Very late relapse of medulloblastoma

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A case of 47-year-old woman with a local relapse of medulloblastoma 23 years after initial presentation is reported. At the age of 24, the patient underwent resection of medulloblastoma of the right cerebellar lobe, followed by the craniospinal orthovoltage irradiation (3600 R to the brain, and 3000 R to the spinal cord). At the 21st year of follow-up, a second cancer originating in the thyroid gland was diagnosed. Thyroidectomy followed by 131-iodotherapy for the papillary cancer was performed. Two years later she was operated for the recurrence of medulloblastoma at the former site. The patient was unfit for chemotherapy due to poor bone marrow reserve following the previous treatment. The reirradiation of the posterior cranial fossa was performed postoperatively. The patient was given 45 Gy in 25 fractions to the recurred tumour volume with 2 cm margin within 41 days. The treatment was performed by 6 MV photons with conformal technique and noncoplanar beams arrangement. The patient is disease free 15 months after relapse of medulloblastoma.

The following problems are discussed: late relapse of medulloblastoma, secondary cancers after craniospinal irradiation, and retreatment of CNS tumours.

key words: medulloblastoma, late relapse, radiation-induced cancers, retreatment of CNS tumours

INTRODUCTION

The period of risk for relapse of medulloblastoma is not established. We present a case of a woman with medulloblastoma located in the cerebellar hemisphere, which recurred 23 years after initial surgery, followed by radiation therapy. The long survival time makes it possible to analyse the late sequel of the initial treatment. This question includes radiation-induced malignancy. A report on a very late relapse is connected with a discussion about the retreatment of CNS tumours.

CASE REPORT

A 24-year-old woman underwent a right suboccipital craniotomy for a right cerebellar lobe tumour. The pathologic diagnosis was medulloblastoma (Fig. 1). A shunt was placed preoperatively. The subtotal resection was followed by the whole neuraxis irradiation with the orthovoltage technique, which was performed outside our institution. The dose to the posterior fossa was 3600 R in 18 fractions. The spinal cord dose was 3000 R. The dose to the brain and to the spine was specified at the depth of 4 cm from the occipital bone and from the skin, respectively. Dizzy attacks, significant hearing impairment, memory deterioration, SOMA (Subjective, Objective, Management and Analytical) [18] Grade 3 (complete, permanent) alopecia, skin atrophy and pigmentation change as well as SOMA Grade 2 (symptomatic but not dysfunctional) subcutaneous fibrosis followed the treatment.
At the 21st year of follow-up, ultrasound examination revealed the presence of the solitary nodules in the right lobe of the enlarged thyroid gland. On the assumption that it is a nodular goitre, one lobe with isthmus was excised. The specimen revealed a papillary carcinoma. Then the patient underwent total thyroidectomy. The histopathology confirmed microcarcinoma also in the left lobe of the thyroid gland. After surgery the whole body isotopic study was performed, but did not reveal any metastases. Radioactive 131-I was used to identify residual thyroid tissue and to ablate it. TSH suppression was administered. Whole body isotopic study carried out 10 months after thyroidectomy did not reveal any remnants or metastases of the thyroid cancer.

Twenty-three years after the initial treatment of medulloblastoma and two years after the thyroidectomy, the patient developed strong dizzy attacks, right facial numbness and unsteady gait within 3 months. The patient was admitted to the hospital, where lateral nystagmus and cerebellar ataxia were diagnosed. Magnetic resonance imaging (MRI) showed a tumour of the right lobe of the cerebellum, laterally to the site of origin. A total resection was performed. The excision specimen was diagnosed as a medulloblastoma (Fig. 2A, B). Postoperatively, the dizzy attacks gradually decreased but remained. First, the adjuvant chemotherapy was considered for this patient. Unfortunately, the systemic chemotherapy could not be used due to the decrease in the bone marrow reserve after radioactive iodine treatment and previous extensive irradiation. Finally, she was given 45 Gy in 25 fractions to the recurred tumour volume with 1–2 cm margin (smaller one in the contact with brainstem) within 41 days. The treatment was conducted by 6 MV X-rays with conformal technique and noncoplanar beams arrangement. The patient was given steroids during radiotherapy as a requirement. The patient remained well 16 months after the operation of relapse. Her neurological status slightly improved. MRI performed 15 months after reoperation was without any features of recurrence.

DISCUSSION

Initial treatment results

Despite the use of inadequate (according to the contemporary standards) radiation technique and doses, a long survival after an initial treatment of medulloblastoma was observed. The presumption of the low aggressiveness of the disease therefore should be made. Probably, the presence of prognostic factors other than therapeutic, mostly influenced survival in this case. Occurrence in adulthood, location in cerebellar hemisphere with lateral cerebellar syndrome was noted. Although the prognostic value of these factors was not proven [4, 6, 8], they are related to better prognosis, according to some authors. The site of the relapse was posterior fossa. The completeness of resection at the first presentation probably positively influenced survival and reduced detrimental effect of too low dose delivered for the posterior fossa. The dose less than 50 Gy
and incompleteness of resection are documented factors predicting the posterior fossa recurrence [3, 8]. The posterior fossa, alone or in addition to the other sites is the most frequent site of tumour recurrence, in 17–22% and 34–57%, respectively [3, 4, 8, 20, 30]. The only data giving the same frequency of posterior fossa and spinal failures are related to children or reduced dose delivered to the spinal axis [9, 27]. Although metastases outside the CNS occur rarely, the probability becomes higher with the local recurrence. Previously, some authors claimed that ventricular shunting was a reason of dissemination [3], but the retrospective research conducted in children did not prove this hypothesis [2].

**Initial treatment complications**

While the real contribution of administered radiotherapy in prolongation of survival is difficult to establish, the emergence of many severe treatment sequel in the follow-up period has been documented. Alopecia, brainstem necrosis, postradiation myelitis, delete of cognitive function and hearing impairment are listed in literature about late toxicity [6, 8]. Significant hearing impairment and skin side effects were observed in the presented case. The Hearing loss was frequently observed before era of 3-D conformal radiotherapy (3-D CRT). It was due to destruction of the cochlear hair cells and ischaemic changes of the vessels. These conditions did not improve after medication [10, 15]. The use of 3-D CRT, especially the intensity modulated radiation technique in the boost now allows to spare the cochlea in most cases [10, 13].

Most authors have reported the impairment of intellectual function in children after craniospinal irradiation, even after posterior fossa irradiation only [11, 25]. These sequelae are correlated with the young age at radiation and the dose delivered [11]. Because of few adult patients with medulloblastoma, it not possible to draw any firm conclusions. The data based on cohorts of long-term survived patients with glioma did not show clear correlation between radiotherapy and cognitive function decline [26]. But most reports indicate that worse memory occurs after radiotherapy [16]. This subjective memory deterioration was also observed in this case.

It is reasonable to believe that late complication in the patient was due to the papillary cancer of the thyroid gland. There are many reports about increased risk of thyroid cancer after radiation exposure in childhood, independently of the indication for radiotherapy [14, 24]. Age at radiation and dose are the most significant risk modifiers [14]. The data reporting cases of adults irradiated, estimated risk of thyroid cancer lower than in children, especially under age of five [24]. The incidence is linearly related to the dose in the low doses range, probably under 2 Gy. At higher doses dose-risk relationship becomes rather constant. This great predisposition of thyroid gland to radiation-induced tumourigenesis at low doses explains the occurrence of the cancer even if the thyroid gland is outside the irradiation field [14]. The radiation-induced thyroid cancers appear after more than 5 years. The peak of morbidity falls about 15 years and decreases 19–20 years after exposure, but persists throughout a patient’s lifetime [24]. The inadequate technique of irradiation, which involved one posterior orthovoltage X-ray field delivering many scattered radiation doses, is the most probable reason for this sequel in the presented case. Treatment of the spine with one posterior photon field should be avoided. Namely, high exit dose is the reason of side effects in the thyroid gland and surrounding organs. The use of electrons and the low level of cranio-spinal junction are required [21].

**Time and treatment of relapse**

The very late occurrence of relapse in the presented case is uncommon, however not exceptional. Although the median time to recurrence is 30–37 months, late relapses are not infrequent [6, 20]. The posterior fossa recurrences 10 and 19 years after treatment were observed [1, 4]. Concerning the 5-year disease-free survival rate amounts 41–61% and decreases to 27–48% after 10 years [6, 20], the important question is how long should we follow medulloblastoma survivors. The period of risk for relapse of medulloblastoma is not clearly defined. Some authors are consistent with so called Collins’ low. According to this low, children are considered as cured if they survive without recurrence a period equal to the age at diagnosis plus 9 months [4, 5, 23]. However, there are also data in disagreement with this theory [17, 22]. Approval of the Collins’ rule makes us use imaging studies in adult patients for many years with doubtful benefits. Lefkowitz [17] stated that yearly-performed imaging studies are ineffective because neurologic symptoms most often are the first sign of recurrence. The other argument for discontinuation of evaluation is the short survival after recurrence despite an early relapse detection [17, 28]. Probably this opinion is changing in the light of new data where the multimodality treatment consisted of systemic chemotherapy and modern radiotherapy techniques in addition to surgery results in prolonged survival after recurrence [29]. Although, based on previous data, median survival after recurrence is 12 months, the longer interval from initial presentation and the use of systemic chemotherapy was associated with better and longer response [30]. The effectiveness of chemotherapy in
addition to surgery and reirradiation in the treatment of recurrent medulloblastoma was documented. It improved median survival time after recurrence to 24 months and increased the patient’s survival rate for over two years [19, 29]. The main problem with the use of systemic agents for these patients is limited bone marrow reserve after previous craniospinal irradiation. Indeed, the planned systemic chemotherapy was not used in the presented case because of poor bone marrow reserve due probably to both the previous craniospinal irradiation and the treatment with radioactive isotope. The significant hearing impairment was the other factor limiting the use of chemotherapy (platinum-based schedules) in this patient.

Reirradiation of brain tumours is rarely performed because of risk of severe complications and small benefits in term of survival [26]. For late recurrences of brain tumours, a modest neurological improvement and prolonged survival from relapse is possible with reirradiation [7, 12]. The long period from initial treatment and availability of modern radiation techniques encouraged us to perform the second course of radiotherapy for this patient.

CONCLUSIONS

The 5-year follow-up in medulloblastoma survivors is not sufficient considering the risk of very late relapse of medulloblastoma and the extended incidence of radiation-induced malignancies. Successive retreatment of the recurrence can be performed.

REFERENCES


