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Original Article

Docetaxel, Oxaliplatin with Capecitabine (TEX Regimen) in Metastatic Gastric and Gastroesophageal Adenocarcinoma: A Prospective Single-Arm Observational Study from a Tertiary Cancer Center in Kashmir

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Abstract

Background Metastatic gastric and gastroesophageal adenocarcinoma (MGGEAC) is a challenging disease with limited treatment options. The Taxotere, Eloxatin, and Xeloda (TEX) regimen has shown promising results in several clinical trials. There exists a dearth of data pertaining to the efficacy and tolerance of the treatment approach in the populace of Kashmir.

Methods This study was performed at the Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir. Patients with MGGEAC received treatment with biweekly TEX regimen that included docetaxel 50 mg/m^2-D1, oxaliplatin 85 mg/m2-D1, and capecitabine 1250 mg/m^2/day, twice daily orally, for 14 days. The effectiveness of the regimen was assessed based on the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), along with the prognostic factors, safety, and tolerability of the regimen.

Results The ORR was 63.5% after four cycles. The median PFS and OS were 9.1 and 13 months, respectively. Univariate and multivariate analysis showed that a higher number of sites of metastases is associated with poor PFS. The TEX regimen was well tolerated. The most observed grade 3 to 4 toxicities were neutropenia (36.7%), anemia (20%), fatigue (20%), and febrile neutropenia (16.7%).

Conclusion Using the TEX regimen in MGGEAC showed better response rates and a slightly longer PFS. A higher number of sites of metastases is a poor prognostic factor in MGGEAC, as seen in our study. The toxicity profile shows that the regimen is tolerable. We recommend a randomized controlled study comparing CapeOx with TEX to test this regimen further.

Keywords
- gastric cancer
- TEX regimen
- docetaxel
- oxaliplatin
- capecitabine
- prognostic score

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Introduction

Globally, gastric cancer accounts for 5.7% of new cases (5th most common) and 8.7% of deaths due to cancer per year (3rd most common).[1] Nonmetastatic gastric and gastroesophageal junction adenocarcinoma are managed by combined therapeutic modality (surgery, chemotherapy, and radiotherapy).[2] The 5-year overall survival (OS) of localized gastric cancer is 31% that has remained stable over the last three to four decades.[3] Metastatic disease has an extremely poor prognosis with a 5-year OS of less than 5%.[2] According to Globocan 2020, gastric cancer is the sixth most common cancer in India. India has a yearly estimate of 68,000 new cases of gastric cancer, which leads to around 50,000 deaths.[4,5] Kashmir has a high incidence of gastric cancer (4th most common), accounting for 7.6% of all cancers and it exceeds the national average in India.[6,7] The metastatic disease is managed primarily by palliative intent chemotherapy with surgery and radiotherapy reserved for selected indications. Systemic chemotherapy results in better response rates, slightly prolonged survival, and improved quality of life.[8]

Immunotherapy, either alone or in combination with chemotherapy, has now replaced chemotherapy as the first-line treatment for metastatic gastric and gastroesophageal adenocarcinoma (MGGEAC) in Western countries.[9–11] However, due to its high cost, chemotherapy remains the standard of care for patients in low-middle income countries like India. Platinum and 5-fluorouracil (5-FU)/analogue combination is considered the gold standard first-line regimen in this setting. The DCF regimen (docetaxel, cisplatin, 5-FU) slightly improves response rate and survival, but with higher toxicity, it provides an additional option for physically fit patients.[12,13] To reduce the toxicity, while maintaining the efficacy, different regimens were tried. One such regimen referred to as the fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) regimen has reported improved ORR with an acceptable toxicity profile.[14–16] The modification of this regimen with the substitution of 5-FU with capecitabine (Taxotere, Eloxatin, and Xeloda [TEX] regimen) has been tested by many investigators.[8,14,17,18]

In Kashmir, the diagnosis and treatment of MGGEAC are often challenging due to limited healthcare resources; however, efforts are being made to improve the management of these cancers in the region, including the development of specialized cancer centers and increased access to screening and diagnostic services.[6] Overall, MGGEAC represents a significant burden of disease in Kashmir, and improving awareness, prevention, and treatment strategies for these cancers in the region is a critical public health priority.

The aim of our prospective observational study is to assess the effectiveness, safety, and tolerability of the TEX regimen in treating MGGEAC in the Kashmir region. The study seeks to assess the ORR, PFS, and OS of patients with MGGEAC-treated with this regimen. This information can guide clinical practice and contribute to evidence-based treatment guidelines for patients with MGGEAC.

Methods

Patient Selection

This prospective observational study was conducted in MGGEAC patients registered at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir from November 2017 to December 2018. Patients who had been newly diagnosed with MGGEAC or were developing metastatic disease after receiving definitive treatment with radical surgery and chemoradiation, and who fulfill the following inclusion criteria, were included in the study. Inclusion criteria were (1) age more than 18 years and less than 70 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status less than 2, (3) no prior palliative chemotherapy, and (4) measurable disease and sufficient renal, hepatic, and bone marrow function. However, patients with uncontrolled medical illness, psychiatric illness, and pregnant or lactating women were excluded from the study.

Study Design and Treatment Protocol

Eighty-five patients were enrolled in the study. History with clinical examination was performed before enrolment. Baseline complete blood count, blood chemistries, electrocardiogram, and serum tumor markers (Carcinoembryonic antigen (CEA), CA19–9) were analyzed. All the enrolled patients underwent Oesophagogastroduodenoscopy (OGD) scopy and histopathological confirmation of disease. A contrast-enhanced computed tomography (CECT) scan of the thorax, abdomen, and pelvis was performed 2 weeks before starting the treatment. After enrolment, patients received the TEX regimen as follows: docetaxel 50 mg/m^2 (1 hour infusion), followed by oxaliplatin 85 mg/m^2 (2 hours infusion) on day 1, and capecitabine 1250mg/m^2/day twice daily for 14 days by oral route. The cycle was repeated every 14 days. Administration of prophylactic treatments, such as antiemetics and corticosteroids, was based on standard recommendations and physician assessment. Granulocyte colony-stimulating factor was used for secondary prophylaxis. Treatment continued as long as the disease progressed, there was unacceptable toxicity, or the patient refused treatment. Dose modifications were performed according to published guidelines.

Assessment of Response and Tolerability

The patients were evaluated for their response to chemotherapy after each treatment cycle. They underwent a CECT scan after completing four cycles of chemotherapy or earlier if the physician deemed it necessary. The scans were evaluated by at least two observers and confirmed by an independent radiologist. The assessment of radiological response was determined using the RECIST 1.1 criteria.[19] Results were stratified as complete response (CR), partial response (PR), stable disease, or progressive disease. The period of PFS was calculated from the commencement of chemotherapy until the first indication of disease progression or death. In the absence of any such events, the last follow-up date was considered as the end-point for PFS measurement. The OS period was calculated from the

beginning of chemotherapy until the patient's death due to any cause, or until the last follow-up date if the patient was still alive. Toxicity assessments were conducted in each cycle using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. OS and PFS were further evaluated with univariate and multivariate analyses. A prognostic score proposed by Chau et al, which includes ECOG performance status more than or equal to 2, SAP levels more than 100, presence of peritoneal metastases, and presence of liver metastases were calculated and patients were divided into three groups (no risk factors, one or two risk factors, ≥3 risk factors).[20]

Statistical Analysis

The utilization of descriptive statistics, such as median, frequency, and percentage, was employed to depict categorical variables encompassing age, gender distribution, treatment, and response to treatment. All patients were assessed for the ORR, which was expressed as a percentage and considered as the primary end-point. The secondary end-points were PFS, OS, and safety. PFS and OS were evaluated using Kaplan–Meier survival methods, whereas univariate and multivariate comparisons analysis was done by log-rank test. IBM SPSS version 20.0 (SPSS Inc. Chicago, Illinois, United States) was used for statistical analyses.

Results

Patient Demographics

The study enrolled a total of 85 patients between November 2017 and December 2018. The data from 85 patients diagnosed with gastric ($n = 61$) and gastroesophageal junction ($n = 24$) adenocarcinomas who underwent treatment with the TEX regimen was analyzed. Her2 neu tested positive in 8 out of 38 biopsy samples (►**Table 1**).

Efficacy

Median number of chemotherapy cycles delivered was eight cycles (1–15). After completion of four cycles of the TEX regimen, we evaluated a total of 85 patients and found that one of them achieved a CR, which corresponds to a percentage of 1.2%. Additionally, 53 patients showed a PR, representing a percentage of 62.4%. Thus, ORR was 63.5% (54/85). In 21 patients (24.7%), the disease remained stable. In addition, only 10 patients (11.8%) showed progressive disease (►**Table 2**). Maintenance capecitabine was received by 32 patients (37%) after getting a favorable response on the TEX regimen. Upon progression, 62% of patients (33/53) received second-line chemotherapy. The most common second-line chemotherapy used was single-agent irinotecan (70%).

Having observed clinical responses of the tumor against the TEX regimen after four cycles, next, we evaluated PFS and OS as secondary end-points of our study. The median follow-up period was 10.5 (3–27) months. The duration of median PFS was noted to be 9.1 months (standard error: 1.15, 95% confidence interval [CI]: 6.84–11.23 months). Similarly, the median OS noted was 13 months (standard error: 1.53; 95% CI: 10.01–15.99 months; ►**Fig. 1**).

Table 1 Patient dispositions and demographics

Baseline characteristics	No. of patients (percentage, if required)	
Total no. of patients evaluated	85	
Median age	60 (26–70 years)	
	≤ 60 years	55 (64.7%)
	> 60 years	30 (35.3%)
Sex	Male	70 (82.4%)
	Female	15 (17.6%)
ECOG PS	≤1	75 (88.2%)
	≥2	10 (11.8%)
Location of primary	GE junction/proximal	30 (35.3%)
	Body	24 (28.2%)
	Distal	27 (31.8%)
	No localization	4 (4.7%)
Prior surgery and chemoradiation	No	79 (92.9%)
	Yes	6 (7.1%)
Site of metastases	Nonregional node	38 (44.7%)
	Liver	36 (42.4%)
	Peritoneum	28 (32.9%)
	Lung	7 (8.2%)
No of sites of metastases	1	44 (51.8%)
	≥2	41 (48.2%)
Histology	Adeno	69 (81.2%)
	Signet	16 (18.8%)
Her2Neu (by FISH/IHC)	Positive	8 (9.4%)
	Negative	30 (47.1%)
	Not performed	47 (55.3)
Chau prognostic group	No risk factor	9 (10.6%)
	1/2 risk factor	69 (81.2%)
	3/4 risk factor	7 (8.2%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry.

Table 2 Tumor response to Taxotere, Eloxatin, and Xeloda (TEX) regimen after completion of four cycles

Number of eligible patients	85
No of patients performed response assessment scan	78
Radiologic response	Frequency (%)
Complete response	1 (1.2)
Partial response	53 (62.4)
Stable disease	21 (24.6)
Progressive disease	10 (11.8)
Overall response rate	54 (63.5)
Clinical benefit rate	75 (88.2)

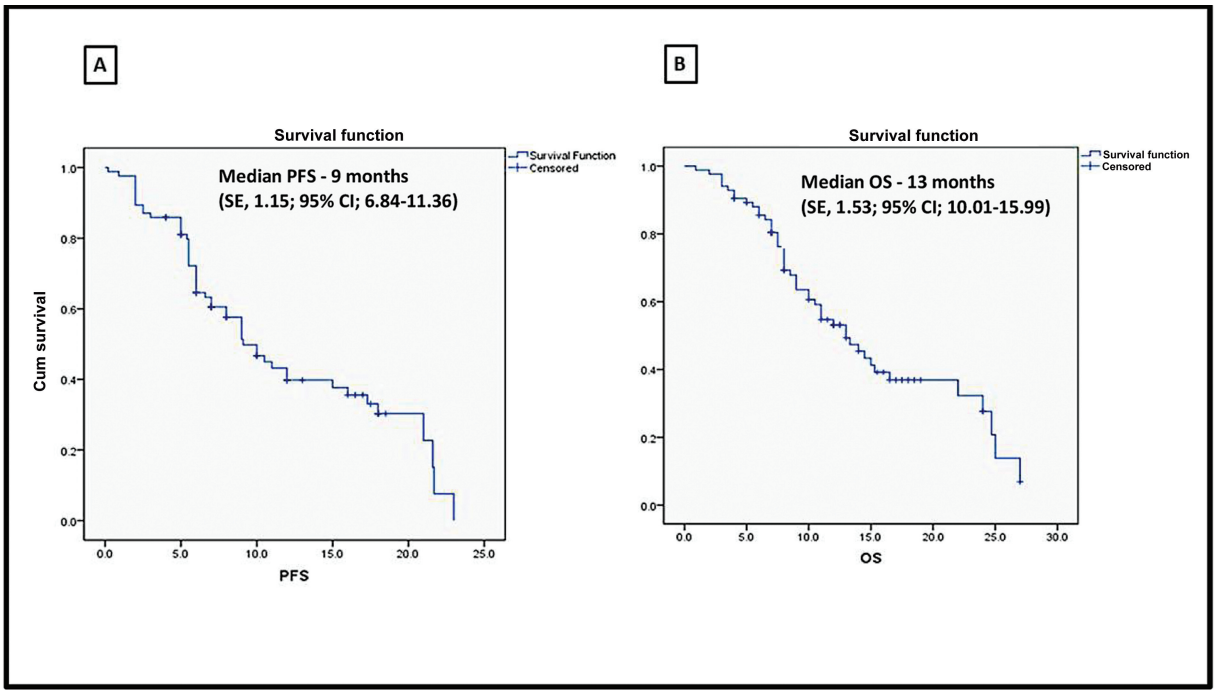

Fig. 1 Kaplan–Meier curve for progression-free survival (PFS) (**A**) and overall survival (OS) (**B**). CI, confidence interval; SE, standard error.

Univariate Analysis of OS and PFS with Prognostic Factor Score

In the univariate analysis, a single metastatic site had shown better progression-free survival (PFS), which retained significance in multivariate analysis (8.5 vs. 2.7 months; *p*-value 0.035). ECOG performance status, presence of nonregional lymph nodal disease, and capecitabine maintenance had significant effects on PFS in univariate analysis, whereas none of these factors showed significance in multivariate analysis. For OS, capecitabine maintenance had shown significance in univariate analysis, but not shown significance in multivariate analysis (►**Tables 3** and **4**).

Assessment of Safety Profile

Next, we checked for TEX regimen safety and tolerability. Neutropenia was the most observed grade ¾ toxicity (36.7%). Anemia and fatigue were the second most common toxicity, affecting 20% of the participants. Febrile neutropenia and

Table 3 Univariate and multivariate analyses of PFS

Characteristics	PFS (months)	*p*-Value (univariate analysis)	*p*-Value (univariate analysis)
Age		0.338	0.986
≤ 60	6.271		
> 60	4.987		
Gender		0.681	0.731
Male	5.999		
Female	5.259		
ECOG PS		0.011	0.175
0.1	10.026		
≥2	1.232		
Location of primary		0.927	0.578
GE junction/ Proximal	6.134		
Body	6.020		
Distal	6.367		

Table 3 (*Continued*)

Characteristics	PFS (months)	*p*-Value (univariate analysis)	*p*-Value (univariate analysis)
No localization	3.996		
Histopathological reports		0.848	0.140
Adeno	5.820		
Signet ring cell	5.438		
TB		0.588	0.418
N	6.181		
> ULN	5.078		
ALP		0.126	0.233
< 100 U/L	7.015		
> 100 U/L	4.243		
Presence of nonregional nodal metastases		0.043	0.345
Yes	7.678		
No	3.580		
Presence of peritoneal metastases		0.149	0.324
Yes	3.672		
No	7.587		
Presence of liver metastasis		0.632	0.234
Yes	5.109		
No	6.150		
No. of sites of metastases		0.045	0.035 (HR: 0.017, 95% CI: 0.000–0.759)
1	8.525		
≥2	2.734		
Chau prognostic score		0.244	0.117
No risk factors	2.065		
1,2 risk factors	4.525		
3,4 risk factors	10.298		
Capecitabine maintenance		0.004	0.857
Yes	7.776		
No	3.483		

Abbreviations: ALP, ALP: Alkaline phosphatase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GE, gastroesophageal junction; HR, hazard ratio; PFS, progression-free survival; TB, Total bilirubin; ULN, Upper limit of normal.

sensory neuropathy were reported in 16.7 and 8.3%, respectively. There were no deaths related to the treatment. Twenty-four of the patients required dose reductions (►**Table 5**).

Discussion

Systemic treatment in MGGEAC aimed to improve survival, pain control, quality of life, and nutritional intake. The Cochrane meta-analysis[13] showed that systemic chemotherapy improves median survival and response rate compared with placebo. The combination chemotherapy regimen is superior to single-agent chemotherapy in terms of survival and response rate with slightly increased toxicity.[21] There is no ideal first-line chemotherapy regimen, which could be either a doublet of a platinum agent with 5-FU/analogue, or a triplet of docetaxel combined with platinum and 5-FU/analogue. The selection is based on patient performance status, general health, comorbid illnesses, and patient preference.[22]

Docetaxel-based triplet regimens for advanced gastric cancer have become more common following the results of the V-325 trial of Van Cutsem et al 2006, which concluded that the use of DCF resulted in improved clinical outcomes and survival compared with only CF regimen,[14] but with higher frequency of adverse events (82% severe neutropenia,

Table 4 Univariate and multivariate analyses of OS

Characteristics	OS (months)	*p*-Value (univariate analysis)	*p*-Value (multivariate analysis)
Age		0.479	0.341
≤ 60	7.760		
> 60	6.689		
Gender		0.953	0.344
Male	7.284		
Female	7.164		
ECOG PS		0.053	0.111
0,1	10.996		
≥2	3.453		
Location of primary		0.992	0.760
GE junction/proximal	6.834		
Body	7.220		
Distal	7.633		
No localization	7.209		
Histopathological reports		0.486	0.147
Adeno	8.014		
Signet ring cell	6.434		
TB		0.670	0.109
N	6.715		
> ULN	7.733		
ALP		0.726	0.826
< 100 U/L	7.579		
> 100 U/L	6.869		
Presence of nonregional nodal metastases		0.088	0.290
Yes	9.183		
No	5.265		
Presence of peritoneal metastases		0.471	0.124
Yes	6.126		
No	8.322		
Presence of liver metastasis		0.987	0.813
Yes	7.244		
No	7.204		
No. of metastases		0.080	0.312
1	10.209		
≥2	4.239		
Chau prognostic score		0.851	0.280
No risk factors	6.215		
1,2 risk factors	6.569		
3,4 risk factors	8.888		
Capecitabine maintenance		0.001	0.874
Yes	10.064		
No	4.384		

Abbreviations: ALP,—; ECOG PS, Eastern Cooperative Oncology Group performance status; GE, gastroesophageal junction; OS, overall survival; TB,—; ULN,—.

Table 5 Adverse events

Toxicity	Any grade Number (%)	Grade 3 and 4 Number (%)
Hematological		
Neutropenia	31 (51.7%)	22 (36.7%)
Anemia	35 (58.33)	12 (20%)
Thrombocytopenia	17 (28.3%)	8(13.3%)
Febrile neutropenia (Grade 3 and 4 only)	–	10 (16.7%)
Nonhematological		
Fatigue	35 (58.3%)	12 (20%)
Sensory neuropathy	17 (28.3%)	5 (8.3%)
Diarrhoea	17 (28.3%)	4 (6.7%)
Mucositis	12 (20%)	4 (6.7%)
Hand foot syndrome	24 (40%)	4 (6.7%)
Anorexia	24 (40%)	3 (5%)
Nausea and vomiting	18(30%)	3 (5%)

29% febrile neutropenia and 49% severe gastrointestinal adverse events).

To reduce the toxicity of the DCF regimen, while maintaining its efficacy, researchers introduced a modified DCF regimen.[23–25] Another approach was to substitute cisplatin with oxaliplatin and 5-FU with capecitabine, which is called TEX regimen.[14,18] A comparison of the REAL-2 meta-analysis and ML17032 trial has revealed that capecitabine-based combinations offer improved OS when compared with 5-FU.[26] Al-Batran et al data showed decreased toxicity with oxaliplatin compared with cisplatin-based chemotherapy.[27]

A trial using the FLOT regimen[15] for MGGEAC reported an ORR of 57.7%, median PFS, and OS of 5.2 and 11.1 months, respectively. Grade 3/ 4 toxic effects were neutropenia (48.1%), leukopenia (27.8%), diarrhea (14.8%), fatigue (11.1%), and febrile neutropenia in 3.8%.

According to Srinivasalu et al,[28] ORR, 1-year PFS, and higher-grade toxicities were 52, 60, and 33%, respectively, in the FLOT group. Febrile neutropenia and thrombocytopenia were the most common toxicities. Another trial[29] concluded that the docetaxel, oxaliplatin, and 5-fluorouracil regimen (docetaxel + FOLFOX 7) provided a high response rate (72%) at the cost of increased toxicity (72% grade ¾).

Stein et al[18] conducted a study which revealed that the TEX regimen resulted in an overall response rate (ORR) of 43%. The study also found that the median PFS was 6.9 months, and the OS was 13 months. The most common higher grade toxicities were diarrhea (30%), nausea/vomiting, and infections.

A study conducted by Tata Memorial Hospital in Mumbai, India, analyzed the TEX regimen in MGGEAC. The ORR was 55.2%, and a clinical benefit rate was 80.8%. The median event-free survival was 6.34 months and the median OS was 15.3 months.[8] The most common higher grade adverse events were hand-foot syndrome (22.5%), neutropenia (19.2%), diarrhea (17.7%), anemia (9.6%), and neuropathy (7.2%).

Van Cutsem et al[14] randomly assigned patients with MGGEAC into three arms—TE, TEF, and TEX. ORR, median PFS, and median OS in the TEX arm were 25.6%, 5.55 months, and 11.30 months respectively. Febrile neutropenia was reported in 9% (TEX) of patients. Other toxicities were similar across the arms.

Our study is prospective, and to the best of our knowledge, it is the largest study to feature the TEX regimen in the region of Kashmir. We reported a higher ORR (63.5%) and better median PFS (9.1 months) in comparison with published literature. Median OS (13 months) was comparable.[8,14,15,18,28,29] Single site of metastases had shown better PFS in our study.

Neutropenia and anemia of grade ¾ were noticed in 36.7 and 20% of patients, respectively. Additionally, only 16.7% of patients had febrile neutropenia. These toxicities are comparable with other studies of FLOT and TEX regimens and much lesser compared with the DCF regimen. Additionally, the incidence of nonhematological toxicities was lower compared with the modified DCF regimen[23,24] and was comparable with other studies of FLOT and TEX regimen.[8,14,15,18,28,29] These findings suggest that the TEX regimen may be associated with a lower risk of certain toxicities, making it a potentially viable treatment option for patients with MGGEAC.

Merits of our study were prospective nature, real-world setting, adequate patient numbers, daycare delivery of chemotherapy, avoidance of peripherally inserted central catheter line and its complications, lesser toxicity, and better response rates. This is the first study from Jammu and Kashmir, supporting the use of the TEX regimen.

The limitations of the study were primarily observational nature, shorter follow-up, and no comparison arm. We did not use trastuzumab in this study because it is not combined with three-drug regimens in other trials.

Conclusion

In MGGEAC, the TEX regimen gives superior response rates and numerically higher PFS. A higher number of sites of metastases is a poor prognostic factor in MGGEAC, which has been seen in our study. The trial needs a longer follow-up for updated results, and we recommend a randomized controlled study comparing CapeOx with TEX to test this regimen further.

Ethics

The Ethical Standards by the Institutions and National Research Committee, Helsinki Declaration of 1964, and subsequent amendments or equivalent standards have been complied with for all procedures undertaken in this study. The study was approved by the Institutional Ethics Committee of SKIMS, Soura, Jammu & Kashmir (Protocol number 65/2018 dated 07.07.2018), and conducted in compliance with protocol after written informed consent to participate in the study was taken from all patients before enrolment.

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Conflict of Interest
None declared.

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