Post-treatment maturation of medulloblastoma in children: two cases and a literature review

Xuanxuan Wu*, Yudong Zhou*, Lusheng Li, Ping Liang and Xuan Zhai

Abstract
We herein report two cases of post-treatment maturation of medulloblastoma (MB). We also conducted a literature review to summarize the clinical and pathologic features of MB maturation. From January 1992 to February 2017, 52 patients with MB underwent surgical resection followed by radiotherapy and chemotherapy. Tumor cell maturation was identified in two patients who underwent a second surgery. We conducted a systematic search of PubMed and identified six such cases. In both of our patients, the pathologic type was MB with extensive nodularity (MBEN). Both patients underwent radiotherapy and chemotherapy. The tumor differentiated to gangliocytoma in both patients. In the overall analysis that also included the six cases identified in the literature, the pathologic types were classic MB \( (n=1) \), desmoplastic/nodular MB \( (n=2) \), MBEN \( (n=3) \), and unclassified MB \( (n=2) \). MB differentiated into the following types: gangliocytoma \( (n=2) \), ganglioglioma \( (n=1) \), melanocyte \( (n=1) \), neuronal differentiation \( (n=2) \), and classic MB \( (n=1) \). Desmoplastic/nodular MB and MBEN can differentiate into less malignant cells types after radiotherapy and chemotherapy. Maturation of MB may be affected radiotherapy and chemotherapy.

Keywords
Medulloblastoma, maturation, chemotherapy, radiotherapy, surgical resection, malignancy

Date received: 30 November 2017; accepted: 29 May 2018

Introduction
Medulloblastoma (MB) is the most common primary malignant brain tumor in children. Under the current World Health Organization (WHO) classification, Department of Neurosurgery, Children’s Hospital of Chongqing Medical University, Chongqing, China

*These authors contributed equally to this work.

Corresponding author:
Xuan Zhai, Department of Neurosurgery, Children’s Hospital of Chongqing Medical University, No. 136 Zhongshan 2nd Road, Yuzhong, Chongqing 400014, China. Email: zhaixuan@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
MB is categorized into four distinct variants: classic MB (CMB), desmoplastic/nodular MB (DMB), MB with extensive nodularity (MBEN), and large cell/anaplastic MB. Treatment options include surgical resection, chemotherapy, and radiotherapy. Patient survival is affected by several factors, including the disease stage upon diagnosis, the extent of surgical removal, adjuvant therapy, and the pathologic type. We herein report two cases of pediatric MB with post-treatment maturation. We also conducted an extensive search of the literature to identify similar cases and herein discuss the pathologic maturation of MB, chemotherapy, radiotherapy, and prognosis. These cases are being reported to provide surgeons and oncologists with an understanding of the treatment of MB in clinical practice.

Materials and methods

We retrospectively reviewed the medical records of all patients who received treatment for MB in our institution from January 1992 to February 2017. We also searched the published literature in PubMed (January 1990–June 2017) for reports of the result of MB maturation. The search keywords were “medulloblastoma,” “differentiation,” “maturation,” “gangliocytoma,” “ganglioglioma,” and “neuron.” Publications meeting all of the following criteria were included in the final review: patient age of ≤14 years; pathologic diagnosis of MB using a surgically resected specimen; and, if a second pathological diagnosis was not available, elimination of MB with recurrence or distant metastasis. The following clinical data were collected: age at symptom onset, sex, treatment prior to diagnosis, specific diagnosis, sequence of treatments performed, time of MB maturation, result of MB maturation, follow-up, and outcome. The references of all identified articles were also manually searched for additional studies.

No ethics committee review was required for this study. Verbal informed consent was obtained from the patients’ parents.

Results

Case identification

From January 1992 to February 2017, 52 patients with MB underwent treatment at our department. Post-treatment maturation was identified in two patients (Tables 1 and 2).

Case 1

A 13-month-old girl presented with a 3-day history of vomiting and somnolence. Her clinical examination findings were normal. Laboratory investigation showed electrolyte imbalance. Computed tomography of the brain showed a 5-cm heterogeneous lesion in the posterior fossa. The fourth ventricle was not visible, and the third and lateral ventricles were dilated. External ventricular drainage was performed to control the patient’s symptoms. Magnetic resonance imaging (MRI) revealed a 5-cm lesion in the right cerebellar hemisphere (Figure 1(a)). Subtotal cerebellectomy was performed because of the high vascularity of the mass. Pathologic examination showed an MBEN (Figure 1(c)) with the following immunohistochemical features: synaptophysin (++)+, neurofilament (−), neuron-specific enolase (++), CD57 (+), glial fibrillary acidic protein (+), NeuN (++), vimentin (+), and Ki67 (+) (85%). She was treated first with chemotherapy using the protocol described by Rutkowski et al. The chemotherapy drugs were cyclophosphamide (800 mg/m²/d), cisplatin (75 mg/m²/d), and vincristine (1.5 mg/m²/d). The patient developed common post-chemotherapy responses such as alopecia.
| Article                        | Patient no. (sex, age) | Treatment prior to diagnosis | Diagnosis               | Sequence of treatments performed                                      | Time of MB maturation | Result of maturation                        | Follow-up treatment                                                                 | Outcome               |
|-------------------------------|------------------------|------------------------------|-------------------------|-------------------------------------------------------------------------|-----------------------|---------------------------------------------|-----------------------------------------------------------------------------------|-----------------------|
| Kudo et al. 1990              | 1 (F, 11 y)            | Tumorectomy                  | MB                      | 1) chemotherapy + second operation 2) radiotherapy 3) third operation    | 44 mo                 | Neuronal differentiation; glial differentiation | Radiotherapy + chemotherapy                                                      | Died at 15 y         |
| Cai et al. 2000               | 2 (M, 3 mo)            | Gross total resection        | DMB                     | 1) chemotherapy 2) subtotal resection + second recurrent tumor resection | 8 mo                  | CMB                                         | Radiotherapy + last operation                                                      | Died at 25 mo         |
|                              | 3 (M, 3 y)             | Subtotal resection           | MB                      | 1) chemotherapy 2) radiation therapy 3) second resection                | 8 y                   | Mature neuronal elements                     | N/NM                                                               | Alive for >11 y       |
| Kubota et al. 2009            | 4 (F, 8 y)             | Emergency open biopsy with ventricular drainage | CMB                     | 1) chemotherapy 2) radiation therapy 3) radical surgical resection      | 3 mo                  | Melanotic or melanocytic MB/ gangliocytoma or ganglioneurocytoma | Mega-dose chemotherapy + third operation | Survived for >24 mo   |
| Chelliah et al. 2010          | 5 (M, 22 mo)           | Complete resection           | MBEN                    | 1) chemotherapy 2) second resection 3) radiation therapy 4) craniotomy and intraoperative biopsies | 10 y                  | Gangliocytoma                               | N/NM                                                               | N/NM                  |
| Valvi and Ziegler 2017        | 6 (M, 10 mo)           | External ventricular drainage + limited resection + gross total resection | DMB (SHH)               | 1) chemotherapy + biopsy 2) radiation therapy 3) one cycle of consolidation of chemotherapy 4) further resection | N/NM                  | Ganglioglioma                               | Two consolidation chemotherapies                                                  | Survived for >6 y     |
| Present cases                 | 7 (F, 13 mo)           | External ventricular drainage + partial resection | MBEN                    | 1) chemotherapy 2) radiation therapy 3) complete resection              | 31 mo                 | Gangliocytoma                               | None                                                               | Survived for >6 y     |
|                              | 8 (F, 24 mo)           | Subtotal resection           | MBEN                    | 1) chemotherapy 2) radiation therapy 3) complete resection              | 6 mo                  | Gangliocytoma                               | Consolidation chemotherapy                                                      | Survived for >2 y     |

MB: medulloblastoma; DMB: desmoplastic/nodular medulloblastoma; SHH: sonic hedgehog subgroup; CMB: classic medulloblastoma; MBEN: medulloblastoma with extensive nodularity; N/NM: none or not mentioned; F: female; M: male.
Table 2. Comprehensive therapy of patients in the literature (n=6) and in the current report (n=2).

| Article            | Patient no. | Operative treatment                                                                 | Chemotherapeutics and dosage          | Irradiated site and irradiation dose | Tumor site/posterior cranial fossa | Whole brain | Whole spinal cord |
|--------------------|-------------|------------------------------------------------------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|-------------|------------------|
| Kudo et al. 1990   | 1           | Subtotal tumorectomy; second operation; third operation                            | Vincristine (0.3 mg, 0.2 mg, 0.75 mg) | ACNU (30 mg, 20 mg, 100 mg)          | 50 Gy                             | 30 Gy       |
| Cai et al. 2000    | 2           | Gross total resection; subtotal resection; second recurrent tumor resection         | Vincristine (NM)                      | VP-16 (NM)                            | 16 Gy                             | 19.2 Gy     | 19.2 Gy          |
|                    | 3           | Subtotal resection; second resection                                               | Vincristine (NM)                      | Lomustine (NM)                        | 20 Gy                             | 30 Gy       |
| Kubota et al. 2009 | 4           | Emergency open biopsy with ventricular drainage; radical surgical resection         | Vincristine (1.5 mg/m²)              | Etoposide (NM)                        | 32.5 Gy                           | 21 Gy       | 21 Gy            |
| Chelliah et al. 2010 | 5          | Complete resection; second resection                                               | Vincristine (NM)                      | Children’s Oncology Group Protocol ACNS0334 | 4500 rads                         |             |                  |
| Valvi and Ziegler 2017 | 6         | External ventricular drainage; limited resection; gross total resection             | Children’s Oncology Group Protocol ACNS0334 |                                         |                                   |             |                  |
| Present cases      | 7           | External ventricular drainage; partial resection                                     | Vincristine (1.5 mg/m²/d)            | Methotrexate (5g/m²/d)                | 16 Gy                             | 36 Gy       | 36 Gy            |
|                    | 8           | Subtotal resection; recurrent tumor resection                                      | Vincristine (1.5 mg/m²/d)            | Methotrexate (5g/m²/d)                | 19.3 Gy                           | 36 Gy       | 36 Gy            |

NM: not mentioned.
and myelosuppression. She underwent secondary radiotherapy (craniospinal irradiation at a dose of 36 Gy in 20 fractions followed by posterior fossa boost at 16 Gy in 11 fractions). Thirty months after the first surgery, a repeat MRI scan showed a 3-cm residual mass in the posterior fossa (Figure 1(b)). The patient underwent microsurgical tumor resection. Pathologic examination showed gangliocytoma cells in scattered clusters on a background of neurogliocytes (Figure 1(d)). At the last follow-up 6 years later, the patient was healthy.

Case 2

A 2-year-old girl presented with a 20-day history of headache and a 4-day history of vomiting and somnolence. Physical examination revealed an ataxic gait. Laboratory examination showed no abnormalities. MRI revealed a 4.5-cm mass with enhanced signals in the left cerebellar hemisphere (Figure 2(a)). Pathologic examination after subtotal tumor resection revealed an MBEN (Figure 2(c)). She then underwent systemic chemotherapy.
with cyclophosphamide (800 mg/m^2/d), cisplatin (75 mg/m^2/d), and vincristine (1.5 mg/m^2/d) according to the protocol described by Rutkowski et al.\textsuperscript{3} Repeat MRI 6 months later revealed a relapsing lesion in the cerebellar hemisphere (Figure 2(b)), but the patient had no neurologic deficits. Pathologic examination of the resected tumor revealed morphological features characteristic of gangliocytoma (Figure 2(d)). The patient underwent craniospinal radiation (36 Gy in 18 fractions) followed by boost to the posterior fossa (19.8 Gy in 11 fractions). The patient was alive and well upon the last visit 3 years later.

**Literature search**

We identified five publications that reported six cases of histologically confirmed MB with post-treatment maturation (4 boys, 2 girls) (Tables 1 and 2).\textsuperscript{4-8} The patients’ mean age was 7.8 years (range, 3 months to 11 years). The MB subtypes were DMB (n=2), MBEN (n=1), CMB (n=1), and

---

**Figure 2.** Imaging and pathological findings of Patient 8. (a) Preoperative imaging. T2-weighted magnetic resonance imaging (MRI) shows a hypointense mass, approximately 4.5 cm in size, in the left cerebellar hemisphere. (b) Imaging obtained after subtotal resection and chemotherapy and radiotherapy. T2-weighted MRI shows a new hypointense mass, approximately 1 cm in size, in the original location. (c) First pathological examination. Medulloblastoma with extensive nodularity contains a nodular area composed of small cells in continuity with the fibrillary region (hematoxylin and eosin, 100×). (d) Pathological examination after comprehensive therapy. Mature ganglion cells are seen in clusters on an astrocytic background (hematoxylin and eosin, 400×).
Maturation occurred after combined radiotherapy and chemotherapy in five patients and after chemotherapy alone in the remaining patient. MB differentiated into the following types: gangliocytoma (n=2), ganglioglioma (n=1), melanocyte (n=1), neuronal differentiation (n=2), and CMB (n=1). The duration from pathologic verification of the initial MB to maturation ranged from 3 months to 11 years. Two patients died, and one survived for >11 years.

Discussion

The annual incidence of childhood central nervous system tumors is estimated at 5 per 100,000 children.9 MB is the most common malignant central nervous system tumor in childhood and is 10 times more likely to be diagnosed in children than in adults.9 MB is accompanied by headache, ataxia, high intracranial pressure, brain stem dysfunction, or nerve root or spinal cord compression caused by a space-occupying lesion. In general, MB is highly invasive and prone to metastasis. Maturation of MB has been reported, but only as scattered case reports. We have herein presented two cases of MB maturation at our institution and described six additional cases identified in a literature search.

Under the WHO classification, MB is categorized into four types: CMB, DMB, MBEN, and large cell/anaplastic MB.2 DMB contains nodular, reticulin-free zones characterized by neuronal maturation. The reticulin-free zones have a reduced nuclear:cytoplasmic ratio and contain fibrillary matrix cells with a neuronal appearance. These nodules are surrounded by dense, mitotically active cells that produce a dense intercellular reticulin-positive network of fibers. MBEN accounts for <3% of all cases of MB and is often seen in children aged ≤3 years.1 MBEN has a relatively good prognosis. Compared with DMB, MBEN has an expanded lobular architecture: the reticulin-free zone is typically elongated and rich in neuropil-like tissue. The reticulin-free zone also contains small cells that resemble the cells of central neurocytoma. The internodular component is reduced in some areas. In a study of 82 patients, Garre et al.10 showed that MBEN was present in 15% (12/82) and that DMB was present in 12% (10/82); additionally, MBEN was associated with Gorlin syndrome in 5 of 12 patients. Their study showed an association of both Gorlin syndrome-associated MBEN and sporadic DMB with mutations in the PTCH1, SMOH, and SUFUH genes.11–13 Their study also indicated that MBEN and DMB have the potential for maturation. In both of our cases, the tumors that eventually matured were MBEN upon the first surgery. In the overall analysis that also included the six cases found in the literature search, DMB and MBEN accounted for 62.5% (5/8) of all cases and showed a high trend toward differentiation and maturation. MB differentiated into the following types: gangliocytoma (n=2), ganglioglioma (n=1), melanocyte (n=1), neuronal differentiation (n=2), and CMB (n=1). Gangliocytoma (WHO grade I) is well-demarcated and usually consists of large, mature neurons with a small glial component.10,14 Ganglioglioma (WHO grade I–III) is a rare tumor composed of both neuronal and glial components and characterized by large, mature neoplastic neurons; the glial component consists of astrocytic or oligodendroglial cells.15 Gangliocytoma (n=2), ganglioglioma (n=1), and neuronal cells (n=2) are less malignant than MB; thus, DMB and MBEN could differentiate into less malignant cell types.

Differentiation of MB could be the result of radiotherapy and chemotherapy or may represent intrinsic properties of the MB.16 Bernert et al.17 reported a pathologically
confirmed case of ganglioglioma differentiation with neither radiotherapy nor chemotherapy. Crawford and Levy\textsuperscript{18} also reported a case of myogenic differentiation without adjuvant therapy, indicating an intrinsic potential for differentiation.

Adjuvant therapy, including chemotherapy and radiotherapy, varies based on the pathologic and molecular classifications.\textsuperscript{1,19} Chemotherapy is an important part of postoperative treatment of MB. In certain cases, chemotherapy could spare the patients from irradiation and the detrimental effects of irradiation on development. When adequate resection is not possible, chemotherapy should be guided by pathologic and molecular typing. The chemotherapy after radiotherapy is a cisplatin-based regimen that is administered for four to nine cycles.\textsuperscript{20} The chemotherapy includes induction chemotherapy and consolidation chemotherapy.\textsuperscript{5} Induction chemotherapy typically consists of cisplatin, vincristine, and cyclophosphamide in combination with mesna and etoposide. Consolidation chemotherapy includes high-dose carboplatin and thiotepa. Salet et al.\textsuperscript{21} reported a case of Ewing sarcoma that differentiated into ganglioneuroblastoma and displayed neuronal maturation after chemotherapy. In our overall analysis that included the two patients at our institution and the six cases identified in the literature search, all patients received chemotherapy, suggesting that chemotherapy could affect maturation of MB cells.

Radiotherapy is the mainstay of treatment in patients aged >3 years. The regimen involves craniospinal irradiation at a total dose of 23.4 Gy followed by local boost to the posterior fossa at a total dose of up to 54.0 to 55.8 Gy.\textsuperscript{22} Patients aged <3 years undergo chemotherapy first in an effort to avoid or at least postpone radiation, but this may decrease survival.\textsuperscript{23} Stokman et al.\textsuperscript{24} quantitatively evaluated radiotherapy-induced oral mucositis and found that epithelial cell maturity shifted from immature to mature due to radiotherapy. Previous studies have indicated that irradiation can affect cell maturation. In the current study, seven of eight patients (87.5\%) underwent radiotherapy, suggesting that radiotherapy may affect mutation of MB cells. A variety of attempts have been made to reduce irradiation dosages.\textsuperscript{25,26} Large doses of radiotherapy may kill tumor cells but could also lead to mutation of tumor cells and further differentiation.\textsuperscript{27} Molecular subgrouping has already been applied to clinical trials involving a variety of adjuvant therapy schemes, and this classic scheme is likely to be modified or supplanted by a scheme based on molecular subgroups.\textsuperscript{28}

MB is a highly malignant brain tumor with a poor prognosis in children. In a European study from 2000 to 2007, the 1-, 3-, and 5-year survival rates of pediatric patients with MB were 81\%, 63\%, and 56\%, respectively.\textsuperscript{29} The prognosis is the worst in infants and improves with increasing age.\textsuperscript{29} Survival has improved since the adoption of molecular classification. Schwalbe et al.\textsuperscript{30} stratified patients with MB into those with favorable risk, standard risk, high risk, and very high risk, and the corresponding 5-year progression-free survival rates were 91\%, 81\%, 42\%, and 28\%, respectively. In the current study, our literature review showed that one patient remained alive for >11 years, and the two patients in our institution survived for >2 and >6 years, respectively. In these two cases, MB differentiated into less malignant gangliocytoma after radiotherapy and chemotherapy. We are continuing to follow up both patients.

**Conclusion**

DMB and MBEN are more likely to differentiate into less malignant cell types.
Maturation of MB may be affected by radiotherapy and chemotherapy.

Acknowledgement
We are grateful to Dr. Jin Zhu, Department of Pathology, and Dr. Yong Qin, Department of Radiology, for providing the relevant figures for these cases.

Disclosure of conflict of interest
The authors declare that there is no conflict of interest.

Funding
This research was funded by the Key Project of the Chongqing Natural Science Foundation (cstc2015jcyjbx0144).

References
1. Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. Crit Rev Oncol Hematol 2016; 105: 35–51.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016; 131: 803–820.
3. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 2005; 352: 978–986.
4. Kudo M, Shimizu M, Akatsu Y, et al. Gangliogial differentiation in medulloblastoma. Acta Pathol Jpn 1990; 40: 50–56.
5. Cai DX, Mafra M, Schmidt RE, et al. Medulloblastomas with extensive posttherapy neuronal maturation. Report of two cases. J Neurosurg 2000; 93: 330–334.
6. Kubota KC, Itoh T, Yamada Y, et al. Melanocytic medulloblastoma with ganglio-neurocytomatosus differentiation: a case report. Neuropathology 2009; 29: 72–77.
7. Chelliah D, Mensah Sarfo-Poku C, Stea BD, et al. Medulloblastoma with extensive nodularity undergoing post-therapeutic maturation to a gangliocytoma: a case report and literature review. Pediatric Neurosurg 2010; 46: 381–384.
8. Valvi S and Ziegler DS. Ganglioglioma arising from desmoplastic medulloblastoma: a case report and review of literature. Pediatrics 2017; 139.
9. Schueller U, Heine VM, Mao J, et al. Acquisition of granule neuron precursor identity is a critical determinant of progenitor cell competence to form Shh-induced medulloblastoma. Cancer Cell 2008; 14: 123–134.
10. Garre ML, Cama A, Bagnasco F, et al. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome—a new clinical perspective. Clin Cancer Res 2009; 15: 2463–2471.
11. Taylor MD, Liu L, Raffel C, et al. Mutations in SUFU predispose to medulloblastoma. Nat Genet 2002; 31: 306–310.
12. Kool M, Korshunov A, Remke M, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 2012; 123: 473–484.
13. Lafay-Cousin L, Smith A, Chi SN, et al. Clinical, pathological, and molecular characterization of infant medulloblastomas treated with sequential high-dose chemotherapy. Pediatr Blood Cancer 2016; 63: 1527–1534.
14. McLendon RE and Provenzale J. Glioneuronal tumors of the central nervous system. Brain Tumor Pathol 2002; 19: 51–58.
15. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114: 97–109.
16. Suresh TN, Santosh V, Yasha TC, et al. Medulloblastoma with extensive nodularity: a variant occurring in the very young-clinicopathological and immunohistochemical study of four cases. Child's Nerv Syst 2004; 20: 55–60.
17. Bernert BF, Roman A, Carboni P Jr, et al. Gangliogial differentiation in a medulloblastoma with extensive nodularity. J Bras Patol Med Lab 2013; 49: 433–436.
18. Crawford JR and Levy ML. Medulloblastoma with myogenic
differentiation: a rare medulloblastoma variant in a young child. BMJ Case Rep 2015; 2015.
19. Aristizabal P, Burns L, Rivera-Gomez R, et al. Medulloblastoma with extensive nodularity: tailored therapy in a low-resource setting. J Pediatr Hematol Oncol 2017; 39: 299–301.
20. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children’s Cancer Study Group PNET-3 Study. J Clin Oncol 2003; 21: 1581–1591.
21. Salet MC, Vogels R, Brons P, et al. Maturation toward neuronal tissue in a Ewing sarcoma of bone after chemotherapy. Diagn Pathol 2016; 11: 74.
22. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006; 24: 4202–4208.
23. Kann BH, Park HS, Lester-Coll NH, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. JAMA Oncol 2016; 2: 1574–1581.
24. Stokman MA, Spijkervet FK, Wymenga AN, et al. Quantification of oral mucositis due to radiotherapy by determining viability and maturation of epithelial cells. J Oral Pathol Med 2002; 31: 153–157.
25. Yoon JH, Park KD, Kang HJ, et al. Treatment of pediatric average-risk medulloblastoma using craniospinal irradiation less than 2500 cGy and chemotherapy: single center experience in Korea. World J Pediatr 2017; 13: 367–373.
26. Wahba HA, Abu-Hegazy M, Wasel Y, et al. Adjuvant chemotherapy after reduced craniospinal irradiation dose in children with average-risk medulloblastoma: a 5-year follow-up study. J BUON 2013; 18: 425–429.
27. Cebulska-Wasilewska A, Krzysiek M, Krajewska G, et al. Retrospective biological dosimetry at low and high doses of radiation and radioiodine impact on individual susceptibility to ionizing radiation. Genome Integr 2017; 8: 2.
28. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. Acta Neuropathol 2016; 131: 821–831.
29. Kohler BA, Ward E, McCarthy BJ, et al. Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011; 103: 714–736.
30. Schwalbe EC, Lindsey JC, Nakjang S, et al. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. Lancet Oncol 2017; 18: 958–971.