Original Article

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Intensity Modulated Radiation Therapy versus Supportive Care in Malignant Pleural Mesothelioma: A Pilot Study for Treatment Outcomes and Cost-Effective Expectations

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor. The outcome of treatment of Egyptian MPM patients is not satisfactory and its cost-effectiveness is questionable.
Aim: The study aimed to test the treatment outcome and cost-effectiveness of intensity modulated radiation therapy (IMRT) in unresectable MPM patients who exhausted the standard treatment modalities.
Methods: Twenty-four eligible patients were randomized (1:1) to either a control group receiving best supportive care (BSC) or an intervention group receiving IMRT to the tumor volume. Quality of life (QoL) was assessed by the European Organization for Research and Treatment of Cancer QoL questionnaires QLQ-C30 and QLQ-LC13 (lung cancer module). Tumor progression was monitored by serial computerized tomography scans. Assessment was done at enrollment and after 4 months. Incremental cost-effectiveness ratio (ICER) was calculated for BSC vs. IMRT. The output data of the ICER were total costs, overall survival (OS), progression-free survival (PFS) for each treatment modality.
Results: The median OS did not differ significantly between IMRT and BSC (13 versus 11 months, respectively; p=0.117) while the median PFS was significantly longer with IMRT (6 versus 4 months, respectively; p=0.009). The IMRT group demonstrated a significant deterioration in their final QoL scores compared to baseline. IMRT had an incremental cost of 5912 USD per patient with an incremental effectiveness of 4 months of PFS, providing an ICER of 6.260.
Conclusion: Although it may be associated with longer PFS, IMRT in MPM with intact lung is likely detrimental and not cost-effective.

Keywords: Malignant pleural mesothelioma, Intensity modulated radiation therapy, Quality of life, Cost-effectiveness, Egypt
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INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive tumor related to exposure to asbestos fibers [1]. The number of MPM patients in Egypt is progressively increasing [2]. Asbestos is a known material that was used in mummification by ancient Egyptians [3]. It was used previously in many products and it is known that prolonged exposure for many years causes MPM [4]. Lifetime risk of developing MPM is thought to be 8 to 13% in those with prolonged exposure to asbestos [5]. A study that reported 40 years as a median age of diagnosis of MPM in Egypt, illustrated the massively polluted residential areas with subsequent disease impact on younger Egyptian population relative to the international figures [6].

MPM has a median overall survival (OS) of only about one year [7]. Till now MPM is not a curable disease and its treatment is difficult due to advanced disease at presentation [8, 9]. Surgery, radical radiotherapy and chemotherapy are still the main lines of treatment [10]. Gene therapy, immuotherapy, photodyamic therapy or hyperthermic chemoperfusion of the pleura are still investigational [11, 12].

The challenging issue in treating MPM in Egypt is the unsatisfactory treatment outcome relative to the high financial cost of surgery, chemotherapy and radiotherapy. The role of intensity-modulated radiation therapy (IMRT) in MPM is questionable. The National Cancer Comprehensive Network version 3.2017 guidelines did not recommend radiotherapy in MPM in the context of intact lung, but it may be considered with caution under strict dose limits of organs at risk or Institutional Review Board approved protocols [13].

The economic difficulties in Egypt and the unmet national health care budget motivated the research team of the current study to investigate the feasibility of

IMRT in Egyptian MPM patients who exhausted all lines of chemotherapy and are not candidate for surgery.

METHODS

This pilot study was conducted at the International Medical Center, Cairo, Egypt. All patients admitted to the Oncology Department from May 2015 to January 2016 were assessed for eligibility prior to inclusion in the study. The end point was to assess the feasibility of treating Egyptian MPM patients with IMRT through monitoring the treatment outcomes and cost-effective expectations.

Eligibility requirements

Inclusion criteria included histopathological diagnosis of epithelioid MPM, stage I to III, age from 18 to 60 years, performance status (PS) = 0 to 1 by the Eastern Cooperative Oncology Group performance status scale, adequate lab values (complete blood count, kidney and liver functions tests), absence of any co-morbid disease and adequate baseline pulmonary function tests in the contra lateral intact lung. Forced expiratory volume in the first second (FEV1), FEV1/ forced vital capacity (FVC), maximum voluntary ventilation (MVV) and residual volume (RV) / total lung capacity (TLC) should be >2 liters, >50%, >50% of predicted and <50%, respectively. Patients who didn't meet the threshold criteria were excluded from the start. Eligible patients were scheduled for split lung function testing to ensure that the patient will be left with at least 1 liter of FEV1 in the contra lateral intact lung.

Patient must not be eligible for any surgical interference either by extrapleural pneumonectomy or pleurectomy/decortication. Patient should have progressive or unresponding tumor to all standard chemotherapy protocols (gemcytabine/cisplatin and pemetrexed/carboplatin) or those who achieved maximum response to chemotherapy and still not candidate for surgery.

Patient should have mesothelial tumor that can be encompassed in a well-tolerated radiation field by IMRT either rapid arc or step and shoot method (maximum gross tumor volume not exceeding 4 cm, absence of metastasis in the contralateral mediastinal, contralateral internal mammary, contralateral supraclavicular lymph nodes and absence of direct extension of the tumor to the contralateral pleura) as decided by independent radiation therapy committee in the International Medical Center who revised the previous criteria before randomization and ensured absence of any difference in tumor volume/distribution between the two groups.

Exclusion criteria included mixed histology and sarcomatous type of mesothelioma, stage IV disease, extensive stage I, II, III disease that cannot be encompassed in a tolerable IMRT field and previous extrapleural pneumonectomy or pleurectomy/ decortication. Naïve patient who had not received any previous chemotherapy for MPM and those with past history of cancer or concomitant second primary cancer were excluded.

A Signed informed consent was obtained from all participants and the study protocol was approved by the Institutional Review Board of the Clinical Oncology Department, International Medical Center dated March 2015. The study was conducted in accordance with Declaration of Helsinki and Good Clinical Practice guidelines. The study registration number in Cure and More Egyptian National Research Consortium is RWN006.

Clinical effectiveness

Patients who fitted the inclusion criteria were randomly assigned through opaque envelopes one to one randomization into two groups. The control group received best supportive care (BSC) without any oncologic interference and the intervention group received IMRT on the ipsilateral chest wall of MPM.

All patients in IMRT group were simulated on acuity simulator Varian mode. The planning system used was Eclipse version 13.6 3D planning. Patients were treated on linear accelerator true beam Varian type (FF) three energies 6, 10, 15 MV (FFF) high intensity 6, 10 MV. During simulation, every patient was immobilized by a vacuum body mattress in a supine position with his arms raised above the head on a resting plate prior to computed tomography simulation.

Computed tomography cuts were taken every 3 mm. An initial planning target volume (PTV) (PTV-CT) was defined as a rind composed of 5mm around the clinical target volume (CTV) including pleura mesothelioma, chest wall of the entire hemithorax and any lymph node greater than 1.5cm in the ipsilateral hilar, mediastinal and subcarinal groups. The PTV-CT began superiorly at the thoracic inlet and continued inferiorly until the insertion of the diaphragm into approximately the T12 or L1 vertebral body. The average thickness of the PTV-CT was 25-45 mm. The prescribed tumor dose was 40-49.5 Gy with the following organs at risk dose constraints: mean lung dose below 20–21 Gy, V40 $\leq$ 70% and mean dose $\leq$ 35% for the heart, mean dose $\leq$ 34% for the esophagus and maximum dose $\leq$ 60 Gy for the brachial plexus. The IMRT treatment plans were assessed through comparing the tumor volume and organs at risk doses with the standard guidelines recommended doses for target volume delineation and normal tissue constraints.

Both study groups were compared in terms of median OS, median progression free survival (PFS), one year survival and PFS at 4 and 6 months. Quality of life (QoL) was assessed at baseline and at 4 months. Cost-effectiveness of the treatment procedures was assessed in USD. The median time to disease progression was the length of time from the start of treatment modality after enrollment till half of the patients developed disease progression. The MPM tumor dimensions were measured at the time of enrollment and after 4 months then every two months using computed tomography scan of the chest until tumor progression. The median OS was the length of time from the date of diagnosis till the death of half of the patients [14].

Quality of life was assessed by applying the Arabic version of the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaires QLQ-C30 version 3.0 and the lung cancer module QLQ-

LC13. The questionnaires were downloaded from the EORTC website after terms and conditions agreement [15]. The questionnaires were applied at the time of enrollment and 4 months later. The initial and end summary scores of QLQ-C30 and QLQ-LC13 in both treatment groups were calculated according to the EORTC guidelines and compared.

Toxicity of IMRT was not assessed as a separate entity because the items of QLQ-LC13 evaluated all the expected symptoms likely to be related to IMRT.

Resource use and cost

The analysis was conducted from the perspective of the health care system and included direct medical and non-medical costs incurred by the health care. The costs of BSC and IMRT were estimated. The following costs were estimated: diagnostics, computed tomography simulation, consultation, contouring, positioning, planning and plan verification, review visits and treatment delivery. The output data of the incremental cost-effectiveness ratio (ICER) was total costs, mean OS and mean PFS. Incremental cost-effectiveness ratios were calculated for IMRT versus BSC.

Statistical Methods

The collected data was revised, coded, tabulated and introduced to a personal computer using the Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Continuous variables were expressed as mean and standard deviation or as median and interquartile range in cases of skewed distributions. Categorical variables are expressed as frequencies and percentages. Survival rates were estimated and graphed using the Kaplan-Meier method. Log rank test was used to compare time-to-event variables by levels of a factor variable. Differences between independent groups were tested using the student *t* test. In cases in which the samples were paired, the paired *t* test was used. Fisher's exact test was used to examine the relationship between categorical variables when the expected count is <5 in more than 20% of cells. A p-value < 0.05 was considered statistically significant

RESULTS

Baseline characteristics of patients are illustrated in table 1. No significant statistical differences were observed between the two study groups.

All patients developed progressive disease and were followed up until death except one patient (1/12, 8.3%) in IMRT group who was alive with no evidence of progressive disease at last follow up.

There was no significant statistical difference in the median OS between BSC and IMRT groups (table 2). On the other hand, PFS in IMRT group was significantly longer than in BSC group. The 1-year survival rate for BSC group was 41.7% while for IMRT group it was 66.7%. At 15 month, the survival rate was 0% for BSC group compared to 16.7% for IMRT group. At 4 months, the PFS rate for BSC group was 16.7% while for IMRT group it was 66.7%. At 6 month, the PFS rate was 0% for BSC group, compared to 25% for IMRT group.

Table 1. Baseline patients' characteristics

	BSC group (n=12)	**IMRT group** (n=12)	**P value**
	No (%)	**No (%)**	
Gender			
Male	10 (83.3)	11 (91.7)	1
Female	2 (16.7)	1 (8.3)	
Tumor location			
Left	4 (33.3)	4 (33.3)	1
Right	8 (66.7)	8 (66.7)	
Stage			
I	1 (8.3)	2 (16.7)	1
II	10 (83.3)	9 (75)	
III	1 (8.3)	1 (8.3)	
ECOG PS			
1	8 (66.7)	8 (66.7)	1
2	4 (33.3)	4 (33.3)	
	Mean (±SD)	**Mean (±SD)**	
Age	52 (±7.5)	52.2 (±6.5)	0.93
Pulmonary functions			
FEV1 [Liters]	2.7 (0.63)	2.72 (0.56)	0.96
FEV1/FVC	72.9 (7.96)	73.2 (6.23)	0.94
MVV	86 (13.7)	84.9 (16.9)	0.93
RV/TLC	43.8 (11.2)	44 (10.36)	0.87

BSC: Best supportive care, **IMRT**: Intensity-modulated radiation therapy, **ECOG PS**: Eastern Cooperative Oncology Group performance scale, **FEV1**: Forced expiratory volume in the first second, **FEV1/FVC**: FEV1/ forced vital capacity, **MVV**: maximum voluntary ventilation, **RV/TLC**: residual volume / total lung capacity

Table 2. Overall survival and progression-free survival

	BSC group	**IMRT group**	**p value***
	Estimated median in months (95%CI)		
Overall survival	11 (7.61-14.4)	13 (11.3-14.7)	0.117
Progression-free survival	4 (NR)	6 (4.82-7.18)	0.009

BSC: Best supportive care, **IMRT**: Intensity-modulated radiation therapy; **CI**: Confidence interval; **NR**: Not reached; * Log rank test

All patients completed the EORTC QLQ-C30 at baseline and at 4 months (table 3). The final QLQ-C30 summary score was significantly higher in the BSC group compared to the IMRT group indicating better QoL in the BSC group. The decline and the percent of decline from baseline to final QLQ-C30 summary score was significantly higher in the IMRT group compared to the BSC group indicating more QoL deterioration in the IMRT group.

Table 3. EORTC QLQ-C30 summary score and QLQ-LC13 score in both groups

		BSC group	IMRT group	P value *
		Mean (±SD)	Mean (±SD)	
EORTC QLQ-C30 summary score				
	Baseline	71.58 (5.01)	71.67(5.82)	0.514
	At 4 months	60.75 (3.21)	46.66(3.99)	0.003
	Change from baseline	- 10.83	- 25.01	0.0003
	Percent of change from baseline	- 15.12	- 34.89	0.0002
EORTC QLQ-LC 13 score				
	Baseline	86.13(4.37)	83.77(4.96)	0.611
	At 4 months	80.13 (4.98)	62.83(4.21)	0.041
	Change from baseline	- 6	- 20.94	0.003
	Percent of change from baseline	- 6.96	- 24.99	0.0001

BSC: Best supportive care, **IMRT**: Intensity-modulated radiation therapy, **EORTC QLQ**: European Organization for Research and Treatment of Cancer QoL questionnaire, **QLQ- LC13**: quality of questionnaire for lung cancer; * Student t-test

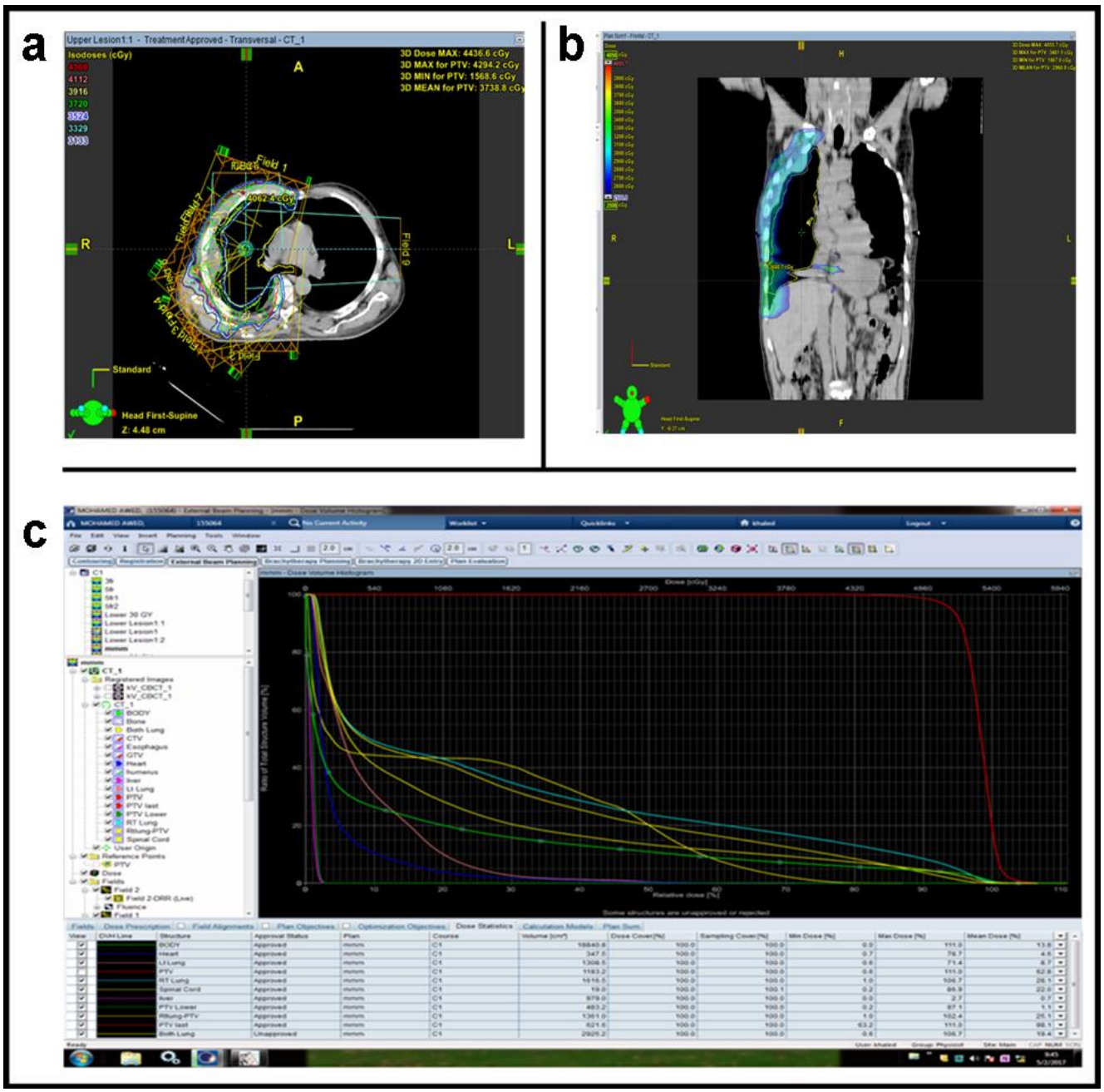

Figure 3. **a**: Eight fields of step and shoot IMRT in a 50 years old male patient with right side malignant pleural mesothelioma, epithelioid type. The patient received systemic chemotherapy with pemetrexed and ciplatin for total 6 cycles and he was not candidate for surgery, **b**: Dose distribution in a coronal section demonstrating homogenous dose distribution. Mean dose to the PTV=2960.8 cGy, **c**: Dose volume histogram demonstrating acceptable normal tissue dose constrains.

The final QLQ-LC13 score was significantly higher in BSC group compared to IMRT group indicating more symptoms deterioration with IMRT. The decline and the percent of decline from baseline to final QLQ-LC13 summary score were significantly higher in IMRT group compared to BSC group indicating more deterioration in the chest symptoms with IMRT.

Two patients from the intervention group and three from the control group were treated with step and shoot IMRT. Dosimetric parameters of the treatment plans demonstrated that the mean and standard deviation of radiotherapy doses to the target volume and the organs at risk are within acceptable limits for both groups regardless the IMRT modality (figures 3a, 3b, 3c and table 4).

Table 4. Radiotherapy doses (in cGy)

	No.	Mean	±SD	Minimum	Maximum
Spinal cord	12	1880.0	701.4	746.8	3196.1
Both lungs	12	1275.0	278.0	1017.0	1837.2
PTV	12	4240.5	334.7	3735.5	4838.3
Liver	12	1193.8	1123.9	10.1	2970.8
Heart	12	1849.60	974.38	250.30	3160.40

IMRT had an incremental cost of 5911.86 USD per patient with an incremental effectiveness of 4 months of progression free survival, providing an ICER of 6.260 (table 5).

Table 5. Average cost (in USD)

	BSC	IMRT
Direct medical cost	1000	6704.7
Direct non-medical cost	123.82	330.98
Total cost	1123.82	7035.68

USD: United States Dollar, **BSC**: Best supportive care, **IMRT**: Intensity-modulated radiation therapy

DISCUSSION

In 2005, a report from the Egyptian National Cancer Institute and Abbassia Chest hospital described a 4-fold increase in the number of MPM patients over 4 years [16]. In an institutional-based data at Ain Shams University Clinical Oncology Department in Egypt between 2010 and 2015, MPM cases represented about 26.5% of the yearly reported thoracic malignancy cases and about 2.6% of the yearly reported cancer cases in the same period (unpublished data).

Treatment results of Egyptian MPM patients are not satisfactory. In patients with MPM, radiotherapy can be used as a part of multimodality regimen; however, radiotherapy alone is not recommended.

Baldini reported that the role of radiotherapy in unresected mesothelioma is still questionable. Toxicity is usually unacceptable. Some data reported that treatment with IMRT may be tolerable [17]. On the contrary, Rosenzweig et al stated that 56% out of 36 MPM cases were operated with pleurectomy/ decortication prior to IMRT while 44% did not undergo resection. The 1-year and 2-year survival rates were 75% and 53% in operated patients while it was 69% and 28% in non-operated patients respectively. The final conclusion of Rosenzweig et al was that treating the intact lung with pleural IMRT in patients with MPM is a safe and feasible treatment option with acceptable rate of pneumonitis [18].

The data of the current study agree with the report of Baldini [17]. In our study, there was no significant median OS benefit for the IMRT group versus the control group (13 vs. 11 months, p=0.117) while the IMRT group demonstrated a highly significant median PFS vs. the control group (7.5 vs. 4.3 months, p=0.009). However, improved PFS of the IMRT group was at the cost of increased toxicity and QoL decline as evident by the symptom assessment using the EORTC QoL questionnaires.

The one year survival for the IMRT group in the current study is comparable to that reported by Rosenzweig et al [18] (66.7% vs. 69%). However Rosenzweig et al did not correlate the survival benefit of IMRT for MPM with QoL and economic outcomes as was done in the current study.

Up till now, no formal well designed randomized phase III trials evaluating the impact of IMRT on the QoL of MPM patients with intact lung. de Graaf-Strukowska et al suggested that future studies including radiotherapy for the treatment of mesothelioma should include formal measures of QoL and symptom control [19].

In the current study, the EORTC questionnaires were used as it is a validated method for evaluating the QoL of cancer patients. Moreover, the items of the symptom score in the questionnaire are the same items that can be used to monitor the acute and late effects of thoracic radiotherapy. Eliciting a comparison between the initial and final results of EORTC QLQ-C30 and QLQ-LC13 revealed non-significant difference between both groups at baseline evaluation. However, final comparison between both groups revealed a statistically significant deterioration of the scores in the IMRT group compared to the control group. These results suggest that IMRT in MPM in the context of intact lung is likely a detrimental procedure.

For the time being, no study touched the issue of cost-effectiveness of IMRT in unresected MPM patients. van Zandwijk et al stated that current guidelines do not deal with cost implications (cost-effectiveness) of the diagnostic and treatment approaches of MPM patients [20]. In this study, we have shown that despite the non-significant difference between two treatment groups as regards OS, IMRT is apparently a cost-effective treatment as regards PFS for patients with MPM, However, improved PFS in the IMRT group was at the cost of increased toxicity and poor QoL which makes the cost-effectiveness of IMRT in terms of PFS of MPM patients a questionable issue.

Conclusion

Piloting IMRT in unresected MPM patients had no OS advantage. The improvement in PFS was at the cost of increased toxicity and poor QoL and the procedure is not expected to be cost-effective in Egyptian patients.

Conflict of interest

The authors have no conflict of interest to declare.

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