiotherapy in children with low-grade brain tumours: treatment results and toxicity

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The proceedings from the 3rd Congress of the Polish Society of Radiation Oncology. Technical, Biological, and Clinical Advances in Radiotherapy, 13–16 October 2004, Bydgoszcz and ESTRO 23, 24–28 October 2004, Amsterdam.

Summary

Background The conformal radiotherapy technique is a particularly important method for the treatment of children with localized low-grade brain tumours, whose prognosis, with regard to long-term survival is often excellent and should be accompanied by the smallest possible risk of toxicity.

Aim The results of 3-D conformal radiotherapy in children with low-grade astrocytoma and craniopharyngioma, treated in our department to present.

Materials/Methods Between 1997–2001, 20 children, aged between 3.5 and 18 years, with low-grade brain tumours (8 craniopharyngioma and 12 low-grade astrocytoma) were treated with conformal radiotherapy. In the craniopharyngioma group, all patients were irradiated owing to tumour recurrence, after multiple surgeries, and were seriously handicapped before the commencement of radiotherapy. Patients with astrocytoma were treated after chemotherapy, partial surgery or biopsy only.

Results All patients with craniopharyngioma survived with no recurrence (5) or with a stable disease state (3). Radiation related complications were not observed. Four patients with astrocytoma died, due to progressive disease (3) or chemotherapy related complications (1). Two patients are living with dissemination to the CNS, 4 with no recurrence and 2 have stabilized. Late complications after radiotherapy were not observed.

Conclusions Three-dimensional radiation therapy is a safe and successful method for the combined treatment of children with low-grade brain tumours. The risk of radiotherapy related complications is relatively low.

Key words **conformal radiotherapy • brain tumours • craniopharyngioma • astrocytoma • children**

Full-text PDF: http:/www.rpor.pl/pdf.php?MAN=7660

Word count: 1511
Tables: 2
Figures: –
References: 18

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Background

CNS tumours constitute approximately 20% of all paediatric neoplasms. Low-grade astrocytomas account for nearly one-half of all brain tumours in children. They are a heterogenous group of tumours, with an overall survival rate as high as 80–100%. Craniopharyngiomas represent less than 10% of intracranial neoplasms in children and adolescents and one half of sellar tumours. Despite recent progress in neurosurgery and development of new chemotherapy protocols, radiotherapy is still an important method in the treatment of CNS tumours in children [1].

Conformal radiotherapy techniques are performed using multiple treatment fields, each shaped to conform to a "beam's eye" view of the target volume. This allows for a high homogenous dose of irradiation to be delivered to the tumour region while minimising the doses to normal tissue. This is particularly important for children with localized low-grade brain tumours whose prognosis regarding long-term survival is often excellent and should be accompanied by the smallest possible risk of toxicity [2,3].

Aim

The aim of this work was to present the results of three-dimensional conformal radiotherapy in children with low-grade brain tumours, treated in our department.

Materials and Methods

Between 1997 and 2001, 20 children, aged 3.5–18 years, 8 with craniopharyngioma and 12 with low-grade astrocytoma, were treated with conformal radiotherapy techniques in our Radiotherapy Department. Neurosurgery and chemotherapy were carried out in the Children's Memorial Health Institute in Warsaw.

All patients with craniopharyngioma were referred to radiotherapy, due to tumour recurrence after multiple surgeries, and were seriously handicapped before the onset of radiotherapy.

Patients with astrocytoma were treated after partial surgery (3) or biopsy only (9) or after chemotherapy (7).

Radiotherapy was delivered using a linear accelerator with an energy of 6 or 15 MV. The total dose at the ICRU reference point was 54 Gy in 30 fractions for all patients.

Orfit masks were used for head immobilisation in all cases. After preliminary simulations, the patients underwent CT examinations in their treatment position. The 3-D treatment planning was performed with a 3-D treatment planning system, TMS-Helax. The gross tumour volume (GTV) included the tumour itself or the tumour bed with residual tumour. The CTV included the GTV with an added margin of 1.0 cm. The planning target volume (PTV) included the CTV surrounded by an additional margin of 0.5 cm in three dimensions.

Beam position, dimensions and shape were planned using the beams eye view. All patients were treated by an isocentric technique, using photon beams generated by a Megatron KD2 accelerator (Siemens). Most patients were treated with three or more noncoplanar fields. The irradiated volume was matched to the planned volume by using individual blocks. Three-dimensional dose distributions were calculated with the help of our TPS. Minimal, maximal and average doses to the PTV as well as the maximal dose to organs of risk was reported, together with dose-volume histograms. Simulations of the treatment plan were performed using an Oldelft simulator, and simulator radiographs were produced. The post verification films were taken during the first irradiation. The portals were compared with simulator films and the DRRs by a dedicated computer program. In most cases (90%), no correction of field position or shielding was required.

Neurologic/hormonal late complications of radiotherapy were graded according to the Bloom scale (4).

Results

The observation period was closed on the 31.01.2003. The median time of follow up, from commencement of radiotherapy until the last observation, was 48 months (from 4 to 80).

All patients with craniopharyngioma are living with no recurrence (5) or with a stable disease state (3). No radiotherapy related complications, according to the Bloom scale, were observed.

Four patients with astrocytoma died. In 3 patients, progression of nonoperable tumours after 6, 9 and 12 months occurred. Those patients survived

Table. 1. Craniopharyngioma patients – characteristics and treatment results.

No	Sex	Age at time of diagnosis (years)	Surgery (year)	Status before RT	Age at time of RT	RT (year)	Present status	Follow up (months)
1	M	4	1995 1997	Hypophysis insuff. Partially blind	6	1992	NED Hypophysis insuff. HRT Partially blind	78
2	F	3	1988 1990	Hypophysis insuff. Totally blind	12	1997	SD Hypophysis insuff. Osteoporosis, HRT Totally blind	67
3	M	5	1996 1996 1998	Hypophysis insuff. Partially blind	7	1998	SD Hypophysis insuff. HRT Partially blind	60
4	M	13	1997 1999	Hypophysis insuff. Diabetes insipidus	15	1999	NED Hypophysis insuff. HRT	48
5	F	3	1996 1999	Pubertas praecox Hypophysis insuff.	5	1999	NED Hypophysis insuff. HRT	48
6	M	5	1997 1999	Hypophysis insuff.	8	2000	NED Hypophysis insuff. HRT	44
7	M	4	1996 1997 1998	Hypophysis insuff. Totally blind	8	2001	SD Hypophysis insuff. HRT Totally blind	32
8	F	4	1997 2001	Hypophysis insuff. HRT	7	2001	NED Hypophysis insuff. HRT	32

NED – no evidence of disease; SD – stable disease; HRT – hormone replacement therapy; RT – radiotherapy.

from 1 to 13 months. One died owing to complications of chemotherapy. Two are living with metastases to the supratentorial and spinal regions, diagnosed 6 and 16 months post radiotherapy. Both were treated for the stabilisation of symptoms using multiagent chemotherapy regimes including: Adriamycin, Ifosfamid and Vepesid. Four children are living with no recurrence and 2 have stabilized, as confirmed by MRI.

No late complications of radiotherapy, evaluated according to the Bloom scale, were observed.

Patient status and treatment results are presented in Tables 1 and 2.

Discussion

Conformal radiotherapy techniques as 3-D conformal radiotherapy, or stereotactic radiotherapy for smaller tumours, have become the standard for the care of children and adults with relatively noninvasive intracranial tumours.

For patients after subtotal resection of craniopharyngioma, 3-D conformal radiotherapy or more precise techniques, such as stereotactic radiotherapy, were widely applied. Results from those treatment methods are excellent, with 5–10 year overall and disease-free survival rates as high as 90% and 80% respectively [5–9]. In most expert opinions, external irradiation should be applied early in the treatment course, and following limited surgical resection, in order to limit the severe toxicity that has been reported following maximal tumour resection and repeated surgeries [10,11]. In our material, all patients with craniopharyngioma were refered for radiotherapy owing to tumour recurrence after multiple surgeries and were seriously handicapped before radiotherapy began.

In the St. Jude Children's Research Hospital, experience with paediatric patients treated for craniopharyngioma showed that children treated by surgery lost a mean of 9.8 points on the IQ scale while those treated using combined-mo-

Table 2. Astrocytoma patients – characteristics and treatment results.

No	Sex	Age at time of diagnosis	Surgery (year)	Chth	RT		Status before RT	Present status	Follow up (months)
					Year	Age			
1	M	9	1996 (partial)	No	1997	9	No deficits	NED No deficit	80
2	M	14	1997 (biopsy)	No	1997	14	Epilepsy	Progression 1998 DDD 1999	+20
3	M	10	1997 (biopsy)	No	1997	10	Hemiparesis N.VII paresis	NED No deficit	78
4	F	6	1997 (biopsy)	Yes (progression)	1997	6	Somnolence	DDD 1998	+12
5	M	13	1993 (part) 1994 (part) 1998 (shunt)	Yes	1998	18	Visual deficits Quadriparesis	Dissemination (chemotherapy) LWD	60
6	F	10	1998 (biopsy)	No	1998	10	N.VI paresis	DDD 1999	+12
7	M	14	1998 (biopsy)	Yes	1999	15	Epilepsy N.VI paresis	Dissemination (chemotherapy) LWD	48
8	F	11	1993 (part) 1998 (part)	Yes (progression)	1999	17	Ataxia	DDC (chemotherapy related)	+2
9	M	3	1988 (part) 1999 (part)	No	1999	14	N.VI paresis	NED	50
10	M	2	1994 (partial)	Yes	1999	6	Hypophysis insuff.	SD Hypophysis insuff.	50
11	F	2	1998 (biopsy)	Yes (progression)	1999	3.5	No deficits	NED Thyroid insuff. HRT	48
12	M	5	1999 (partial)	Yes (progression)	1999	5	Nystagmus	SD	46

NED – no evidence of disease; SD – stable disease; LWD – living with disease; DDD – died due to disease; DDC – died due to complications; HRT – hormone replacement therapy.

dalities lost only 1.25 points. Patients in the surgery group, who had relapses, lost a mean of 13.1 points. The loss of 10 points was considered to be clinically significant. The surgery group also had more frequent neurologic, opthalmic and endocrine complications [7]. These findings are in agreement with our data, wherein 4 children were partially or totally blind following repeated surgical procedures.

It has now been established that limited surgery and radiotherapy cause lesser or comparable consequences. Newer radiation planning and delivery techniques have made combined modality a good initial option for most patients with craniopharyngioma.

For most children with low-grade astrocytoma, the treatment of choice is surgery. Complete resection rates are approximately 80% for hemispheric and cerebellar tumours and 40% for diencephalic tumours. Complete or subtotal resection leads to long term disease-free survival in more than 80% of children [12]. These patients are recommended to continue under surveillance alone [13]. Radiotherapy might be beneficial for patients with bulky residual tumours or with deep midline tumours that are surgically inaccessible. The overall survival rates for those patients range between 33% and 75% at 10 years [12]. Stereotactic irradiation techniques and 3-D conformal radiotherapy are well established in adults, but data regarding childhood low-grade gliomas is scarce [14].

Merchant et al. treated 38 children with fractionated conformal radiotherapy and, after a median follow-up of 17 months, only 4 tumours relapsed. Acute toxicity was low [15]. Saran treated 14 children with conformally guided stereotactic radio-

therapy and achieved a 3-year local progression-free survival rate of 87%, and an overall survival rate of 100%. Four of 12 children with neurological deficits improved while 5 remained stable [16].

In our data, radiotherapy was applied in the cases of 12 children with low-grade astrocytoma after partial resection or biopsy only. Four of these patients are living with no evidence of disease and 2 with MRI proven, stable disease.

The occurrence of metastatic disease in the CNS for low-grade astrocytoma is a rare event and occurs in only 5–10% of cases. With improvements in neuroimaging, this phenomenon is being reported with increasing frequency, and as a consequence, craniospinal irradiation needs to be considered for these patients [14]. In our material, 2 patients are living with dissemination in the CNS, diagnosed 6 and 16 months after radiotherapy. Both were successfully treated with salvage chemotherapy, including Adriamycin, Ifosfamid, Vepesid.

The role of chemotherapy in the treatment of patients with low-grade astrocytoma should be established. Platinum based chemotherapy applied in young (<5 years) children with symptomatic hypothalamic and chiasmatic tumours, delays the use of irradiation. For older symptomatic patients conformal radiotherapy remains the standard therapy [17]. In our material, 7 children were treated initially by chemotherapy while 4 progressed and one died due to an adjuvant chemotherapy related complication.

The use of local irradiation alone did not significantly effect IQ scores over time. The tumour itself is an important cause of patient's decline in IQ, and is more often observed in younger patients [17,18].

Up to the present time, we have not observed any late complications related to radiotherapy, though longer follow-up periods are necessary.

Conclusions

Three-dimensional radiation therapy is a safe and successful method for the combined treatment of children with low-grade brain tumours. Radiotherapy should be applied early in the course of treatment for patients with craniopharyngioma and following limited surgical resection to avoid severe toxicity of repeated surgery. Conformal radiotherapy is the treatment of choice for patients with astrocytoma, when total resection of tumour is not possible. The risk of radiotherapy related complications is relatively low.

References:

1. Skowrońska-Gardas A: Evaluation of radiotherapy for pediatric CNS tumours. Expert Rev Neurother, 2003; 3: 491–500
2. Adams E, Suter B, Warrington A et al: Design and implementation of a system for treating paediatric patients with stereotically-guided conformal therapy. Radiother Oncol, 2001; 60: 289–97
3. Loeffler I, Kooy H, Tarbell N: The emergence of conformal radiotherapy: special implications for pediatric neuro-oncology. Int J Radiat Oncol Biol Phys, 1999; 44: 237–38
4. Bloom H, Wallace E, Henk J: The treatment and prognosis of medulloblastoma in children: a study of 82 verifed patients. Am J Roentgenol, 1969; 105: 43–62
5. Khafaga Y, Jenkin D, Kanaen I et al: Craniopharyngioma in children. Int J Radiat Oncol Biol Phys, 1998; 42: 601–6
6. Habrand J-L, Ganry O, Couanet D et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. Int J Radiat Oncol Biol Phys, 1999; 44: 255–63
7. Merchant T, Kiehna E, Sanford R et al: Craniopharyngioma: The St. Jude Children's Research Hospital experience 1984–2001. Int J Radiat Oncol Biol Phys, 2002; 53: 533–42
8. Varlotto J, Flickinger J, Kondzolka D et al: External beam irradiation of craniopharyngiomas: long term analysis of tumour control and morbidity. Int J Radiat Oncol Biol Phys, 2002; 54: 492–99
9. Stripp D, Maity A, Janss A et al: Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. Int J Radiat Oncol Biol Phys, 2004; 58: 714–20
10. Kalapurakal J, Goldman S, Hsieh Y et al: Clinical outcome in children with reccurent craniopharyngioma after primary surgery. Cancer J, 2000; 6: 388–93
11. Kalapurkal J, Goldman S, Hsieh Y et al: Clinical outcome in children with reccurent craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. Med Pediatr Oncol, 2003; 40: 214–18
12. Freeman C, Farmer J-P, Montes J: Low-grade astrocytomas in children: evolving management strategies. Int J Radiat Oncol Biol Phys, 1998; 41: 979–87
13. Fisher B, Leighton C, Vujovic O et al: Results of policy of surveillance alone after surgical management of pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys, 2000; 51: 704–10

14. Kortman R-D, Timmermann B, Taylor R et al: Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Strahlenther Onkol, 2003; 179: 509–20

15. Merchant T, Zhu Y, Thompson S et al: Preliminary results from a phase II trial of conformal radiation therapy for pediatric patients with localized low-grade astrocytoma and ependymoma. Int J Radiat Oncol Biol Phys, 2002; 52: 325–32

16. Saran F, Baumert B, Khoo V et al: Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood. IInt J Radiat Oncol Biol Phys, 2002; 53: 43–51

17. Fouladi M, Wallace D, Langston J et al: Survival and functional outcome of children with hypothalamic/chiasmatic tumors. Cancer, 2003; 97: 1084–92

18. Debus J, Kocagöncü O, Höss A et al: Fractionated stereotactic radiotherapy (FSRT) for optic glioma. Int J Radiat Oncol Biol Phys, 1999; 44: 243–48