RESEARCH ARTICLE

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Survival and Prognostic Determinants after IMRT and 3D Radiotherapy in Metachronus Bone – Only Spinal Metastasis of Breast Cancer: A Prospective Phase II Trial

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Abstract

Objectives: Oligometastasis is a distinctive subset of osseous metastatic breast cancer, represented by single or few detectable metastatic osseous lesions. A more advanced radiotherapy approach can be considered in those bone-only diseases. We analysed different predictive factors affecting the 5-year survival after palliative radiotherapy in patients with bone-only metastatic breast cancer. **Methods:** This prospective multicentre phase II study included 60 breast cancer patients with metachronus osseous oligometastasis in the period from January 2019 to January 2024. **Result:** The mean age of our patients was 49.55±6.39 (40-67), and the median follow-up time was 45 months. The mean survival time from metastasis and radiotherapy was 41.11 (36.33-45.89), and 49.64 (44.11-55.16), respectively. The three-year bone survival rate was 81.7% and the five-year survival rate was 79%. In the univariate analysis, the significant prognostic factors that were associated with poor OS were: age more than 50 years old, multiple metastasis, higher level of LDH , anemic patients, triple negative disease, 3D planning and dose less than 3000/10GY. Multivariate analysis confirmed 2 independent prognostic factors for longer survival: triple-positive histology (p=0.0001), and intended radiation dose more than or equal 30 Gy (p=0.028). **Conclusion:** Prolonged radiotherapy fractionation schedules improve survival in triple positive bone-only metastatic breast cancer with controlled primary. Simple blood tests should not be routinely done in those patients.

Keywords: breast cancer- metastasis- bone- radiotherapy

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Introduction

Only a minority of patients (< 10%) has stage IV breast cancer at diagnosis. However, a significant percentage will develop metastasis during the course of the disease, especially to lungs, pleura, liver, lymph nodes and bones [1, 2].

Bone is the most frequent site of breast cancer metastasis, reaching up to 60–80% of metastatic breast cancer (MBC) patients. Bone involvement is the inaugural site of metastatic disease in 25–40% of MBC patients, two thirds of them presented in the spine [3].

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects including pain, spinal cord compression, hypercalcemia, and pathologic fracture [4]. The goals of palliative radiotherapy of bone metastases are pain relief, preservation of function, and maintenance of skeletal integrity along with an increase in the survival rate [5-7].

Decreasing the tumor size with interruption of the biomolecular pain cycle for pain relief are the radiobiological aims of radiotherapy in more radiosensitive tumor subtypes [8].

An updated review of patients with previously unirradiated painful bone metastases revealed pain relief equivalency following 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions and a single 8 Gy fractions. However, single-fraction (SF) RT was associated with a higher incidence of reirradiation to the same painful site than multiple fractionation schedules [4]. It has been clinically and radio biologically documented that the relief of symptoms occurs within 2–4 weeks post radiation [9, 10], and the local control at 1 and 2 years was 90.3% and 82.4%, respectively, with tolerable toxicity [11].

Intensity modulated radiotherapy (IMRT) can provide high-dose radiation to the target volume while more preservation provides adjacent at-risk organs with higher local control and subsequent higher survival [12]. Trove et al. [13] in a prospective phase 2 trial in oligometastatic breast cancer with bone metastasis administrated IMRT and SBRT to osseous metastasis whose primary tumor was controlled, the 2 years OS was 95%.

Age, performance state, associated comorbidities, hormonal state, and previous treatments are important

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prognostic and predictive factors for survival. Smaller tumor burden was associated with a much higher survival rate, but a large individual variation also was documented [14, 15].

The aim of this study

It was to investigate the overall survival rate and the predictive factors affecting the overall survival after palliative radiotherapy in patients with metachronus 1-5 osseous spinal metastases of breast cancer origin.

Materials and Methods

This prospective phase II one-arm, multicenter trial was carried out in Radiotherapy Departments, South Egypt Cancer Institute, Assuit University, and the Clinical Oncology Department, Assuit University, during the period from January 2019 to January 2024. It involved 60 breast cancer patients with metachronous bone only metastasis. The Ethical Committee of South Egypt Cancer Institute approved the study protocol (no.542).

Eligibility criteria

The patient must have histological confirmation of breast adenocarcinoma. Radiographic manifestation of metachronous bone metastasis (1-5) in the axial spine was required including plain radiographs, radionuclide bone scans, or magnetic resonance imaging. The primary tumor should be controlled, and the patients must be ≥18 years of age.

Exclusion criteria

Patients who were under 18 years of age, male patients and those with another solid or hematological tumor or metastases other than bone.

Pre-treatment assessment

Diagnosis of osteolytic bony lesion was based on CT, magnetic resonance imaging (MRI) or bone scintigraphy findings. MRI is mandatory before IMRT plan. If necessary to confirm the diagnosis of metastatic disease, bone biopsy was performed. Staging included computed tomography of the thorax, abdomen and pelvis. Pain assessment was done before the start of the radiotherapy by VAS score in which a score range from 0-10, Where 0 indicating no pain while 10 representing the worst possible pain. Mild pain was assigned a score (1-4), moderate pain a score of (5-6), extreme pain a score of (7-8), and heavy pain a score of (9-10).

Blood tests

Lactate dehydrogenase (LDH), albumin, hemoglobin, C-reactive protein (CRP), calcium, and alkaline phosphatase (ALP) were part of routine blood chemistry. Normal LDH was defined as 140-208 U/L (normal albumin 3.5-5.5 g/ dL high ALP ≥105 U/l; normal CRP <5 mg/l; low hemoglobin <11.7 g/dl; normal calcium 8.6-10.3 mg/dL. Normal cancer antigen (CA) 15-3 was defined as 0-25 kIE/l.

Target volume delineation

IMRT technique GTV: include all the visible metastatic lesions in the affected vertebra/vertebrae (if possible), CTV: include the whole affected vertebra/ vertebrae, PTV: add arbitrary 6mm around the CTV(Figure1) .we chose such PTV margin to mimic the standard clinical practice, as little consensus exists for such limited margin [16].

3D technique CTV: include the metastatically affected vertebral body or bodies and the adjacent intervertebral discs. A caudally and cranially adjacent vertebral body is also included. PTV: 1 cm expansion of the CTV isotopically, and it should be covered by the 90% isodose line.

The radiotherapy fractionation schedules based upon PS-adjusted modeling, the dose was: 40 GY in 20 fractions, 30 GY in 10 fractions, 20 GY in 5 fractions, and 8 GY in 1 fraction.

Mode of delivery

Based on clinician prognosis predictions, planning was done by 3D radiotherapy or IMRT. IMRT was applied only on thoracic and lumber metastasis whose dose constrains for lung, heart or kidneys don't meet or patients with chronic cardiac or lung disease for more preservation of organs at risk, treatment planning was done by ELEKTA Monaco platform (TPS, version 6.1.2.0) and delivered by Linac Synergy platform. With 4-, 6- or 10-MV photons energy in all patients.

Statistical analysis

Data were analysed using the Statistical Package for Social Science (SPSS), version 26.0 for Windows. Qualitative data were expressed as frequency and percentage, while quantitative data were expressed as mean ± SD or median and range according to normality of data after testing its distribution by the Shapiro-Wilk test.

Survival analysis was done using a Log rank test to calculate overall survival. Univariate cox regression analysis was performed to identify the prognostic factors associated with overall survival, and significant variables were entered in a multivariate backward LR cox regression analysis to calculate the adjusted hazardous ratio. The level of significance was considered at P value < 0.05.

Results

Patient, tumour characteristic and blood tests analysis

We enrolled 60 patients in our study, all of whom have metachronous metastasis with controlled primary. As listed in Table 1, the mean age of our patients was 49.55±6.39 (40-67), and 56.7% of them (n=34) were less than 50 years old. The median follow up time was 45 ranging from 14 to 100 months. 23.3 % of them (n=14) of our patients have performance III. 81.7% (n=49) of the studied patients received more than or equal 3000GY/10fx radiotherapy dose, while 18.3% of them received less than 3000GY/10fx. 53.3% (n=32) of the studied patients were treated by IMRT and 46.7% of them (n=28) treated by 3D. IMRT dose was more than or equal 3000GY/10 fractions, except 5 patients with PS III received 2000GY/5 fractions. 26.7 % of the studied patients had triple negative disease,

Table 1. Characteristics of Studied Patients

Variables	N=60	%
Age (years)		
≤50	34	56.7
≥50	26	43.3
Mean ± SD (range)	49.55±6.39 (40-67)	
PS		
II	46	76.7
III	14	23.3
Target		
One target	49	81.9
More than one target	11	18.3
Solitary		
One metastasis	39	65
Multiple metastasis	21	35
Opioid	36	37.9
Positive	39	65
Negative	21	35
Hormonal state		
Triple-negative	16	26.7
Triple-positive	44	73.3
Treatment of metastasis		
Chemotherapy	18	30
Hormonal	42	70
Radiotherapy modality		
IMRT	32	53.3
3D	28	64.7
Radiotherapy dose		
≥3000/10	49	81.7
<3000/10	11	18.3

Data were expressed as frequency and % or mean ± SD

Table 2. Investigation and Outcome of Studied Patients

Variables	N=60	%
Investigations		
Albumin		
Normal	29	48.3
High	31	51.7
CBC		
Normal	30	50.0
Anemic	30	50.0
ALP		
Normal	46	76.7
High	14	23.3
CRP		
Normal	25	41.7
High	35	58.3
LDH		
Normal	49	81.7
High	11	18.3
CA15-3		
Normal	39	65.0
High	21	35.0

while 73.3% of them had triple positive respectively. 65% of the studied patients (n=39) had solitary bone metastasis, while 35 % of them (n=21) had multiple metastasis. Regarding treatment of metastasis, 42 patients received hormonal therapy, while 18 patients received chemotherapy. All the studied patients underwent primary surgery and received adjuvant radiotherapy, 16 patients (26.7%) received adjuvant chemotherapy (triple negative disease). As shown in Table 2. 50% of our patients (n=30) were anemic. High ALP documented in 23.3% of the studied patients (n=14), and CA15-3 was high in (35%) of them (n=21). The median pain score before the onset of the treatment was 7(4-10) and after 36 months it reduced to 5 (0-9). Twenty three patients developed distant metastasis mainly to the lungs and the liver. The median time to start the systemic chemotherapy was 10 months, while twenty seven patients developed widespread osseous metastasis after a median time of 6 months after palliative radiotherapy. The prescribed palliative radiotherapy dose was received by all of our patients without interruption. Regarding post radiation skeletal related events, two patients complicated by pathological fractures and equipped with thoracic surgical corset. One patient developed spinal cord compression, and he was managed by dehydrating measures and palliative radiotherapy.

Survival analysis with its associative prognostic factors

The mean survival time from metastasis was 41.11 (36.33-45.89), while the mean survival time after palliative radiotherapy was 49.64 (44.11-55.16) Table 3. The three years bone survival rate was 81.7% and the five-year survival rate was 79% (Figures 2). Thirteen patients died in this study, the cause of death in the majority of our patients was widespread disseminated organ metastasis, except in two patients that developed bedsores and complicated by deep venous thrombosis and pulmonary embolisms.

Table 4 shows, the mean OS for patients received dose more than or equal 3000/10 or less, was 56.85 (53.40 -60.31) and 3.78 (2.99-4.58) respectively p< 0.001. For IMRT, it was 56.37(51.51-61.23) and 3D, it was 40.88 (30.74-51.03) p=0.008. Regarding hormonal state, the mean OS for triple negative and positive was 25.27(10.87-39.66) and 57.70 (54.59-60.81) p<0.001. In univariate analysis, the significant prognostic factors that were associated with higher OS were: patients with age less than 50 years old, with solitary metastasis, normal LDH, normal CBC, triple-positive disease, and IMRT. These significant variables were entered in a multivariate cox logistic regression model and the significant poor prognostic variables were: patients received a dose

Table 3. Overall Survival (OS) among Studied Patients

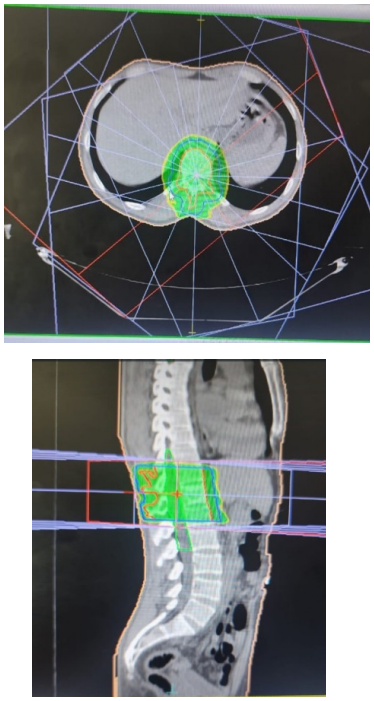
Variables	
Mean OS (95% CI)	
Survival from radiotherapy	49.64 (44.11-55.16)
Survival from diagnosis of metastasis	41.11(36.33-45.89)

The median follow-up time is 45, ranging from 14 to 100 months

Table 4. Factors associated with Overall Survival (OS) among the Studied Patients

Variables	Mean OS (95% CI)	P-Value*
Age (years)		
≤50	54.94 (49.49-60.41)	0.036
≥50	42.94 (33.11-52.77)	
PS		
II	57.93 (55.13-60.73)	<0.001
III	5.72 (3.79-7.65)	
Solitary		
One metastasis	58.84 (56.61-61.07)	<0.001
Multiple metastases	28.27 (16.54-39.99)	
target		
One target	51.96 (46.46-57.46)	0.062
multiple targets	39.18 (22.90-55.46)	
Hormonal state		<0.001
Triple – negative	25.27 (10.87-39.66)	
Triple- positive	57.70 (54.59-60.81)	
Albumin		
Normal	50.18 (42.36-58.00)	0.894
High	49.20 (41.44-56.95)	
CBC		
Normal	56.38 (51.54-61.22)	0.015
Anemic	42.80 (33.41-61.22)	
ALP		
Normal	57.93 (55.13-60.73)	<0.001
High	5.72 (3.79-7.65)	
CRP		
Normal	46.12 (36.48-55.75)	0.323
High	51.98 (45.47-58.48)	
LDH		
High	24.09 (8.03-40.14)	<0.001
Normal	55.5251.31-59.72)	
CA15-3		
Normal	58.84(56.61-61.7	
High	28.27 (16.54-39.99)	
Treatment of metastasis		
Chemotherapy	36.32 (22.87-49.77)	0.003
Hormonal treatment	54.83 (50.01-59.65)	
Opioid		
Positive	54.21 (48.83-59.58)	0.032
Negative	41.56 (30.38-52.73)	
Radiotherapy dose		
≥3000/10	56.85 (53.40-60.31)	<0.001
<3000/10	3.78 (2.99-4.58)	
Radiotherapy modality		
IMRT	56.37 (51.51-61.23)	0.008
3D	40.88 (30.74-51.03)	

95% CI (confidence interval); *Log rank test



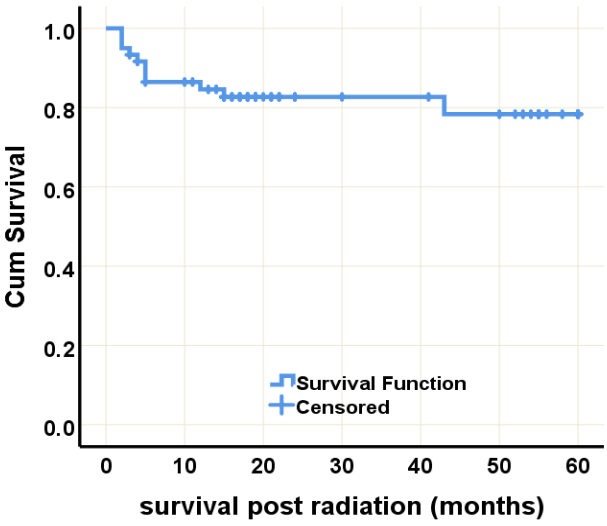
Fiqure1. 95% Dose Distribution IMRT on Thoracic and Lumber Metastasis with 6 mm PTV

less than 3000/10GY (HR=21.57) and patients with triple- negative disease (HR=6.32), as shown in Table 5. Three variables (albumin, CRP and number of targets) were not predictors for survival and lost significance (p= 0.323, 0.0620, 0.894, respectively).

Discussion

3D radiotherapy has been widely used for several years as an effective modality for the treatment of bone metastasis.

Although there is limited literature on the evaluation



3-year survival was 81.7%
5-years survival was 79.0%

Figure 2. Kaplan Meir Curve for Post-Radiation Survival among the Studied Patients

Table 5. Prognostic Factors Related to Overall Survival (OS) among the Studied Patients

Predictors	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.17 (1.07-1.28)	<0.001		
Solitary				
One metastasis	Reference	0.001		
Multiple metastases	32.21 (4.0-105.5)			
CBC				
Normal	Reference	0.033		
Anemic	5.32 (1.14-24.68)			
LDH				
High	Reference	<0.001		
Normal	11.27 (3.24-39.15)			
Hormonal state				
Triple- positive	Reference	<0.001	Reference	0.014
Triple-negative	21.34 (4.51-50.67)		6.32 (1.96-44.20)	
CA15-3				
Normal	Reference	0.001		
High	32.30 (4.0-100.6)			
Treatment of metastasis				
Chemotherapy	Reference	0.009		
Hormonal treatment	5.21 (1.51-17.93)			
Radiotherapy dose				
≥3000/10	Reference	<0.001	Reference	0.01
< 300010	72.97 (8.85-60.4)		21.57 (2.06-90.16)	
Radiotherapy modality				
IMRT	Reference	0.021		
3D	6.07 (1.31-28.25)			

Cox regression analysis; HR, hazard ratio; 95% CI, 95% confidence interval

of the effect IMRT on metastatic breast cancer, only one other study, to the best of our knowledge, has reported the outcome of IMRT regarding survival in solitary bone metastasis of breast cancer. Treating palliative, frail patients for preservation the organs at risk and avoiding long term toxicity, shouldn't interfere with the idea of simple, fast treatment path. However, ring style treatment system Halcyon 2.0(Varian Medical System Inc., Palo Atlo, USA) with flatting filter free and rapid gantry and collimation rotation becoming slandered devices don't take longer [17].

Studies that used advanced radiotherapy technique

Trovo et al. [13], prospective phase 2 trial , administrated IMRT and SBRT in of oligo-bone metastasis of breast cancer, whose primary tumour was controlled, ≤5 metastatic sites,. SBRT consisted of 30-45 Gy in 3 fractions, while IMRT was delivered to a total dose of 60 Gy in 25 fractions. The 2 years OS was 95% [13]. In our series, 3 years survival was 81.7%, we can explain their higher survival rate by many factors, this trial depend up on FDG-PET/CT for staging, (89%) of Trovo et al. [13], patients received concomitantly chemoradiation therapy for treatment of bone metastasis and The majority of patients (Forty-four)were treated with SBRT.

Few other studies have analysed the role of SBRT in oligometastatic disease including metastatic breast cancer patients [17-19]. In accordance with our hypothesis, studies in the literature showed that young patients with low tumour volume, limited osseous only metastatic hormonal positive breast cancer, achieved the maximum benefit from SBRT to all metastatic sites [7, 18, 20]. which was comparable to our prognostic factors for prolonged survival, e.g. young patients (less than 50 years old) with, oligometastatic bone (1-5 metastasis) and hormonal receptor- positive cancer.

In the randomized exploratory trial, conducted by Milano et al. [19], hypofractionated stereotactic radiation (50 Gy in 10 fractions) was performed to all sites of disease in 48 breast cancer patients with 1-5 extracranial metastases. The authors observed that some patients who had only bone metastases rather than visceral metastases and low tumour burden (volume and number of lesions) survived longer than 10 years [18]. Five-year survival in our study was high (79%). Also, extended survival can be anticipated most likely for patients with hormonal positive disease. Further research for calculation 10-year survival is recommended.

Studies that used conventional or conformal radiotherapy techniques

Additionally, similar to the JCOG1017 PRIM-BC trial.com, Scoresetti et al. [20] Compared the responses to SBRT (30-60 Gy in 3-4 fractions or 16-24 Gy in single fraction) and conventional RT (8 Gy in single fraction or 30 Gy in 10 fractions) in 99 patients with 1-5 metastatic lesions in mixed primary after controlled primary malignancy. Amongst these, about 33.5% patients had bone metastasis. The median OS in the SBRT group was 41 months versus 28 months in the conventional RT group (P=0.090; where P<0.20 designates a positive trial) [19]. Our results documented that the mean survival of IMRT VS 3D radiotherapy was 56.37 and 40.88 months respectively (p=0.008).

Nieder et al.'s [21] retrospective study included 57 consecutive female patients with bone metastases from breast cancer who received 2-D or 3-D palliative radiotherapy. The median survival from palliative radiotherapy was 32 months. This finding is not consistent with our study as the mean survival time after palliative 3D radiotherapy was 40.88, while the mean survival after IMRT and 3D radiotherapy was 49.64 months. In our series, the five- yeas survival rate was 79% while in Nieder et al.'s [21] study, the five-year survival rates were 13 % . It was attributed to good prognostic factors in our study (metachronus disease with controlled primary, significant percentage of patients had PS II , triple positive disease and using advanced radiotherapy techniques. In a different study, the median survival time after bone metastases diagnosis was 28 months in women with bone-only metastases [13].

Studies that analysed the prognostic factors and survival outcome

In our database a dose of more than 30 GY was associated with prolonged survival, the mean OS in those patients was 56.85 months (53.40-60.31), while the median survival in Nieder et al. [21] was 29 months after ≥30 Gy. As in the current study, using an IMRT technique for planning with more preservation of lung and kidneys (organs at risk) in thoracic and lumber vertebral metastasis, might lead to better tumour control and higher survival.

Turanli and Cetin [22] reported a study of breast cancer with bone metastasis treated between 2004 and 2007, Only 24 out of 129 patients received palliative radiotherapy. Normal serum CA 15-3 level and postmenopausal status associated with significant prolonged survival, hormone receptor and HER2 status were not significant. Conversely, in our study the age of patients and CA15-3, lost significance, while triple negative disease was associated with poor survival comparable to the results reported by Nieder etal. [21].

Regarding survival in patients who received hormonal or chemotherapy for metastasis, Turanli and Cetin study classified their patients into two groups according to initial metastasis treatment modalities; group I (patients who received hormonal therapy) and group II (patients who received chemotherapy followed by endocrine therapy) [23]. All patients received bisphosphonates, whereas only 24 patients required palliative radiotherapy during the course of their disease. In groups I and II, and the median overall survival was 41 and 40 months (p=0.79).In our study the mean survival after treatment of metastasis (chemotherapy or hormonal) was 36.32 (22.87-49.77) and 54.83 (50.01-59.65) p=0.003.

In contrast to the results published in the M.D. Anderson Cancer Center [17]. Where the analysis included 314 patients managed between 1997 and 2008, about (33.5%) patients had bone only metastasis. The multivariate analysis showed that longer survival was in painless solitary bone metastases, while in our cohort these parameters lost significance.

Limitation of the study

Our registry-based population approach introduces some limitations as this research is centring on survival time. Thus, other factors such as dosimetry for organ at risk, quality of life, neurologic deficits, were not documented in this analysis. Second, a possible methodological defect in our study was the heterogeneity in patients selection between IMRT and 3D radiotherapy. As such, these analyses with clearly small sample sizes and short follow-up may not yield accurate conclusions in this subgroup of patients, future trials with longer follow-up and larger sample sizes are recommended, more prospective comparative studies will be needed to validate our findings, and better understand which patients are likely to benefit most from this regimen concerning also on progression free survival. Other studies may focus on molecular subtyping to offer additional guidance on proper patient selection and prediction of treatment response, aiming to have the fast ring style system IMRT in the near future.

In conclusion, palliative RT helps to obtain a satisfactory rate of 5-year survival in in metachronus oligo- spinal bone metastasis of breast cancer. To achieve optimal results, it should be chosen in a high dose to selected patients with favourable prognostic factors particularly for those with triple-positive disease. In spite of the restricted margins in IMRT plan, the survival rate did not achieve a significant difference from 3D radiotherapy. It might attributed to a heterogeneity in subgroup of patients.

Author Contribution Statement

AAY is the main author of the manuscript and made contributions to the protocol design.AAY and AE Analyzed, interpreted the data, and drafted the manuscript. AA and SE provided support regarding the statistical analysis and discussion. A A and SE were responsible for data analysis and manuscript revision. All authors have reviewed and approved the final version of the manuscript

Acknowledgements

Not applicable

Data Availability

The datasets analyzed during the current study are

available from the corresponding author on request

Ethical Declaration

The study was approved by SECI ethics committee and an informed written consent was taken from all patients.

Conflict of Interests

The authors indicated no potential conflicts of interest.

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