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ORIGINAL ARTICLE

Malignant pleural effusions: Are we better than the past?

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ABSTRACT

Objective: Malignant pleural effusion (MPE) is indicative of advanced-stage disease and a poor prognosis in almost all cancer types. Lung and breast cancers are the predominant malignancies causing MPE, collectively representing over 60% of the total. In recent years, cancer has become a type of chronic disease, with advancements in diagnostic tools and treatment strategies. Our objective was to assess the evolution of primary diagnoses, survival rates, and associated variables among individuals with MPE in recent years.

Materials and Methods: A retrospective search was conducted on the demographics, comorbidities, primary cancer sites, diagnostic interventions, and laboratory results of patients diagnosed with MPE between January 1, 2005, and July 30, 2018.

Results: Of the 663 patients who have MPE, the female/male ratio was 373/290. The mean age was 59.2 ± 14.0 at the time of diagnosis. The most common cancers were lung cancer (30.9%), breast cancer (23.3%), and gastrointestinal system cancers (16.62%). It was observed that the rate of MPE due to lung cancer increased gradually over the years. Initially, breast cancer constituted the most prevalent diagnosis in 28.2% of cases, whereas lung cancer rose to the top as the most prevalent in the second and third five-year periods (28.9% and 37.4%, respectively). Overall, the median survival time was 2.07 months. Kaplan-Meier analysis also revealed that survival times did not change significantly over fourteen years.

Conclusion: Advances in diagnostic methods and treatment modalities have altered the most common primary cancer causing MPE in recent years but have not contributed to survival time.

Keywords: pleurisy, effusion, diagnosis, lung, malignancy.

INTRODUCTION

Malignant pleural effusion (MPE), refers to malignant involvement of the pleural space, is the second most common cause of exudative pleural effusion, following parapneumonic effusions [1]. It affects approximately 15% of all cancer patients during the course of those diseases [2]. MPE indicates advanced disease and reduced survival in almost all cancer types. Although it may vary depending on the type of primary cancer, the median life expectancy ranges from 1 to 12 months [2-4]. The most common cancers causing MPE are lung and breast cancers, which together account for more than 60% of all cases [5].

Advances in diagnostic tools and treatment modalities have transformed cancer into a chronic disease. The average survival of patients, even in the metastatic stage, significantly improved [6]. Five-year survival of metastatic breast cancer increased from 10% to 27% during the last 40 years [7]. Similarly, the median overall survival of metastatic colorectal cancer doubled in the previous two decades [8,9]. Moderate progress was also present

in lung cancer, and 5-year survival rates approached 20% [6,10].

The management of pleural effusion aims not only to provide definitive treatment but also to control symptoms and allow time for the treatment of the underlying disease [11]. Options include serial thoracentesis, chest tube or indwelling pleural catheter placement, pleurodesis, and pleurectomy [2]. Despite improvements in the management of MPE as well as treatment options for primary cancers, MPE is still associated with a reduced lifetime expectancy, regardless of the primary site. We aimed to evaluate the changes in primary diagnoses, survival rates, and related factors in patients with MPE from 2005 to 2018 in our institution.

MATERIALS AND METHODS

Study design

We retrospectively reviewed MPEs between 01.01.2005 and 30.07.2018. We obtained the pathological reports from the database of the pathology department. MPE was defined as the detection of tumor cells in the cytopathological examination of pleural fluid or pleural biopsy material. We obtained the demographic data, comorbidities, primary cancer sites, diagnostic interventions, and laboratory results at the time of diagnosis from the database of our hospital. Survival status, and date of death data were double checked from the database of the hospital and the Death Notification System (DNS) of the Turkish Ministry of Health.

Statistical analysis

We present the descriptive statistics for continuous variables as mean ± standard deviation, or median, minimum-maximum values based on the normality assumption of distributions. In order to specify significant variables for survival time, we split the data into five-year periods. For survival analysis, we considered five-year periods as strata, and then we applied univariate stratified Cox regression to determine the candidate variables for multiple stratified Cox regression models. The variables with a p-value<0.25 in univariate models are taken as candidate variables for the multiple Cox regression model. We also present the survival probabilities for 1-year, 2-years, 3-years, and 4-years, median survival times, and survival curves based on the final Cox regression model. The survival analysis part was conducted using R (R Core Team, 2021) [12], "survival" [13], "ggplot2" [14], and "survminer" [15] packages. The other analysis was using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., 2015). The results are condisered statistically significant if the p value is< 0.05.

Ethical approval

Researchers assure that the study fully complies with the Declaration of Helsinki. The clinical research ethics committee of Hacettepe University Faculty of Medicine approved the study protocol (GO 18/883, 25.09.2018).

RESULTS

Of the 663 patients with MPE, 56% were female, and the female/ male ratio was 1.29 (373 and 290, respectively). The mean age was 59.2±14.0 years at the time of diagnosis. Among those 277 patients whose smoking status information can be accessed, 164 had a smoking history, and 113 were non-smokers. At the time of analysis 21, (4.3%) patients were alive, and 462 (95.7%) were dead. Since the Ministry of Health started using a properly organized DNS in 2013, we could not achieve reliable survival data of 180 patients from previous years. The demographic data of the study population is shown in Table 1.

Table 1. Demographics

Characteristics	2005-2009 (N= 281)	2010-2014 (N= 207)	2015-2018 (N= 175)	Total (N= 663)
Mean Age (years±SD)	57.3 (14.2)	59.8 (14.0)	61.5 (13.4)	59.2 (14.0)
Gender (Female) N, (%)	175 (62.3)	105 (37.7)	93 (53.1)	373 (56.3)
Smoking N, (%) (N= 277)	53 (59.6)	64 (66.6)	47 (51.1)	164 (59.2)
Mortality N, (%) (N= 483)	124 (94.7)	177 (97.8)	161 (94.2)	462 (95.7)
Lung cancer (%)	78 (27.8)	62 (30.0)	65 (37.1)	205 (30.9)

The most common diagnoses were lung cancer (30.9%), followed by breast cancer (23.2%) and gastrointestinal system (GIS) cancers (16.6%) overall (Table 2). Breast cancer was the most prevalent diagnosis in the first 5-year period (28.2%), while lung cancer became the most common diagnosis in the second and third 5-year periods (28.9% and 37.4%, respectively) (Figure 1). Evaluation of factors associated with death showed that elder age (HR: 1.010) and low serum protein levels (HR: 1.496) were associated with shorter survival. GIS and hematologic cancers reduce the time to death 1.441 and 1,157 times compared to lung cancers, respectively (Table 3).

Examination of mortality data over 5-year periods showed that there was no significant difference in survival. Although the rate of 1-year survivors is higher in Groups 2 and 3 than in Group 1, death rates have converged over the years. The median survival was 2.07 months overall. Kaplan-Meier analysis also revealed that there was no significant change in survival times during five-year periods over 14 years (Table 4, Figure 2).

DISCUSSION

Current study confirmed that lung cancer is the most common tumor causing MPE. The fraction of lung cancer among cancers causing MPE has increased over the years, and that of breast cancer has decreased. Elder age and low serum protein levels were associated with shortened survival. While GIS and hematologic cancers with MPE were more risky for reduced survival compared to lung cancer, the lifespan was longer in breast cancers. Despite the minor increase in 1-year survival time, which did not reach statistical significance, survival time did not change during the 14 years.

In the late 1990s, Sahn et al. reported that lung cancer (36%), breast cancer (25%), and lymphoma (10%) were the most common cancer types associated with MPE [16]. In a large-scale research conducted almost 20 years later, the most common causes of MPE were determined to be lung (37%), breast (16%), hematological (10%), and unknown origin (10%) [17]. These results indicate that breast cancer is the second-leading cause of MPE, although its impact is decreasing, whereas lung cancer preserves its leading role. The results of our

Table 2. Distribution of primary tumors

Lung 205 (30.9%)		Non-lung 458 (69.1%)							
	Breast 154 (23.2%)	GIS 110 (16.6%)		Gynecology-Urinary 69 (10.4%)		Hematology 43 (6.5%)		Others 82 (12.4%)	
Adenocarcinoma	148 (22.3%)	Gastric	59 (8.9%)	Ovary	47 (7.1%)	Lymphoma	32 (4.8%)	Mesothelioma	31 (4.7%)
NSCLC	29 (%4.4)	Pancreas	24 (3.6%)	RCC	7 (1.1%)	MM	6 (0.9%)	CUP	29 (4.4%)
SCLC	22 (3.5%)	Colorectal	19(2.9%)	Endometrium	5 (0.8%)	ALL	2 (0.3%)	Sarcoma	9 (1.2%)
Squamous cell carcinoma	6 (0.9%)	Cholangiocarcinoma	4 (0.6%)	Bladder	4 (0.6%)	CLL	2 (0.3%)	Malignant melanoma	4 (0.6%)
		Esophagus	2 (0.3%)	Prostate	3 (0.5%)	AML	1 (0.2%)	Thyroid	3 (0.5%)
		Small intestine	1 (0.2%)	Tuba uterina	1 (0.2%)			Yolk sac	2 (0.3%)
		Gall bladder	1 (0.2%)	Cervics	1 (0.2%)			Cutenous SCC	1 (0.2%)
					1 (0.2%)			Parotis	1 (0.2%)
								Thymus	1 (0.2%)
								PNET	1 (0.2%)
								Cystadenocarcinoma	1 (0.2%)

GIS: Gastrointestinal system, NSCLC: Non-squamous cell lung cancer, SCLC: Small cell lung cancer, MM: Multiple myeloma, ALL: Acute lymphocytic leukemia, CLL: Chronic Lymphocytic leukemia, AML: Acute myeloid leukemia, RCC: Renal cell carcinoma, CUP: Cancer of unknown primary site, SCC: Squamous cell carcinoma, PNE: Primitive neuroectodermal tumor

Table 3. Factors related with reduced survival

	Univariate Cox Regression	Multiple Cox Regression**	HR (95% CI)	p-value
	HR (95% CI)	p-value		
Age of diagnosis	1.005 (0.998-1.012)	0.148	1.010 (1.002-1.017)	0.014
Gender (M/F)	1.448 (1.203-1.742)	<0.001	-	-
Smoking	1.199 (0.914-1.573)	0.191	-	-
Lactate dehydrogenase	1.000 (1.000-1.000)	0.363	-	-
Pleural glucose	1.000 (0.999-1.000)	0.26	-	-
Pleural protein	1.000 (0.996-1.004)	0.992	-	-
Serum protein	0.707 (0.641-0.779)	<0.001	0.669 (0.627-0.779)	<0.001
Organ systems				
Gastrointestinal system	1.705 (1.300-2.235)	<0.001	1.441 (1.079-1.926)	0.013
Hematologic malignancy	1.413 (0.952-2.096)	0.086	1.157 (0.752-1.780)	0.507
Breast cancer	0.649 (0.503-0.837)	0.001	0.619 (0.471-0.814)	0.001
Gynecologic-Urologic malignancy	0.939 (0.677-1.301)	0.704	0.709 (0.493-1.019)	0.063
Others	0.936 (0.680-1.288)	0.683	0.949 (0.679-1.325)	0.758

**In the final model, the year period is considered as strata. Therefore, the stratified Cox regression results were given.

Table 4. Survival rates up to 5 year-periods

Survival	2005-2009 (Group 1)	2010-2014 (Group 2)	2015-2018 (Group 3)	OVERALL
1-year (%)	16.47	25.51	22.81	21.89
2-year (%)	9.01	13.88	10.03	11.02
3-year (%)	6.49	6.40	7.12	6.69
4-year (%)	3.69	2.92	4.92	3.79
Median (months)	1.57	1.87	2.30	2.07

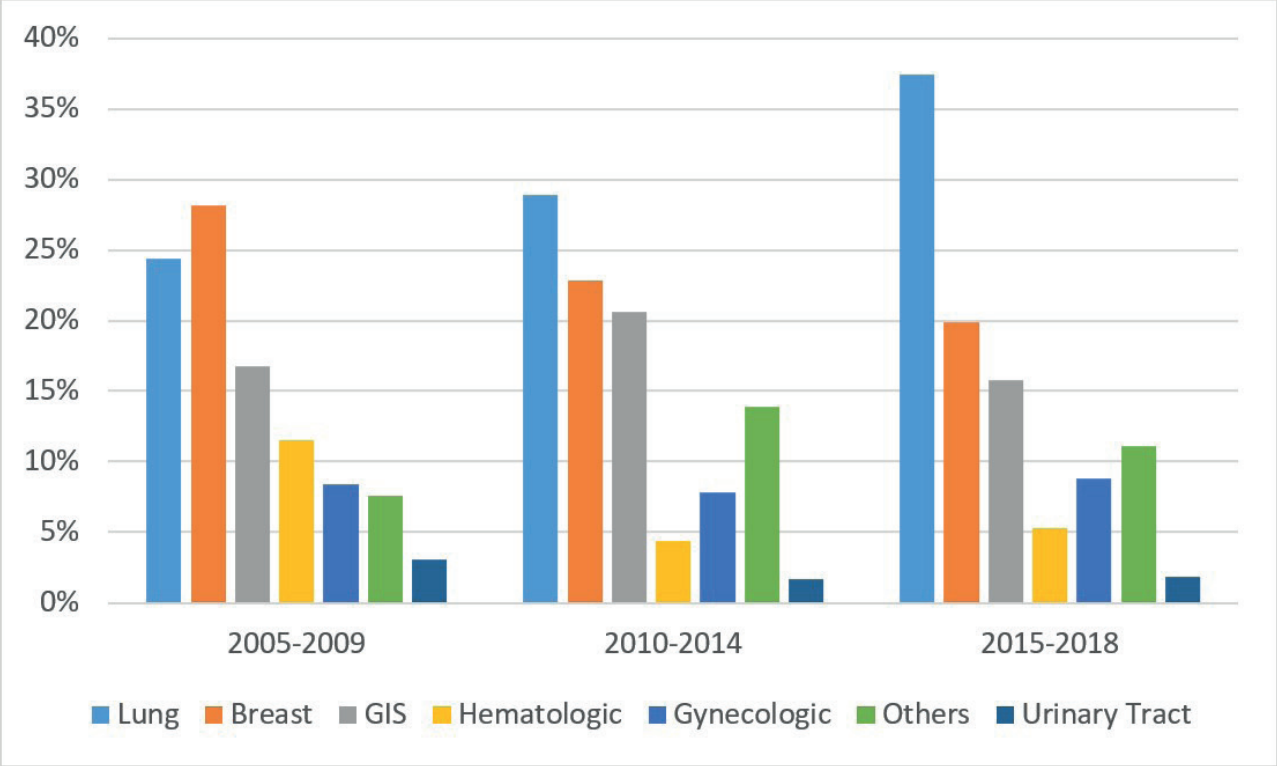

Figure 1. Diagnoses by five-year periods

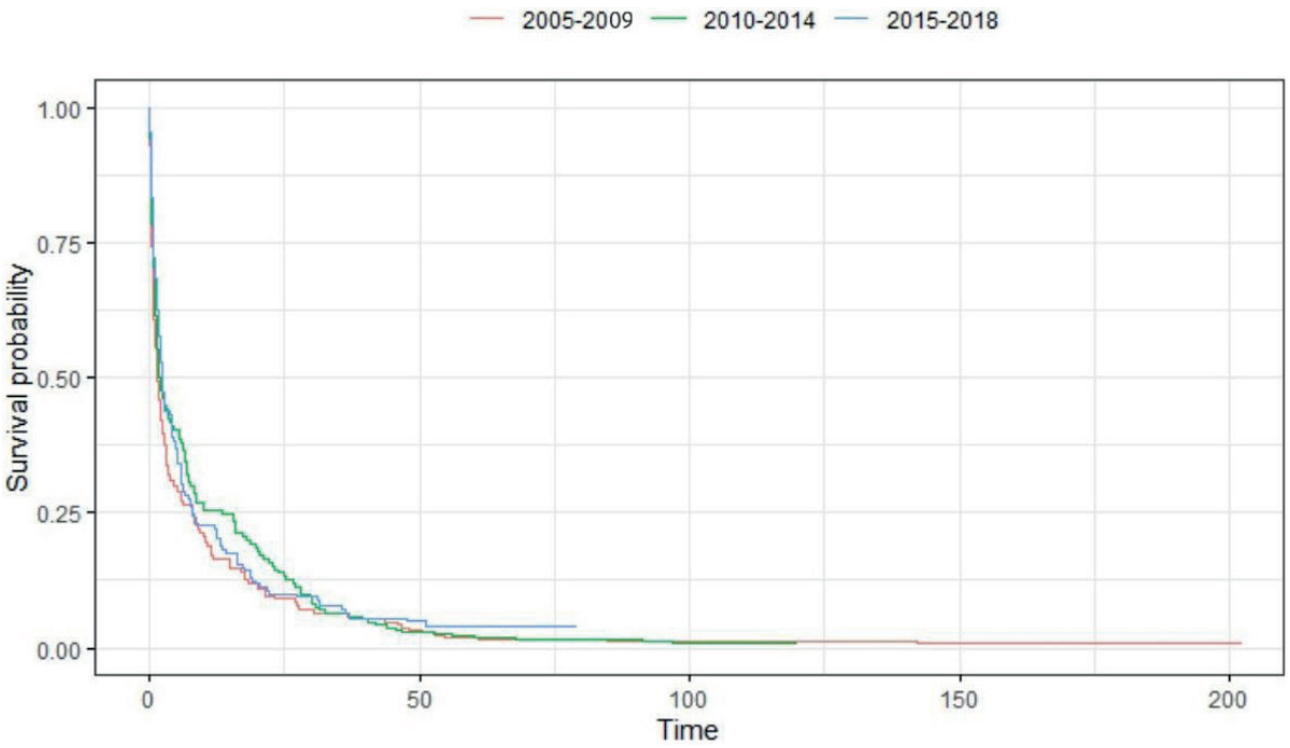

Figure 2. Kaplan-Meier analysis of survival by five-year periods

study appear to be in accordance with previous research, with the exception that gastrointestinal malignancies rank third. Analyses of 5-year intervals revealed a rise in the incidence of lung cancer, a decrease in breast cancer, and no change in the other malignancies. This finding may be related to the established breast cancer screening program. Indeed, Bleyer et al. have shown that screening with mammography contributes to early detection and has reduced the diagnosis of advanced breast cancer over the past three decades [18].

Extensive research has been conducted on the factors associated with the prognosis of MPE. First, the primary tumor site constitutes an independent risk factor for survival. While chemotherapy-sensitive malignancies, including breast cancer, and hematologic malignancies have a more favorable prognosis, solid tumors like lung, GIS, urologic cancers, and sarcomas are associated with a shorter life time [19-21]. In our study, GIS cancers with MPE were associated with a lower survival rate than lung cancer with MPE. Contrary to the literature, hematological malignancies with MPE were also associated with a slightly shorter survival compared to lung cancers with MPE. This may be due to the different grades of diseases included in our study and previous studies.

Other predictors of mortality were sought in the clinical state and laboratory results of individuals. Performance, age, and blood and pleural fluid test results have all been associated with mortality [2,19,20,22]. Being elder and having low serum protein levels were found to be associated with decreased life expectancy in our study. These parameters may be associated with the performance status of the patient rather than the tumor's behavior. In fact, the scores generated to predict survival in MPE utilize not only the laboratory values induced by the tumor but also the patient's performance [19]. Although LENT [19] and PROMISE [23] scores have been reported to be useful in predicting survival, doubt exists due to their limited clinical use and lack of validation in different studies. Due to the reciprocal impact of laboratory data and characteristics such as general health, comorbidities, and nutritional status on each other, it appears difficult to determine which is the main cause and to develop a simple survival prediction model.

In their 1966 article, Ariel et al. stated that while the average life expectancy for colon cancer and MPEs of unknown primary is 3 to 4 months, patients with breast, ovarian cancers and lymphoma have an improved prognosis [24]. Similarly, in the 1970s, the average MPE survival rate was about 16 months

for breast and mesothelioma malignancies and 6 months for lung and other solid cancers [25,26]. Despite the fact that new treatment methods for many cancers have resulted in longer survival in recent years, it is difficult to state that significant progress has been made in the treatment of MPE. Although it varies depending on the primary tumor site, with the best prognosis for ovarian tumors and the worst prognosis for the lungs, the average survival time remains between 3 and 12 months [2,27]. We also found no change in the mean lifespan after diagnosis across the 14-year research period. When prognostic factors are also considered, it becomes apparent that the development of MPE is an indicator of the progression of cancer from a local to a systemic disease, regardless of the primary site, and that it impairs the overall health status.

Our study's strengths include a significant number of patients over an extended period of time. In addition, describing the primary tumor's site in great detail and analyzing the change in mortality over time adds value to this study. Important limitations include the retrospective design, the inability to access the data of some patients due to deficiencies in the death notification system, and the absence of performance score and symptom data.

MPE remains associated with a poor prognosis despite advances in diagnostic procedures and treatment modalities. Indicators of a poor prognosis in MPE are closely associated with the primary tumor, clinical features, and laboratory findings. Unfortunately, the intended increase in MPE's average survival has not been realized. Hopefully, further research and progress in the management of MPE will contribute to better survival in the future.

Author contribution

Study conception and design: OK, and ZTS; data collection: OK, and FT; analysis and interpretation of results: OK, SÖ, and EÖ; draft manuscript preparation: OK, SÖ, FT and ZTS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (GO 18/883, 25.09.2018).

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Conflict of interest

The authors declare that there is no conflict of interest.

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