Original Article

Evaluation of treatment results and access to health support of malignant pleural mesothelioma patients in Cappadocia

Ipek Pinar Aral

Clinic of Radiation Oncolog, Nevsehir State Hospital, Nevsehir, Turkey

Abstract

Aim: Malignant Pleural Mesothelioma (MPM) is frequently observed due to erionite in Cappadocia. In this study, patients who live in Cappadocia region and were treated in Nevsehir State Hospital were evaluated.

Material Method: In this study, the data of 22 patients admitted to Nevşehir State Hospital and diagnosed with MPM between 15.7.2009-27.08.19 were evaluated retrospectively. The patients' overall survival (OS), progression-free survival (PFS) and access to health support were examined.

Results: The median follow-up period was 26 (range 1-153) months. The median age of the patients at the time of diagnosis was 65 years (range 36-86). Only 2 (9.1%) patients were localized / operable at the time of diagnosis; three patients (13.6%) were metastatic and 17 (77.3%) were in-operable. The female / male ratio of our patients was 1/1. The 3 patients (13.6%) were diagnosed at Nevşehir State Hospital, and 19 patients (86.4%) were diagnosed outside the Cappadocia. During the follow-up period, 19 patients (86.4%) deceased and 3 patients (13.6%) were alive. The median OS of the patients was 19 (range 1-133) months. The relapse was observed in 19 patients (86.4%). The median PFS value is 10 (range 1-126) months.

Conclusion: There is not enough infrastructure in Cappadocia in terms of diagnosis and treatment of MPM. The people of Cappadocia need to be supported in terms of access to MPM treatment. The OS of MPM has not improved significantly over the past 40 years.

Keywords: Cappadocia; malignant mesothelioma; malignant pleural mesothelioma

INTRODUCTION

Malignant Pleural Mesothelioma (MPM) is a rare malignancy that originates from mesothelial cells. Although most cases occur in pleura, it may also develop in peritoneum, pericardium, and tunica vaginalis (1). Since no early stage symptom is seen, patients are usually diagnosed at an advanced stage (2). Overall survival (OS) for untreated patients is foreseen around 12 months, and for treated patients, regardless of the treatment, is around 18 months (3). Despite improvements in chemotherapy, radiotherapy and surgery, no significant survival increase was observed in mesothelioma in the last 30 years (2).

The most important risk factor is asbestos exposure. Asbestos is a silicate mineral that is present in nature (4). Erionite is one of the most aggressive subtypes of asbestos. Mesothelioma is frequently observed due to the erionite found in zeolite stones that are used in the construction of houses in Cappadocia (3). In addition, oncogenic SV-40 virus and genetic mutations such as p53, p14, p16 and NF2-MERLIN have been implicated in the development of the disease (4). The latent period from exposure to the development of mesothelioma is approximately 20-40 years (5,6).

The single modality (chemotherapy, radiotherapy or surgery) does not have sufficient effect on the survival of patients. Therefore, multimodal treatment is recommended for patients in good condition. However, aggressive treatment approaches are questioned as they cause serious morbidity (7). Combined platinum + pemetrexed therapy is preferred in the first step. However, the effect of these medicines is usually short-term. New systemic treatment approaches are needed. For this purpose, agents such as bevacizumab are used in patients who relapse after chemotherapy and have promising results (8).

In this study, patients who live in endemic Cappadocia region and are treated in Nevsehir State Hospital were evaluated. The patients' overall survival, progression-free survival (PFS) and access to health services were examined.

MATERIAL and METHODS

In this study, the data of 22 patients admitted to Nevşehir State Hospital, diagnosed with malignant pleural mesothelioma between 15.7.2009-27.08.19 were evaluated retrospectively.

Patient interview information, patient files and electronic system data were used for the study. Patients' demographic status, date of diagnosis, details of treatment, responses to the treatment and their recent status were noted. The study was conducted in accordance with the Helsinki Declaration, which was approved by the Ethics Committee of Nevsehir Public Hospital in September 2019 (File number: 26171210-020).

The primary endpoint is overall survey and progression free survey. The date of diagnosis was used as the starting date for the overall survey and PFS. As the endpoint for OS; the last follow-up date for the living patients, the exitus date for the ex. As the endpoint for PFS; the first event date for recurrence and distant metastasis is the last follow-up date for patients without recurrence. The study included adult patients with malignant mesothelioma who had pathological evidence and whose information was fully accessible. Patients with missing file and follow-up information were excluded.

Statistical analyses

Data were calculated using SPSS 24. escriptive statistics for continuous (quantitative) variables; mean, standard deviation, minimum and maximum values are expressed, while categorical variables are expressed as number (n) and ratio (%). The suitability of the variables to the normal distribution was evaluated by visual and analysis methods and nonparametric tests were used because they did not fit the normal distribution. Chi-square and Fisher's exact tests were used to determine the demographic characteristics of the patients. Spierman's rank correlation test was used for univariate correlation analysis. Mann-Whitney U test was used for independent statistical analysis of two groups and Kruskall Wallis test was used for 3 and more independent groups. Kaplan Meirer was used for univariate survey analysis and log rank test was used. In multivariate analyzes, Cox regression test was used. Statistically significant limit was accepted as less than 0.05.

RESULTS

The median follow-up period was 26 (range 1-153) months. The median age of the patients at the time of diagnosis was 65 years (range 36-86). Only 2 (9.1%) patients were localized / operable at the time of diagnosis; Three patients (13.6%) were metastatic and 17 (77.3%) were inoperable. Of the two patients evaluated as localized –operable, one was operated and the other rejected the operation. The female / male ratio of our patients was 1/1; 11 patients (50%) were female and 11 patients (50%) were male. The 12 patients (54.5%) localized in the right lung and 10 patients (45.5%) localized in the left lung. Only 3 patients

(13.6%) were diagnosed at Nevsehir State Hospital, and 19 patients (86.4%) were diagnosed outside Cappadocia. Twenty (90.9%) of the patients received CT and 2 patients (9.1%) did not undergo CT due to their general condition and comorbid disease. Cisplatin + pemetrexed (68.2%) were administered to 15 patients and carboplatin + pemetrexed were applied to 5 patients (22.8%). When the first-line CT response was evaluated, no involvement was observed in PET-CT in 8 patients. Complete response was seen in 8 patients (36.4%), partial response in 6 patients (27.3%), stable response was seen in 2 patients (9.1%) and progression in 4 patients (18.2%). Two patients underwent pemetrexed maintenance therapy after the first step. After relapse, 16 patients (72.7%) underwent second-line CT. As second line, 5 (22.7%) patients had pemetrexed-based regimens and gemcitabine-based regimens were administered to 11 (68.7%) patients. The demographic data and treatment details of the patients are summarized in Table 1.

Table 1. Patient Demographics		
Stage	localized / operable	2 (9.1%)
	Inoperable	17 (77.3%)
	Metastatic	3(13.6%)
Gender	Female	11(50%)
	Male	11(50%)
Site	Right	12 (54.5%)
	Left	10 (45.5%)
First –Line CT	Cisplatin + pemetrexed	15 (68.2%)
	Carboplatin + pemetrexed	5 (22.7%).
	No CT	2(9.1%)
First-line CT response	Complete Response	8 (36.4%)
	Parsiel Response	6 (27.3%)
	Stable	2(9.1%)
	Progression	4 (%18.2)
Second-line CT	Pemetrexed-based	5 (31.2%)
	Gemcitabine-based	11 (68.7%)
Last Status	Ex	19 (86.4%)
	Alive	3 (13.6%)
CT: Chemotherapy		

During the follow-up period, 19 patients (86.4%) died and 3 patients (13.6%) survived. The median OS of the patients was 19 (range 1-133) months (Figure 1). The 1-year OS value is 68.2%; the 2-year OS value is 47.1%. The relapse was observed in 19 patients (86.4%). The median PFS value is 10 (range 1-126) months (Figure 2). The 1-year PFS value is 36.4%; the 2-year PFS value is 23.5%.
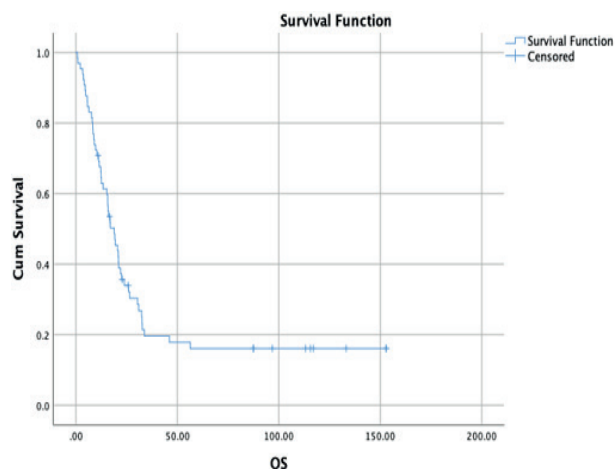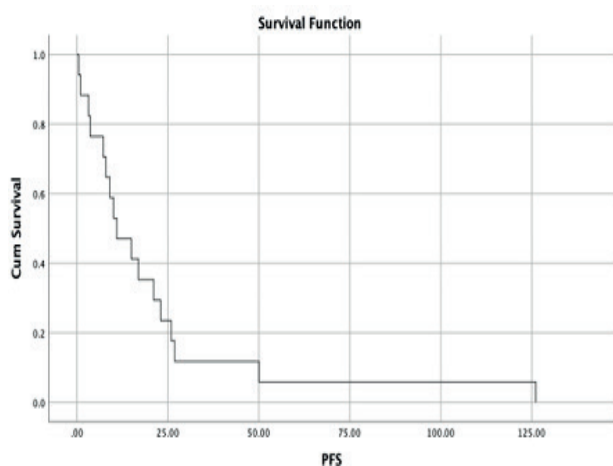
Figure 1. OS evaluation of patients

Figure 2. PFS evaluation of patients

Considering the factors affecting OS, the stage (p=0.38), the gender of patient (p=0.65), the localization of the disease on the right or left (p=0.23) side, whether the protocol applied in the first step is cisplatin + pemetrexed or carboplatin + pemetrexed (p=0.40) Secondary CT protocols (p=0.11) and whether or not receiving RT (p=0.97) did not significantly affect OS.
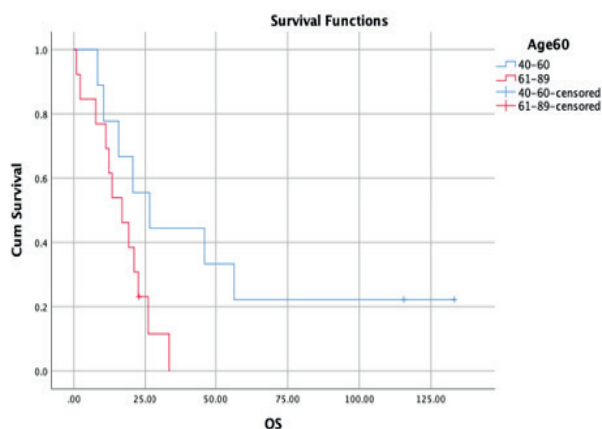

Figure 3. Being over 60 at the time of diagnosis adversely affected OS

The relationship between OS and age at the time of diagnosis was significant (p=0.048). The median OS value of 9 patients under the age of 60 at the time of diagnosis was 26 (range 8-133); the median OS of 13 patients over 60 years was 16 (range 1-33). Increased patient age at the time of diagnosis significantly reduced overall survival (Figure 3).

The first line CT response was significantly affected OS (p=0.001). The median OS of the patients with CR response in first-line was 41 (range 10-133) months. PR was median 10 (range 2-115) months, stable was 14 (range 9-16) months, and progression was median 8 (range 1-16) months (Figure 4).
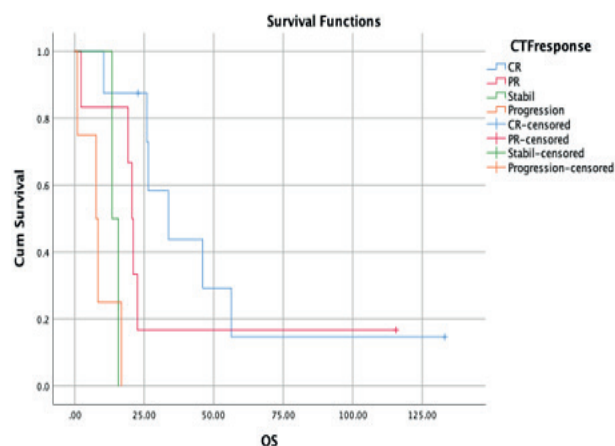

Figure 4. Evaluation of the relationship between first-line CT response and OS

When the factors affecting PFS were evaluated, the stage (p=0.44), the gender of patient (p=0.50), the localization of the disease on the right or left (p=0.33), whether the first-line protocol was cisplatin + pemetrexed or carboplatin + pemetrexed (p=0.30), there was no significant effect. The age of the patients at the time of diagnosis had a significant effect on OS, but there was no significant effect on PFS (p=0.30).

DISCUSSION

In current study, the median age of the patients at the time of diagnosis was 65 years (range 36-86). The female / male ratio of our patients was 1/1. Only 3 patients (13.6%) were diagnosed at Nevşehir state hospital, and 19 patients (86.4%) were diagnosed outside Cappadocia. The median OS of the patients was 19 (range 1-133) months. OS was only affected significantly by age at diagnosis and first −line CT response. The median PFS value is 10 (range 1-126) months. Among the variables we examined, there is no parameter that has a significant effect on PFS.

Malignant mesothelioma due to occupational exposure has been reported more frequently in men than in women (2,9). However, the rate of male and female was found to be similar in studies conducted in Cappadocia (3). Because mesothelioma is caused by the stones that are being used in the construction of houses. In this study, the ratio of male to female was 1/1, similar to previous assessments

in Cappadocia. In addition, survival rates in women have been reported to be higher in the literature (6,9). However, in our study, gender had no significant effect on the OS and PFS.

In patients with mesothelioma, advanced age is a negative prognostic factor (10,11). In accordance with the literature, in our study group, overall survival decreased in patients with age at the time of diagnosis. But there was no significant relationship between age and PFS.

Maximum surgical cytoreduction is recommended in patients diagnosed in early stage and those who are in good condition (12-14). Only two of 22 patients admitted to our hospital were found to be eligible for surgery. Decortication was performed in one patient and the other patient refused surgery.

In newly diagnosed mesothelioma patients, both survival and quality of life are improved with chemotherapy. Pemetrexed and platinum are recommended as first-line CT in patients with good performance (ECOG ≤2) (12,15,16). Carboplatin is recommended instead of cisplatin in patients who are thought to be unable to tolerate cisplatin. Carboplatin is generally better tolerated. In current analysis, Cisplatin + pemetrexed (68.2%) were administered to 15 patients as first-line CT and carbo pemetrexed to others. The addition of carboplatin or cisplatin to pemetrexed had no significant effect on the OS and PFS.

Second-line CT has limited effect in patients with mesothelioma. There is no standard second-line chemotherapy protocol (3,16). For the second line, CT may be considered pemetrexed again in patients that receiving pemetrexed in first- line CT and in remission for more than 6 months (12). Additionally, vinorelbine and gemcitabine are often preferred in the second line (17,18). As second line, 5 (22.7%) patients whose median PFS is 7.2 months had pemetrexed- based regimens. The eleven patients whose median PFS is 5.3 months had gemcitabine-based regimens.

In patients who are in poor general condition, single agent CT (ECOG 2) or palliative support (ECOG 3-4) may be considered (12). In our study, two patients did not undergo CT due to general condition disorder and comorbidity. Only supportive treatment was given. Their OS values are 3 and 4 months.

Prophylactic RT has been tried to prevent spread of disease in the surgical tract after biopsy. For this purpose 21 Gy/3 frx or 20 Gy / 4 frx could be applied. Today, prophylactic RT is not applied frequently. However, fistula tract is included in the adjuvant RT field (19,20). In this study, it was not possible to evaluate whether the patients received prophylactic RT or not. There is no RT center in Cappadocia, patients don't have an easy access to radiotherapy. The patients are admitted to the hospitals outside the province for RT. The patient files and electronic system did not have sufficient data for prophylactic RT.

Palliaive RT is an effective treatment in symptomatic patients (8 Gy 3 one fraction, 4 Gy 3 five fractions, or 3 Gy 3 10 fractions) (21-23). In our study, 22 patients received RT for palliative purposes. Unfortunately, in this patient group, detailed data about TR dose and irradiated fields information could not be obtained. Patients received radiotherapy in different cities according to their social support. In this region where mesothelioma is endemic, the presence of RT center will be beneficial in terms of access to the treatment and inclusion of the results to the literature.

Only 3 patients (13.6%) were diagnosed at Nevşehir State Hospital, and 19 patients (86.4%) were diagnosed outside Cappadocia. As is seen, there is not enough infrastructure and awareness for the diagnosis of MPM. There are eight State Hospitals in the Cappadoccia region and 7 of those hospitals do not have oncology service. Only a medical oncologist worked at the Nevşehir State Hospital for a period of 18 months. The majority of the patients in this study received treatment at that time. In addition, there is no RT center in the region. MPM patients in Cappadocia do not have sufficient support in terms of diagnosis, surgery, chemotherapy and radiotherapy.

The study has some important limitations. First of all, the number of patients is limited and retrospective. Smoking information of the patients is not in the electronic system and file data. The pathology reports of most patients lacked subtypes (sarcomatoid, epithelioid, etc.) and their effect on OS and PFS could not be studied. The patients included in the study reside in the endemic Cappadocia region. However, it is not known how many patients lived in Tuzköy-Sarıhıdır-Karain or how many years they lived there. Response assessment information was not available for all patients receiving second-line CT. Furthermore, patients receiving RT do not have dose-volume histogram information.

CONCLUSION

Overall survival of MPM didn't improve significantly over the past 40 years. There is not enough infrastructure in terms of diagnosis and treatment of MPM in Cappadocia region. The habitants of Cappadocia need to be supported in terms of access to MPM treatment.

REFERENCES

1. Hiriart E, Deepe R, Wessels A. Mesothelium and Malignant Mesothelioma. J Dev Biol 2019;7:7.

2. Taioli E, Wolf AS, Camocho- Rivera M, et al. Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. PloS one 2015;10:0145039.

3. Petrelli F, Ardito R, Conti B, et al. A systematic review and meta-analysis of second-line therapies for treatment of mesothelioma. Respiratory Med 2018;141:72-80.

4. Bibby AC, Tsim S, Kanellakis N, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016;25:472-86.

5. Bibby AC, Tsim S, Kanellakis N , et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment Eur Respir Rev 2016;25:472-86.

6. Taioli E, Wolf AS, Camacho-Rivera M, et al. Women with malignant pleural mesothelioma have a threefold better survival rate than men. Ann Thorac Surg 2014;98:1020-4.

7. Ceresoli GL, Gridelli C, Santoro A. Multidisciplinary Treatment of Malignant Pleural Mesothelioma. The Oncologist 2007;12:850-63.

8. Scherpereel A, Wallyn F, Albelda SM, Munck C. Novel therapies for malignant pleural mesothelioma. Lancet 2018;19:161-72

9. Tsao AS, Lindwasswer O, Adjei AA, et al. Current and Future Managament of Malignant Mesothelioma: A consensus Report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer and Mesothelioma Applied Research Foundation. J Thorasic Oncology 2018;13:1655-7.

10. Amin W, Linkov F, Landsittel DP. Factors influencing malignant mesothelioma survival: a retrospective review of the National Mesothelioma Virtual Bank Cohort. F1000 Res 2018;7:1184.

11. Koyuncu A, Koksal D, Ozmen O, et al. Prognostic factors in malignant pleural mesothelioma: a retrospective study of 60 Turkish patients. J Cancer Res Ther 2015; 11:216-22.

12. Kindler HL, Ismaila N, Armato SG, et al.Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Practice Guidline. J Clinical Oncology 2018; 13:1343-73.

13. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. J Thorac Oncol 2007;2:957-65.

14. Rusch VW, Piantadosi S, Holmes EC. The role of extrapleural pneumonectomy in malignant pleural mesothelioma. A Lung Cancer Study Group trial. J Thorac Cardiovasc Surg 1991;102:1-9.

15. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21:2636-44.

16. Nowak AK. Chemotherapy for Malignant Pleural Mesothelioma: a Review of Current Management and a Look to the Future. Ann Cardiothorac Surg 2012;1:508-15.

17. Zauderer MG, Kass SL, Woo K, et al. Vinor- elbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-4.

18. Zucali PA, Perrino M, Lorenzi E, et al. Vinor- elbine in pemetrexed-pretreated patients with ma- lignant pleural mesothelioma. Lung Cancer 2014;84:265-70.

19. Nagendran M, Pallis A, Patel K, et al. Should all patients who have mesothelioma diagnosed by video-assisted thoracoscopic surgery have their intervention sites irradiated? nteract Cardiovasc Thorac Surg 2011;13:66-9.

20. Lee C, Bayman N, Swindell R, et al. Pro- phylactic radiotherapy to intervention sites in me- sothelioma: A systematic review and survey of UK practice. Lung Cancer 2009;66:150-6.

21. Macleod N, Price A, O'Rourke N, et al. Ra- diotherapy for the treatment of pain in malignant pleural mesothelioma: A systematic review. Lung Cancer 2014;83:133-8.

22. MacLeod N, Chalmers A, O'Rourke N, et al. Is radiotherapy useful for treating pain in mesothelioma?: A phase II trial. J Thorac Oncol 2015;10:944-50.

23. MacLeod N, Kelly C, Stobo J, et al. Pain in malignant pleural mesothelioma: A prospective characterization study. Pain Med 2016;17:2119-26.