Therapeutic aggressiveness in the oncological patient at the end of life: Experience in a tertiary hospital.

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Abstract

Background: The fundamental therapeutic objective in advanced or metastatic cancer is the control of symptoms without detriment to quality of life. Several studies show that cancer patients continue to receive cancer treatment until the last month of life, and this is related to poor-quality care.

Methods: This was a retrospective observational study conducted over a period of three years in a tertiary hospital. Data from deceased patients treated in the medical oncology unit for a solid tumour diagnosis were collected from January 1, 2016, to December 31, 2018. Demographic variables related to the tumour, treatment and death were also collected. For descriptive statistics, percentages with frequencies (categorical variables) and medians (continuous variables) were used. The nonparametric Kruskal–Wallis test was used for dichotomous variables, and the Mann–Whitney test with the Bonferroni correction was used for between-group comparisons of independent samples. The SPSS 20.0 program was used for statistical analysis.

Results: In total, 1611 patients were analysed; 40.16% and 17.94% of patients received treatment in the last 30 and 14 days of life, respectively. The median time from the last treatment to death was 39 days. By tumour location, breast cancer had the highest percentage of patients in active treatment in the last month of life (55.26%) and the lowest median from the last treatment to death (28 days). By age range, the group ≥ 75 years had the highest median (59 days) with a statistically significant difference compared to groups aged <75 years. A total of 76.22% of patients died in the hospital setting, of which 6.89% died in palliative care units.

Conclusions: The location of the primary tumour and age can influence decision-making in terminal cancer. The administration of cancer treatment in the final stages of life seems to have no benefit in terms of survival and can negatively influence the quality of life of patients. It is necessary to prioritize palliative care and early management by specialized units in the final phases of life.

1. Introduction

Despite constant progress in the field of oncology, cancer continues to be a highly lethal disease and to cause great morbidity. Approximately 9.6 million cancer-related deaths and 18.1 million new cases were noted 2018, according to the World Health Organization, and the number of diagnoses is estimated to reach 29.5 million by 2040 (1).

In recent decades, there have been great advances in the treatment of cancer with the development of precision medicine. New drugs have been created and incorporated into routine clinical practice, expanding the available therapeutic arsenal (2, 3). Among these new therapies, directed molecular therapies (e.g., monoclonal antibodies, immunotherapy) are notable, along with their new toxicity profiles and better dosages that contribute to prolonging the duration of treatments in advanced stages (4, 5).

Although increased survival is desirable, the main therapeutic objective in advanced or metastatic disease is to control symptoms and improve the quality of life of the patient. Therefore, the use of aggressive therapies at the end of life, an increasingly common practice, is a controversial issue (2, 6–11). Additionally, it has been observed that this objective is not achieved in patients who start with a poor functional status (3, 6). That is why the guidelines of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) do not recommend the use of antineoplastic treatments in patients without previous benefit and/or with an ECOG score ≥ 3.

Therapeutic aggressiveness in terminal cancer patients is related to poor-quality care (12). Thus, the objective to achieve in these last stages of the disease must be to guarantee quality care that includes decision-making and psychological support, symptom control and palliative care (3, 13). However, data from national and international studies show that today, patients with end-of-life cancer continue to receive active treatments in the last month and even in the last 14 days of life (3, 8, 14, 15).

2. Objetive

To analyse patients with solid tumours in the final stages of life, the time elapsed between the prescription of the last active treatments and their death in a tertiary hospital was used as an indicator of therapeutic aggressiveness.

3. Materials And Methods

Study design and population

This was a monocentric retrospective observational study that included all patients with solid tumours treated in the Medical Oncology service of a tertiary hospital who died between January 1, 2016, and December 31, 2018. All patients who received active systemic treatment (oral or intravenous chemotherapy, monoclonal antibodies, targeted therapies) and who had data on the date on which the last treatment was received and the date of death were included. Patients undergoing hormone therapy were excluded. Other exclusions included minors, those with haematological malignancies, those lost to follow-up, and those who received only radiotherapy or were treated only due to their participation in a clinical trial, since they were subsequently referred to their hospital of origin. The clinical data of the patients were collected from the Diraya computerized clinical history system. Data on intravenous treatments were analysed in the Farmis–Oncofarm program (version 11.38). The dates of death were obtained from the single Health History (version 6.9) and confirmed in the National Institute of Statistics.

Statistical analysis

Data on the demographic variables (sex, age), variables related to the primary tumour and the treatment received (origin of primary tumour, number of lines of treatment, date of last treatment) and death (date

and place) were collected. For descriptive statistics, we used absolute percentages and frequencies for categorical variables and the median for continuous variables.

The population did not follow a normal distribution (Kolmogorov–Smirnov test, $p < 0.05$). The nonparametric Kruskal–Wallis test was used for the analysis of dichotomous variables (sex and age). The variable “age” was distributed in ranges, creating the variable “age in ranges”. Between- group comparisons were carried out using the Mann–Whitney test for two independent samples with the Bonferroni correction, controlling the error rate. In this case, $p = 0.05$ was considered significant when divided by the number of combinations of the different age groups.

All statistical analyses were performed with the SPPS 20.0 program (Statistical Package for the Social Sciences).

4. Results

Between 2016 and 2018, a total of 8,353 new patients were treated in the Medical Oncology service. The number of patients who died during this period was 1937, of which 1611 were included in the study. The remaining 326 were excluded for having received only palliative care at diagnosis (N = 193), for being lost to follow-up or for having abandoned treatment by choice (N = 133) (Figure 1).

Regarding the general characteristics of the total population analysed (N = 1611), we found that the tumour with the highest representation was lung cancer (N = 504), followed by digestive tract tumours (N = 474) and genito-urinary (N = 142) tumours, with the least representation being tumours of cutaneous origin (N = 18) and those of unknown origin (N = 4). Regarding sex, the proportions of men and women were 63.7% and 36.3%, respectively, with a median age of 65 years for men and 62 years for women (Table 1).

Within the group of 1611 patients who received treatments, the median time elapsed from the last treatment to death was 39 days. In the analysis by pathology, this median was lower in breast cancer (28 days), lung cancer (32 days) and sarcomas (33 days). Regarding the analysis by sex, we observed that the median in men was 41 days, while that in women was 37 days, with tumours with the lowest median being for cutaneous tumours in men, at 25 days, and breast cancer in women, at 28 days (Table 2).

A total of 40.16% (N = 647) of patients received active treatment in the last 30 days of life, of which 17.94% (N = 289) did so in the last 14 days of life. Breast cancer was the location with the highest percentage of patients in active treatment in the last month of life, with 55.26% treated in the last 30 days and 30.70% in the last 14 days. In contrast, the percentages of patients with tumours of genito-urinary origin treated in the last 30 days of life (27.5%) and in the last 14 days of life (7%) were lower (Figure 2).

In the analysis by age ranges (Table 3), the group aged ≥ 75 years differed from the rest of the age groups, having the highest median number of days between last treatment and death, at 59 days, and a statistically significant difference compared with the groups comprising patients <75 years of age

(Mann–Whitney U, p <0.005) (Table 4). The medians of the groups of patients by age range who received treatment in the last 14 days differed (Kruskal–Wallis test, p = 0.012), with a statistically significant difference being evident between the groups of patients aged 40–49 and 60–74 years (Mann–Whitney U, p <0.001) (Table 4).

Regarding the percentage of patients who received treatment in the last month and the last two weeks of life, the group of patients ≥ 75 years were the minority, at 29.41% and 10.4%, respectively (Figure 3).

Patients received a median of two lines of treatment (interquartile range 2). A total of 34.88% (N = 562) received one line of treatment, 31.47% (N = 507) received two lines, 17.75% (N = 286) received three lines, and 10.05% (N = 162) received four lines. Breast cancer was the pathology with the most lines of treatment received, with a maximum of nine lines (Figure 4).

To evaluate the quality of care at the end of life in our centre, the place of death of our patients was also analysed: 23.77% died at home, and 76.22% died in the hospital setting, of which 6.89% did so in areas specializing in palliative care, 3.41% in the emergency room and 61.64% in conventional hospitalization floors or other areas (Figure 5). We do not know the place of death of 4.28% of the patients analysed because these data were not included in the computerized medical records.

5. Discussion

Quality palliative care should be the priority in patients with advanced terminal disease. Generally, we consider that a disease is in the final stage when the patient is in his or her last six months of life. However, in patients with cancer, it is increasingly difficult to determine this time with precision, since it can be influenced by various factors (the theoretical estimate of life expectancy, the functional status of the patient, comorbidity, and social environment). For this reason, in many cases, the interruption of treatment is delayed, perpetuating a situation of therapeutic aggressiveness (8, 13).

The identification of indicators of quality of care can be useful to evaluate whether we are providing quality care at the end of life. In this sense, several factors have been described, such as the administration of chemotherapy in the last weeks of life, the need for hospitalization, consultations with emergency services, admission to the intensive care unit (ICU) and referral to palliative care teams (3, 6–13).

It is considered that quality care for palliative cancer patients should depend on the administration of chemotherapy in the last two weeks of life being less than 10% and the start of a new regimen in the last month of life being less than 2% (8).

With the objective of identifying indicators of quality of care in patients with cancer at the end of life and possible related factors, we conducted a retrospective study compiling the total number of oncological patients in active treatment who died in our centre between 2016 and 2018 and relating them with data on demographic variables, the primary tumour and treatments received.

Based on the indicators of therapeutic aggressiveness indicated by Earle (8), we established the median time in days from the last treatment received until death and the percentage of patients who had received active treatment in the last month and last 14 days of life as the main variables. We observed that 17.94% of patients were in active treatment in their last 14 days of life, results that were clinically relevant when the sample size analysed was taken into account. In the literature, there are retrospective studies that show results similar to ours (13, 14), while others reflect a less aggressive approach at the end of life according to indicators such as the use of intravenous chemotherapies in the last month of the life and the place of death (15, 16). Even so, the great heterogeneity between the populations studied, the sample size and the variables analysed in each of these studies makes them difficult to compare.

The analysis by age group and location of the primary tumour shows that in patients < 75 years of age and in patients with breast cancer, there is a greater tendency towards therapeutic aggressiveness. This could be related to the degree to which the subjectivity of the physician can influence decision-making in the most advanced stages of the disease. In this sense, age could be an influential factor at the time when active treatment is or is not continued in the terminal stage. In their study, Baena et al. (3) included the prescribing oncologist as an independent variable, observing a greater individual tendency to prescribe active treatments in the later stages of the disease.

The type of neoplasm, the available therapeutic options, its form of administration and dosage could influence these results. The new therapeutic arsenal developed in recent years is based mainly on targeted therapy, usually with less toxicity than chemotherapy (5, 18). This could lead to a rethinking of the current concept of “therapeutic aggressiveness”.

The objective of palliative chemotherapy is to improve the quality of life of patients; however, it is not achieved in those who start with a poor functional status and is capable of worsening the situation in patients with good functional status, by adding complications derived from toxicities. A recent systematic review and meta-analysis (4) of ten randomized controlled clinical trials evaluated the risks and benefits associated with active oncological treatment against the initiation of palliative care in the last phases of advanced terminal disease, concluding that active treatment did not demonstrate an impact on overall survival and was associated with an increase in toxicity and, therefore, a greater deterioration of quality of life, which increases emergency room visits, hospital admissions and death outside the home. In our study, we observed that the majority of patients died in the hospital setting and disconnected from palliative care. A total of 23.77% of patients died at home; however, we could not ensure that this was related to well-being and quality of life since we do not know which patients were linked to home hospitalization and palliative care services. It is possible that having a powerful palliative care service with high accessibility facilitated the passage of patients to these units before what was actually done, with the consequent improvement in the quality of life of the patients.

As the main limitations of our study, we highlight its retrospective design and the difficulties in collecting information to define indicators of therapeutic aggressiveness and related factors, such as the distinction between subgroups of patients with oral or intravenous treatment, the record of visits to the emergency

room, admissions to the ICU, admissions to nononcological facilities, admissions to external centres, the date of referral to the palliative care unit, the chemosensitivity of the tumour or the functional status of the patient measured by validated scales such as ECOG or Karnofski. Even so, we believe that our data provide information on clinical relevance in our field, since we handle a volume of patients much higher than most of the published studies, in addition to conducting our analysis with real-life data from a large sample of patients that allows us to propose hypotheses about factors that may influence a greater or lesser therapeutic aggressiveness.

6. Conclusions

Our data show that the location of the primary tumour and age can be influential factors in therapeutic decision-making at the end of life. The administration of cancer treatment in the final stages of life seems to have no benefit in terms of survival and can negatively influence the quality of life of patients. It is for this reason that the identification of indicators of therapeutic aggressiveness can be useful to improve the management and quality care of terminal cancer patients. Referral to specialized palliative care units and early management should become a priority in the final phases of life.

Declarations

Ethics approval and consent to participate

This research was carried out in accordance with Regulation (EU) 2016/679 regarding the protection of natural persons with respect to the processing of personal data and the free circulation of these data and Organic Law 3/2018 of 5 December, Protection of Personal Data and guarantee of digital rights.

All information regarding personal identification was removed from the dataset before analysis. As this was a retrospective observational study based on data from medical records, without physical participation of patients and all deceased, informed consent was not requested.

The study was approved by the Ethics Coordinating Committee of Biomedical Research of Andalusia (Application code: S2000340).

Consent for publication

According to the Ethics Coordinating Committee of Biomedical Research of Andalusia, no publication consent is required as all data used in this manuscript refers to deceased patients.

availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

competing interests

The authors declare that they have no competing interests.

author contributions

Data acquisition: Castilla M.A., Salvador J.

Statistical analysis: Castilla M.A.

Drafting of the manuscript: García C., Morales R.

Manuscript revision: All authors reviewed the manuscript.

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Tables

Table 1

General characteristics of the patients: tumour location, frequency and median age at death.

	GLOBAL		MAN		WOMAN	
Tumour location	Frequency N (%)	Age (median, range)	Frequency N (%)	Age (median, range)	Frequency N (%)	Age (median, range)
Lung	504 (31.28)	66 (29-89)	407 (39.67)	67 (34-89)	97 (16.58)	63 (29-81)
Digestive System	474 (29.42)	65 (33-89)	307 (29.92)	66 (33-89)	167 (28.55)	64 (33-89)
Genito-Urinary	142 (8.81)	71 (28-86)	128 (12.48)	71 (28-86)	14 (2.39)	71 (57-84)
Breast	114 (7.08)	58.50 (30-87)	0 (0)	NOT	114 (19.49)	58.50 (30-87)
Gynaecological	93 (5.77)	61 (35-88)	0 (0)	NOT	93 (15.90)	61 (35-88)
Sarcoma	91 (5.65)	50 (18-80)	46 (4.48)	49.50 (18-74)	45 (7.69)	50 (19-80)
Head and neck	62 (3.85)	60 (33-84)	50 (4.87)	60 (33-84)	12 (2.05)	60 (47-84)
Central Nervous System	56 (3.48)	56.50 (22-79)	39 (3.80)	56 (22-73)	17 (2.91)	57 (27-79)
Neuroendocrine	53 (3.29)	64 (32-82)	36 (3.51)	63 (32-82)	17 (2.91)	65 (34-72)
Dermatology	18 (1.12)	63.50 (34-81)	13 (1.27)	64 (34-81)	5 (0.85)	63 (46-69)
Unknown origin	4 (0.25)	61.50 (43-70)	0 (0)	NOT	4 (0.68)	61 (43-70)
TOTAL	1611 (100)	64 (18-89)	1026 (63.7)	65 (18-89)	585 (36.3)	62 (19-89)

Table 2

Time from last treatment to death by location and sex

	GLOBAL		MAN		WOMAN	
Location	Frequency (%)	Days (median, min-max)	Frequency (%)	Days (median, min-max)	Frequency (%)	Days (median, min-max)
Lung	504 (31,29)	32 (1-928)	407 (39.66)	32 (1-928)	97 (16.58)	30 (1-236)
Digestive System	473 (29,42)	51 (1-1097)	307 (29.92)	55 (1-1097)	167 (28.54)	40 (1-609)
Genito-Urinary	142 (8.81)	55.5 (6-520)	128 (12.47)	54 (6-520)	14 (2.39)	65.5 (8-227)
Breast	114 (7.07)	28 (0-1044)	0 (0)	0 (0)	114 (19.48)	28 (0.1044)
Gynaecological	93 (5.77)	50 (1-732)	0 (0)	0 (0)	93 (15.89)	50 (1-732)
Sarcoma	91 (5.64)	33 (2-431)	46 (4.48)	28 (2-135)	45 (7.69)	36 (2-431)
Head and neck	62 (3.84)	36.5 (0-321)	50 (4.87)	32 (0-321)	12 (2.05)	56 (3-152)
Central Nervous System	56 (3.47)	34.5 (1-151)	39 (3.80)	32 (1-161)	17 (2.90)	50 (8-102)
Neuroendocrine	53 (3.29)	34 (1-248)	36 (3.50)	32 (2-248)	17 (2.90)	44 (1-188)
Dermatology	18 (1.11)	34.5 (5-137)	13 (1.26)	25 (5-113)	5 (0.85)	70 (9-137)
Unknown origin	4 (0.25)	42 (1-71)	0 (0)	0	4 (0.68)	42 (1-71)
TOTAL	1611	39 (0-1097)	1026	41 (0-1907)	585	37 (0-1044)

Table 3 Median number of days between last treatment and death by age in ranges		
Age	Frequency (number, %)	Days (median, range)
< 40	71 (4,40)	34 (1-197)
40-49	133 (8.25)	29 (0-437)
50-59	383 (23,77)	35 (0-510)
60-74	735 (45,62)	40 (0-746)
≥ 75	289 (17,94)	59 (2-1097)
TOTAL	1611 (100)	39 (0-1097)

Table 4 Between-group comparative analysis of medians to death since last treatment by age					
Age	< 40	40-49	50-59	60-74	≥ 75
< 40		p =0.42	p =0.66	p =0.37	p <0.005
40-49			p =0.082	p <0.005	p <0.005
50-59				p =0.002	p <0.005
60-74					p <0.005
≥ 75					
p value calculated with the Mann–Whitney U test (p <0.005 Bonferroni correction)					

Figures

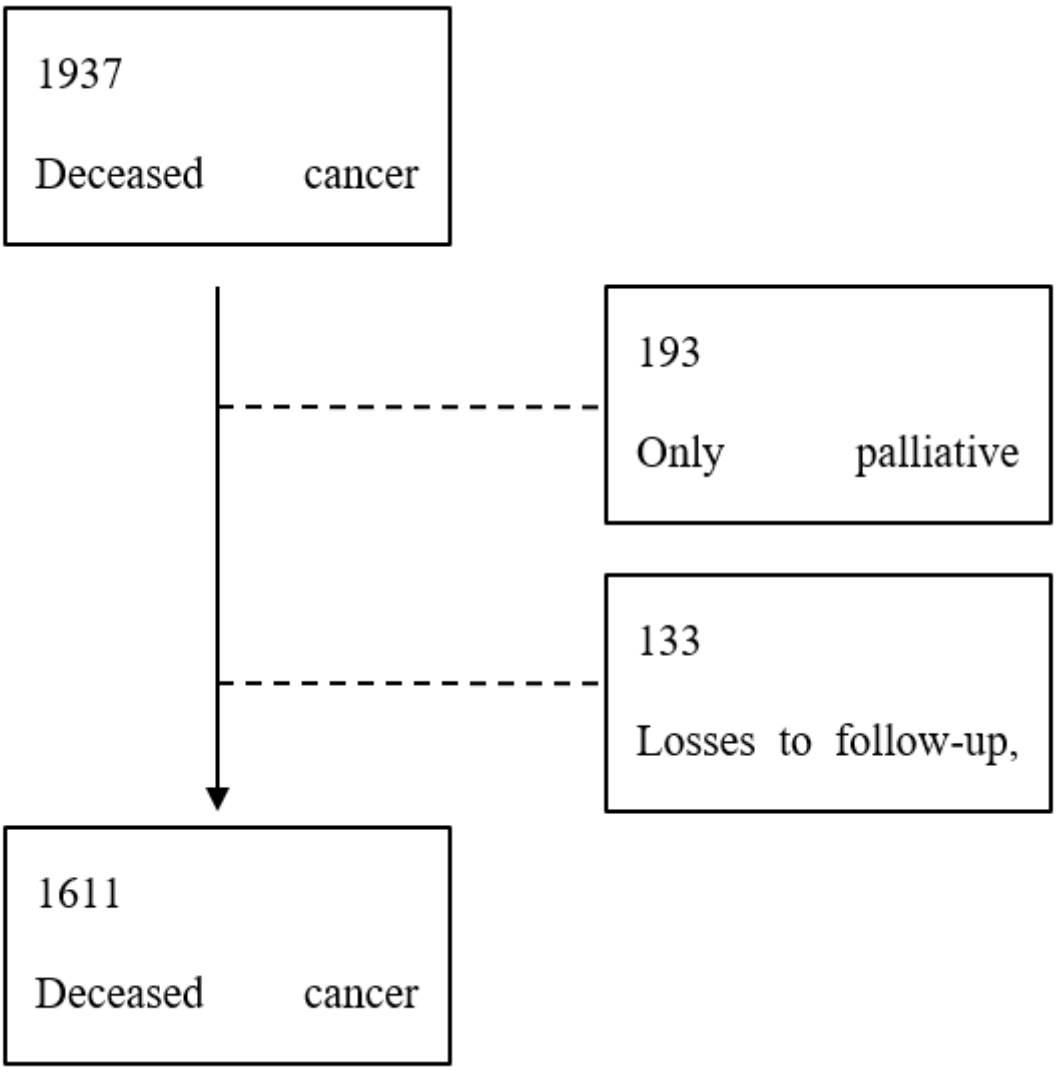

Figure 1

Design and selection of patients

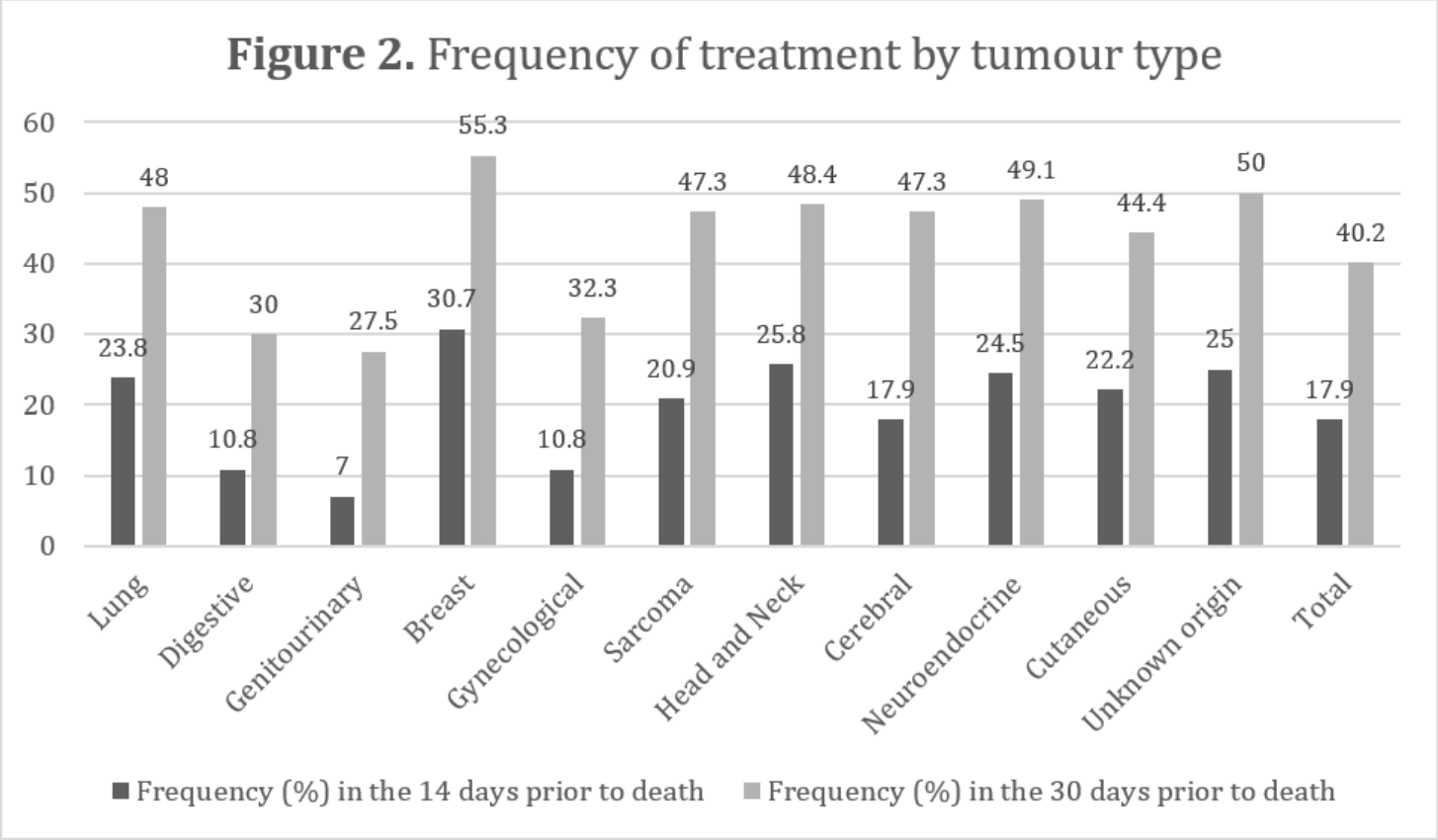

Figure 2

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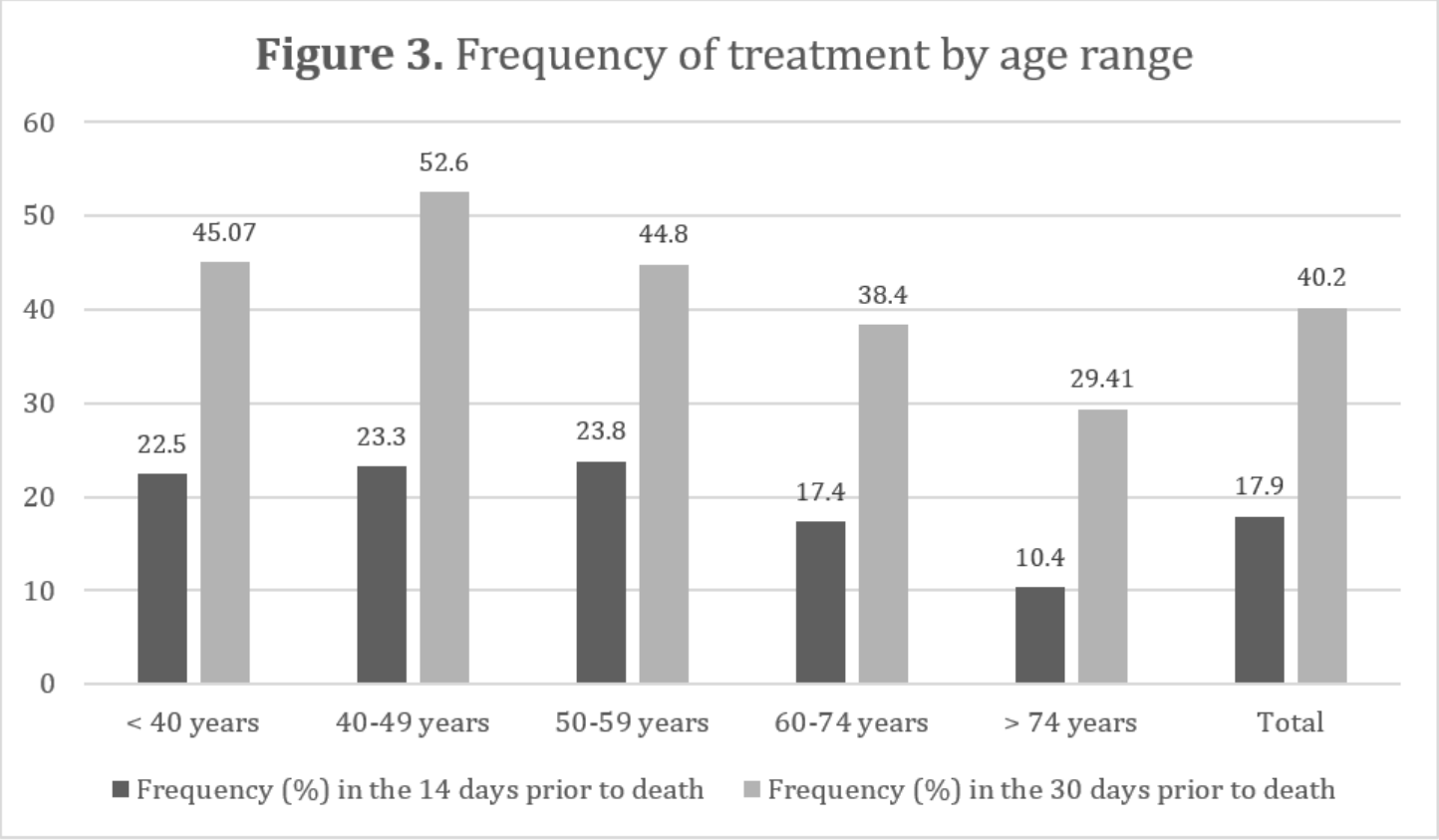

Figure 3

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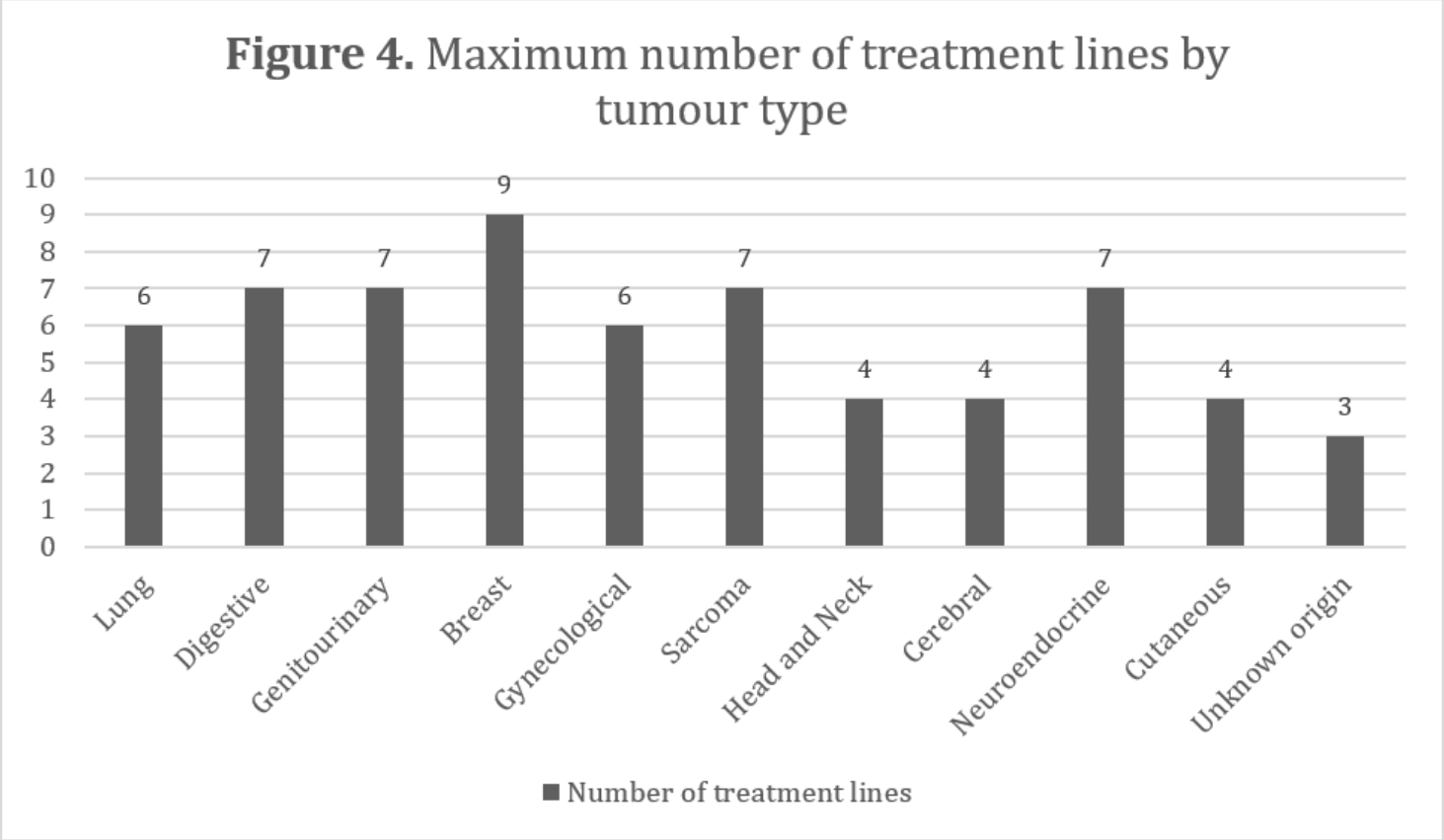

Figure 4

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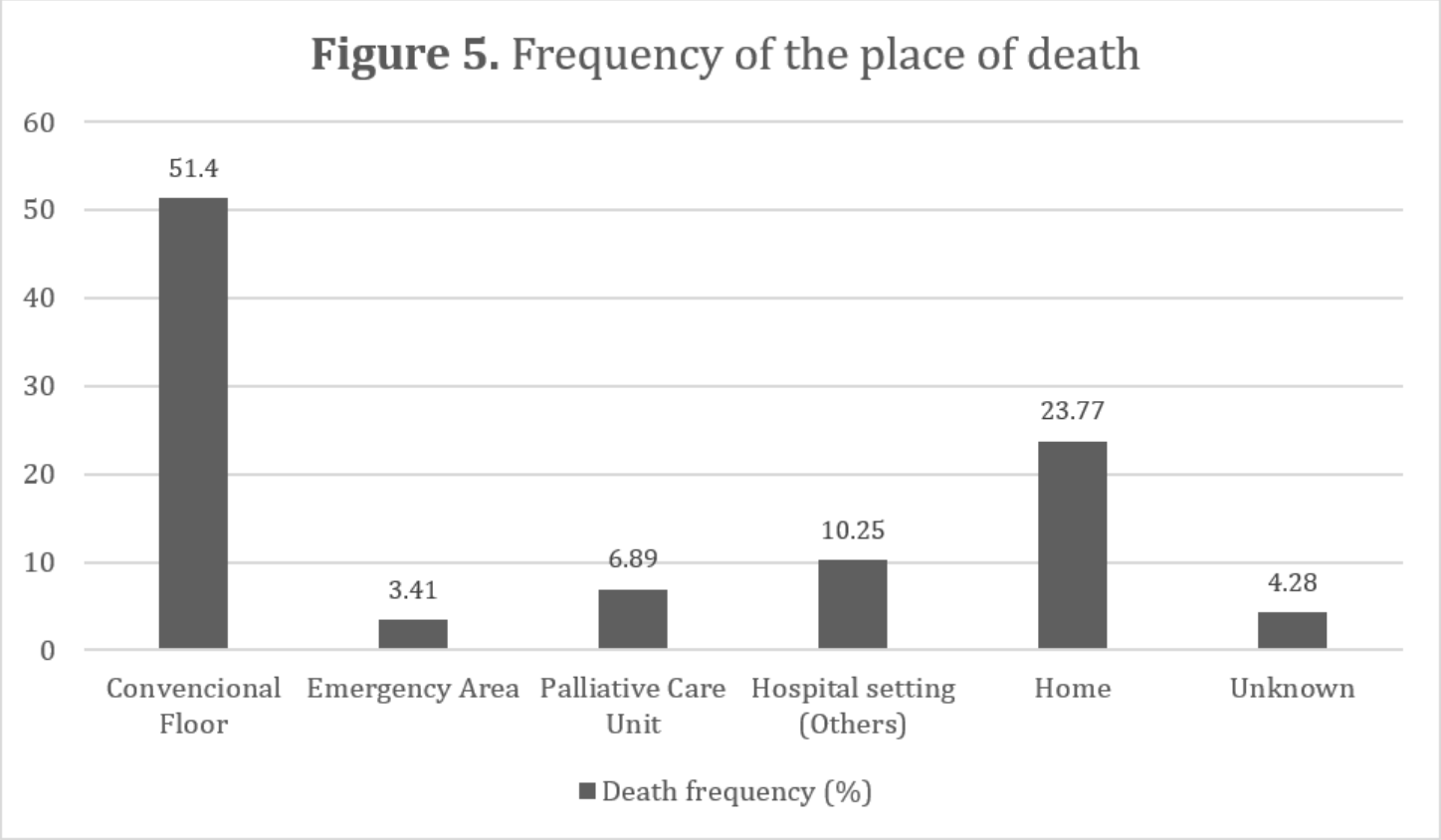

Figure 5

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