Recurrence pattern and Survival analysis in patients undergoing radiotherapy IMRT technique for medulloblastoma

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Research

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Abstract

Objective The technique of radiotherapy is associated with the recurrence pattern and prognosis of postoperative treatment for medulloblastoma. Our aim was to assess recurrence patterns and survival in patients with medulloblastoma between three-dimensional conformation (3D-CRT) and intensity modulated radiotherapy (IMRT). To analyze the factors affecting the prognosis, such as the use of 3D-CRT or IMRT, the time interval of surgical and radiotherapy, whether there is chemotherapy and chemotherapy regimen.

Methods In this study, 36 patients with medulloblastoma were conducted investigating and data were analyzed from May 2009 to September 2017. The median survival of each group was calculated for different clinical stages,pathological types and treatment methods. The PFS and OS for patients curves were derived by Kaplan-Meier estimation, and which were calculated using the Cox proportional hazards model between the IMRT and 3D-CRT treatment groups.

Results Up to the follow-up date, 7 of the 9 patients in the 3D-CRT group had recurrence and 9 of the 27 patients in the IMRT group had recurrence. The 2-year and 5-year PFS of the IMRT group were 74.1% and 65.8%, and which of the 3D-CRT group were 55.6% and 22.2%, respectively. The PFS was significantly higher for patients treated with IMRT compared with 3D-CRT ($P<0.05$). The 2-year overall survival rates of the IMRT group compared with the 3D-CRT group were the same, the 5-year overall survival rate of the IMRT group was higher than that of the 3D-CRT group, however, there was no statistical difference. The PFS and OS for patients with low-risk groups were better than those of the high-risk group ($P<0.05$). There was no statistical difference between the M2 group and the M3 group in the 2-year and 5-year OS($P>0.05$). There was no statistical difference in the chemotherapy-free group, the EP chemotherapy regimen and the temozolomide (TMZ) chemotherapy group in the 2-year and 5-year PFS and OS($P>0.05$). The results of multivariate Cox proportional hazards model analysis showed that the residual, recurrence or metastasis before radiotherapy were independent prognostic factors affecting PFS($P<0.05$). Radiotherapy mode was negatively correlated, although there was no statistical significance($P=0.061$).

Conclusions IMRT can reduce the risk of spinal cord recurrence compared with 3D-CRT, especially the low rate of spinal cord recurrence. The development of the technique of radiotherapy was associated with improvements in medulloblastoma prognosis.

Introduction

Medulloblastoma (MB) is a central nervous malignancy that occurs in children and young adults. MB is frequently located in the posterior fossa. Radiotherapy of the craniospinal irradiation (CSI) techniques and chemotherapy are the standard treatments after operation of medulloblastoma [1].

To our knowledge,IMRT, volumetric-modulated arc therapy (VMAT), Tomotherapy (TOMO) and other modern radiotherapy technologies are obviously better than 3D-CRT and conventional radiotherapy technologies in terms of dose distribution in the target volume and normal tissue protection [2–

4].Previous study have shown that 3D-CRT avoiding failures related to radiotherapy uncertainties to some extent, but there are still 1/3 failures statement[5]. Previous study had shown the pattern of failure associated with medulloblastoma patients treated with proton radiation therapy was similar to the pattern of failure in patients treated with photon radiation therapy [6].Howerver, there are few reports about recurrence patterns after radiotherapy.

In this paper, the recurrence patterns of 36 cases of medulloblastoma admitted to our hospital after radiotherapy were analyzed,and the survival was further analyzed to provide a clinical basis for the selection of radiotherapy techniques.

Materials And Methods

Patients and treatments

A total of 36 patients with medulloblastoma in hospital were enrolled and who were confirmed by pathology after surgery between May 2009 and September 2017.All patients received imaging of the entire neuraxis with magnetic resonance imaging (MRI) before craniospinal irradiation (CSI). Definitions of clinical target volume (CTV) are based on imaging aspects. We designed a clinical target volume (CTV) for CSI containing the spinal canal, which identified on computed tomography (CT) and T2-weighted magnetic resonance imaging (T2-MRI).Clinical data obtained from a retrospective review of charts including the patient's sex, age, risk status, interval time between surgery and radiation.After completion of radiation therapy, patients routinely underwent imaging of the entire neuraxis.Patients with evidence of recurrent disease were discussed in a multidisciplinary collaboration before salvage therapy.

Radiation therapy and chemotherapy

Patients were scanned using a GE Light Speed 16-slice computed tomography (CT) Scanner with 3.0-mm slice thickness and were treated in the prone or supine position.The planned system used the Eclipse11.0 planned system (Varian Medical Systems Inc. Palo Alto, CA). A total of 2-3 isocenters were set.Patients with 3D-CRT plan were positioned in the prone position and the whole brain field was irradiated by two parallel pairs of traditional 90°and 270°.The lower boundary of the whole brain field intersects with the upper boundary of the spinal field, and the whole brain field collimator rotates at a certain angle to match the scattered penumbra of the spinal field.The junction layer of the cerebral spinal cord underwent three 1cm shifts (5th, 10th and 15th). Patients in IMRT group were supine or prone, and the spinal cord planning target volume (PTV) was designed with five field coplanar designs of 320°, 340°, 0°, 20° and 40°, and the collimator angle was 0°.For patients with long PTV in the spinal cord, the PTV in the spinal cord was divided into upper and lower parts, and the overlap area of the upper and lower parts was about 2cm.In IMRT group, the angle of the two whole brain field collimator was about 85° and 95°, which could optimize the dose of the cerebrospinal junction and reduce penumbra at the millimeter level, so that only one 1cm shift was needed for the whole cerebrospinal junction.The dose distribution of 3D-CRT plan and IMRT plan is shown in Fig 1.

The radiotherapy dose was 26-36 Gy in the whole brain and spinal cord, and the dosage of local tumor bed or residual and recurrent lesions was 54-60 Gy.The chemotherapy regimen was treated with 4-8 cycles of EP (Etoposide + Cisplatin) or 8-12 cycles of oral administration of temozolomide (TMZ) after craniospinal irradiation.

Follow-up and measurements

The imaging data of 36 patients with medulloblastoma were studied and evaluated by two experienced radiologists to observe the recurrence and metastasis after radiotherapy.The patients were followed up by telephone and examination at the hospital. PFS was defined as the time from the start of radiotherapy to the disease progression of the patient or the last follow-up.OS was defined as the time from the beginning of radiotherapy to the death of the patient or to the follow-up.The survival data in 3D-CRT group and IMRT group were analyzed.

Statistical analysis

All calculations were performed with SPSS version 22.0 for Windows software.The Kaplan-meier method was used for survival analysis, and the log-rank method was used to compare the survival differences between groups. The Cox proportional hazards regression model was used to determine prognostic factors on PFS and OS.P 0.05 was considered statistically significant.

Results

Patient characteristics

Characteristics of the patients are shown in Tab 1.Among all 36 cases, 19 males(52.8%) and 17 females (47.2%), the age at diagnosis was from 3 years to 52 years old with a median age of 10.5 years old. The follow-up period was up to December 6, 2019, with a median follow-up period of 60.5 months (27.4-149.7 months).The median follow-up time of 3D-CRT group and IMRT group was 111.3 months (76.6-149.7 months) and 45.6 months (27.4-89.3 months),respectively.3-DCRT irradiation group was used from May 2009 to August 2013, and IMRT irradiation group was used from September 2013 to September 2017.The interval time of surgery and radiotherapy was 4 weeks, 8 weeks and 12 weeks.The examination before radiotherapy for tumor residue and spread was divided into non-spread group (M0), local residual group (M2) and cerebrospinal fluid spread (M3).EP regimen and TMZ regimen were used for adjuvant chemotherapy.

Recurrence rules

At the time of last follow-up, there were 7 cases of recurrence in the 3D-CRT group, including 4 cases of spinal cord spread,there were cases of spinal cord spread in the IMRT group and there was only 1 case of spinal cord spread. The disseminated magnetic resonance of the spinal cord presents as solitary single (Fig. 2a), or as diffuse meningeal thickening (Fig. 2c), or as space-occupying lesions in the spinal cord (Fig. 2b).There was 1 case of vertebral metastasis in the 3D-CRT group (Fig.2d), and the magnetic

resonance T1 showed abnormally low signal shadow of multiple cones, while there were 2 cases of vertebral metastasis in the IMRT group, of which 1 case was shown in figure 2e, and the PET/CT showed high metabolism of single vertebral body. There were 1 case of frontal lobe metastasis in the 3D-CRT group and 1 case in the IMRT group，respectively (Fig. 2f and Fig. 2g).The remaining sites of recurrence were in situ (Fig. 2h) or intracranial disseminated lesions (Fig. 2i).

Survival analysis

According to the statistical analysis of the survival of 36 patients with medulloblastoma, the 2-year and 5-year PFS of the IMRT group were 74.1% and 65.8%, respectively, while the 2-year and 5-year PFS of the 3D-CRT group were 55.6% and 22.2%, respectively. The IMRT group was superior to the 3D-CRT group in PFS ($p < 0.05$).There was no difference between the 2 -year and 5-year OS of the two groups($p > 0.05$).The results of the two groups are shown in Fig 3 and Tab 2.

Compared with interval (4 or 8 weeks) between surgery and radiotherapy,there was no statistical difference in both PFS and OS.The interval < 12w group was better than the > 12w group ($P < 0.05$),but there was no difference in OS between the two groups($p > 0.05$). The 2-year and 5-year PFS of the non-disseminated group (M0) were better than the local residual group (M2) and the CSF disseminated group (M3) ($P < 0.05$).There was no statistical difference in PFS between M2 group and M3 group ($p >0.05$).The M0 group was better than the M2 and M3 groups($P < 0.05$),and there was no statistical difference in OS between the M2 and M3 groups($p > 0.05$).There was no statistical difference among the chemotherapy-free group, EP chemotherapy regimen and TMZ chemotherapy group in the 2-year and 5-year PFS and OS groups($p > 0.05$).The comparison of survival analysis of the above groups is shown in Tab 2.

Radiotherapy technique, interval time between surgery and radiotherapy,and whether residual, recurrence or metastasis before radiotherapy are the main factors affecting PFS. The results of multivariate Cox regression model analysis show that residual, recurrence or metastasis before radiotherapy is an independent prognostic factor affecting PFS($P < 0.05$).However, radiotherapy mode was negatively correlated, although there was no statistical significance($P=0.061$).Cox regression analysis of each group is shown in Tab 3.

Discussion

Medulloblastoma (MB) is a common malignant tumor in children. It is a malignant and invasive embryonic tumor that occurs in the cerebellum or fourth ventricle and accounts for 12–25% of all CNS tumors. The main treatment of medulloblastoma is surgery. Postoperative radiotherapy can significantly reduce the recurrence and prolong the survival rate of patients. A recent study has shown that supine position for CSI was found to have similar survival outcomes compared with the prone position[7].A multicenter study found that modern radiotherapy techniques can enhance the dose uniformity in the target area, especially the spinal cord target area [2]. However,there is little research on survival related to technology. Our study found that the IMRT radiotherapy dose of spinal cord recurrence was only 1 case, while the 3DCRT group had a relatively high recurrence rate of 3 cases. A number of other studies have

found that [8, 9], IMRT and VMAT overlap planning design allows for more positioning errors, which may be another advantage of IMRT in craniospinal irradiation. This is different from the pattern of recurrence after proton radiotherapy. One study found [6], the rate of extracranial recurrence, especially spinal cord recurrence, was higher after proton radiotherapy. However, our study suggested that the rate of spinal cord recurrence and metastasis after IMRT radiotherapy for medulloblastoma was very low. The previously reported incidence of vertebral metastasis is not high [10]. Our study suggests that vertebral metastasis is not uncommon, and various imaging techniques such as MR and PET-CT can play a role in diagnosis.

It was found that the following factors are important in rate of survival: radiotherapy technique, time interval between surgery and radiotherapy, assessment of pre-radiotherapy, chemotherapy intervention.

Firstly,whole brain and spinal cord technique is safe and feasible to use whole brain field irradiation. One study found [5], the application of left and right brain field in the whole brain and spinal cord was effective for penetrating irradiation, and only 1 of the 76 patients with 3D-CRT technology developed the failure of the sieve plate area. However, our study found that 2 out of 36 patients with medulloblastoma developed frontal lobe metastasis, which was considered as a possible failure of the sieve plate area. With the progress of radiotherapy technology, especially the development of VMAT and TOMO program for the treatment of whole brain and spinal cord technology [11, 12], the dose distribution in the target region was more uniform than that of 3DCRT and IMRT.

Secondly,whether the time interval between surgery and radiotherapy affects prognosis is still controversial.Del Charco[13] indicated that the 5-year local control rate of < 45 days was 89%, while that of > 45 days was only 68%. And another study had shown that early postoperative radiotherapy could even be harmful[14]. The 5-year PFS was 0%, 85%, and 75%, respectively, for intervals from surgery to radiotherapy of < 3 weeks, 3–5 weeks and ≥ 6 weeks was 0%, 85%, and 75%, respectively. Our study found that the PFS was significantly shortened when the interval time between surgery and radiotherapy was more than 12 weeks, suggesting that the interval time between surgery and radiotherapy for medulloblastoma should not be more than 12 weeks at the latest.

Thirdly,radiotherapy is an important part of the comprehensive treatment of medulloblastoma. The presence or absence of postoperative residual and spread is an important factor affecting the prognosis [15]. The prognosis of patients is poor when it is disseminated and planted along the cerebrospinal fluid. According to the different states of Chang's staging system before radiotherapy [16],the patients were divided into stage M0 - stage M4. M0: no tumor metastasis was found;M1: only tumor cells were found in cerebrospinal fluid;M2: tumor cells are confined to the brain;M3: presence of CSF metastasis;M4: there are distant metastases outside the nervous system. The survival conditions were markedly different from period to period. Our study also found that the survival of the non-disseminated group (M0) was the best, while the survival of the partial residual group (M2) and the CSF disseminated group (M3) was poor. Since all the patients in this study were aged ≥ 3 years, the M0 group was the low-risk group, while the M2 groups and the M3 groups were the high-risk groups. Modern installments have been added to

molecular biology's classification in a more refined way [17], and molecular typing was not studied in this study due to the defects of the samples.

Lastly,Postoperative chemotherapy is an important part of the comprehensive treatment of medulloblastoma, and a number of studies have suggested that postoperative chemotherapy can improve the survival of patients with medulloblastoma [18, 19]. Research from National Cancer Data Base shown that[19], the 5-year survival rate of the adjuvant chemotherapy group was significantly higher than that of radiotherapy alone, which was 86.1% and 71.6%, respectively. Recent research suggests that preoperative chemotherapy can also yield survival benefits [20].In terms of the choice of chemotherapy regimen, the combination of three drugs may be more effective [21],lomustine(CCNU), cisplatin, and vincristine or cyclophosphamide, cisplatin, and vincristine are more commonly used.Our study indicated that there was no statistical difference in PFS and OS in the chemotherapy group,the chemotherapy-free group,the EP chemotherapy group and the TMZ chemotherapy group. Our study also clarified that single drug or double drug combination chemotherapy could not make patients with medulloblastoma benefit from postoperative chemotherapy.

Multivariate Cox regression analysis showed that recurrence, residual or spread before radiotherapy was an independent prognostic factor affecting PFS.This also explained, to some extent, the significant shortening of PFS in patients with medulloblastoma more than 12 weeks after surgery and radiotherapy, which may be due to the increased proportion of local recurrence or spinal cord dissemination due to the extended interval, thus affecting the disease-free survival of patients. However, radiotherapy is a negative correlation factor, indicating that IMRT technology can reduce the negative survival effect caused by recurrence spread to a certain extent.

In summary, IMRT technology has advantages over 3D-CRT technology in total cerebral spinal radiation, especially the lower spinal cord recurrence rate. The interval time between surgery and radiotherapy should be no more than 12 weeks.PFS and OS were higher in patients without residual, recurrence and spread before radiotherapy. Chemotherapy with TMZ alone or EP combined with both drugs did not increase survival. Multivariate analysis showed that the pre-radiotherapy status was an independent factor, and IMRT technology could reduce this survival effect. This study is a retrospective analysis. There may be a certain selection bias, no molecular typing analysis. We expect a large scale of domestic case registration and follow-up observation to obtain more comprehensive and reliable clinical data, so as to provide a more reliable basis for our clinical decision.

Abbreviations

IMRT:intensity modulated radiotherapy; 3D-CRT:three-dimensional conformation ; VMAT:volumetric-modulated arc therapy; TOMO:tomotherapy ;PFS: progression-free survival; OS: overall survival; MB:medulloblastoma ; TMZ :temozolomide; MRI :magnetic resonance imaging; CT:computed tomography; CSI:craniospinal irradiation ; CTV:clinical target volume; PTV:planning target volume;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent for scientific usage of clinical data was obtained from all patients included in the study.

Availability of supporting data

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Hao Chang and DongJie He drafted the manuscript. ZiShen Zhang improved the patients immobilization. QiMing Wang, ZongYan Yu, participated in data collection and helped to analyze the data. DeQuan Yu, PinTing Zhao prepared the plan design. QiuJu Shao participated in the coordination of the study. All authors read and approved the final manuscript.

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Tables

Tab 1 The clinical characteristics of the 36 patients with medulloblastoma

Characteristics	Groups	n	Proportion（%）
Gender	Male	19	52.8
	Female	17	47.2
Radiation technical	3D-CRT	9	25.0
	IMRT	27	75.0
Time[a]	≤4w	7	19.4
	＞4w	29	80.6
Time[b]	≤8w	21	58.3
	＞8w	15	41.7
Time[c]	≤12w	26	72.2
	＞12w	10	27.8
Status before radiation	M0	18	50.0
	M2	12	33.3
	M3	6	16.7
Chemotherapy	None	14	38.9
	EP	16	44.4
	TMZ	6	16.7

[a].The interval time of surgery and radiotherapy is four weeks.[b].The interval time of surgery and radiotherapy is eight weeks.[c].The interval time of surgery and radiotherapy is twelve weeks.

Tab 2 Survival analysis of the 36 patients with medulloblastoma

Characteristics	groups	PFS (2y/5y,%)	P value	OS(2y/5y,%)	P value
Radiation technical	3DCRT	55.6/22.2	0.043	88.9/44.4	0.476
	IMRT	74.1/65.8		88.9/62.1	
Time[a]	≤4w	100.0/80.0	0.128	100.0/75.0	0.148
	>4w	62.1/43.4		86.2/51.2	
Time[b]	≤8w	81.0/43.8	0.328	90.5/56.7	0.576
	>8w	53.3/46.7		86.7/51.9	
Time[c]	≤12w	80.8/55.1	0.027	88.5/62.5	0.113
	>12w	40.0/30.0		90.0/40.0	
Status before radiation	M0	88.9/82.5	0.003[1] 0.004[2]	100.0/79.9	0.016[3] 0.016[4]
	M2	58.3/22.2	0.852	91.7/33.3	0.727
	M3	33.3/33.3		50.0/50.0	
Chmotherapy	None	71.4/45.7	0.810[5] 0.579[6]	85.7/40.4	0.809[7] 0.664[8]
	EP	68.8/48.9	0.752	100/63.6	0.808
	TMZ	66.7/66.7		66.7/66.7	

[a].The interval time of surgery and radiotherapy is four weeks.[b].The interval time of surgery and radiotherapy is eight weeks.[c].The interval time of surgery and radiotherapy is twelve weeks.

[1].M0 *vs* M2;[2].M0 *vs* M3;[3].M0 *vs* M2;[4].M0 *vs* M3;[5].None *vs* EP;[6].None *vs* TMZ;[7].None *vs* EP;[8].None *vs* TMZ.

Tab 3 Multivariate Cox regression analysis of the PFS for patients with medulloblastoma

	B	SE	Wald	*p*	HR	95% CI
	-0.962	0.513	3.514	0.061	0.382	0.140-1.045
Interval time of surgery and radiotherapy	0.653	0.540	1.461	0.227	1.921	0.666-5.540
Status before radiation	0.823	0.367	5.035	0.025	2.278	1.110-4.675

Figures

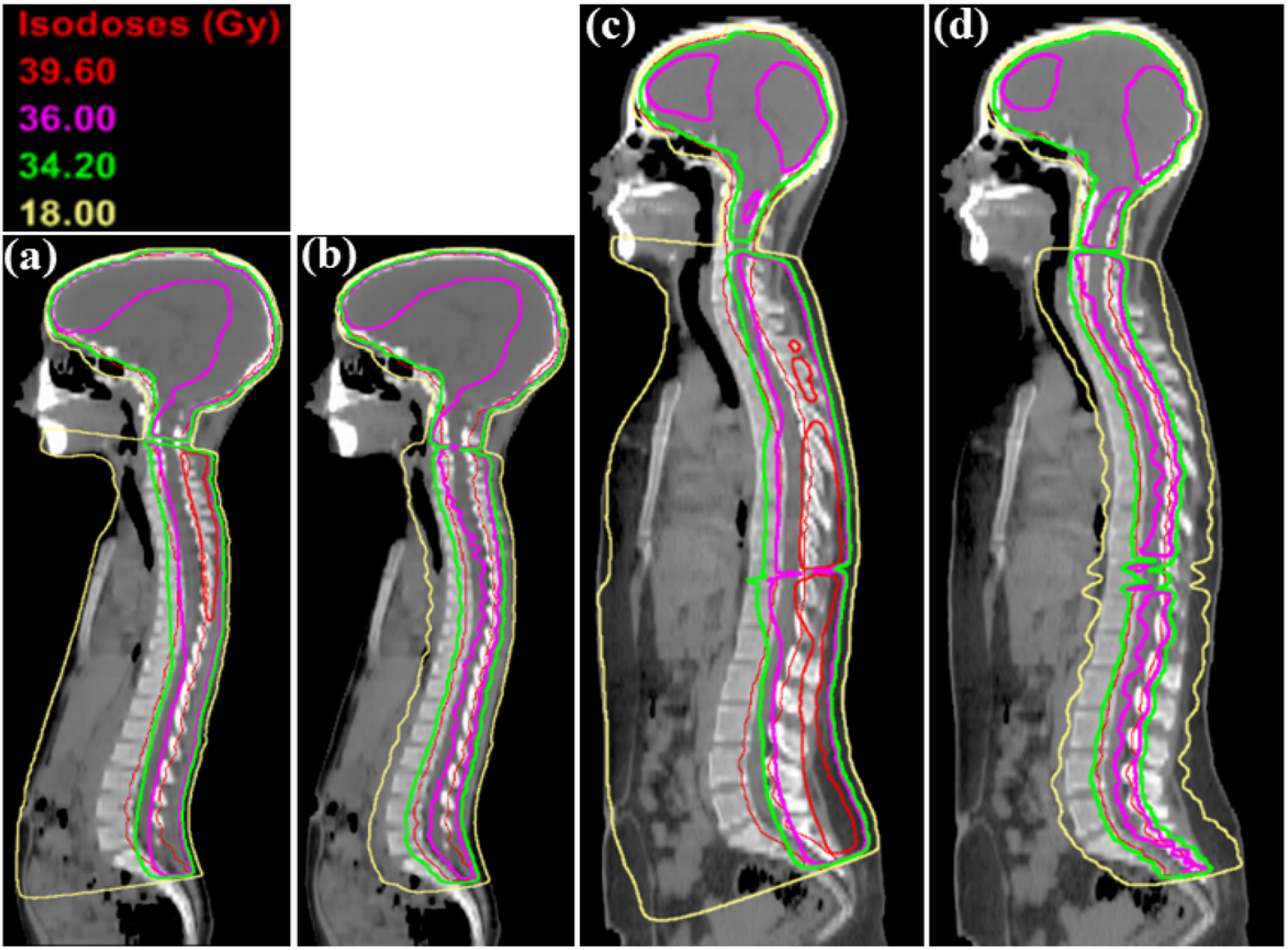

Figure 1

Sagittal view shows the dose distribution for two patients.(a) and (c) show doses distribution of 3-DCRT plan in children and adults. (b) and (d) show doses distribution of IMRT plans in children and adults.The yellow line represents the 18 Gy isodose curve,the green line represents the 34.2 Gy isodose curve,and the purple line represents the 34.2 Gy isodose curve.

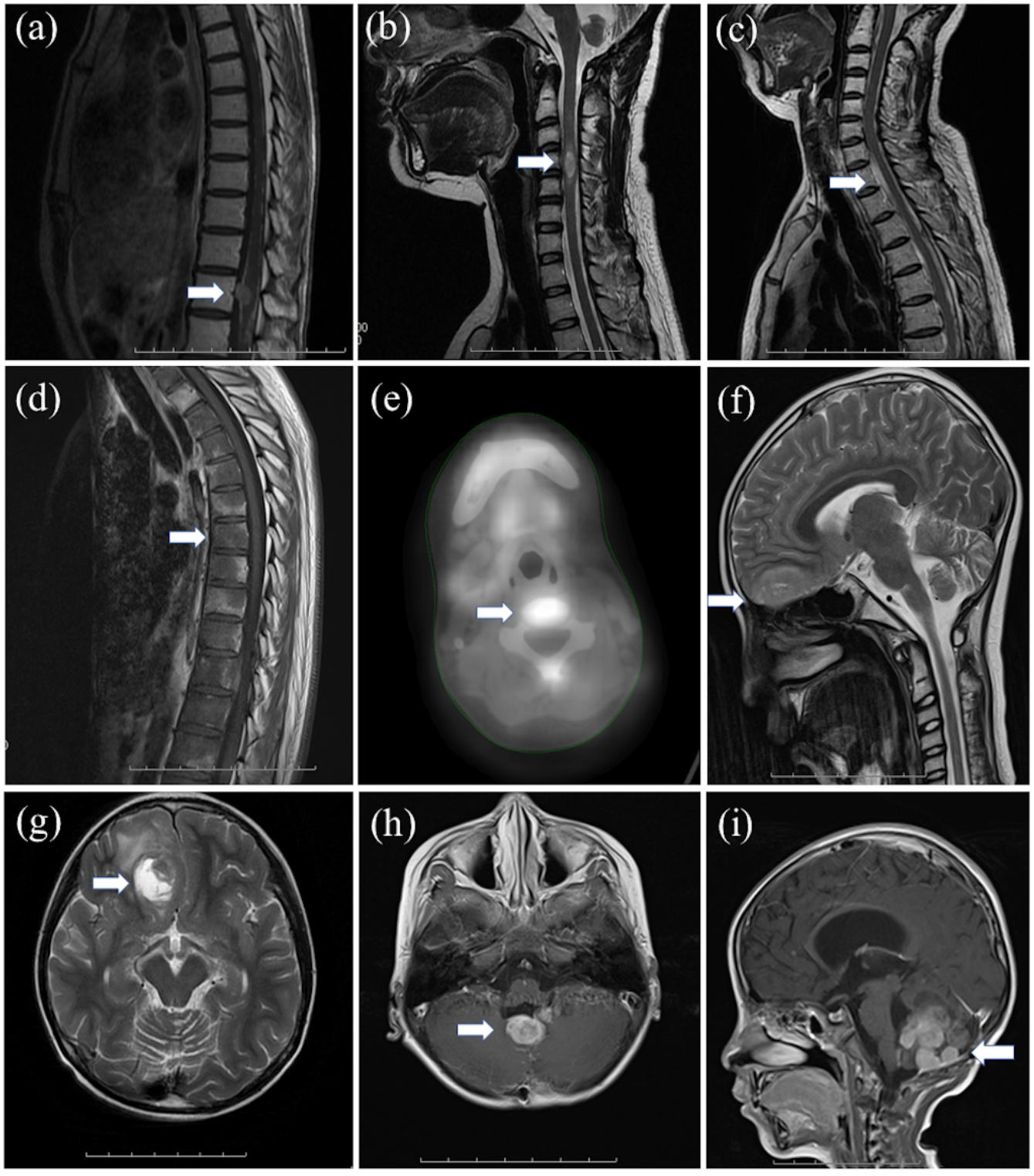

Figure 2

Relapse cases of medulloblastoma patients.(a,b,c) MRI imaging data indicate cases of spinal cord spread.(d,e) Imaging data are shown for bone metastasis.(f,g) MRI imaging data are shown patients with plate area recurred.(h,I) MRI imaging data are demonstrated Recurrent in situ and posterior fossa. The white arrow points to the site of tumor recurrence or metastasis.

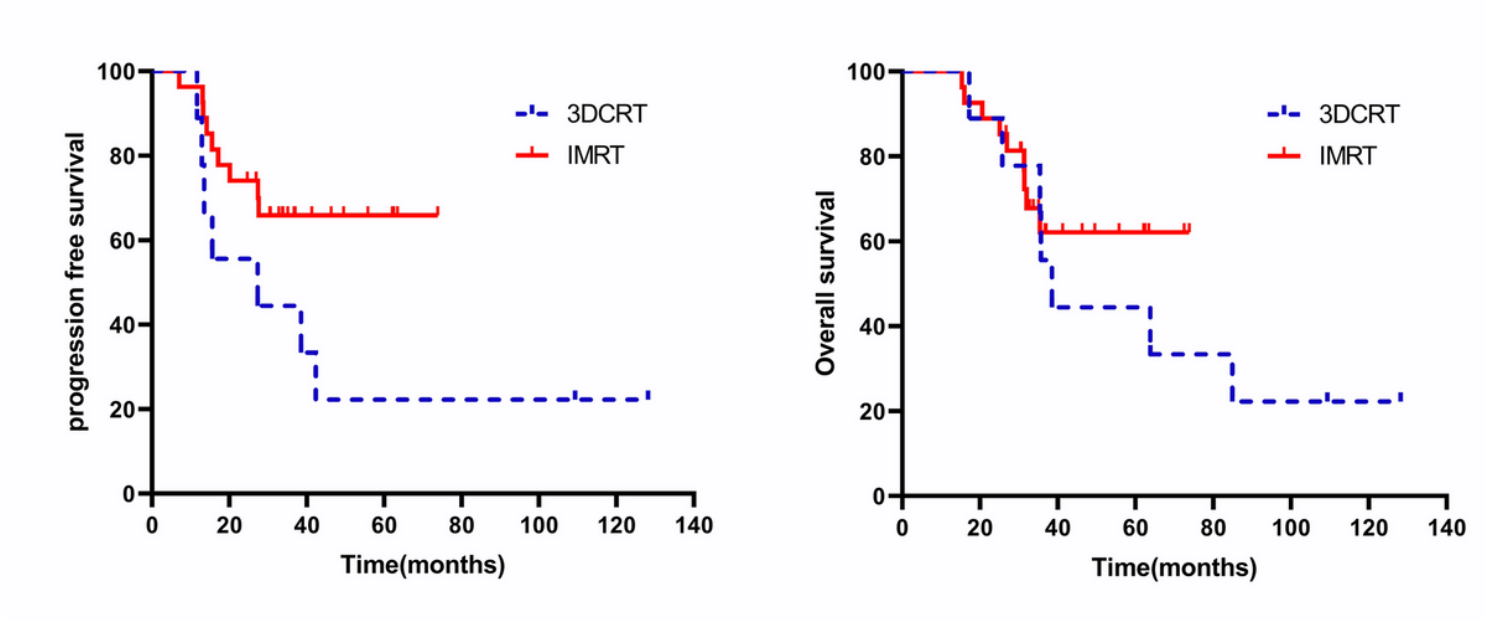

Figure 3

Survival outcomes. Survival curves showing progression-free survival and overall survival rates after radiation beginng.