Clinical Outcome and Prognostic Factors of Malignant Spinal Dumbbell Tumors

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Abstract:

Introduction: To investigate the clinical outcome and prognostic factors of malignant spinal dumbbell tumors (m-SDTs).

Methods: We retrospectively reviewed the clinical outcome of 22 consecutive cases of m-SDTs and analyzed the prognostic factors associated with worse outcome.

Results: Nineteen of the 22 cases were managed with surgery (86%), and gross total resection (GTR) was achieved in four cases (21%). The duration of overall survival (OS) ranged from 3 to 140 months, with a median survival time of 15.3 months. The 5 year OS rate was 55.6%. In multivariate analysis, histological subtype (high-grade malignant peripheral nerve sheath tumor) (hazard ratio [HR] 14.9, $p = 0.0191$), GTR (HR 0.07, $p = 0.0343$), and presence of local recurrences (HR 11.2, $p = 0.0479$) were significant and independent predictors of OS.

Conclusions: On the basis of clinical data, we propose that GTR and prevention of local recurrence may improve the clinical outcome of m-SDTs.

Keywords:

Malignant spinal tumor, dumbbell tumor, prognostic factors

Spine Surg Relat Res 2018; 2(4): 317-323

dx.doi.org/10.22603/ssrr.2018-0004

Background

Spinal tumors can take the form of dumbbell-shaped tumors, as originally described by Heuer[1]. The term "dumbbell tumors" is usually used for separate but connecting tumors that have more than two separate regions, including those in the intramedullary, intradural, epidural, and paravertebral spaces. Because of their unique locations, the clinical characteristics of spinal dumbbell tumors (SDTs) are different from those of spinal tumors of other types, and therefore, SDTs require attention in terms of treatment strategies and clinical outcome.

Approximately 18% of spinal tumors are SDTs[2]. Among SDTs, benign tumors such as schwannomas are dominant, whereas malignant SDTs (m-SDTs), including malignant peripheral nerve sheath tumors (MPNSTs), are uncommon[3]. As a result, there are minimal data on the clinical outcome of m-SDTs. Generally, the clinical behavior of m-SDTs depends on the biological nature of the tumors, and clinical experience shows that m-SDTs, particularly MPNSTs, may grow rapidly[4,5]. Therefore, management of m-SDTs is a challenging issue in the field of spinal diseases.

In the present report, we retrospectively reviewed the clinical outcome of 22 cases of m-SDTs. We analyzed the clinical features, the modalities of treatment, and the clinical outcome of these cases, aiming to determine factors associated with overall survival (OS) in patients with m-SDTs.

Materials and Methods

Clinical data

We retrospectively reviewed the records of 22 consecutive patients with m-SDTs. Our institutional review board approved this study. All patients were treated at our hospital from 1995 to 2016. The following clinical data were collected from each patient's medical records: demographic details, diagnostic and therapeutic information, tumor pathology, surgical details, postoperative tumor recurrence, and survival. The surgical variable was defined by the surgeon's

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Received: January 23, 2018, Accepted: February 24, 2018, Advance Publication: April 27, 2018

Table 1. Clinical Characteristics of 22 Patients with Malignant Spinal Dumbbell Tumors.

Characteristic	Value
Age at diagnosis in years	
Mean	44.8±3.1
Range	3-80
Sex	
Male	12
Female	10
Tumor location	
Cervical	10
Thoracic	7
Lumbar	4
Sacral	1
Tumor size	
<5 cm	6
≥5 cm	16
Eden's classification	
I	0
II	6
III	14
IV	2
Histology	
MPNST	
High grade	9
Low grade	4
Hematopoietic	
Malignant lymphoma	2
Plasmacytoma	1
Others	6

MPNST: malignant peripheral nerve sheath tumor

assessment of the procedure as palliative, intralesional, or en bloc. Palliative procedures were defined by limited decompression or stabilization without any oncologic intent. An intralesional resection involved violation of the tumor capsule, that is, piecemeal resection. En bloc resection referred to the circumferential isolation of the tumor without violation of its border or capsule. The surgical margins of the tumor resection were classified into en bloc tumor resection with wide margin, en bloc tumor resection with marginal margin, and intralesional resection. Gross total resection (GTR) (no macroscopic evidence of residual tumor), subtotal resection (more than 90% resection), and partial resection (less than 90% resection) were defined on the basis of postoperative magnetic resonance imaging (MRI) findings. The surgeries were performed by an operation team with two board-certified spine surgeons.

Pathological examination

Specimens were obtained for evaluation from all patients, and histopathological analysis was used to establish the final diagnosis. Pathological grading of MPNSTs was performed by independent and experienced pathologists in accordance with the criteria described by Ducatman et al., and the tumors were classified as high grade or low grade[6]. High-grade tumors are characterized by fasciculated cells with hyperchromatic nuclei and frequent mitotic figures. Low-grade tumors are characterized by decreased cellularity and fewer hyperchromatic cells, mitotic figures, and tumor necrosis compared with high-grade tumors.

Long-Term Follow-up

Recurrence of m-SDTs was defined as the appearance of new lesions or regrowth of the remaining tumor, that is, an increase in observed tumor volume over two consecutive imaging studies performed after tumor removal or radiotherapy. For detecting distant metastasis, computed tomography, MRI, positron emission tomography (PET) scan, and bone scintigraphy were performed. OS was defined as the time from initial surgery or radiotherapy until death.

Statistical analysis

Rate of OS was estimated using the Kaplan-Meier method, whereas differences in prognostic parameters were evaluated by the log-rank test. A Cox proportional hazards model was used for multivariate analysis. JMP version 10 software was used for statistical analysis. Probability values were obtained from two-sided tests, with statistical significance defined as $p < 0.05$.

Results

Clinical demographics

The mean age of patients with m-SDTs was 44.8 ± 3.1 years. There were 12 men and 10 women. Locations of the m-SDTs included the cervical vertebrae (n = 10), thoracic vertebrae (n = 7), lumbar vertebrae (n = 4), and sacral vertebrae (n = 1). Maximal lesion diameters ranged from 2 to 20 cm; the mean maximal diameter was 6.8 ± 3.8 cm. In 16 cases, the maximal diameter was greater than 5 cm. Based on Eden's classification, the tumor location in the axial plane was type II in 6 cases, type III in 14, and type IV in 2. Regarding the histology of malignant SDTs, we found 13 cases of MPNST, 2 of malignant lymphoma, and 1 each of extraskeletal Ewing's family of tumors, hemangiopericytoma, hemangioendothelioma, malignant myoepithelioma, neuroblastoma, malignant solitary fibrous tumor, and plasmacytoma. MPNSTs were classified as low grade in four cases (30%) and as high grade in nine cases (70%). A summary of the patients' clinical demographics is presented in Table 1.

Treatment

Nineteen of the 22 cases were managed with surgery (86%). Among the surgically treated cases, en bloc tumor resection with wide margin and en bloc resection with marginal margin were carried out in only 1 patient each (4.5%), whereas the remaining 17 patients underwent intralesional

Table 2. Clinical Data of 22 Patients with Malignant Spinal Dumbbell Tumors.

Patient	Age	Sex	Follow up (mo)	Histology	Size ≥5 cm	Surgery	Rtx	Ctx	Local recurrence	Distant metastasis	Alive
1	42	M	6	MPNST (high)	yes	intra, PR	Conv	no	no	no	no
2	71	F	42	MPNST (high)	yes	no	CIRT	no	yes	no	yes
3	20	M	140	MPNST (low)	yes	intra, GTR	no	no	yes	no	yes
4	70	M	5	MPNST (high)	yes	intra, STR	no	no	no	yes	no
5			88	MPNST (high)	yes	marginal, en		no	yes	yes	no
	2	F				bloc	no				
6	37	M	8	MPNST (high)	yes	no	no	yes	no	no	no
7	69	F	120	MPNST (low)	no	intra, GTR	no	no	yes	no	yes
8			13	MPNST (high)	yes	wide, en		yes	no	no	no
	35	M				bloc	no				
9	40	M	9	MPNST (high)	yes	intra, PR	CIRT	no	no	yes	no
10	48	M	23	MPNST (high)	yes	intra, PR	CIRT	yes	no	yes	yes
11	10	M	50	EFT-extraskeletal	yes	intra, STR	Conv	yes	yes	yes	no
12		M	11	Hemangiopericyto	yes			no	no	yes	no
	47			ma		intra, STR	Conv				
13		F	56	Hemangioendothel	yes			no	yes	no	yes
	37			ioma		intra, STR	no				
14		F	15	Malignant	yes			yes	no	no	yes
	80			lymphoma		no	no				
15	75	M	8	Plasmacytoma	no	intra, PR	yes	yes	yes	no	no*
16		F	61	Malignant	no			yes	yes	no	yes
	71			lymphoma		intra, STR	no				
17		F	15	Myoepithelial	yes			yes	yes	no	yes
	34			Carcinoma		intra, PR	CIRT				
18	3	F	34	Neuroblastoma	yes	intra, STR	no	yes	yes	no	yes
19	47	M	13	MPNST (low)	no	intra, PR	CIRT	no	yes	no	yes
20		F	22	Solitary fibrous	no			no	yes	no	yes
	78			tumor		intra, STR	no				
21	11	F	3	MPNST (high)	yes	intra, PR	Conv	no	no	no	yes
22	46	M	15	MPNST (low)	no	intra, STR	no	no	yes	no	yes

mo: months, Rtx: radiotherapy, Ctx: chemotherapy, MPNST (high): high-grade malignant peripheral nerve sheath tumor, MPNST (low): low-grade malignant peripheral nerve sheath tumor, EFT: Ewing's family of tumor, intra: intralesional, GTR: gross total resection, STR: subtotal resection, PR: partial resection, Conv: conventional radiotherapy, CIRT: carbon-ion radiotherapy, * Died of another disease (myocardial infarction)

resection (91%). Overall, four cases achieved GTR (21%). Chemotherapy was given to nine patients, seven of whom had undergone tumor resection and two of whom had not. The best response to chemotherapy was partial response in five cases, stable disease in three cases, and progressive disease in one case. Nine patients received radiotherapy, four received conventional radiotherapy, and five received carbon-ion radiotherapy (CIRT) with curative intent. In terms of clinical setting, eight patients received postoperative adjuvant radiotherapy and one patient received CIRT as radiosurgery. A summary of the clinical data is shown in Table 2.

Local control, distant metastasis, and overall survival

Local recurrence was observed in nine cases (41%) after a median follow-up period of 3 months (range 1 to 15 months). Remarkably, among cases of MPNST, seven patients (78%) with high-grade tumor experienced recurrence. In contrast, four patients with low-grade malignancies had no tumor recurrence at the final follow-up. Importantly, a patient with high-grade MPNST treated by CIRT as radiosurgery had not developed local recurrence for 42 months at the time of this writing. Regarding distant metastasis, lung metastasis was observed in four patients, two of whom also developed bone metastasis. Intraspinal/intracranial metastasis was seen in two additional patients. At final follow-up, eight patients died of their malignancy and one died of myocardial infarction. The duration of OS ranged from 3 to 140 months, with a median survival time of 15.3 months. The 3 and 5 year OS rates were 66.7% and 55.6%, respectively (Fig. 1).

Clinical factors associated with OS

Next, we evaluated the prognostic significance of various clinical factors, including tumor size, histological subtype (high-grade MPNST or SDTs of other histological types), degree of removal (GTR or not), presence or absence of chemotherapy, CIRT, and local recurrence. As shown in Fig. 2, high-grade MPNST and presence of local recurrence were associated with poorer OS (p = 0.0129 and p = 0.001, respectively). Median OS was 8.7 months for patients with

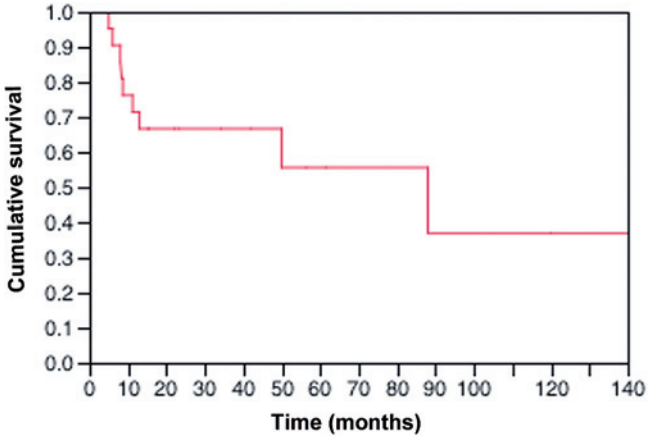

Figure 1. Kaplan-Meier survival curve for 22 cases with malignant spinal dumbbell tumors, showing a median survival time of 15.3 months.

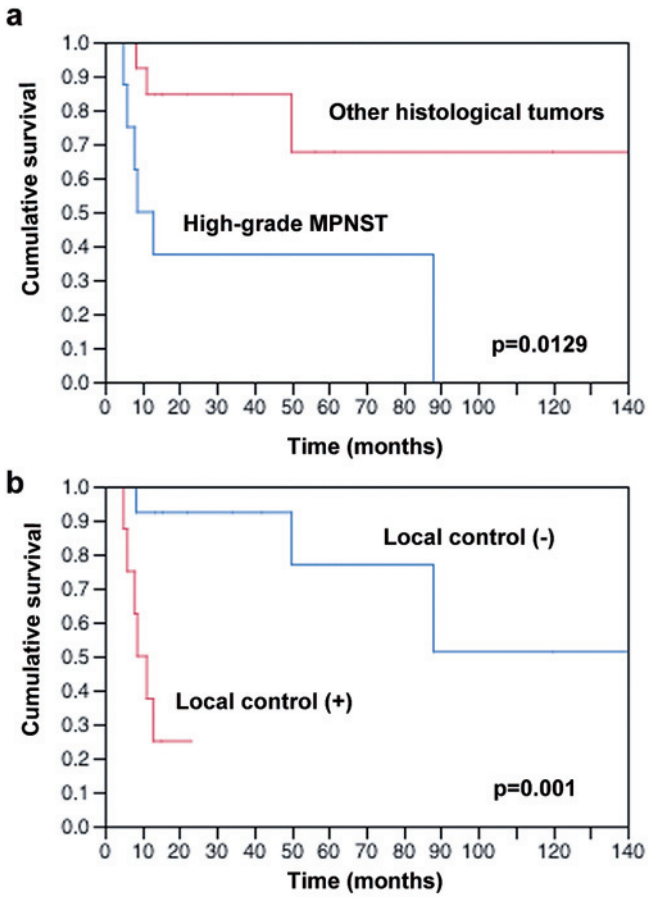

Figure 2. Association between predictive factors (histological subtypes and local recurrence) and poor prognosis in malignant spinal dumbbell tumors. Kaplan-Meier survival curves based on histological subtype (a) and presence or absence of local recurrence (b). Log-rank tests were used to determine statistical significance, with $p < 0.05$ defined as significant.

high-grade MPNST and 22.1 months for those with SDTs of other histological types. Meanwhile, median OS was 8.7 months for patients with local recurrence and 42 months for those without local recurrence. On the contrary, no significant difference in OS was noted between tumor size (p = 0.186), degree of removal (p = 0.375), presence or absence of chemotherapy (p = 0.691), and CIRT (p = 0.968). In univariate analysis, histological subtype (high-grade MPNST) (hazard ratio [HR] 6.67, 95% confidence interval [CI] 1.01-44.2, p = 0.0389) and presence of local recurrence (HR 6.66, 95% CI 1.02-44.3, p = 0.0389) were significant and independent predictors of OS (Table 3). According to multivariate analysis, histological subtype (high-grade MPNST) (HR 14.9, 95% CI 1.5-396, p = 0.0191), degree of removal (GTR) (HR 0.07, 95% CI 0.0016-0.835, p = 0.0343), and presence of local recurrence (HR 11.2, 95% CI 1.02-370, p = 0.0479) were significant and independent predictors of OS (Table 4).

Table 3. Univariate Analysis of Clinical Factors in Relation to Overall Survival.

Clinical factors	Hazard ratio	95% CI	p value
Tumor size ≥5 cm			0.14
Histology			
(High-grade MPNST)	6.67	1.01-44.2	0.0389*
GTR (yes)			0.68
CIRT (yes)			0.26
Chemotherapy (yes)			0.78
Local recurrence (yes)	6.66	1.00-44.3	0.0389*

CI: confidence interval, MPNST: malignant peripheral nerve sheath tumor, GTR: gross total resection, CIRT: carbon-ion radiotherapy, *: p<0.05

Table 4. Multivariate Analysis of Clinical Factors in Relation to Overall Survival.

Clinical factors	Hazard ratio	95% CI	p value
Tumor size ≥5 cm	0.48	0.024-12.6	0.61
Histology			
(High-grade MPNST)	14.9	1.5-396	0.019*
GTR (yes)	0.007	0.0016-0.835	0.0343*
CIRT (yes)	0.11	0.004-0.90	0.062
Chemotherapy (yes)	0.58	0.11-2.86	0.50
Local recurrence (yes)	11.2	1.02-370	0.0479*

CI: confidence interval, MPNST: malignant peripheral nerve sheath tumor, GTR: gross total resection, CIRT: carbon-ion radiotherapy, *: p<0.05

Case Presentation

Case 9

A 40-year-old man presented with a spinal dumbbell MPNST in the cervical spine (Eden's type III), with a chief complaint of a mass in the left neck. Neurological examination showed progression of numbness and muscle weakness in his left extremities. The mass was 9 cm in size, and axial T2-weighted MRI showed a mixed-intensity mass with unclear boundaries in the epidural and paravertebral spaces (Fig. 3a). On PET scan, the lesion showed increased isotope uptake (SUVmax = 5.5) (Fig. 3b, arrows). The patient un-

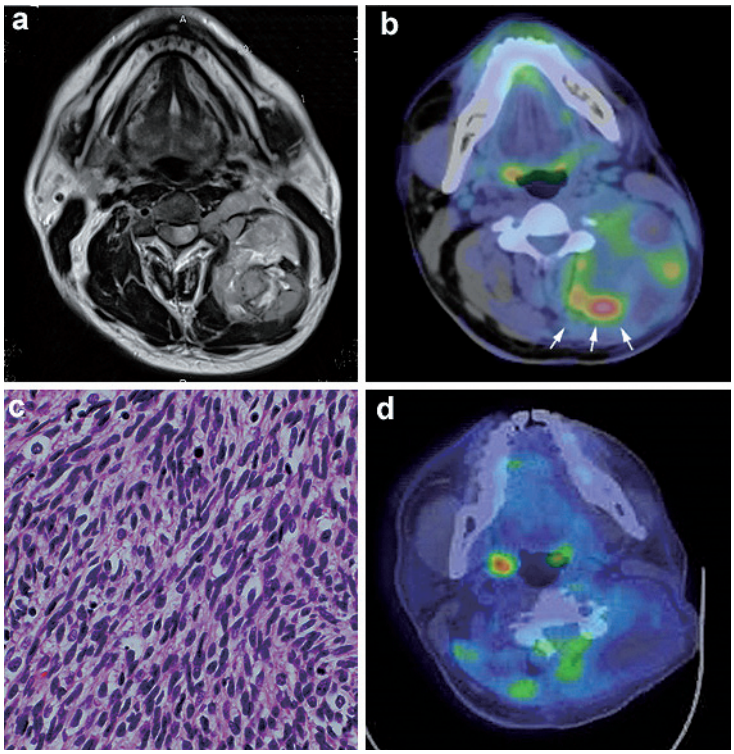

Figure 3. Case 9. A spinal dumbbell MPNST in the cervical spine in a 40-year-old man. (a) Axial T2-weighted MRI showed a mixed intensity mass with unclear boundaries in the epidural and paravertebral space (Fig. 3a). (b) PET scan showed increased isotope uptake (SUVmax=5.5) in the tumor (Fig. 3b, arrows). (c) Postoperative pathology confirmed the diagnosis of high-grade MPNST. H&E, original magnification×400. (d) PET scan after treatment of carbon-ion radiotherapy revealed a reduction of isotope uptake (SUVmax=2.0) in the tumor.

derwent a partial laminectomy and resection of the epidural tumor by a posterior approach. Postoperative pathology showed the proliferation of spindle cells arranged in fascicular pattern with nuclear atypia, confirming the diagnosis of high-grade MPNST (Fig. 3c). Subsequently, the patient was treated by CIRT. Five months after surgery, multiple lung and bone metastases were detected, whereas no obvious local recurrence was observed on MRI and isotope uptake within the tumor was reduced (SUVmax = 2.0) (Fig. 3d). The patient died 9 months after surgery.

Discussion

Fewer than 10% of SDTs are m-SDTs[2], and as a result there remains insufficient clinical information about this tumor type. Indeed, in the majority of m-SDTs, GTR is very difficult or impractical because of the complexity of the surrounding anatomy, suggesting that m-SDTs might be associated with worse clinical outcomes compared with other types of spinal tumors. However, only a limited number of studies have attempted to identify the clinical features of m-SDTs[7]. Our report focused on the clinical outcomes of m-SDTs, and hence, we believe that this study may contribute to the understanding of this rare form of spinal tumor.

The evidence for the effective treatment of m-SDTs is scant. It has been suggested that GTR, preferably with negative margins, should improve the outcome of malignant spinal tumors such as MPNST[8]. However, GTR has been performed at a significantly lower rate for SDTs (60%) compared with intradural (79%), extradural (85%), and paraspinal (77%) tumors[9]. Consistent with this, the rate of GTR in our series was only 21% (4/19). Importantly, we found that GTR was one of the independent favorable predictors for OS in multivariate analysis. Thus, GTR might confer a survival benefit independently of other covariates, including adjuvant therapies such as radiotherapy and chemotherapy. Therefore, we consider that GTR, if technically feasible, is a reasonable goal in the treatment of m-SDTs[10]. Interestingly, we found the significant differences in feasibility of GTR between histological subtype (MPNST vs. others, p = 0.028). However, we considered that our data set was too small to draw a solid conclusion relating to this issue. With regard to the location of the tumors, there was no significant difference in OS between tumor location (cervical vs. others, p = 0.12).

Given the challenging nature of m-SDT treatment, alternatives to surgery have recently emerged. One promising modality is CIRT, which is considered to show superior

treatment outcomes and dose distribution for malignant spinal tumors compared with photon beam therapy[11]. Remarkably, Matsumoto et al. reported that CIRT for primary spinal sarcomas resulted in 5 year local control and OS rates of 79% and 52%, respectively[12]. Indeed, in the present study, five patients received CIRT and experienced no severe adverse events, and in multivariate analysis, CIRT showed a favorable effect on OS, though it was not significant (HR 0.11, 95% CI 0.004-0.90, $p = 0.062$). These findings suggest that CIRT is both effective and safe for the treatment of patients with m-SDTs.

In this case series, MPNST with high-grade malignancy was a strong and independent poor prognostic factor. Remarkably, seven out of nine patients with high-grade MPNST died of their disease. In contrast, none of the patients with low-grade MPNST experienced recurrence or distant metastasis, suggesting an urgent need for systemic treatments such as chemotherapy for patients with high-grade MPNST. However, the role of adjuvant chemotherapy for high-grade MPNST continues to be a subject of debate[13]. In this study, the administration of chemotherapy did not lead to improved survival. Thus, the use of adjuvant chemotherapy for high-grade MPNST remains an individual decision based on the estimated risk of recurrence, the performance status of the patient, and the willingness of the patient to undergo toxic treatment with uncertain benefit[14].

We experienced three cases of m-SDTs with hematopoietic origin. Interestingly, one was a rare case of dumbbell-shaped intraspinal plasmacytoma. Zappe et al. reported a solitary dural plasmacytoma associated with neurological symptoms, and, as was the case in our study, the diagnosis was not suspected before surgery[15]. The optimal management of hematopoietic m-SDTs is not known; however, we consider that patients with severe spinal instability, spinal deformity, or spinal cord compromise will require surgical intervention followed by postoperative radiation and chemotherapy. In contrast, m-SDTs of malignant lymphomas including Hodgkin's disease can usually be managed nonoperatively with pain control and conventional radiation therapy and chemotherapy, because lymphadenomatous tissue responds well to radiotherapy and chemotherapy and good clinical response and improved neurological function have been anticipated[16].

Conclusion

In this report, we document our experiences with m-SDT, a rare type of malignant tumor with an unusual form in the spine. Although we recognize that the limitations of this study include its retrospective nature as well as the heterogeneity of the cases and lacks of certain new findings and ideas, we nevertheless clearly demonstrated that GTR of m-SDTs provided significant long-term benefits in survival, independent of a number of other covariates. However, GTR of m-SDTs was often challenging because of the surrounding anatomical structures. In this regard, we also observed that the use of CIRT, an emerging radiotherapeutic technique, decreased recurrence and increased survival in patients with m-SDTs. Quite clearly, more effective systemic approaches other than conventional chemotherapy, for instance molecular targeted medicines, are needed to improve the clinical outcome of m-SDTs.

Conflicts of Interest: The authors declare that there are no relevant conflict of interest.

Sources of Funding: This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (#15K10499).

Author Contributions: YM, KK, and JF conceived of the study, collected data, and drafted the manuscript. ME, HS, AM, and NS participated in the design of the study. KI and SO participated in imaging editing and collection. SB, MH, and YN helped in drafting the manuscript. All authors read and approved the final manuscript.

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