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Role of Soluble Mesothelin Related Peptide (SMRP) Tumour Marker as a Prognostic Value of Mesothelioma Patients Pre and Post Operative

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Abstract: **Background:** Soluble mesothelin-related peptides (SMRP) are a potential tumor marker for malignant mesothelioma. It that has been proposed for differential diagnosis from pleural metastatic cancer, as well as prognosis and treatment monitoring of malignant pleural mesothelioma (MM). **Aim of The work:** To Study the Value of SMRP as a tumor marker in prediction the response to treatment and the prognosis in patient of malignant mesothelioma who undergone pleurectomy decortication as more accepted surgical procedure in comparison to who only had chemotherapy. **Patient and Methods:** Through a clinical trial started from April 2017 till November 2018 With a minimum follow-up of 6 months was required and up to 12 months, there were sixty patients of mesothelioma. First thirty underwent pleurectomy decortication during their management. In the remaining thirty only chemotherapy was the only therapeutic decision. Serum samples collected pre and post management in each group. Change of SMRP was studied as a predictor of overall survival and the quality of life in according to degree of pain and dyspnea control. **Results:** There were no statistically significant differences in according to demographic criteria in both groups. Which was essential for accuracy of the study. Most of the patients were epitheloidmesothelioma, there were only three sarcomatoid MPM in the study. There was statistically significant difference in according to the percentage of change of SMRP in between surgery and chemotherapy (p value;0.04) which reflected on survival of P/D patients as its median was 22 months. According to mortality there were 6 in surgical group and 11 in chemotherapy group. Change of SMRP also correlated with statistical significant difference in according to pain and dyspnea (pre & post operative) (p value; 0.03 and 0.01 respectively) with no significant difference in patients had chemotherapy. **Conclusion:** SMRP may be a useful tumor marker for detecting the progression of malignant mesothelioma and expecting the response to treatment in according to overall survival and post operative quality of life.

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Key words: Mesothelioma, SMRP, Pleurectomy / decortication, prognosis

1. Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor with a poor survival rate that arises from the surface cells of the pleura. MPM primarily caused by exposure to asbestos (**1).** Previously considered as a rare tumor, MPM has become a very important public health issue, and its incidence is expected to continue to increase. Current therapeutic options for MPM are limited (**2).**

Patients with MPM generally present with shortness of breath and chest pain. The clinical signs of MM are unspecific, but MM is usually associated with the presence of exudative effusions (**3).**

The risk of MPM due to asbestos is related to the duration of exposure and cumulative dose (**4**). Early diagnosis offers the best hope for a favourable prognosis; however, the early and reliable diagnosis of MPM is extremely difficult as only 5% of patients present with stage IA disease (**5**).

The incidence of MPM revealed a gradual increase in number of cases in Europe over the last 40 years with male: female ratio has changed from 1:1 to 4:1 and it is expected that the incidence of MPM will continue to rise till approximately 2020 ***(6).***

The relatively late discovery of most cases is due to the long interval between exposure of asbestos and development of mesothelioma with latency period of

30 to 45 years. So, because of its carcinogenic property, the use of asbestos has been banned in many developed countries, but some developing countries such as China and India still permit its usage ***(7)***

The incidence in Egypt is expecting to rise in the following years, the total estimated cases are (207, 238, 456) in (2020, 2025, 2050) respectively ***(8).***

Immunohistochemical diagnosis of epithelioid mesothelioma in pleural biopsy or surgically resected specimens has been actively pursued, using markers such as podoplanin, calretinin, WT-1, cytokeratin 5, thrombomodulin, and mesothelin (**9).**

Mesothelin is a 40 kDa cell surface glycoprotein that is highly expressed in MM, pancreatic cancers, ovarian cancers, and some other cancers. Mesothelin is synthesized as a precursor 69 kDa protein and forms two proteins, the membrane-bound mesothelin and a soluble megakaryocyte potentiating factor (**10**).

The SMRP is related to the mesothelin family of molecules. Mesothelin is a 40-kD cell surface glycosylated phosphatidylinositol-anchored glycoprotein, which functions in cell-to-cell adhesion **(2).** SMRPs can be detected in blood, and have been found highly increased in the blood of patients with mesothelioma (**1**).

Patients who are ultimately considered for surgery should have a good performance status, minimal comorbidities, epithelioid histology, and stage I or perhaps stage II (without nodal involvement) disease. Patients with sarcomatoid histology, biphasic histologies, or extrapleural nodal involvement (stage III-IV) have poor outcomes (**11**).

Because MPM is often diagnosed late, it has a poor prognosis with five-year survival is still approximately 8 %. It occurs mainly in older men (median age at diagnosis, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20-40 years later) ***(12).***

Median survival for untreated malignant pleural mesothelioma is usually less than 1 year, survival figures must always be interpreted with caution and be compared with the average survival of nine months with supportive care alone. ***(13).***

In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected MPM includes: Computed Tomography (CT) of the chest with contrast, Thoracentesis for cytologic assessment of the effusion, Pleural biopsy (eg, thoracoscopic biopsy, preferred) ***(14).***

However, cytologic samples are often negative even when patients have MPM ***(15)***. Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status ***(16).***

Study by Muers et al., 2008 (17) showed that chemotherapy alone is not able to improve on the results obtained with simple symptomatic treatment, in terms of mean survival rate.

In our study we investigated the ability of SMRP to predict the overall survival and the effect of pleurectomy/ decortication over chemotherapy for improving quality of patients life.

2. Patients and Methods

This study was carried out at thoracic surgery unit at cardiothoracic surgery department at Ain Shams University & other centers of thoracic surgery. Apart of our study was done through outpatient clinic of oncology department in Ain Shams University hospital and other oncology out patient clinics.

The study is a prospective observational non-randomized clinical trial conducted during the period from April 2017 till November 2018 With a minimum follow-up of 6 months was required and up to 12 months. There were 30 patients with pathological proved resectable MPM who had pleurectomy/decortication (+-extended resection which included pericardium, Lymph node and diaphragm) and on the other side there were 30 had only chemotherapy.

Study included patients referred for Ain Shams University hospitals and other centers to undergo surgical management of malignant pleural mesothelioma (group A) & others with newly diagnosed patients and refered to oncology department to have chemotherapy (group B). We intend to choose patients with no other life threating co-morbidity. Disease should be measurable in according to expected adequacy of follow-up through post – operative performance status, post -operative follow up CT chest. ECOG performance status (Eastern Co operative Oncology Group) used to assess how the disease affects the daily living abilities of the patient.

We excluded MPM patients who had other cancers, those undergone extrapleural pneumonectomy (EPP) and patients on immunosuppressive therapy for any cause.

Serum samples of MPM collected pre operatively and pre discharge from hospital in surgical group. In other group samples collected prior to chemotherapy and after finishing all cycles. All samples centrifugated at approximately 1000-3000 rpm for 10-15 min. then the serum immediately store frozen at -80 °C, until further analysis.

Personal data collected include: name, age, sex, body mass index, occupation, residence, history of smoking, associated diseases and asbestos. Full clinical history included risk factors, associated chronic illness, asbestosis exposure, grade of dyspnea and degree of pain.

Pain (categorized according to pain scale) Grade 1: No pain, Grade 2: (MINOR) annoying but not

interfere with daily activities, Grade3: (MODERATE) Interfere significantly & unable to tolerate, Grade 4: (SEVER) disabled to do daily activities. Dyspnea (Grades considered in Questionnaire) ***(18)*** Grade 1: climb stairs without dyspnea, Grade 2: walk any distance without dyspnea, Grade 3: walk more than 100 meter without dyspnea, Grade 4: dyspnea on walk at or less than 100 meter, Grade 5: dyspnea on mild exertion e. g, undressing, Grade 6: dyspnea at rest.

Asking about method of tissue diagnosis (mostly VATs), report of histo-pathology and immunohistochemistry. Asking either the patient had chemotherapy prior to surgery or not, and if he had what its type?

Investigations done included CT chest, full laboratory investigations include: complete blood count, INR, liver function including (including; serum AST, ALT, total bilirubin, albumin) and renal function including (blood urea nitrogen (BUN), creatinine, virology and cross matching tests for blood donors. Operative data includes the surgical technique, operative timing, blood loss & transfusion and specimen type & weight. Postoperative data: included hospital stay, ICU stay, Immediate post operative pain and different methods of its control, postoperative complications including air leak wound infection and Mortality.

SMRP measured using ELISA technique. The concentration of SMRP in the samples is determined by comparing the O. D. of the samples to the standard curve. The sensitivity, specificity and predictive value of SMRP were statistically calculated.

Receiver Operating Characteristic (ROC curve) for Mesomark sensitivity and specificity showed the performance of SMRP.

Radiological response to therapy was assessed using the modified RECIST criteria:

Tumor thickness perpendicular to the chest wall or mediastinum was measured in two positions at the three separate levels on thoracic CT scans. The sum of six measurements defined a pleural unidimensional measure. Patients are divided according their radiological response into regressive (partial response and complete response), stable disease and progressive disease. Radiological (PR) partial response was characterized as ≥30 percent diminish in the sum the longest width of the objective lesions compared with baseline. (PD) progressive disease was characterized as ≥20 percent increment of at least 5 mm in the sum of the longest width of the objective lesions compared with the smallest sum of the longest width recorded **(19).**

Following up patients for 6 months minimum up to12 months postoperatively with outpatient appointments and telephone calls. Patients will be followed for progression through: progression free survival, over all survival, change in pain & dyspnea and follow up CT chest after 6 months and up to 12 months.

Statistical Analysis

All data will be recorded and statistical analysis was performed using SPSS version 20. Data were expressed as mean and standard deviation for quantitative data and percent for qualitative data. After normality test, **T-test** was used to compare parametric quantitative data while **Mann-Whitney test** was used to compare non-parametric data. **Chi-square test** was used to compare quantitative data. **Receiver Operating Characteristic curve** (ROC curve) the sensitivity and specificity showed the performance of SMRP. Mortality to be calculated. The free survival curves and Overall survival curves were plotted utilizing the **method of Kaplan and Meier**. Patients were lost to follow-up, or were alive at the finish of the trial were censored since last known follow-up. **P-value <0.05** was considered significant.

3. Results

Demographic characteristics of patients in both groups.

In surgery group there were there were 18 male and 12 female with mean age 52 years, while in chemotherapy group both sexes are equally distributed with mean age 53.5 years. According to Body mass Index the most occupied category in both groups is 18.5-24.5 followed by patients within <18.5 then patients with BMI within 24.5- 30.

According to ECOG performance status; **grade 0** (fully active and can carry all pre disease performance without restriction) in group A (n 13) & group B (n=10), **grade 1** (restricted in physically strenuous activity but ambulatory and can carry light work) in group A (n= 9) & group B (n=14), **grade 2** (ambulatory and can do his self care but can not do any work) in group A (n= 6) & group B (n=8).

Table 1 showing asbestosis exposure of patients at both groups

	Surgery group		Chemo group	
Asbestosis exposure	Frequency	Percent	Frequency	Percent
NO Exposure	10	16.7	6	10
Suspected	11	18.3	14	23.38
Confirmed	9	15.0	10	16.7

According to side of pathology there are equally distributed (15,15) in surgical group, in chemotherapy group (17 right, 13 left). VATS used to get pleural biopsy in 25 of surgical and 27 of chemotherapy patients. Most of our patients underwent VATs for pleural biopsy (25 in surgery group, 27 in chemotherapy group). These biopsies by histopathologic evaluation there were 27 patient of epitheloid mesothelioma who underwent P/D, 21 who had chemotherapy. Nine patients with biphasic (3 in group A and 6 in group B) and only 3 sarcomatoid patients.

Table (2) showing pain at time of diagnosis

Pain at presentation	Group of surgery		Group of chemotherapy	
	Frequency	Percent	Frequency	Percent
Tolerated	14	46.7	8	26.64
Untolerated & need for potent analgesia	16	53.3	22	73.26

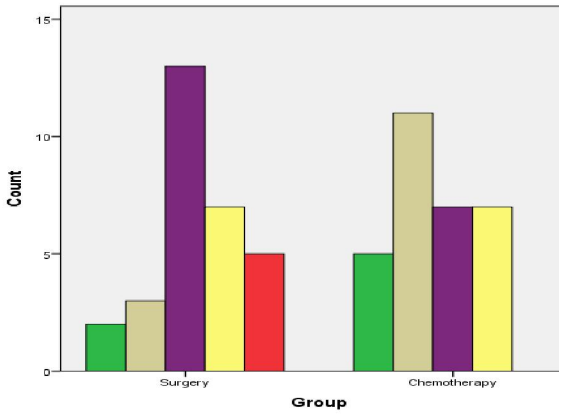

Figure (1) Show dyspnea at time of Presentation

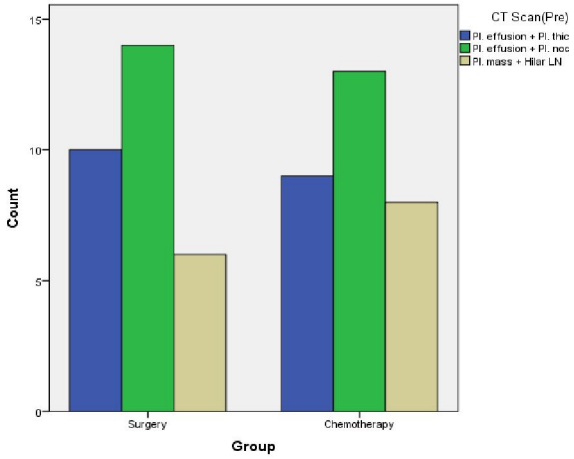

Figure (2): CT scan pre managent

In group of surgery:

All patients underwent pleurectomy /decortication with some variations in according to the involved structures (diaphragm in 13 patients, LN in 14 and pericardium in 6 patients. Mean of operation time is 187 minutes and mean of tumor mass excised was 163.6 mg. Patients stay from 6 to 12 days and they observed for early post operative complications. There was no case re opened for bleeding (mean of blood loss was 503.3 cc). Air leak was variable post operative (No in 4 patients, mild in 15, moderate in 7 and sever in 4. Need for Heimlech valve was in 66.7% of the patients.

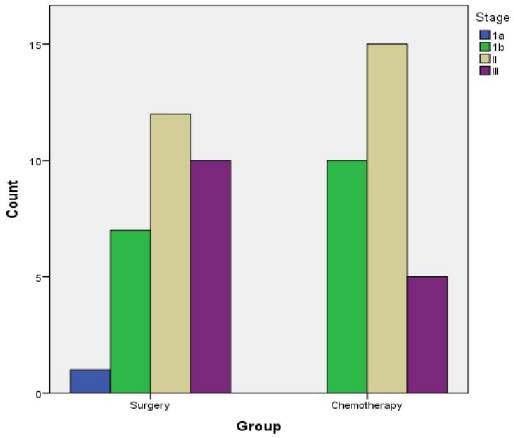

Figure 3: Of Staging in Both groups

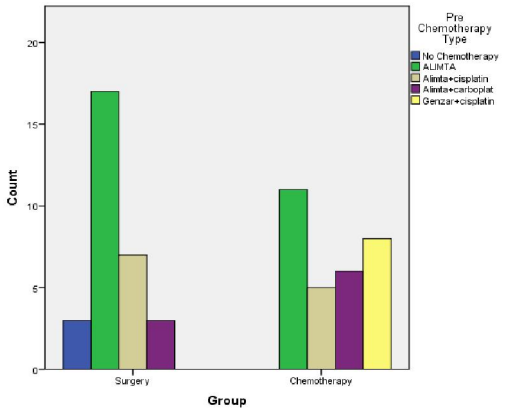

Figure (4) Of chemotherapy as first step managment

Table (3) Baseline SMRP in both groups SMRP (pg/ml)

Group	N	Minimum	Maximum	Mean	Std. Deviation
Surgery group	30	125	800	368.05	33.95
Chemo group	30	112.50	450	265.65	19.16

Follow up of the patients:

1st Laboratory:

Serum SMRP and compare it with pre management values (in each group and in both groups) as shown in the following table.

Table (4): Postoperative SMRP and its change from preoperative values

Group	Variables	Minimum	Maximum	Median	P-value
Surgery	Postoperative SMRP (pg)	0	725	125	
	Change in SMRP (pg)	-450	175	-187.5	<0.001*
	Percentage change in SMRP	-100%	31.82%	-59.97%	
Chemotherapy	Postchemotherapy SMRP (pg)	35	533	160	
	Change in SMRP (pg)	-235	82.50	-90	<0.001*
	Percentage change in SMRP	-83.72%	18.33%	-35%	

Surgery group showed higher median of the change in SMRP than chemotherapy group with high statistical significance (-187.50 pg versus -90 pg, P = 0.002).

Table (5): Comparison of the change in SMRP (pg) between both groups

	Surgery	Chemotherapy	P-value
Median	-187.50	-90	
Minimum	-450	-235	0.002*
Maximum	175	82.50	

Nonparametric Mann-Whiney test was used for comparison. *significant change

2nd point of follow up Survival: progression free survival, over all survival and mortality. (Survival till last follow up OR Mortality)

Table (6) showing survival in both groups

Group	Mortality	Survivors
Surgery	6	24
Chemotherapy	11	19

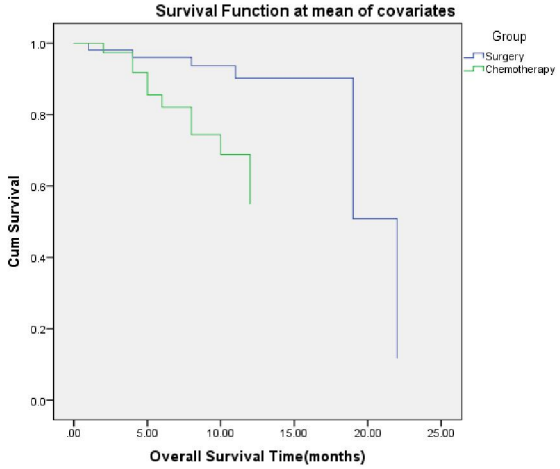

Figure (5) showing: ROC curve showing overall survival in both groups

3rd Radiological follow up: Follow up CT according to modified RECIST.

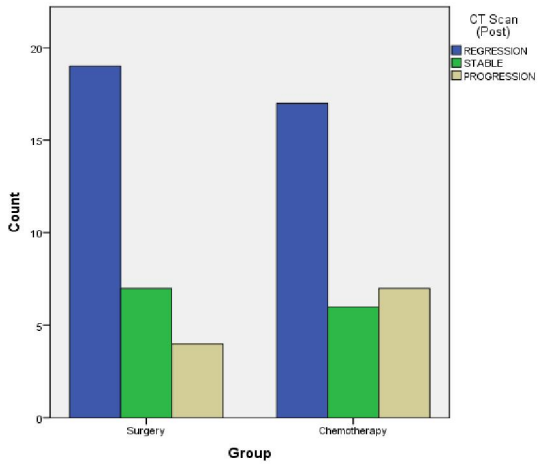

Figure (6) Showing the change of CT findings pre and post man agement in both groups Which showing more regressive in surgery group

Table (7): Postoperative dyspnea grades in comparison to preoperative frequencies in the surgery group

Variables	Postoperative dyspnea		Preoperative dyspnea		P-value
	Frequency	Percent	Frequency	Percent	
No dyspnea	0	0	0	0	0.009*
Mild (grade 1 & 2)	10	33.3	2	6.7	
Moderate (grade 3 & 4)	16	53.3	16	53.3	
Severe (grade 5 & 6)	4	13.3	12	40	

*significant difference

Table (8): Comparison of postoperative degrees of pain between both groups

Degree of pain	Group		P value
	Surgery	Chemotherapy	
≤ Degree 1	14	5	0.01*
	46.7%	16.7%	
> Degree 1	16	25	
	53.3%	83.3%	

*Significant difference

5th Role Of SMRP in prediction of survival

Table (9): The best cutoff values of the percentage change in SMRP to predict survival in both groups (higher sensitivity and specificity)

Groups	Cutoff of percentage change in SMRP		
	Cutoff (If greater than or equal)	Sensitivity	Specificity
Surgery	10%	95%	0%
	83%	20%	100%
Chemotherapy	6.2%	89%	0%
	65.4%	26%	100%

4. Discussion

Our study includes sixty patients who were divided into 2 group. Each one of them include 30 patients. Group A underwent surgery and group B received only chemotherapy.

In study by ***(20)*** include 41 patients of mesothelioma patients underwent the study 27 of them had systemic therapy. Seven patients who underwent surgical resection with negative margins had elevated preoperative SMRP levels that fell to normal postoperatively. Rising SMRP was observed in all patients with radiologic disease progression.

Robinson et al 2005 reported that determination of SMRP levels, as a marker of detecting MM in an asbestos-exposed population, had high sensitivity and specificity. The same group investigated the presence of mesothelin in pleural fluid from 192 individuals (52 MM, 84 non-neoplastic, and 56 non-MM cancers) and peritoneal fluid from 42 patients (seven MM, six non-neoplastic, 14 non-MM cancers, 15 end-stage renal failure). Higher levels of mesothelin were detected in the fluid of patients with MM when compared to either other malignancies or non-neoplastic disease (21)

Our study is a prospective observational non-randomised clinical trial conducted during the period from April 2017 till November 2018. A study by **(19)** cross sectional prospective study included all (i.e. 78) patients with malignant mesothelioma treated at the Institute of Oncology Ljubljana between March 2007 and December 2009.

In our study there were 33 males (18 in surgery group and 15 in chemo. Group) while there were 27 female (12 in surgery and 15 in chemo. Group). ***(19)*** which included 78 patients (57 female and 21 male) with mean age 64.48 years.

History of our patients included methods of tissue biopsy which confirmed diagnosis of mesothelioma. VATS had the major role to get the pleural biopsy in 83.3% of patients of P/D group. That was similar to the Egyptian study by ***(22)*** which discussed the epidemiology of mesothelioma in Egypt through ten-years in multicentres.

Eighty percent of our patients were epitheloid mesothelioma patients (26 in surgery & 22 in chemo group. Fifteen percent of the remainder 20% were Biphasic. Only 5% were sarcomatoid who were exclusive to chemotherapy group. Similarly, Of the 36 patients of ***(study of Dipalma N et al., 2011)*** affected by MM, diagnosed by histology and immunohistochemistry, 29 (81%) had an epithelioid type cancer, 4 a sarcomatoid type (11%), and 3 a mixed type (8%). Stage II and stage Ib of mesothelioma presented in our study in percentage of 45% and 28.3% respectively. Stage III found in 25% of patients of both groups. Distribution of staging among patients in similar studies differs; the forty one patients of study by **Wheatley-Price et al** 2010; Six patients had early-stage disease (stage I/II), 33 patients had advanced disease (stage III/IV), and two patients were incompletely staged **(20, 23).**

In our study, range of pre operative SMRP in surgery group was 125-300 with mean 368 pg/ml (0.9 nanomol/L), while in chemotherapy group the range of SMRP was 112.5 – 450 with mean 265.65 pg/ml (0.66 nanomol/ L). In study by **Wheatley-Price P et al**., 2011, the 8 patients who had surgery the baseline SMRP 20Nm decreased to 9 in follow up with change 56% **(20).**

During P/D of all patients in group A of, our study, the involved structures included diaphragm only resection in 5 patients, diaphragmatic resection and LN which excised in 4 patients. The third category included diaphragmatic resection and pericardial resection in 3 patients. there was a case included resection of pericardium in addition to excisional biopsies from lung, oesophagus and trachea.

Such surgeries prolonged to 240 minutes but the mean of all surgical times was 187 minutes. On contrary, there was no correletation between the weight of surgical specimen excised and time spent in operating room. The mean of specimen weight was 163 gm.

Follow up of the patients included; clinical, radiological and post management SMRP level. All three items compared to pre interventional values. This is over other studies which its upper extent was to reach two lines of this triangle. Example about that is study by ***Dipalma N et al., 2011*** which was pointing to the change in SMRP and neglected the clinical and radiological aspects **(23).**

Study by ***Wheatley-Price P et al 2011*** found that Percentage changes in SMRP levels is a potentially useful marker of disease course. Authors recommended to make findings be validated prospectively for a role as an objective adjunctive measure of disease course in both clinical trials and clinical practice **(20).**

The percentage of change of SMRP between both groups in our study; was statistically significant significant (p value; 0.04). The cross sectional prospective study by ***Franko A et al., 2012*** depend his results on SMRP changes, survival and m RECIST criteria with no data about quality of life of his patients **(19).**

During follow up (CT according to modified RECIST) of the patients in our study we found that 60% of all sample size had regressive course (included complete and partial response), 21.7% of them had stable disease. Progressive course found in 18.3 %. **Wheatley-Price P et al 2011** study described initial radiological reports and also follow up reports according to RECIST and modified RECIST criteria. About initial reports, progressive and regressive courses was equal (8) but stable disease was less than both (5 patients) **(20).**

Postoperative SMRP and its change from preoperative values according to our results; its range between 0- 725 with median 125 pg/ml which decreased from pre operative values by median (-ve 59.97%). On the other side in chemotherapy only group the range of post SMRP was 0-532 with median 135 which decreased from pre chemo values by (median -35%). In each groups there is statistical significant difference (p value <0.001). ***In Wheatley-Price P et al 2011*** the percentage of change in SMRP in patients had systemic therapy (non surgical management) was 25% in regressive subgroup, 11% in the stable one and 99% in the progressive subgroup **(20).**

In our study Mortality occurred follow up of during six patients in P/D group and eleven in chemotherapy group. Median for survival time was 22 months. Mean values of progress free survival in regression, stable and progression response groups are 7.8, 8.2 and 6.25 respectively.

Study by ***Franko A et al 2012*** used Pearson's correlation coefficient to calculate The correlation between survival and SMRP levels. In this study, At the time of censoring, 8 patients were alive and the mean survival for the overall group was 23 months with range between (2.83–86.10) months. No correlation was found between SMRP levels before treatment and survival ($r = 0.028$; $p = 0.87$) **(19).**

In our study by Comparing post operative dyspnea grades in both groups; there was statistically significant difference (p value 0.02). In surgery group patients had grade 2 or less were 33.3%, while in chemo group they were 10%. Others had more than grade 2 were 66.7% in surgery group while they were 90%.

By the same way during Comparison of postoperative degrees of pain between both groups; there was statistically significant (p value 0.01).

twenty five of chemotherapy patients suffering from pain with grade more than 1 while they were 16 in surgery group. Patients with no post operative pain or only grade 1 were (15 in surgery group and 5 in chemo group).

Conclusion

- Our research confirm the Trust of SMRP as a predictive marker of prognosis of an aggressive disease which was in need for more investigations as asked by many other studies.
- Pre management serum SMRP levels correlate with severity of mesothelioma.
- Percentage changes in SMRP are a promising marker of disease course in patients with MM; that changing SMRP levels show high levels or concordance in detecting disease course changes including:
  - ✓ Overall survival
  - ✓ Quality of life
- Relationship between SMRP (pre and post management) and disability resulted from sever pain and dyspnea was of our study benefits.
- If the surgical intervention in form of pleurectomy/ decortication is possible (in according to disease staging and general condition of the patients) will improve the prognosis inspite of post-operative complications.
- Patients received chemotherapy perior to P/D had better results; this add more strength to combined therapy of mesothelioma.

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