

Factors Affecting Mortality at Home and Hospital in Oncology Patients and the Effect of Age

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ABSTRACT Objective: Several factors assessing cancer mortality and impacting the choice of place of death for terminally ill patients have been previously documented. We examined the relationships between several oncological factors, including age, on cancer mortality and the choice of place of death. **Material and Methods:** All patient data were collected retrospectively from hospital computer records and medical chart reviews. A total of 2,183 patients admitted to our hospital over 6 years (September 2013-December 2019) were included. **Results:** A total of 2,183 patients were analyzed, of which 58.5% (n=1,277) of patients died. More deaths occurred in the hospital than at home (n=1,032 vs. n=245). The mean age of patients who died at home was more than those who died in the hospital (mean ages: 68.4±12.5 vs. 63.5±12.5; median ages: 69, range 24-100 vs. 63, range 19-97). The hospital mortality rate of patients <65 years old was statistically higher than patients ≥65 years old. **Conclusion:** We found that a second primary cancer, metastasis, diagnosis from the primary mass, certain cancer diagnoses (such as lungs, stomach, and brain cancers), locally advanced and metastatic stage cancers, certain histological types, late diagnosis (the first application to branches such as chest diseases, emergency, neurosurgery) negatively affected mortality. In addition, we determined that metastatic, locally advanced stage. and patients aged <65 years of age died more frequently in the hospital.

Keywords: Cancer mortality; home care; hospital palliative supportive treatment; home health services

Global Cancer Statistics 2022: The trend projection analysis published in 2023 stated that more than nineteen million new cancer cases were diagnosed in 2020 and approximately ten million deaths annually are predicted to be caused by cancer.¹ Thus, patients facing death in the terminal period have to select the place of death. The majority of patients with cancer prefer home death due to effective programs to keep these patients at home, although this often is not possible.²⁻⁴ Patients with terminal cancer do not have the same chance of dying at home because of certain inequalities, including clinical diseases caused by cancer and individual factors,

demographic and personal variables, and the preservation of the patient's individuality.⁵ Reports have suggested that patients with terminal illnesses more often die at home.⁶

Several recent studies have reported a global surge in cancer occurrence and deaths.⁷ Efforts are being made to strengthen the basic information on life statistics and registration systems in countries with low middle income.⁸ However, programming errors in using these systems and inappropriate death records limit the reliability of the data.⁷ In the absence of data or delays, cancer mortality estimates are usually derived from the information on cancer occur-

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rence (population or clinical registries) or mortality rates in nearby countries with more accessible data.^{7,9} Cancer mortality has been widely accepted as the most crucial measure of progression against cancer.¹⁰ Our study, a small summary of trends in cancer mortality rates based on local data, will constitute a limited value in assessing the fight against cancer. Information on cancer mortality from our country should be considered as a small sample. In our study, local cancer trends played an illuminating role in cancer mortality risk factors, the role of diagnosis, and access to treatment. In addition, our study results could lead to the development of novel treatment strategies by identifying the factors affecting cancer mortality and preferences for the place of death.

MATERIAL AND METHODS

A total of 2,183 patients who were admitted to our hospital over 6 years (September 2013-December 2019) were included. The patient data were obtained from retrospective medical chart reviews and computerized records. Age, gender, complaints about cancer and polyclinic and the date they applied, diagnosis and diagnosis date, stage, places, and dates of death were recorded. All patients were classified as follows: T: tumor stages 1-4, N: nodal spread, N0 and N+. M: the presence of distant metastases, R: recurrence. Then, those with T1 or T2, N0, and M0 were classified as “early stage” and those with T3 or T4, N+, and M0 were classified as “locally advanced stage.”

Patients' names and all identity information were encrypted. The data were analyzed anonymously. The study was conducted retrospectively with the permission of our hospital archive search and the approval of the Recep Tayyip Erdoğan University Ethics Committee (date: March 18, 2020, no: 40465587-050.01.04-52). It was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice.

STATISTICAL ANALYSIS

SPSS (version 22 for Windows, SPSS Inc., Chicago, IL, USA) was used to perform statistical evaluation. Data were analyzed using descriptive methods and their distribution using the Kolmogorov-Smirnov

test. The Mann-Whitney *U* test was used to contrast between groups for quantitative data. Chi-square analysis was used to determine the relationship between qualitative data. Bonferroni correction was used for all other analyses. The statistical significance level was set at $p < 0.01$ and $p < 0.05$.

RESULTS

The mean age of participants was 62.7 ± 13.2 years (17-100), 46.6% ($n=1,018$) were ≥ 65 years of age, and 53.4% ($n=1,164$) were < 65 . In addition, 65.5% ($n=1,430$) of the patients were male, and 34.5% ($n=752$) were female. Mortality and survival rates, sociodemographic and cancer information of patients are shown in Table 1.

The mean age of patients who died was more than those who were alive (mean ages: 64.5 ± 12.7 vs. 60.3 ± 13.6). Of the participants, 38.2% ($n=833$) were metastatic, 34.1% ($n=744$) were locally advanced, 25.2% ($n=551$) were early, and 2.5% ($n=55$) were recurrent stage. Although 94% ($n=714$) of the participants had distant metastases, 6.1% ($n=134$) had single metastases, and 6.2% ($n=1,335$) had no metastases. Patients who died at home were older than those who died in hospitals [mean ages: 68.4 ± 12.5 vs. 63.5 ± 12.5 , and median age: 69 (range: 24-100) vs. 63 (range 19-97)]. Next, 58.5% of the patients ($n=1,277$) died. More deaths occurred in hospitals than at home ($n=1,032$ vs. $n=245$), regardless of the age group (Figure 1). The hospital mortality rate of patients < 65 years old was statistically higher than patients ≥ 65 years old.

The mortality rate was higher in the group aged ≥ 65 years compared with the group aged < 65 years (*). Similarly, the mortality rate was higher in male patients than in female patients (*). The association between death and cancer stage was statistically significant (*). The number of deaths was higher in patients with metastatic and locally advanced than those with early-stage cancer (*). A statistically significant association of mortality with distant metastases was noted (*). The mortality rate was higher in metastases (common, multiple, or single) compared to those without (*). Those who were in the early stages had a higher survival rate than others. These differences

TABLE 1: Sociodemographic and tumor characteristics of the patients (n=2,183).

Variables		Total (n=2,183)* n (%)	Died (n=1,277)** n (%)	Living (n=906)** n (%)	Died <65 years (n=1,164)** n (%) 53.4%	Living ≥65 years (n=1,018)** n (%) 46.6%
Age	Year	62.7±13.2	64.5±12.7	60.3±13.6		
	<i>p value</i>		<0.001			
Age group	<65 years	1,165 (53.4)	632 (54.2)	533 (45.8)		
	≥65 years	1,018 (46.6)	645 (63.4)	373 (41.2)		
	<i>p value</i>		<0.001			
Gender	Male	1,430 (65.5)	970 (67.8)	460 (32.2)	678 (47.4)	752 (52.6)
	Female	753 (34.5)	307 (40.8)	446 (59.2)	486 (64.6)	266 (35.4)
	<i>p value</i>		<0.001		<0.001	
Stage	Early	552 (25.3)	149 (27.0)	403 (73.0)	284 (51.4)	268 (48.6)
	LA	743 (34.0)	382 (51.4)	361 (48.6)	411 (55.3)	332 (44.7)
	Metastatic	833 (38.2)	707 (84.9)	126 (15.1)	440 (52.9)	392 (47.1)
	Relapse	55 (2.5)	39 (70.9)	16 (29.1)	29 (52.7)	26 (47.3)
	<i>p value</i>		<0.001		0.56	
Metastasis	No	1,336 (61.2)	557 (41.7)	779 (58.3)	723 (54.1)	613 (45.9)
	Only	133 (6.1)	103 (77.4)	30 (22.6)	69 (51.9)	64 (48.1)
	Widespread	714 (32.7)	617 (86.4)	97 (13.6)	372 (52.2)	341 (47.8)
	<i>p value</i>		<0.001		0.66	

*Column percentage, **row percentage, LA: Local Advanced.

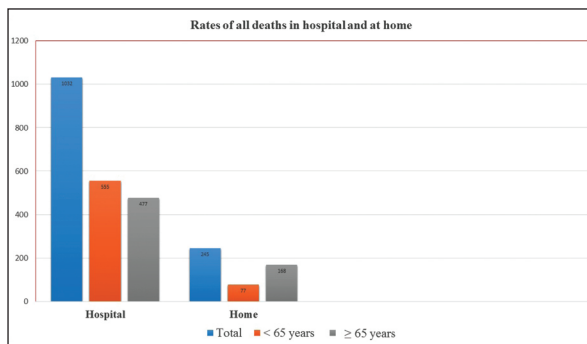


FIGURE 1: Rates of all deaths in hospital and at home. Graphical representation of deaths in the hospital and at home: comparison of <65 and ≥65 age groups with all mortalities.

were not significant when compared in patients aged <65 years and ≥65 years (* $p<0.01$).

Although 12.2% of patients <65 years old died at their homes, the figure was 26.0% for those aged ≥65 years ($p<0.001$). No statistical difference was noted between tumor characteristics and hospital or home mortality ($p=0.098$). Patients with metastatic disease, extensive metastases, and locally advanced disease had higher in-hospital mortality rates (Table 2).

The effect of cancer location on death in patients aged <65 years of age was statistically significant

($p=0.01$). Metastatic patients aged <65 years died more often in hospitals (Table 2). In the <65-year group, hospital deaths were most frequent during the summer, and home deaths were most frequent during the spring, whereas in the ≥65 groups, hospital deaths were most frequent during the summer, and home deaths were most frequent during the autumn.

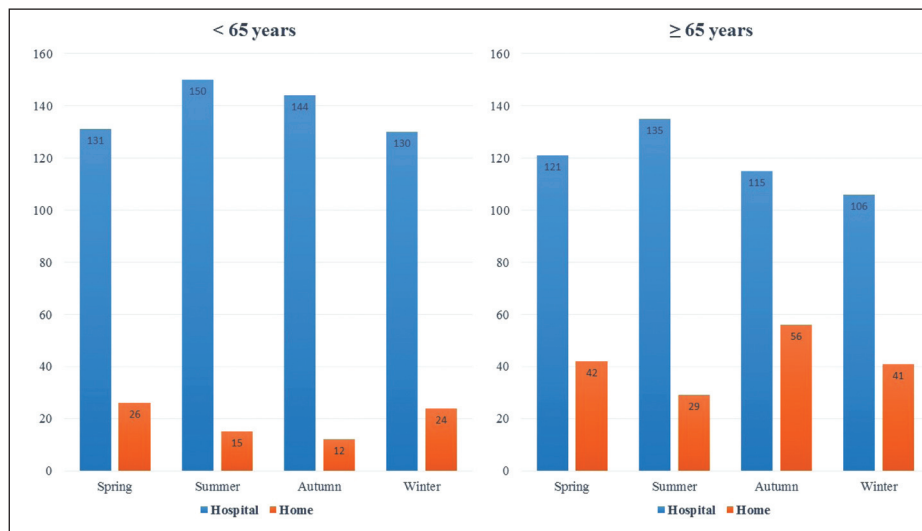
An evaluation of the place of deaths of patients according to the season revealed that in the <65 years group, home deaths occurred most frequently during spring (33.8%) and the least during autumn (15.6%). This rate was statistically significant compared to other seasons ($p=0.031$). Although no statistically significant difference was noted compared with other seasons, the highest number of hospital deaths occurred during summer (27%). Among the ≥65-year-old group, hospital deaths were the highest during summer (28.3%, $n=135$), and home deaths were during autumn (33.3%, $n=56$). The difference was significant ($p=0.017$) (Figure 2).

The primary site of the tumor was the diagnosis site in 94% ($n=2,052$), whereas it was the lymph nodes in 1.2% ($n=27$) and other locations in 4.8% ($n=104$). The place of diagnosis was statistically sig-

TABLE 2: Some sociodemographic data and health status of patients who died in the <65 and ≥65 groups (n=1,277).

Variables		Hospital (n=1,032)*	Home (n=245)*	<65 years (n=632)		≥65 years (n=645)	
		n (%)	n (%)	Hospital n (%)**	Home n (%)**	Hospital n (%)**	Home n (%)**
Deaths		1,032 (80.8)	245 (19.2)	555 (87.8)*	77 (12.2)*	477 (74.0)*	168 (26.0)*
Age (years)	Mean	63.5±12.5	68.4±12.5				
	Median	69 (24-100)	63 (19-97)				
	<i>p</i> value	<0.001		<0.001			
Gender	Male	782 (80.6)	188 (19.4)	425 (76.6)	60 (77.9)	357 (74.8)	128 (76.2)
	Female	250 (81.4)	57 (18.6)	130 (23.4)	17 (22.1)	120 (25.2)	40 (23.8)
	<i>p</i> value	0.75		0.79		0.72	
Cancer location	Lung	450 (83.0)	92 (17.0)	256 (46.1)	24 (31.2)	194 (40.7)	68 (40.5)
	GIS	197 (82.4)	42 (17.6)	109 (19.6)	14 (18.2)	88 (18.4)	28 (16.7)
	GUS	163 (79.5)	42 (20.5)	64 (11.5)	8 (10.4)	99 (20.8)	34 (20.2)
	Breast	68 (81.0)	16 (19.0)	48 (8.6)	10 (13.0)	20 (4.2)	6 (3.6)
	Others***	154 (74.4)	53 (25.6)	78 (14.1)	21 (27.3)	76 (15.9)	32 (19.0)
<i>p</i> value	0.098		0.01		0.89		
Stage	Early	105 (70.5)	44 (29.5)	42 (7.6)	8 (10.4)	63 (13.2)	36 (21.4)
	LA	308 (80.6)	74 (19.4)	158 (28.5)	22 (28.6)	150 (31.4)	52 (31.0)
	Metastatic	590 (83.5)	117 (16.5)	338 (60.9)	43 (55.8)	252 (52.8)	74 (44.0)
	Relapse	29 (74.4)	10 (25.6)	17 (3.1)	4 (5.2)	12 (2.5)	6 (3.6)
	<i>p</i> value	0.002		0.59		0.049	
Distal metastasis	No	432 (77.6)	125 (22.4)	215 (38.7)	34 (44.2)	217 (45.5)	91 (54.2)
	Only	79 (76.7)	24 (23.3)	46 (8.3)	8 (10.4)	33 (6.9)	16 (9.5)
	Multipl	521 (84.4)	96 (15.6)	294 (53.0)	35 (45.5)	227 (47.6)	61 (36.3)
	<i>p</i> value	0.006		0.45		0.037	

*Row percentage; **column percentage; ***Other: Head-neck, brain, skin, sarcoma, lymphoma. GI: Gastrointestinal system, GUS: Genitourinary system, LA: Locally advanced.

**FIGURE 2:** Comparison of places of death in accordance with months and seasons.

nificantly associated with deaths ($p=0.001$). The number of deaths was higher in patients diagnosed by biopsy than in living patients ($p=0.001$). The rela-

tionship between the location of diagnosis, stage, and distant metastasis parameters in living and deceased patients was similar in the <65 and ≥65 groups (Table 3).

Prolonged time to diagnosis was significantly associated with an increased mortality rate. Although 44.3% ($n=966$) of cases were diagnosed early, 55.7% ($n=1,217$) were diagnosed late. Those diagnosed within 3 months from the start of the first complaint about the disease were considered as diagnosed early, and those diagnosed in the later period were considered as diagnosed late. The number of deaths in the late diagnosis group was higher than in the living patients (40.9% vs. 60%, $p=0.001$) (Table 3).

Other parameters associated with mortality included the second primary, cancer stage, distant metastasis, and duration of diagnosis. A statistically significant association was detected between second primary cancer and mortality rate ($p=0.001$). A second primary cancer was found in only 7% of patients ($n=153$). The number of deaths was higher in those with a second primary cancer than in those who lived (67.3% vs. 32.7%).

A significant relationship was detected between cancer location and mortality rate in all patients ($p=0.001$). Deaths were more common in those with lung, brain, stomach, and other cancers than those with other types of cancer ($p=0.001$). In addition, the rate of those who died from breast cancer, prostate

cancer, and lymphoma groups was lower than those living ($p=0.001$).

A statistically significant association was noted between mortality rate and first outpatient admission ($p=0.001$). More deaths occurred among those who first applied for chest diseases, emergency, and neurosurgery than in the living ($p=0.001$). For first admissions to ear, nose, throat, and general surgery departments, the rate of death was lower than the rate of survival ($p=0.001$). Finally, a statistically significant association was detected among mortality rates by histological type ($p=0.001$). The rate of deaths from epidermoid cancer (EC), small cell lung cancer (SCLC), and glioblastoma multiforme (GBM) were higher than those who lived ($p=0.001$). In contrast, the proportion of survivors was higher than the proportion of deaths in breast cancer [invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS)], gynecological tumor, and lymphomas ($p=0.001$).

DISCUSSION

The annual mortality rate of cancer has been increasing worldwide, and the majority of these patients are in the advanced stage.¹¹ The existing treatments are expensive and intrusive. Although home deaths have

TABLE 3: Other parameters associated with mortality.

		Total Patient no (%)		<65 years Patient no (%)		≥65 years Patient no (%)	
		Death	Living	Death	Living	Death	Living
Diagnosed place	Primary tumor	1,170 (57)	882 (43)	564 (52.2)	516 (47.8)	606 (62.3)	366 (37.7)
	Lymph node	17 (63)	10 (37)	13 (65.0)	7 (35.0)	4 (57.1)	3 (42.9)
	Other***	90 (86.5)	14 (13.5)	54 (84.4)	10 (15.6)	36 (90.0)	4 (10.0)
	<i>p value</i>	0.001**		0.001**		0.002**	
Stage	M	707 (84.9)	126 (15.1)	380 (86.4)	60 (13.6)	327 (83.2)	66 (16.8)
	LA	383 (51.5)	361 (48.5)	180 (43.8)	231 (56.2)	202 (60.8)	130 (39.2)
	Early	148 (26.9)	403 (73.1)	50 (17.6)	234 (82.4)	99 (36.9)	169 (63.1)
	Relapse	39 (70.9)	16 (29.1)	21 (72.4)	8 (27.6)	18 (69.2)	8 (30.8)
	<i>p value</i>	0.001**		0.001**		0.001**	
Distant M	Multiple	617 (86.4)	97 (13.6)	327 (88.1)	44 (11.9)	289 (84.5)	53 (15.5)
	Only	104 (77.6)	30 (22.4)	54 (78.3)	15 (21.7)	50 (76.9)	15 (23.1)
	No	556 (41.6)	779 (58.4)	250 (34.5)	474 (65.5)	307 (50.2)	305 (49.8)
	<i>p value</i>	0.001**		0.001**		0.001**	
Diagnosis	Early	523 (40.9)	443 (48.9)				
	Late	754 (60.1)	463 (51.1)				
	<i>p value</i>	0.001**					

Chi-Square Test *row percentage ** $p<0.01$ ***:brain, bone, liver, etc. M: metastasis, LA: locally advanced.

long been the dominant choice of cancer patients, the availability of supportive treatment units in hospitals and services comprising a comprehensive nursing home program could solve this problem.¹²⁻¹⁵ From a cost perspective, different approaches with varying costs are available to provide palliative care to terminally ill patients. However, palliative care at home is cost-advantageous compared to alternative care models.¹⁵

A survey study, in which 59 patients indicated their last place of care for death, revealed that the preferences were 58% at home (if conditions were right), 20% in a hospital, 20% in a nursing home, and 2% elsewhere. Among patients who chose to die in a hospital, 69% died in the hospital, and almost all (94%) who chose to die at home died at home. Their actual places of death and their preferred places before dying were found to slightly vary. Although the change in the preference was insignificant, it tended to be hospital or hospice.¹⁶ In a study of 103,097 oncology patients who died between 2000 and 2004, the prevalence of end-of-life hospice care increased from 5.5% to 15.4%.¹¹ In the present study, the mortality rate in hospitals was higher than that at home, regardless of gender. Patients aged <65 years were also more likely to die in a hospital.

Hospital death rates were higher than home death rates, regardless of gender. In addition, patients aged <65 years were more likely to die in a hospital.

The high number of deaths of cancer patients in hospitals The availability of palliative support services in hospitals explains. Similarly, a recently published study investigating the effect of weekend and summer vacations on mortality in oncology patients demonstrated that the mortality rate of all patients included in the study was statistically significantly higher than the mortality rate at home.¹⁷ This was related to the palliative care service provided to terminally ill cancer patients in the third-level hospital.¹⁷ Patients aged <65 years die more in hospital than those aged ≥65 years because younger patients could need more professional help. Patients in the terminal period could have an increased fear of death. Fear of death is known to be a common feature among palliative care patients. Reducing the fear of death in

dying patients is one of the key goals of palliative care. Older patients have a more moderate approach to death than younger adults.^{18,19}

A report on patients with terminal cancer stated that more than 50% of the patients were elderly, and these elderly oncology patients had more severe symptoms, dysfunction, and comorbidity than younger patients.²⁰ Psychosomatic complaints of these patients, compared to younger patients, often result in medical decisions about themselves being taken by their families. Family decision-making can jeopardize patients' autonomy and hinder their choice of the place to die.²¹ These reasons prevent the elderly from reaching the hospital, whereas the relatively younger ones can go to the hospital in the near term of death. Recent studies have demonstrated that patients can understand the prognosis of the disease over time, which could improve decision support for the place of death.²²

Worldwide, palliative care is conducted by nursing homes, palliative care clinics, or hospital palliative care services. Several models for improving palliative care in hospitals are being investigated.²³ Cancer patients with complaints that require palliation are usually admitted for hospitalization when they present to hospitals. We believe that high death rates in the hospital are ascribed to the palliative support provided by our university hospital for terminal cancer patients. Although palliative care is a novel discipline, it is rapidly integrated into the health systems in our country. In palliative care, similar to life, death is considered as a natural process, and it is aimed at providing the necessary care to incurable patients. The aging population and the increasing prevalence of cancer have increased the need for these units. The majority of palliative care users are cancer patients. In our country, palliative care services are financed by the state and are provided in different services or oncology units of hospitals in all provinces.²⁴

Before discharge from the hospital, the physician of the relevant branch directs the patient to "Home Health Services." The doctor in charge of the home health services unit visits the patient's home once a week and the nurses visit the patient's home once to thrice. Patients who are about to die soon and those with symptoms are visited by doctors and

nurses every day as required, with 24/7 availability. We noted considerably low home mortality rates in our study, which could be due to reasons including loyalty to the old doctor, the necessity of establishing completely new relationships with visiting doctors and nurses, and the discharge of patients without prophylactic methods against life limitations.^{25,26}

An analysis of the relationship between mortality rate and gender revealed that the proportion of survivors was higher in the female group, and the proportion of deaths was higher in the male group. This could be attributed to the decrease in breast cancer mortality rate, which is more common in women, and the high mortality rate of lung cancer, which is more common in men. Breast cancer displayed the highest mortality rate in women, whereas lung cancer in men. Except for the 1990s, cancer-related mortality rates among males increased significantly in all the decades studied.²⁷ In addition, mortality rates in breast and prostate cancers were stated as 17.1% and 12.1%, respectively. Breast cancer mortality varied over time with age. In the 1990s, a non-significant decline in patients younger than 30 years of age was observed, whereas it was the same in women aged 85 years and older, with significantly reduced rates for all ages.²⁸

A statistically significant relationship existed between mortality rate and cancer location. However, this did not exert a significant effect on home or hospital mortality rates. Mortality rates varied significantly with histopathological types. For example, the mortality rate was high in the case of EC or SCLC types in lung cancer and GBM in brain cancers. In contrast, the number of patients with lymphoma or breast cancers who lived in the case of IDC or DCIS was higher. Lung cancer diagnosis is an important independent marker for overall survival.²⁹

We found a significant correlation between the mortality rate and the place of diagnosis. Deaths in the primary tumor and the other group were significantly higher than those who lived, which could be attributed to the ease with which a biopsy could be performed on a large primary mass. Poor survival in the other group is that the metastatic sites biopsied were sites such as liver and brain metastases, which worsened survival.

A significant relationship was noted between patients having a second primary cancer and mortality rate. The number of deaths in the presence of a second primary cancer was higher. Several studies conducted worldwide have reported that the incidence of multiple primary malignant tumors varies between 0.52% and 11.7%, which is associated with a short survival time.³⁰ In our study, 7% of patients had second primary cancer, whereas 93% did not.

Cancer stage is an independent prognostic evidence for overall survival.²⁹ We found a statistically significant relationship between mortality rate and cancer stage. Although the rate of deaths in the metastatic (Stage IV) and locally advanced stage (Stage III) groups was higher, it was higher in patients in the early stage (Stage I and II).

Delays of up to almost a month in diagnosing and treating cancer have been associated with increased mortality rates.³¹ We found that those diagnosed within 3 months from the onset of any complaint that could be associated with the disease were considered as diagnosed early, and those diagnosed later were considered as diagnosed late. The mortality rate was higher in the late-diagnosed group compared to the living group, and the difference was statistically significant.

CONCLUSION

We addressed several factors affecting the mortality rate in oncology patients. These included second primary cancer, presence of metastasis, diagnosis from primary mass, lung, stomach, and brain cancer, locally advanced and metastatic stage, histological type, outpatient clinic (chest diseases, emergency, and neurosurgery branches), and late diagnosis. Contrary to all these known facts, we found that a large proportion of oncology patients died in hospitals.

The hospital care of these patients, who require intensive care in the last days of their lives, is highly expensive for national budgets. Patients with terminal cancer should be provided with sufficient information about end-of-life care preferences. They should be directed to home care services to ensure that they receive supportive treatment at home after discharge. The provision of palliative support is appropriately

designed and delivered every day of the week and every month of the year through home health services or hospitals.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

bers of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sema Yılmaz Rakıcı; **Design:** Sema Yılmaz Rakıcı, Özlem Terzi; **Control/Supervision:** Sema Yılmaz Rakıcı, Songül Özyurt, Zihni Acar Yazıcı; **Data Collection and/or Processing:** Sema Yılmaz Rakıcı, Özlem Terzi; **Analysis and/or Interpretation:** Sema Yılmaz Rakıcı, Özlem Terzi; **Literature Review:** Sema Yılmaz Rakıcı; **Writing the Article:** Sema Yılmaz Rakıcı, Zihni Acar Yazıcı; **Critical Review:** Sema Yılmaz Rakıcı, Özlem Terzi; **References and Fundings:** Sema Yılmaz Rakıcı, Özlem Terzi; **Materials:** Sema Yılmaz Rakıcı.

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