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The Utility of Routine MRI Surveillance Screening in Pediatric CNS Tumor Survivors

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Case Report

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Abstract

Purpose

Surveillance magnetic resonance imaging (MRI) is routinely used to detect recurrence in pediatric central nervous system (CNS) tumors. Frequency of neuroimaging surveillance varies with no standardized approach.

Methods

We sought via a single institution retrospective cohort study to evaluate the frequency of recurrence identified by surveillance neuroimaging versus those detected clinically.

Results

This study included 476 patients; the majority diagnosed with a low-grade glioma (LGG) (n = 138; 29%), high grade glioma (HGG) (n = 77; 16%), ependymoma (n = 70; 15%) or medulloblastoma (n = 61; 13%). Patients with LGG, HGG and ependymoma more commonly had multiply recurrent disease (p = 0.08), with those with ependymoma demonstrating two or more relapses in 49% of cases. Recurrent disease was identified by imaging more often than clinical symptoms (65% vs 32%; p = < 0.01). Mean time to first relapse and subsequent relapse for the entire cohort was 30 months (range 1 day – 24.8 years) and 19.5 months (range 1 week-19.6 years), respectively. Patients diagnosed with meningioma demonstrated the longest mean time to first relapse (74.7 months), whereas those with Atypical Teratoid Rhabdoid Tumor (ATRT) and Choroid plexus papilloma tended to have the shortest time to relapse (8.9 months and 5.5 months, respectively). Overall, 22 patients sustained the first relapse > 10 years from initial diagnosis (9 LGG, 4 medulloblastoma, 3 meningioma, 2 germ cell tumor, 1 pineoblastoma, 1 craniopharyngioma, and 2 other).

Conclusion

With a higher tendency towards detection of tumor recurrence/progression on MRI surveillance in comparison to clinical progression, surveillance imaging should be considered in routine follow up of pediatric CNS tumor survivors. With some relapses > 10 years from initial diagnosis, imaging beyond this time point may be useful in particular tumor types.

INTRODUCTION

Pediatric central nervous system (CNS) tumors encompass both low- and high-grade neoplasms, with the latter being malignant tumors more commonly associated with an inferior prognosis. Magnetic resonance imaging (MRI) is routinely used as a surveillance tool in patents with central nervous system

(CNS) tumors though the timing of imaging is arbitrary [1–4]. While standardized treatments exist for many CNS tumors, surveillance imaging following completion of therapy, particularly beyond 10 years is lacking. Surveillance imaging is utilized to assess response to treatment, obtain baseline evaluations following treatment to aid in detecting asymptomatic recurrent disease, and to assess for late effects of therapy [5]. With earlier detection, treatment of recurrent disease may improve outcome, although this tends to vary based on tumor type. With evolution in treatment approaches, it is difficult to extrapolate the ideal interval of surveillance imaging from prior studies. Furthermore, some older studies used both CT and MRI for surveillance [1, 3, 4, 6–11]. Therefore, conflicting evidence exists regarding optimal timing of surveillance imaging and whether it leads to increased progression free and overall survival (OS). The imaging frequency for surveillance is loosely based on the biological characteristics of the tumor type which considers the aggressiveness or grade of tumor, risk of recurrence, pattern of local or metastatic recurrence and prior treatments utilized. As conflicting evidence exists regarding optimal timing of surveillance imaging, it is often left to the discretion of the primary team.

Controversy exists in the use of surveillance imaging in detecting recurrent CNS tumors in pediatrics. Some studies have demonstrated that asymptomatic recurrences are detected in a minority of cases and early detection may not necessarily improve outcomes especially in patients with high-grade neoplasms [12, 13]. Whereas others have shown that surveillance imaging is beneficial in detecting recurrent or progressive CNS tumors in asymptomatic children and permits more opportunities for salvage therapy [8]. Furthermore, late recurrences tend to encompass one of the leading causes of mortality and can be identified 5–20 years from diagnosis [14, 15].

Surveillance imaging is not perfect though. It has been associated with false positive results which may lead to additional imaging, added costs and worry amongst the patient/family [5, 16, 17]. Imaging may also provide an unclear result with the complexity of treatment changes, radiation necrosis, and pseudo-progression confusing the interpretation. Through this study we aimed to determine how often tumor recurrence was identified by surveillance neuroimaging versus clinically from symptomatic presentation at relapse via a retrospective chart review.

METHODS

A retrospective cohort study was conducted at Lurie Children's Hospital. Lurie Children's Hospital IRB approved this study. Data was extracted from EPIC and collected in REDCap. Data collected included race, gender, age at diagnosis, diagnosis by histology, date of diagnosis, type of treatment received, date of recurrence, mode of detection at recurrence, presentation at recurrence, location of recurrence, intervention after recurrence, survival status, and time to recurrence. Pediatric patients (birth to age 21 years of age) diagnosed with a primary CNS tumor between 1988 and 2011 treated at Lurie Children's Hospital Neuro-Oncology Program were included.

Statistical analysis

Descriptive methods were used to present demographics, tumor histology and age at diagnosis. Continuous variables were reported as mean, standard deviation, median and ranges. Categorical variables were described by frequency and percentage. Characteristics were compared with Z-tests of proportions and T-tests, where appropriate.

RESULTS

During the study period (1988–2011), 476 patients met inclusion criteria and had complete chart information including time to relapse and were included in the study. Of those patients included, 745 recurrences were detected. The majority of patients were Caucasian (*n* = 204, 42.5%), followed by Hispanic/ Latino (n = 56, 12%) or African American (n = 20, 4%). More than half (n = 261, 55%) were male. Low grade gliomas (LGG) accounted for 29% (n = 138) of the cohort, 16% had a diagnosis of high-grade glioma (HGG) (n = 77), 15% ependymoma (n = 70) and 13% medulloblastoma (n = 61) (Table 1). At diagnosis, 58% (n = 233) of patients were treated with a multimodality approach to therapy and 42% (n = 170) were treated with a single line of therapy. Of those, 31% (n = 126) were treated with surgery alone, 10% (n = 40) chemotherapy alone and 1% (n = 4) radiation only. In contrast, 25% (n = 99) were treated with a multimodality approach to therapy including surgery, chemotherapy and radiation, 18% (n = 72) with surgery and chemotherapy, 12% (n = 48) surgery and radiation, and 3.5% (n = 14) chemotherapy and radiation. Whereas at time of recurrence/relapse, 57% (n = 180) patients were treated with one line of therapy and 38% (n = 119) received a combination approach to therapy (Table 1).

Table 1
Patient Characteristics

Patient Characteristics		
	# of Patients	**%**
Race		
Caucasian	204	42.5
Hispanic or Latino	56	11.7
Black or African American	20	4.1
Native American or American Indian	1	0.2
Asian/Pacific Islander	12	2.5
Other	12	2.5
Unknown	175	36.4
Gender		
Male	261	55
Female	217	45
Diagnosis		
Low Grade Glioma	138	29
High Grade Glioma	77	16.2
Medulloblastoma	61	12.8
ATRT	6	1.3
Pineoblastoma	10	2.1
Ependymoma	70	14.7
Craniopharyngioma	26	5.5
PNET	15	3.4
Choroid Plexus Papilloma	3	0.6
Choroid Plexus Carcinoma	2	0.4
Germ Cell Tumor	19	4.0
Meningioma	11	2.3
Other	38	8

Patient Characteristics		
	# of Patients	%
Race		
Treatment (at relapse) (n = 316)		
Surgery	69	21.7
Surgery + Chemotherapy	59	18.6
Surgery + Radiation	34	10.7
Surgery + Chemotherapy + Radiation	26	8.2
Chemotherapy	84	26.4
Radiation	27	8.5
Radiation + Chemotherapy	19	6.0

Sixty five percent of relapses were detected with imaging, in comparison to 32% due to clinical symptoms ($p < 0.01$)(Table 2). Furthermore, 2% were identified with both clinical symptoms and imaging features consistent with relapse/progression. Overall based on diagnosis, imaging tended to detect relapse more often than clinical presentation ($p = 0.05$) (Table 2).

Table 2
Mode of detection of relapse.

Mode of Detection of Relapse				
Total	**# of Patients**	**%**		
Clinical	235	31.5	**P < 0.01**	
Imaging	483	64.8		
Both (clinical and imaging features)	17	2.3		
Unknown	10	1.3		
Diagnosis (p = 0.05)	**Clinical (%)**	**Imaging (%)**	**Both (%)**	**Unknown (%)**
Low Grade Glioma	67 (34.5)	122 (62.9)	5 (2.6)	0
High Grade Glioma	44 (41.5)	55 (51.9)	5 (4.7)	2 (1.9)
Medulloblastoma	29 (35.8)	47 (60.5)	2 (2.5)	1 (1.2)
ATRT	1 (14.3)	5 (71.4)	1 (14.3)	0
Pineoblastoma	4 (22.2)	14 (77.8)	0	0
Ependymoma	33 (21.3)	113 (72.9)	2 (1.3)	7 (4.5)
Craniopharyngioma	10 (23.8)	31 (73.8)	1 (2.4)	0
PNET	6 (22.7)	17 (77.3)	0	0
Choroid Plexus Papilloma	1 (25)	3 (75)	0	0
Choroid Plexus Carcinoma	0 (0)	2 (100)	0	0
Germ Cell Tumors	7 (25.9)	20 (74.1)	0	0
Meningioma	10 (33.3)	20 (66.7)	0	0
Other	23 (39.7)	34 (58.6)	1 (1.7)	0

Patients with LGG, HGG and ependymomas were more commonly found to have multiply recurrent disease (p = 0.08), with those diagnosed with an ependymoma demonstrating two or more relapses in 49% of cases. Patients with meningiomas and ependymoma were more likely to have four or more relapses (17% and 14%, respectively) (Table 3).

Table 3
Number of Relapses by Diagnosis

Number of Relapses by diagnosis (P = 0.08)*	**1** **n(%)**	**2** **n(%)**	**3** **n(%)**	**≥ 4** **n(%)**
Low Grade Glioma (n = 140)	101 (72%)	28 (20%)	6 (4%)	5 (4%)
High Grade Glioma (n = 76)	58 (76%)	13 (17%)	2 (3%)	3 (4%)
Medulloblastoma (n = 61)	49 (80%)	8 (13%)	1 (2%)	3 (5%)
ATRT (n = 6)	5 (83%)	1 (17%)	0	0
Pineoblastoma (n = 12)	7 (58%)	1 (8%)	0	2 (17%)
Ependymoma (n = 71)	37 (52%)	13 (18%)	11 (15%)	10 (14%)
Craniopharyngioma (n = 24)	18 (75%)	9 (38%)	0	1 (4%)
PNET (n = 15)	10 (67%)	2 (13%)	1 (7%)	1 (7%)
Choroid Plexus Papilloma (n = 3)	2 (67%)	1 (33%)	0	0
Choroid Plexus Carcinoma (n = 2)	2 (100%)	0	0	0
Germ Cell Tumors (n = 19)	13 (68%)	5 (26%)	0	1 (5%)
Meningioma (n = 12)	5 (42%)	2 (17%)	3 (25%)	2 (17%)
Other (n = 37)	29 (78%)	4 (11%)	2 (5%)	2 (5%)
***ANOVA p < 0.001**				

Mean time to first relapse for the entire cohort was 2.5 years (range 1 day-24.8 years), with a median of 1.3 years (range 1 week- 2.3 years). Overall 24% (117/485) of the first relapses occurred within 6 months of initial diagnosis and 43% (207/485) within 12 months. Given the heterogeneous diagnoses, as expected variations existed in average time to relapse, with the longest mean time to first relapse of 6.2 years (median 2.1 years, range 1.5 months-24.8 years) in meningioma patients, followed by 3.4 years (median 2.5 years, range 0.36 months- 14.1 years) in LGG patients, 3 years (median 1.6 years, range 0.36 months-20.3 years) in medulloblastoma, 2.7 years (median 1.3 years, range 0.53 months- 16.8 years) in germ cell tumor (GCT), and 2.7 years (median 1.4 years, range 1.8 months- 16.9 years) in pineoblastoma patients. The shortest mean time to first relapse was amongst choroid plexus papilloma (CPP) (5.5 months; median 4.4 months, range 2.8–9.4 months), followed by ATRT (8.9 months, median 4.2 months, range 0.72 months- 2.7 years) (Table 4).

Table 4
Time to relapse by Diagnosis

Time to Relapse By Diagnosis	Time to relapse from diagnosis (months)*	Minimum (months)	Maximum (yr)	Mean time to first relapse (months)*	Mean time to subsequent relapse (months)
All diagnosis	39.75	0.03	27.6	30.19	19.5
Low Grade Glioma	53.4	0.36	25.1	41.2	32.6
High Grade Glioma	19.5	0.03	19	13.6	16.7
Medulloblastoma	36.3	0.36	20.3	36.5	17.5
ATRT	8.5	0.72	2.7	8.9	5.6
Pineoblastoma	28.1	1.84	16.9	32.5	6.7
Ependymoma	39.7	1.38	11.1	21.7	11.4
Craniopharyngioma	37.9	1.74	21.9	27.6	32.3
PNET	22.4	0.72	7.7	20.2	5.0
Choroid Plexus Papilloma	11.0	2.79	2.2	5.5	24.7
Choroid Plexus Carcinoma	14.3	12.85	1.3	14.3	0
Germ Cell Tumors	32.8	0.53	16.7	32.9	10.6
Meningioma	90.2	1.51	27.6	74.7	34.9
Other	31.6	0.99	13.6	27.1	11.1
***ANOVA p < 0.001**					

The maximum time to first relapse was over 10 years in several tumor types including, LGG, medulloblastoma, pineoblastoma, craniopharyngioma, GCT, and meningioma. Of those who had first relapse > 10 years from diagnosis, 9 were diagnosed with a LGG with mean time to relapse 11.9 years from diagnosis (range: 10.7–14.1 years), 4 medulloblastoma with mean time to relapse 14.3 years from diagnosis (range 10.6–20.3 years), 1 pineoblastoma relapsed at 16.9 years from diagnosis and 1 craniopharyngioma relapsed 10.4 years from initial diagnosis. Three patients with meningioma relapsed > 10 years from diagnosis (mean 16.3 years; range 11.4–24.8 years) and two GCT relapsed > 10 years (mean 13.9 years, range 10.9–16.8 years). When selecting out for those who sustained first relapse 5 or more years from diagnosis, it is important to note, this included 33 patients with a LGG (mean time to first relapse 8.2 years, median 7.6 years, range 5.1–14.1 years), 11 patients with medulloblastoma (mean time to first relapse 10.1 years, median 9.3 years, range 5.9–20.3 years), 8 ependymoma (mean time to first relapse 6.7 years, median 6.6 years, range 5.1–8.7 years), 5 craniopharyngioma (mean 7.5 years, median

6.9 years, range 5.2–10.2 years), 4 meningioma (mean 14.3 years, median 12 years range 8.5–24.8 years), 3 GCT (mean 11.4 years, median 10.9 years, range 6.5–16.8 years), 2 HGG (mean/median time 6 years, range 5.3–6.7 years), and 1 PNET (relapse at 7.7 years).

DISCUSSION

CNS tumors are a diverse group of diseases, with time to relapse differing based on histological type. Although the use of surveillance MRI is standard practice in management of children with CNS tumors, challenges exist with frequency of monitoring being dependant on tumor type, disease status, metastatic potential and prior treatments received. Furthermore, factors such as pseudo-progression or radiation necrosis may complicate interpretation of imaging. Despite this, pediatric CNS tumors are at a risk of recurrence and as demonstrated surveillance imaging both in the immediate post treatment phase as well as late surveillance (> 5 years post completion of therapy) are necessary. We demonstrate an overwhelmingly higher tendency towards detection of tumor recurrence or progression earlier by MRI surveillance in comparison to clinical progression (65% in comparison to 32%) for CNS tumors with an overall median time to first relapse of 1.3 years, with the earliest relapse noted at 1 week in a HGG patient and the latest at 24.8 years in a patient diagnosed with meningioma.

Prior meta-analysis examined the utility of surveillance neuroimaging in high grade and low-grade CNS tumors [4, 10]. Most recurrences (65–100%) within these studies were identified by imaging in asymptomatic patients in comparison to up to 35% detected by clinical symptoms [10]. Furthermore, most recurrences were within 5 years of treatment and prompted additional intervention or treatment within the low-grade cohort [10]. Whereas, amongst high-grade tumors, the findings were diverse with evidence lacking guiding the effectiveness of MRI surveillance given the uncertainty of whether earlier detection is beneficial [4]. These prior studies are consistent with our finding where most relapses were detected by imaging, with 63% of the LGG patients and 52% of the HGG recurrence appearing on imaging, although our study demonstrates the continued tendency for relapse beyond 5 years, necessitating further imaging.

Similar to the low-grade cohort published previously, we identified that a large portion of LGG patients tend to develop tumor recurrence within the first 5 years from end of treatment with a mean time to recurrence of 3.4 years (median 2.5 years; range 0.36 months-14 years). In our cohort, 33 (24%) of the LGG patients sustained their first relapse 5 or more years from diagnosis, the remainder (76%) had a first relapse within 5 years from diagnosis. This is slightly lower than the previously reported 90% by 5 years in prior studies [10]. With prior studies demonstrating that 56% of tumor recurrences occur within the first-year post treatment, and more specifically 46% within the first 6-months, our results point to a slightly longer time to recurrence with 24% and 43% within the first 6 and 12 months, respectively.

Most treatment protocols for high-grade pediatric CNS tumors suggest routine follow-up imaging for up to 10 years post treatment. Some studies have suggested that regular follow up within this 10-year period is necessary, but regular imaging beyond 10 years in malignant pediatric CNS tumors, namely

medulloblastoma, ependymoma, primitive neuroectodermal tumor (PNET)/pineoblastoma, ATRT, HGG and diffuse intrinsic pontine glioma (DIPG) may not be needed unless clinical symptoms are present as it has been suggested that recurrences are rare or even non-existent beyond 10 years [18]. In contrast to this, we demonstrate maximal time to relapse exceeding 10 years in several tumor types, including those with high grade feature such as, medulloblastoma, pineoblastoma, and GCT. Although late relapses are less common, imaging beyond 10 years is necessary to capture these patents.

Prior studies demonstrated the longest latency period for relapse in standard risk medulloblastoma being 7.9 years [18, 19], whereas within our cohort the longest time to first relapse was 20 years in a medulloblastoma patient, although the median time to first relapse was 1.6 years. While most would expect earlier recurrences, discontinuation of surveillance imaging beyond 10 years in these patients would miss those with very late recurrences. On the contrary, shorter duration of surveillance imaging may capture most of the relapses in other more aggressive CNS tumors, such as HGG. Representing up to 20% of all CNS tumors in childhood and adolescents, HGG are one of the leading causes of mortality amongst CNS tumors. With most previously reported recurrences (up to 75%) occurring within 1 year of diagnosis (21), our results are consistent with median time to recurrence of 8 months (mean 13.6 months) in HGG patients.

Low grade CNS tumors tend to act as a chronic disease, at times necessitating multiple lines of therapy and posing a risk of late recurrences. Consistent with our findings, surveillance neuroimaging in this population tends to aid in detecting recurrence/progression in the absence of clinical signs and symptoms with > 65% of LGG recurrences identified by imaging in various studies [11, 13, 20, 21]. Early detection in patients without symptoms may translate into tumor detection at a stage that may have less disease bulk and in turn more responsiveness or options for treatments. Prior studies have reported average time to recurrence post initial treatment of 0.33 [11] to 2.33 [13] years for low grade tumors. This is slightly earlier than our reported mean time to relapse of 3.4 years in the LGG cohort. This discrepancy may be in part due to initial treatment strategies, a trend to delayed recurrences in low grade tumors in whom initial surgery achieved gross total resection (GTR) in comparison to those with subtotal resection (STR) is possible. With median times to recurrence in GTR low grade CNS tumors reported in three studies as 0.53 [22], 1.0 [21] and 1.9 [20] years respectively, whereas median time solely by resection reported as 0.64 years in GTR and 0.42 years in STR [23]. With 41 (30%) patients in our LGG cohort treated up front with surgery alone, it is probable that these patients had extensive resections of tumor with little to no residual disease. Thus, the median time to recurrence of 3.4 years may be more in keeping with reports previously published. Continued surveillance post treatment would be beneficial to detect recurrences in these patients.

The benefit to survival of detecting recurrences on imaging is controversial and is likely tumor histology based. A medulloblastoma study found that median OS increased by over 15 months in those patients in whom recurrence was found by imaging, although all patients with recurrence died of their disease [24]. Whereas another study demonstrated a survival advantage in some patients in whom medulloblastoma relapse was identified by imaging in comparison to those who presented with symptoms with a median

survival of 44 months in those detected by imaging and 5 months in those presenting with symptoms [25]. Of those detected with surveillance imaging, four remained alive at 44–75 months [25]. The authors also demonstrated a tendency to less advanced disease in those detected by imaging alluding to the possibility of the disease being more amenable to salvage treatment [25]. In contrast, earlier detection of ependymoma recurrence with surveillance imaging was found to be associated with improved second progression free survival, a tendency towards higher probability of survival and increased opportunities for salvage therapy [26]. Aligning with other studies, asymptomatic relapse detected by surveillance imaging was more common amongst patients with ependymoma. Prior studies demonstrated 65% of ependymoma relapses to be found on surveillance imaging in comparison to 32% by clinical symptoms [26], this is consistent with our results with 73% of ependymoma relapse detected with imaging and 21% clinical symptoms. Surveillance imaging more often identifies relapses in ependymoma patents, and thus permits salvage therapy options as asymptomatic recurrences are more commonly associated with reduced disease burden making the disease more amendable to surgical or other salvage therapy options in those with localized recurrences. It is common that patients with symptomatic recurrent ependymoma present with more widespread disease or greater disease burden making them less amendable to salvage therapies [26–28]. Although the effect on OS is unclear; earlier detection of relapse may provide patients and families with added treatment options and more importantly quality of time together. Unfortunately, survival data was limited in our study, as such, we are unable to make comments pertaining to relapse detection and outcomes.

Asymptomatic recurrence rates have been found to be higher in ependymoma and medulloblastoma patients compared to other tumor types [8, 26]. This suggests that surveillance imaging may be beneficial in these patients although there is not compelling evidence to suggest any improvement in OS in those whom asymptomatic recurrence was detected on imaging compared to those with symptomatic recurrences [8]. Within our cohort, 61% of medulloblastoma patients and 73% of ependymoma recurrences were detected by imaging, supporting that imaging is beneficial for early detection of relapse prior to development of clinical symptoms. Whether this correlates to improved outcomes is unknown.

Although the focus of this study was to discuss the risk of tumor recurrence post treatment, one must also be aware of the added risk of secondary malignancies, meningiomas or HGG in the latter time period. Radiotherapy, a common treatment utilized in many pediatric CNS tumors, is a known risk factor for development of secondary malignancies in the radiated field. The Childhood Cancer Survivor Study (CCSS) demonstrated that the risk of secondary malignancy increased over time, with a cumulative incidence of 3.3% at 25 years and 3.5% at 30 years [29, 30]. Imaging following cancer therapy should adjust focus to account for the second malignancy risk, as risk of tumor recurrence decreases as additional time passes post therapy of childhood CNS tumors.

This study has several limitations relating to it being a single institutional retrospective review. As a retrospective review, we recognize this paper is subject to patient selection and information bias. As a heterogenous group of tumors, although we analyzed and reported details of each histological type and rate of recurrence identified with imaging or clinically, the small sample size limits our ability to interpret

the effect of surveillance imaging on OS or specific responses to treatment based on diagnosis. Furthermore, with limited information on outcomes, we are unable to comment on survival status and the effect of surveillance imaging on disease outcomes.

CONCLUSION

Pediatric CNS tumors are a diverse group of neoplasms, with variation in the likelihood of recurrence dependant on tumor type, location, and treatment regimen. It could be argued that surveillance imaging may be more beneficial for some tumors that are salvageable with known successful treatment approaches at relapse or progression in comparison to those where efficacious recurrent treatment approaches are lacking. Currently, surveillance imaging is institution dependent. Surveillance neuroimaging detects a large proportion of asymptomatic relapses, and may provide lead time for other therapies or investigational trials. Even if that does not translate into increased OS, it may lead to more quality and quantity of life for patients and families.

Declarations

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Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval: This study was approved by Lurie Children's Hospital Research Ethics Board. The study was performed in line with the principles of this ethics approval.

Consent to participate: As a retrospective study, consent was not required.

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