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Original article

Atypical Teratoid Rhabdoid Tumors (ATRT): King Faisal Specialist Hospital and Research Centre experience

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ABSTRACT

Background: Atypical teratoid rhabdoid tumor is an uncommon aggressive central nervous system tumor. All retrospective series have shown a short mean overall survival rate. Considering the rarity of the disease, few prospective clinical trials addressed treatment recommendations for such aggressive tumors, and consequently no definitive treatment guidelines have been established. In this study, we are reviewing our experience in treating atypical teratoid rhabdoid tumor patients.

Methods: We reviewed the medical charts of 43 patients with atypical teratoid rhabdoid tumor who were treated in King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, between 1996 and 2013. We evaluated the overall survival rate and the influence of different clinical features and treatment protocols on survival.

Results: The median overall survival time was 16.9 months (95% Confidence Interval, 5.2–32.9 months) with an estimated 2- and 5-year overall survival of 41.9% ± 9.6 and 27.9% ± 9.2, respectively. Patients receiving trimodal treatment (surgery, chemotherapy, and radiotherapy) exhibited significantly better median overall survival time compared to their counterparts (P value < .001).

Conclusions: Atypical teratoid rhabdoid tumor is rare and aggressive central nervous system tumor. Despite the limitations of the study, our results support several of clinical practice development. Utilization of postoperative radiotherapy and the adoption of trimodal therapy are associated with significant improvement of median survival. Prompt management with aggressive trimodal therapy should be the standard for future treatment protocols.

1. Introduction

Atypical teratoid rhabdoid tumor (ATRT) is an uncommon aggressive central nervous system (CNS) tumor. It tends to occur in children younger than 3 years of age [1–3]. Although ATRT accounts for 2–5% of CNS tumors in pediatric patients, it accounts for around 20% of CNS tumors in children younger than 3 years [1,4]. The incidence of ATRT may be underestimated owing to the similar radiologic and histopathologic features when compared to some other high-grade CNS malignancies such as primitive neuroectodermal tumors. ATRT includes a blend of epithelial, mesenchymal, and primitive neuroectodermal components. Molecular and chromosomal analysis improved identification of ATRT and subsequently influenced the treatment strategy adopted in such patients.

Most of retrospective series have showed a short mean overall

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survival (OS) ranging between 6 and 18 months [2,5,6]. Considering the rarity of the disease, few prospective clinical trials addressed treatment recommendations for such aggressive tumors, and consequently no definitive treatment guidelines have been established. Recently, a few studies reported that patients undergoing trimodal treatment (surgery, chemotherapy, and radiotherapy) had better survival rates [7,8]. Such results were supported by the first prospective clinical trial for patients with ATRT which suggested a 2-year Overall Survival (OS) rate around 70% ± 10% when trimodal treatment was adopted [9].

In the current study, we are reporting our experience in treating ATRT patients and evaluating the influence of different clinical features and adopted treatment protocols on survival rates.

2. Patients and methods

The research study proposal was accepted by the Research Advisory Council (RAC) of King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia. The medical files of 43 pediatric patients (less than 18 years) diagnosed with ATRT between 1996 and 2013 were reviewed. **All** included patients had pathologically proven ATRT with typical morphology and/or immune-histochemical confirmation. All tumors, except for 1, had loss of INI-1 expression (BAF-47, BD Biosciences). Patients were excluded if internal revision of histopathology and or/immunohistochemistry was not feasible. Median age at diagnosis was 1.8 years (mean: 3.4, SD: 4.8) with 30 (69.8%) patients being less than three years at time of diagnosis. Male patients (53.5%) marginally exceeded females (46.5%). Vomiting was the most common presenting complaint (57%) followed by headache (26.9%) and ataxia (16.1%). All patients were evaluated with MRI scan of the entire craniospinal axis. Patients with negative MRI imaging had cerebrospinal fluid (CSF) cytological assessment to rule out CNS spread. Forty-one patients had intracranial primary disease (23 infratentorial, 18 supratentorial), and two patients had primary tumor involving spinal cord. Seventeen patients (39.5%) had disseminated disease. Thirteen of them were grossly detected via MRI scans while four had positive malignant cells in their CSF cytology test (Table 1).

Complete treatment data including surgical intervention, fields, and doses of radiotherapy, and adopted chemotherapy protocols were analyzed (Table 2). All patients underwent surgery: six patients were subjected to biopsy or debulking surgery and 23 patients had subtotal resection while 14 patients had gross total resection (GTR). For obstructive hydrocephaly, ventriculoperitoneal shunt was inserted in 26 patients. Thirteen patients underwent surgery only, while the remaining 30 patients received postoperative chemotherapy and/or radiotherapy. Only 16 patients received trimodal treatment. Chemotherapy was administered in 29 patients (67.4%); 23 (percentage?) received standard malignant rhabdoid tumor protocol, three patients (percentage?) received rhabdomyosarcoma IV protocol, and the remaining three patients (percentage?) received VAIA (vincristine, adriamycin, ifosfamide, and actinomycin-D), baby brain protocol, and VAC (vincristine, actinomycin-D, and cyclophosphamide).

Eighteen (41.9%) patients received radiation therapy (RT). Among the radically irradiated 17 patients, seven patients received focal irradiation. The total radiation dose ranged from 50.4 to 54 Gy in 28–32 fractions (1.6–1.8 Gy per fraction). All patients treated with focal irradiation had no radiological or cytological evidence of disease dissemination. Ten patients received craniospinal axis irradiation (CSI) followed by localized boost. The CSI radiation dose ranged from 30.6 Gy to 36 Gy delivered in 17–20 fractions (1.6–1.8 Gy per fraction). Spinal irradiation boost was given in three patients with radiologic evidence of spinal seeding. The involved sites were boosted to a total dose of 44.8–50.4 Gy to the spinal gross lesions and 50.4–54 Gy to the cranial tumor. Craniospinal irradiation plan was given using 2-dimensional (2-D) or 3-dimensional (3-D) lateral opposed brain and direct posterior spinal fields. For the localized boost treatment, 3-dimensional conformal radiotherapy (3D-CRT), Intensity Modulated Radiotherapy (IMRT), or Volumetric Modulated Arc Therapy (VMAT) technique were used. Only one patient with poor general condition received palliative RT of 5 Gy single fraction to the primary tumor. In fifteen patients (88.2%), radiation therapy was started beyond three years of age. The median overall radiation treatment time was 41 days (range: 38 to 62). The majority of the patients (82.4%) completed their radiation treatment in less than 45 days. Protracted treatment time was mainly attributed to treatment interruption for episodes of neutropenia. After the end of the treatment protocol, patients were followed up every 3–4 months for the first 2 years and biannually thereafter. Unless otherwise dictated by the patients' symptoms, patients had biannual MRI follow-up scans for the brain including or not including the spine.

3. Statistical analysis

OS time was calculated from day of diagnosis to death or date of last contact for those patients who were alive. Kaplan-Meier method was used to calculate OS probabilities, and survival estimates were compared for various risk factors using Breslow (Generalized Wilcoxon) test. Level of significance was set at a value of $P < .05$ and all significance levels were two sided. SPSS for Windows (Version 20; IBM Corporation, Armonk, NY) was utilized for all statistical analyses.

Table 1
Summary of demographics and clinical characteristics.

Category			No. (%)
Age at diagnosis	<3 years		30 (69.8)
	≥3 years		13 (30.2)
Sex	Male		23 (53.5)
	Female		20 (46.5)
Year of diagnosis	1996–2005		19 (44.2)
	2006–2013		24 (55.8)
Tumor location	Infratentorial		23 (53.5)
	Supratentorial		18 (41.9)
	Spine		2 (4.7)
Extent of disease	Local disease (M0)		26 (60.5)
	Disseminated (M+)		17 (39.5)
	Dissemination to	Spine	13 (30.2)
		CSF	4 (9.3)

Abbreviations: (M0) no metastatic disease at diagnosis, (M+) metastatic disease at diagnosis, (CSF) cerebrospinal fluid.

Table 2
Treatment details including combinations of surgery, radiotherapy, and chemotherapy.

Surgery	43 (100%)	Biopsy	6 (14.0%)
		Subtotal resection	23 (53.5%)
		Gross total resection	14 (32.6%)
Chemotherapy	29 (67.4%)	Malignant Rhabdoid Tumor Protocol	23 (53.5%)
		Rhabdomyosarcoma Protocol	3 (7%)
		Baby Brain Protocol	1 (2.3%)
		VAC Protocol	1 (2.3%)
		VAIA Protocol	1 (2.3%)
Radiotherapy	18 (41.9%)	Craniospinal irradiation then focal boost	10 (23.3%)
		Focal irradiation	7 (16.3%)
		Palliative irradiation	1 (2.3%)
Treatment		Surgery alone	13 (30.2%)
		Surgery and chemotherapy	13 (30.2%)
		Surgery and RT	1 (2.3%)
		Surgery, chemotherapy, and RT	16 (37.2%)

Abbreviations: (VAIA) Vincristine, Adriamycin, Ifosfamide, Actinomycin-D. (VAC) Vincristine, Actinomycin-D and Cyclophosphamide.

4. Results

Forty-three patients were included in this study. The median OS time was 16.9 months (95% Confidence Interval, 5.2–32.9 months) with an estimated 2- and 5-year OS of 41.9% ± 9.6 and 27.9% ± 9.2, respectively (Fig. 1).

Two patients died while on treatment. Another 19 patients died during the follow up period, and 22 patients were alive at the date of last contact. Among 41 patients who completed the treatment plan, 34 (82.9%) had progressive disease (PD), five (12.2%) had stable disease (SD), and two (4.9%) were in complete remission (CR). Out of 22 patients who were alive at the last contact, eight were under regular follow-up with well controlled disease, nine were receiving best supportive care, and six were labelled as do not attempt to resuscitate (DNAR). Five patients were lost to follow-up, and one of them was discharged against medical advice.

Though there was a trend for young patients (less than 3 years) to have shorter median OS (15 months) compared to older patients (25.5 months), the difference was not statistically significant with *P* value of .374. Similarly, there was no significant difference in survival between male and female patients or supratentorial and infratentorial location (*P* value of .624 and .711, respectively). Patients who underwent GTR had a longer median survival (79.8 months) compared to those who had less extensive surgeries (15.4 months), yet the difference was not statistically significant (*P* value = .294). Patients receiving tri-modal treatment exhibited significantly better median OS time compared to their counterparts (*P* value <0.001, Fig. 2).

Among the 27 patients treated with tri-modal treatment, 14 patients had localized disease compared to 12 out 16 patients who

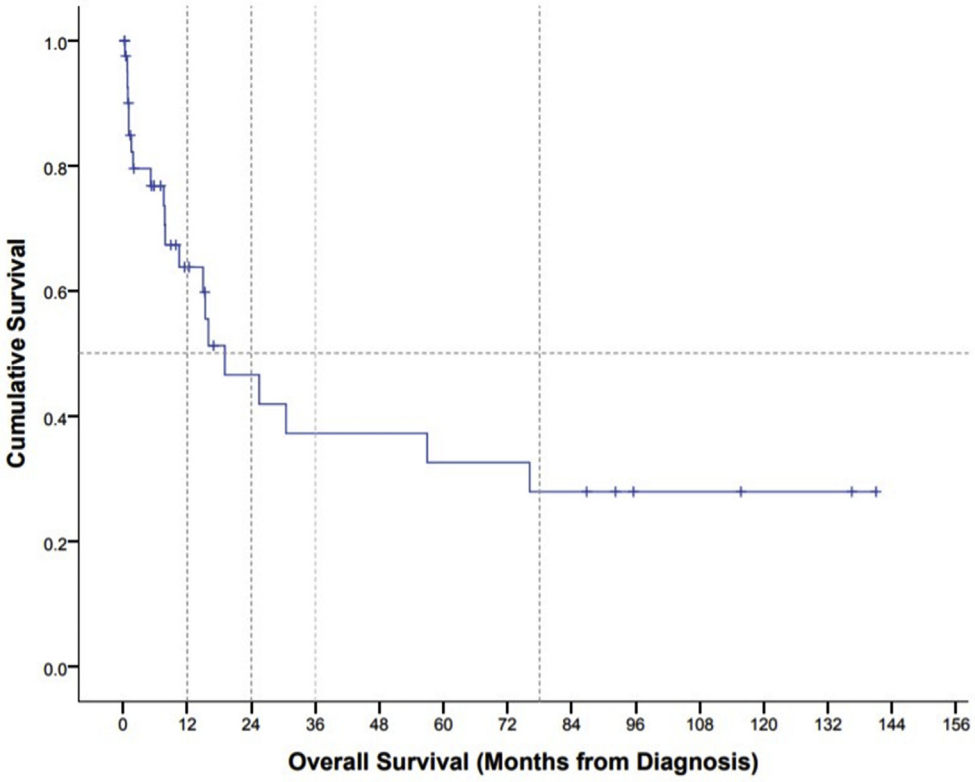

Fig. 1. Overall survival for whole group of patients.

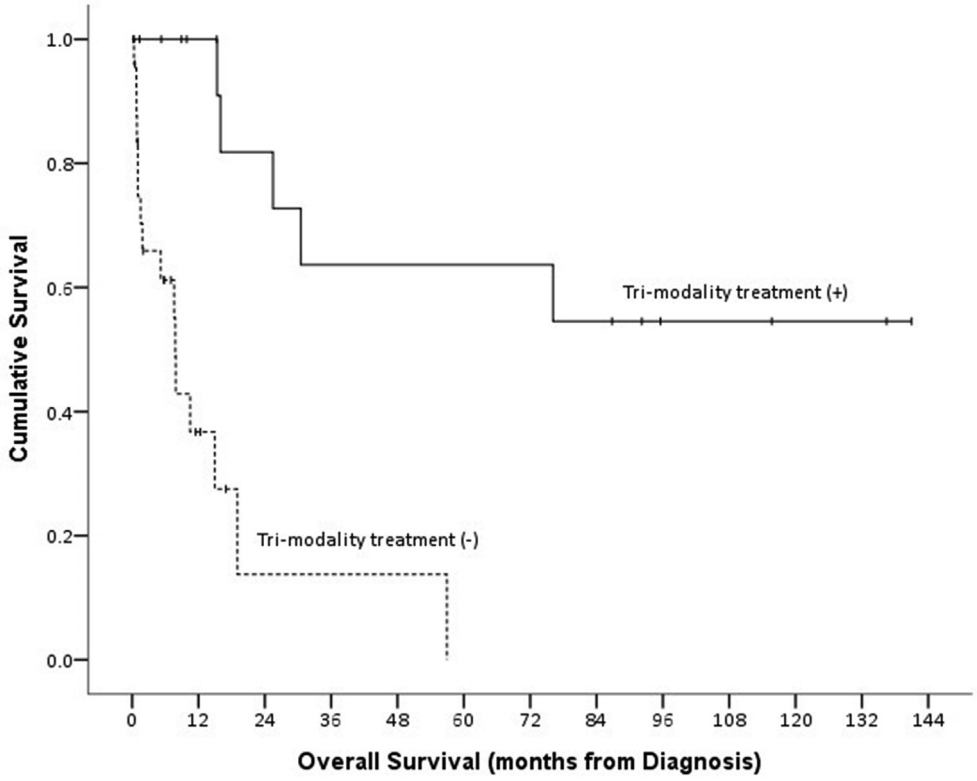

Fig. 2. Difference of mean overall survival for patients who received trimodal treatment versus others.

did not receive trimodal treatment (P value = .133). Only seven patients from the trimodal subgroup had GTR, and the remaining patients had less extensive surgery. Similarly, seven patients among those who did not receive trimodal treatment had GTR (P value = .316).

In a subgroup analysis, those who had radical course of radiation therapy had a significantly better OS as compared to those who did not (P value < .001). Overall survival of patients who received focal radiotherapy was not found to be significantly different from those who had craniospinal axis irradiation (P value = .889). None of the patients included in our study developed serious radiation toxicity. Multi-variable analysis was not feasible owing to the small sample size. Table 3 provides details on median and 5-years overall survival time in different subgroups.

5. Discussion

ATRT is a rare malignant embryonal CNS tumor known for dismal prognosis. The first age-standardized incidence rate is reported to be 1/72,500 persons per year in Austria [10]. In 2012, Lafay-Cousin and colleagues reviewed only 50 ATRT patients from the Canadian population-based registry diagnosed over 12 years [7]. Likewise, using the Surveillance, Epidemiology, and End Results (SEER) International Classification of Disease for Oncology, Chamberlain and colleagues identified a total of 174 ATRT patients diagnosed in 37 years [11]. Similarly, our study reported the clinical outcomes of a relatively limited number of ATRT patients diagnosed at one institute approximately over 2 decades. Over the last 20 years, ATRT treatment strategies have evolved considerably. Operating rooms and procedures have improved. The adoption of early postoperative radiotherapy increased with improvement of techniques from 2-D radiotherapy era to helical tomotherapy. Postoperative intense systemic chemotherapy is increasingly used along with intrathecal chemotherapy. In the current study, infratentorial primary location accounted for 53.5% of the patients, which is comparable to the studies of Dho and colleagues (70%) and Athale and colleagues (47%) [12,13]. In contrast to other publications, we found that the outcome for children less than 3 years old was not significantly worse than those for older children.

We noticed more frequent gross dissemination (30.2%) in our patients compared with western series that suggest 20% of disseminated disease at presentation [14,15]. Lack of awareness of cancer and difficult access to highly specialized health care facilities might explain the relatively higher percentage of advanced stage presentation in our study. In the published literature, positive CSF cytology reached up to 22 - 27%. [13,16] In the current study, CSF cytological evaluation was not performed for patients who had radiological proof for gross dissemination (30.2%). Among patients with radiologic localized disease, 9% had cytological CSF dissemination. In Strother and colleagues' study, positive CSF cytology was found to be 8% [17]. CSF cytology is mandatory in ATRT staging workup as it may influence the management decision. Unlike other published series, the current study showed no survival difference for patients with disseminated disease as compared to those with localized disease [18,19]. The adoption of CSI in many disseminated disease patients might have contributed to the reduction of the difference in survival between the 2 subgroups.

The median overall survival (OS) for the entire cohort in our study is 16.9 months (95% confidence interval [CI], 5.2–32.9 months) which is comparable to series (14.3 months (CI, 11.9–16.6 months) in Fischer-Valuck BW and colleagues report [19] and 17.3 months in the Athale et al. study [13]. Maximum safe resection was attempted in all patients. Vascular tumors and primary tumor extending to adjacent critical structures were the main reasons for suboptimal resection. There is strong evidence of multimodal treatment improving survival for patients with ATRT [19]. Yet, the

Table 3
Comparison of overall survival with respect to different **clinical** factors.

Factors of interest			number	Overall Survival time (months) median (95% CI)	5-years Overall Survival	*p*-value
Age at diagnosis	<3 years		30	15.0 (1.6–28.3)	34.5 ± 11.4	0.374
	≥3 years		13	25.5 (1.5–49.4)	13.9 ± 12.8	
Gender	Male		23	16.0 (1.0–30.9)	10.0 ± 9.3	0.624
	Female		20	76.1 (0.01–170)	44.4 ± 13.9	
Extent of disease at presentation	Local disease		26	56.9 (0.01–147.5)	38.4 ± 18.1	0.795
	Disseminated		17	16.0 (9.1–22.8)	24.6 ± 10.5	
Tumor location[a]	Supratentorial		18	19.0 (13.5–24.5)	20.4 ± 12.4	0.711
	Infratentorial		23	19.0 (7.9–30.2)	32.9 ± 12.7	
Tri-modality Treatment	Negative		27	7.8 (7.3–8.3)	0%	<0.001
	Positive		16	91.8 (58.7–124.9)[b]	54.5 ± 15.0	
Extent of surgery	Biopsy/subtotal resection		29	15.4 (8.9–21.8)	19.4 ± 9.8	0.294
	Gross total resection		14	79.8 (40–119.5)[b]	45.1 ± 18.1	
First line chemotherapy protocol	Malignant Rhabdoid Tumor protocol		23	30.5 (0.1–96.9)	40.9 ± 12.2	0.619
	Other Protocols		6	15.4 (7.6–23.2)	0%	
Radiation[c] therapy	None		25	7.8 (7.4–8.3)	0%	0.001
	Radical		17	76.1 (–)[d]	47.1 ± 13.9	
	Radiation field	Focal	7	25.5 (–)[d]	50.0 ± 20.4	0.889
		CSI then boost	10	76.1 (28.5–123.7)	45.0 ± 19.0	
Year of diagnosis	1996–2004		15	15.4 (4.4–26.3)	0%	0.545
	2005–2013		28	25.5 (8.0–42.9)	34.0 ± 11.7	

[a] Spinal primary location was not included in the comparison.
[b] Mean survival time.
[c] One patient received palliative radiotherapy.
[d] Median (95% CI) could not be calculated.

extent of surgical excision remains an independent factor that influences treatment outcome [7,10]. In our study, although not statistically significant, patients who had GTR had a longer median follow up (79.8 months, range 40–119.5) compared to those who had less extensive surgery (15.4 months, range 8.9–21.8). Surgical impact was diluted by the use of combined modality or trimodal treatment in 31 (72.1%) and 16 (37.2%) patients, respectively, and by the fact that primary GTR was achieved in a proportion of patients with inherit poor prognosis because of initial disease dissemination.

Several studies used diverse combinations of intravenous chemotherapy and intrathecal chemotherapy or high-dose chemotherapy followed by autologous stem-cell rescue with variable results [6,9,13,20]. A meta-analysis by Athale et al. [13] revealed that even without gross total resection, patients who received multi-agent chemotherapy protocols did better, particularly in those younger than 3 years who were spared radiation therapy. The scarcity of the disease and the overall poor quality of evidence made standard treatment regimen in ATRT poorly defined. The role of high dose chemotherapy with autologous-stem cell transplant remains uncertain and its use should be well-adjusted based on the overall toxicity of therapy. The majority of our patients received malignant rhabdoid tumor protocol of chemotherapy. The treatment protocol was well tolerated. The currently available promising target therapies including tazemetostat, Alisertib, and palbociclib were not in effect during the treatment period of the study [21–23].

Early studies that aimed to omit radiation in ATRT patients less than 3 years of age, were associated with a dismal prognosis. The treatment paradigm has changed, and several small cohort studies have reported the significant benefit of adjunct radiation [6,16]. The use of radiation therapy in addition to surgical resection as a treatment for ATRT has increased from 22.3% to 38.4% of cases between 1973 and 2004 [11]. Around 40% of our cohort patients received postoperative radiotherapy with significant improvement of overall survival in those patients as compared with those who did not receive radiotherapy. Similarly, Tekautz et al. 2005 reported that radiation was associated with prolonged survival in older children and adult ATRT patients, while younger children benefited only if they received radiation therapy early in the course of treatment [16]. Buscariollo et al. (2012) reported better overall survival in patients who received initial radiation therapy when compared to those who did not [1]. The relatively small number of patients hindered further exploration of the independence of radiotherapy effect or influence of radiation field on overall survival. Following radiotherapy, neurocognitive toxicities and second malignancies are anticipated [19], especially in patients treated with CSI, and longer follow up is needed.

In agreement with many recent reports [6,9,14,20,24], patients treated with multimodal treatment had significantly better OS compared to patients who had less treatment. The recent increased use of multimodal treatment at our institute might have contributed to the longer median survival, though it is not significant, in patients treated between 2005 and 2013 compared to patients treated earlier.

Like all retrospective studies, our study had the limitation of including a cohort of patients treated over a protracted period with relatively heterogeneous treatment strategies, as well as incomplete data regarding acute radiation-induced toxicities and chemotherapy protocol modifications. Other drawbacks of this study were the lack of molecular categorization and the small sample size.

In conclusion, ATRT is a rare and aggressive CNS tumor. Despite the limitations of the study, our results support the recent advances in the treatment of ATRT. In the current study, utilization of postoperative RT and the adoption of trimodal therapy is associated with significant improvement of median survival. Prompt management with aggressive trimodal therapy should be the standard for future treatment protocols.

Informed consent

No informed consents were obtained since this is a retrospective review of data and all data items collected were already documented in medical charts as part of the patients' care documentation.

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Datasets availability

Data of interest collected from the patients' medical records were secured as governed by institutional policies on patient confidentiality and privacy. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was submitted to the Institutional Review Board of King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, and was approved by the Research Advisory Committee with Approval Number 2111074.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Visual abstract

Supplementary data to this article can be found online at https://doi.org/10.1016/ijpam.2020.06.004.

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