Article published online: 2020-06-10

ORIGINAL ARTICLES CLINICAL ONCOLOGY

Brazilian Journal of Oncology

The discontinuation of antitumor treatment and the advance directives in cancer patients

A interrupção do tratamento antitumoral e as diretivas antecipadas em pacientes com câncer

Pedro Grachinski Buiar[1], Jose Roberto Goldim[2], Vania Naomi Hirakata[3]

ABSTRACT

Objectives: Advance directives (AD) are one of the main pillars of patients' autonomy and can impact directly the quality of life, dignity and rights of the dying patient. Despite this, advance directives face many barriers to be created, implemented and followed. The moment of discontinuation of active anticancer therapy is an important landmark in the palliative evolution of cancer patients. The aim of this study is to investigate if the discontinuation of antitumor treatment could influence rates of advance directives. **Methods:** A single-center retrospective case-notes review study with 321 randomly selected patients of a Single Brazilian tertiary oncology center. Qualitative and quantitative data were collected and analyzed to compare two groups of patients, one group with advance directives registered and another group without directives. **Results:** The rate of advance directives was 22.7%, and in 82.3% of subjects, the decision of treatment discontinuation occurs on the same day or before the AD manifestation. In multivariable analysis, 82.5% of patients with advance directives were in the doctor´s office at the occasion of the discontinuation of their anticancer therapy compared with 64.4% of the patients without directives (RR 1.88; 95%CI 1.019-3.496). The most cited "living will" was the desire "to die at home" (30%), and 10% of those manifesting this directive actually died at home. **Conclusion:** The discontinuation of antitumor treatment may be a window for end of life and advance care plan discussions, raising the rates of advance directives. Doctor's office is a better place than emergency rooms, wards and intensive care units for the discussion about end of life aspects and advance directives.

Keywords: Advance directives; Medical oncology; Palliative care; Living wills.

---

1. Instituto Sul Paranaense de Oncologia, Oncologia Clínica - Ponta Grossa - Paraná - Brazil.
2. Hospital de Clínicas de Porto Alegre, Bioethics - Porto Alegre - Rio Grande do Sul - Brazil.
3. Hospital de Clínicas de Porto Alegre, Biostatistics - Porto Alegre - Rio Grande do Sul - Brazil.

Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.
Correspondence author: Pedro Grachinski Buiar.
E-mail: pgbuiar@gmail.com

Received on: August 20, 2019 | **Accepted on:** April 18, 2020 | **Published on:** June 10, 2020
DOI: https://doi.org/10.5935/2526-8732.20200006

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.
(http://creativecommons.org/licenses/by-nc-sa/4.0/).

RESUMO

Objetivos: As diretivas antecipadas (DA) são um dos principais pilares da autonomia dos pacientes e podem afetar diretamente a qualidade de vida, a dignidade e os direitos do paciente que está morrendo. Apesar disso, as diretivas antecipadas enfrentam muitas barreiras a serem criadas, implementadas e seguidas. O momento da descontinuação da terapia anticâncer ativa é um marco importante na evolução paliativa de pacientes com câncer. O objetivo deste estudo é investigar se a descontinuação do tratamento antitumoral poderia influenciar as taxas de diretivas antecipadas. **Métodos:** Estudo retrospectivo de notas de caso em um único centro com 321 pacientes selecionados aleatoriamente em um centro de oncologia terciária único brasileiro. Dados qualitativos e quantitativos foram coletados e analisados para comparar dois grupos de pacientes, um grupo com diretivas antecipadas registradas e outro sem diretivas. **Resultados:** A taxa de diretivas antecipadas foi de 22,7% e, em 82,3% dos indivíduos, a decisão de descontinuação do tratamento ocorre no mesmo dia ou antes da manifestação da DA. Na análise multivariável, 82,5% dos pacientes com diretivas antecipadas estavam no consultório no momento da descontinuação da terapia anticâncer, em comparação com 64,4% dos pacientes sem diretrizes (RR 1,88; IC95% 1,019-3,496). A “declaração de vontade” mais citada foi o desejo de “morrer em casa” (30%) e 10% dos manifestantes dessa diretiva morreram em casa. **Conclusão:** A descontinuação do tratamento antitumoral pode ser uma janela para discussões sobre o fim da vida e os planos de cuidados avançados, aumentando as taxas de diretivas antecipadas. O consultório médico é um lugar melhor do que as salas de emergência, enfermarias e unidades de terapia intensiva para a discussão sobre aspectos do fim da vida e diretivas antecipadas.

Descritores: Diretivas antecipadas; Oncologia médica; Cuidado paliativo; Declaração de vontade.

INTRODUCTION

Advance directives (AD) are an essential part of the Advance Care Plan (ACP), which aims to improve patient care, quality of life, and reduce health costs.[1] The formulation of an AD involves a behavioral change and a better understanding of the context of a terminal disease, taking into account the values, beliefs and objectives of the patient.[2] The prevalence of advance directives in the USA ranged from 5-37% but this number can reach 70% in samples affected by terminal conditions.[3-6]

The benefits of advance directives include reduction of in-hospital mortality rates, higher levels of patient satisfaction, the accomplishment of patient’s wills, and reduction of depression and anxiety in end-of-life, for patients and their relatives.[7-12] The relevance of AD grows exponentially as we look at the current reality of Oncology and the “chronification” of disease. The process of “chronification” of disease put the ADs into a risk of being undervalued or postponed. That leads us to a potentially negative impact with unwanted costs in a collapsing global health system.[13-16]

Every oncologist treating incurable cancer patients in daily practice recognizes the impact of the discontinuation of anticancer treatment and the beginning of the called Best Supportive Care (BSC) modality of treatment. Despite this, there is a lack of data regarding the association of discontinuation of antitumor treatment with advance directives elaboration and implementation. The primary objective of this study is to evaluate if the moment of discontinuation of antitumor treatment could influence the rates of advance directives.

METHODS

Study design and patients

We perform a retrospective study involving cancer patients in palliative treatment at a university hospital in Brazil. Convenience sampling was made by the registry number of their medical records generated by the hospital’s electronic system. Eligibility criteria included patients over 18-years-old at the time of disease, an incurable disease (at diagnosis or at progression) and ongoing palliative treatment. Patients with cognitive impairment or documented inability to make decisions were excluded. For data analysis, the patients were divided into two groups, one with and another without advance directives. The cases were followed from the time of diagnosis of the incurable condition until death.

We select the first living will declaration directly manifested by the patients and documented in their medical record as the advance directive to consider in the analysis. This could refer to any will regarding the place of permanence, place of death, and treatment measures as cardiopulmonary resuscitation, mechanical ventilation, chemotherapy, enteral tubes, dialysis, broad-spectrum antibiotics and blood transfusions.[17-19] Demographic characteristics were compared between the two groups. Clinical variables included tumor primary site, clinical stage at diagnosis by TNM 7th ed.,[20] performance status by ECOG (Eastern Cooperative Oncology Group) classification at diagnosis, age, sex, educational level, marital status, palliative antitumor treatment dispended, intensive care unit admissions, time intervals from the incurable diagnosis to the discontinuation of the antitumor treatment and beginning of *Best Supportive Care*. The final outcomes included the medical specialty in the last medical contact, cause of death, place of death, life- sustaining measures received and time intervals to the limitation of therapeutic resources (also called *Do-Not-Resuscitate order*) and death.

As a definition of Best Supportive Care (BSC) we consider any palliative treatment, excluding antineoplastic treatments.[21,22] As a definition for the limitation of therapeutic resources, we used the documentation in medical records of the contraindication to aggressive measures, something equivalent to do-not-resuscitate orders.

The study was analyzed and approved by the Ethics and Research Committee of our Institution and is registered in the Brazilian National Database for Scientific Research (Plataforma Brazil) with the number CAAE 71559817.6.0000.5327.

Data collect

Data were collected retrospectively from electronic medical records by direct analysis of documented information. For patients dying outside the hospital and no death registry in the electronic system, an active search was conducted by telephone contact to assess the outcome details. The patients included in this historical cohort were selected from the attendances realized between 2013-2017 and the data were analyzed between October 2017 and June 2018.

Statistical Analysis

Quantitative variables were described by mean and median. The distribution of the qualitative variables was analyzed using percentages. The statistical analysis was performed with SPSS v.18 using the *t*-test for continuous variables and the chi-square test for categorical variables. The two groups were compared using uni and multivariable logistic regression. The performance status was dichotomized in ECOG 0-3 *vs* ECOG 4. Places, where the active treatment was discontinued, were also dichotomized in outpatient scenario (mainly doctor's office) and inpatient setting (including the emergency department, wards and ICU). An adjusted Poisson's regression analysis was done for place and performance status at the moment of the discontinuation of anticancer treatment. To determine the sample size we calculated at least 300 patients estimating approximately 25% prevalence of advance directives, providing 80% power to detect a 2.0 hazard ratio for the association between AD and other variables, with a significance level of 5%. We added 10% of possible losses to reach the final sample size. The missing data were managed with pairwise deletion. A *p*-value below 0.05 was considered statistically significant.

RESULTS

A total of 390 electronic medical records were accessed and 321 subjects confirmed all eligibility criteria and were included in the analysis. The demographic characteristics of the groups with and without advance directives were balanced and summarized in Table 1. The prevalence of advance directives was 22.7% and 74% of subjects received at least one cycle of antitumor treatment, a high rate based on literature evidence.[23]

The group with AD correlated more with the registry of treatment discontinuation compared versus the no AD group (87.7% *vs* 77.6%) and temporal correlation analysis found that the treatment discontinuation decision occurs on the same day or before the first AD manifestation in 82.3% of cases.

Looking at the moment of treatment discontinuation, the place at this moment seems to correlate in a different way between the groups with and without ADs, as demonstrated in Figure 1. The group with advance directives was more correlated with the outpatient scenario than the group without advance directives (82.5% *vs* 64.4%, respectively; RR 1.88; 95%CI 1.019-3.496; *p*=0.043) by multivariate regression. The same analysis did not show a significant association between ECOG performance status (0-3 *vs* 4) and the two groups in the moment of BSC beginning (*p*=0.137).

An analysis, independent of the advance directive status, was performed to access the correlation between performance status and place where BSC was implemented. A statistically significant correlation was found between better performance status (PS ECOG 0-3) and the outpatient scenario in comparison with hospitalized patients (RR 1.835; 95% CI 1.387-2.429; *p*<0.0001), as demonstrated in Figure 2.

There was no statistical difference in outcomes between the groups with and without an AD. The outcomes included the limitation of therapeutic resources, place of death, receipt of blood components, ICU admissions, invasive palliative procedures (drainage of cavities, biliary tract and derivation of intestinal transit in the majority),

Table 1. Characteristics of Patients with and without advance directives.

Total 321 pts*	**Without Advance Directives**	**With Advance Directives**	**P-value**
	248(77,2%)	**73(22,7%)**	
Age (median)	68	69	0,946[a]
Gender			
Female	138(55,6%)	35(47,9%)	0,972[a]
Male	110(44,4%)	38(52,1%)	
Years in school			
< 8 years	134(54%)	39(53,4%)	0,977[a]
8 - 11 years	63(25,4%)	19(26,0%)	
> 11 years	51(20,6%)	15(20,5%)	
Marital Status			
Married	152(61,3%)	38(52,1)%	0,366[a]
Single	76(30,6%)	28(38,4%)	
Divorced	20(8,1%)	7(9,6%)	
Primary Site of the Tumor			
Upper Gastrointestinal Tract	55(22,2%)	15(20,5%)	0,991[a]
Lung	48(19,4%)	15(20,5%)	
Breast	23(9,3%)	6(8,2%)	
Lower Gastrointestinal Tract	46(18,5%)	13(17,8%)	
Others	76(30,6%)	24(32,9%)	
Clinical Stage at Diagnosis			
1	7(2,8%)	2(2,7%)	0,993[a]
2	34(13,7%)	8(11%)	
3	67(27,0%)	18(24,7%)	
4	140(56,5%)	45(61,6%)	
PS ECOG at Diagnosis*			
0	38(15,7%)	12(16,7%)	0,593[a]
1	113(46,7%)	38(52,8%)	
2	51(21,1%)	10(13,9%)	
3	35(14,5%)	12(16,7%)	
4	5(2,1%)	0	
Palliative Chemotherapy			
Yes	184(74,2%)	54(74%)	0,970[a]
No	64(25,8%)	19(26,0%)	
BSC registry**			
Yes	191(77,6%)	64(87,7%)	0,077[a]
No	55(22,4%)	9(12,3%)	
PS ECOG at BSC#			
0 – 3	112(58,6%)	47(74,6%)	0,137[a]
4	79(41,4%)	16(25,4%)	
Place at BSC#			
Outpatient	123(64,4%)	52(82,5%)	0,043[a]
Inpatient+	68(35,6%)	11(17,5%)	

[a] Wald Chi-square test. *Total n=314 pts, due to 7 missing data. **Total n=319 pts, due to 2 missing data (Total patients with BSC registry: 255 due to 11 missing values of AD). # 254 patients due to 1 missing information of PS ECOG and Place at BSC. + Inpatient includes Emergency department, clinical wards, and Intensive Care Unit (ICU). PS ECOG, Eastern Cooperative Oncology Group Scale of Performance Status. BSC, Best Supportive Care.

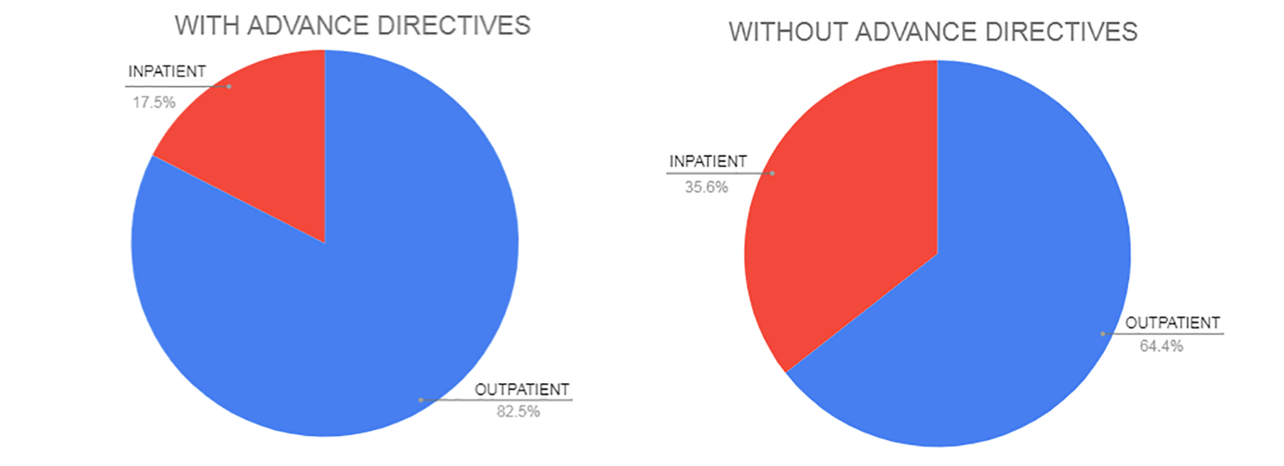

Figure 1. Places at discontinuation of active treatment and initiation of *Best Supportive Care*. This graphic illustrates the differences of scenarios between the groups with and without advance directives when *Best Supportive Care* was initiated.

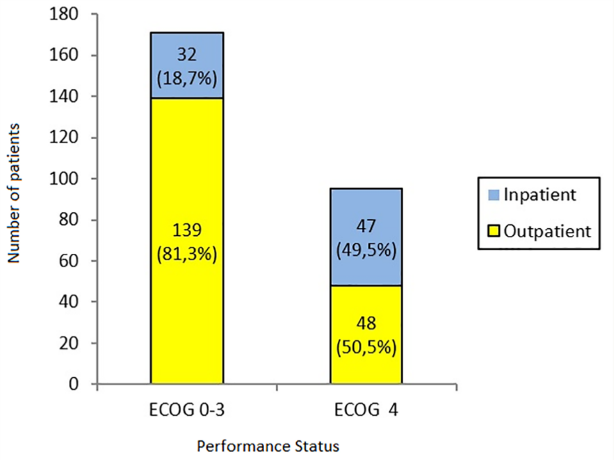

Figure 2. Distribution of patients by place and performance status at the moment of BSC decision (n=266). This graphic illustrates the correlation of outpatient scenario with better performance status scores. ECOG: Eastern Cooperative Oncology Group. Inpatient: Emergency, intensive care unit and wards included.

the specialty at last assistance, cause of death, orotracheal intubation, mechanical ventilation, artificial parenteral hydration and enteral nutrition, and use of broad-spectrum antibiotics did not differ between groups with and without AD (Table 2). The time interval between the palliative diagnosis and the start of BSC, limitation of therapeutic resources, and death also did not differ between the two groups. The median interval from palliative diagnosis to death differed by 3 days between the groups with and without advance directives. The most cited first living will was the "desire to die at home", representing almost 30% of the registries. Among those patients that reported this desire, 13.6% died at home, compared with 64% of in-hospital deaths.

DISCUSSION

The positive correlation between the group with advance directives and the outpatient scenario in the moment of discontinuation of anticancer treatment could be explained by a greater sense of security, confidence and stronger relation with the assistant professional.[24,25] These factors facilitate the transition to a BSC approach and also improve the chance of discussions about the advance care plan and advance directives providing patients with more autonomy. The emergency, wards and ICUs environment interfere negatively in the compliance and elaboration of an advance care plan and advance directives. A good and early advance directive can reduce visits to the emergency department (as illustrated by the 14.8% *vs* 18.5% deaths in the emergency), and could also reduce stress and possible iatrogenic measures as stated by the literature.[26-28]

Despite no correlation founded between the performance status and ADs documentation, in daily practice, we observe that the more debilitated patients are less capable to discuss advance care plan and manifest their advance directives. The prognostic impact that poor performance status carries may reinforce mercy feelings by oncologists and/or family members.[29] A deleterious practice called collusion may occur in this scenario and it refers to the attitude of put aside the patient's autonomy and restricts the decision process to relatives and medical team, hiding the truth and facts from the major interested person.[30]

A fact that suggests the presence of collusion in this study population is that despite low rates of ADs, low rates of life-sustaining measures were verified. We also know that patients on PS ECOG 4 also have more cognitive dysfunctions and weaknesses that may compromise their interest and ability to formulate advance directives in time to honor their

Table 2. Outcomes of patients with and without advance directives

Outcomes	Wthout advance directives	With advance directives	P-value
Place at Limitation of Therapeutic resources (n=267*)	201(100%)	66(100%)	
Clinical Wards	96(47,8%)	23(34,8%)	0,230^a
Emergency	53(26,4%)	21(31,8%)	
Doctor's office	44(21,9%)	19(28,8%)	
ICU	7(3,5%)	3(4,5%)	
Place of death(n=293*)	232(100%)	61(100%)	
Palliative Unit in the Hospital	109(47%)	31(50,8%)	0,905^a
Emergency	43(18,5%)	9(14,8%)	
Clinical Wards	38(16,4%)	11(18%)	
Home	25(10,8%)	5(8,2%)	
Other	10(4,3%)	2(3,3%)	
ICU	7(3%)	3(4,9%)	
Patients that received Blood transfusions	136(54,8%)	41(56,2%)	0,841^a
Patients with ICU admission	14(5,6%)	5(8,3%)	0,509^a
Patients that received Palliative Procedures	48(20,3%)	17(25%)	0,409^a
Last assistance specialty (n=260*)	204(100%)	56(100%)	
Medical Oncology	101(48,7%)	26(46,4%)	0,738^a
Emergency	42(20,2%)	9(16,1%)	
Palliative Care	30(14,7%)	13(23,2%)	
Internal medicine	23(11,3%)	6(10,7%)	
Intensive Care	7(3,4%)	2(3,6%)	
Other	1(0,5%)	0	
Cause of Death (n=255*)	200(100%)	55(100%)	
Progression of Disease	163(81,5%)	47(85,5%)	0,396^a
Infectious	28(14%)	7(12,7%)	
Vascular	6(3%)	1(1,8%)	
Other	3(1,5%)	0	
Limitation of therapeutic resources			
Yes	195(79,6%)	65(89%)	0,085^a
No	50(20,4%)	8(11%)	
Life-sustaining measures			
Cardiopulmonary resuscitation	4/231(1,7%)	1/61(1,6%)	0,961^a
Invasive Airway	11/231(4,8%)	3/61(4,9%)	0,960^a
Parenteral Hydration	144/221(65,2%)	36/59(61%)	0,555^a
Artificial Enteral Nutrition	55/220(25%)	17/58(29,3%)	0,505^a
Broad spectrum antibiotics	103/222(46,3%)	30/59(50,8%)	0,543^a
Interval between Palliative Diagnosis and Death (median in days)	464	461	0,296^b

(A) Pearson chi-square test; (B) Log Rank (Mantel-Cox) Test *Varied values due to missing data in medical records for each outcome ICU, Intensive Care Unit.

living wills.[31] The independent analysis correlating patients in PS ECOG ≤3 with the outpatient scenario in comparison with PS ECOG 4 (RR 1.835; p<0.0001) corroborates this argument.

The 22.7% prevalence of advance directives found in our study is below that described in North America but is consistent with data from other localities.[3-6,32-34] We highlight some possible explanations as a low educational level in our sample (more than 50% without the basic educational level completed), the recent history of use of ADs in Brazil, its low dissemination in the health system, and the information bias inherent to retrospective studies.

Where the oncologic patients have died is an important topic. A large cross-national study involving people with cancer found a large variety of in-home deaths ranging from 12-57%.[35] In this study, 13% of patients died at home despite being the most cited first directive recorded. Of the 22 patients who registered a directive expressing the will to die at home only three (13.6%) actually did, compared to fourteen (63.3%) dying in the hospital. This data clearly indicates the difficulty in honoring this type of living will, suggesting the multifactorial influence acting on the final results. One of the multiple factors for this discrepancy is the low prevalence of outpatient hospice care the Brazilian public health system, a factor that is correlated with more deaths in the setting of choice.[36] Other factors may include losses of ADs in the transition between different health teams, lack of a standardized AD registry and inefficient ways to keep it easily accessible.[37,38]

Although the literature indicates a correlation of the advance directives with a reduction in the adoption of aggressive and life-sustaining measures in the terminal setting, in this study the presence of living wills did not statistically correlate with less life-sustaining treatments.[39] This could be due to underestimation of AD caused by discussion without adequate documentation, difficulty in talking with patients about therapeutic limitations leading to relative-guided decisions, and simply beliefs by family members and physicians that some life-sustaining measures could have a positive impact on the lifetime of a terminally ill patient, generating the high rates of parenteral hydration and broad-spectrum antibiotics. Finally, in accordance with literature evidence, our data show no difference in the survival curves between the groups with and without advance directives.[40-41]

CONCLUSION

We must consider that, like any observational study, this research is subject to observational study biases and the results serve as a hypothesis generator. Although it is not able to directly establish a causal relationship, it provides a statistically significant correlation between advance directives registration and the outpatient setting when the anticancer treatment was discontinued, something based on the theoretical rationale. This type of observational data brings the possibility to change practice improving care of palliative cancer patients by discussions and elaboration of advance directives, patients the opportunity to have their wills honored. Finally, we should always keep in mind the multifactorial pattern that influences the composition of advance directives and impaired solid base evidence in this field of research. (Figure 1).

Advanced directives in Brazil, Latin America and all around the world need to be further studied from a clinical perspective, in addition to the legal and psychological view. More prospective large-scale studies are needed to add data to the literature, including intervention studies. The present study is the first to demonstrate that the place of discontinuation of antitumor treatment affects the advance directives rates, and is the first study assessing the reality of advance directives amongst oncologic patients in Brazil.

This conclusion is important if we consider the current development of the therapeutic arsenal and the prolongation of patient survival, with a concomitant gain in quality of life and "chronification" of disease. It brings a natural tendency to postpone the discussion of the advanced care plan to a later moment after all therapeutic lines had failed. The transition to best supportive care could represent a window for discussions about end of life, for the valorization of patient's autonomy, self-determination, and to preserve dignity in the death and dying process. In addition, this study suggests that the outpatient scenario is the best for the elaboration of advance directives. Medical assistants should always discuss the aspects of the end of life care with their patient, preferably in the office and on the most appropriate occasions. The focus should always be on dignity and respect for the desires of the patient, from the beginning to the end.

ACKNOWLEGMENTS

We thank all the palliative patients of our institution, for the possibility of using their medical records for doing science and give information and results to other patients around the world.

AUTHOR'S CONTRIBUTION

Pedro Grachinski Buiar: Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

Jose Roberto Goldim: Data analysis and interpretation, Final approval of manuscript, Manuscript writing.

Vania Naomi Hirakata: Data analysis and interpretation.

REFERENCES

1. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff. 2008 May/Jun;27(3):759-69.

2. Fried TR, Redding CA, Robbins ML, Paiva A, O'Leary JR, Iannonne L. Stages of change for the component behaviors of advance care planning. J Am Geriatr Soc. 2010 Dec;58(12):2329-36.
3. Jones AL, Moss AJ, Harris-Kojetin LD. Use of advance directives in long-term care populations. NCHS Data Brief. 2011 Jan;1(54):1-8.
4. Yadav KN, Gabler NB, Cooney E, Kent S, Kim J, Herbst N, et al. Approximately one in three US adults completes any type of advance directive for end-of-life care. Health Aff. 2017 Jul;36(7):1244-51.
5. Silveira MJ, Wiitala W, Piette J. Advance directive completion by elderly Americans: a decade of change. J Am Geriatr Soc. 2014 Apr;62(4):706-10.
6. Silveira MJ, Kim SY, Langa KM. Advance directives and outcomes of surrogate decision making before death. N Engl J Med. 2010 Apr;362(13):1211-8.
7. Degenholtz HB, Rhee Y, Arnold RM. The relationship between having a living will and dying in place. Ann Intern Med. 2004 Jul;141(2):113-7.
8. Levi BH, Green MJ. Too soon to give up: reexamining the value of advance directives. Am J Bioethics. 2010 Apr;10(4):3-22.
9. Teno JM, Gruneir A, Schwartz Z, Nanda A, Wetle T. Association between advance directives and quality of end-of-life care: a national study. J Am Geriatr Soc. 2007 Feb;55(2):189-94.
10. Pautex S, Herrmann FR, Zulian GB. Role of advance directives in palliative care units: a prospective study. Palliat Med. 2008 Oct;22:835–41.
11. Davison SN. End-of life care preferences and needs: perceptions of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010 Feb;5(2):195–204.
12. Kelley AS, Wenger NS, Sarkisian CA. End of life care preferences and planning among older Latinos. J Am Geriatr Soc. 2010 Jun;58(6):1109–16.
13. Kardamanidis K, Lim K, Cunha C, Taylor LK, Jorm LR. Hospital costs of older people in New South Wales in the last year of life. Med J Aust. 2007;187(7):383–6.
14. Moorin RE, Holman CDJ. The cost of in-patient care in Western Australia in the last years of life: a population based data linkage study. Health Policy. 2008;85(3):380–90.
15. Access Economics (AUS). Population ageing and the economy. Canberra: Department of Health and Aged Care - Australian Government; 2001.
16. Bercovitz A, Gruber-Baldini AL, Burton LC, Hebel JR. Healthcare utilization of nursing home residents: comparison between decedents and survivors. J Am Geriatr Soc. 2005;53(12):2069–75.
17. Anker SD, Coats AJ, Morley JE. Evidence for partial pharmaceutical reversal of the cancer anorexia-cachexia syndrome: the case of anamorelin. J Cachexia Sarcopenia Muscle. 2015 Dec;6(4):275-7.
18. Ezeoke CC, Morley JE. Pathophysiology of anorexia in the cancer cachexia syndrome. J Cachexia Sarcopenia Muscle. 2015 Dec;6:287-302.
19. Toscani F, van der Steen JT, Finetti S, et al. End of Life Observatory-Prospective Study on Dementia Patients Care (EoLO-PSODEC) research group. Critical decisions for older people with advance dementia: a prospective study in long-term institutions and district homecare. J Am Med Dir Assoc. 2015;16(6):535.e13-20.
20. Sobin LH, Gospodarowicz MK, Wittekind CH. TNM classification of malignant tumours. 7th ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2010.
21. Hui D, De La Cruz M, Mori M, Parsons HÁ, Kwon JH, Torres-Vigil I, et al. Concepts and definitions for "supportive care," "best supportive care," "palliative care," and "hospice care" in the published literature, dictionaries and textebooks. Support Care Cancer. 2013 Mar;21(3):659-85.
22. Koedoot CG, Oort FJ, Haan RJ, Bakker PJ, Graeff A, Haes JC. The content and amount of information given by medical oncologists when telling patients with advanced cancer what their treatment options are. Palliative chemotherapy and watchful-waiting. Eur J Cancer. 2004 Jan;40(2):225-35.
23. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol. 2004 Jan;22(2):315-21.
24. Mack JW, Cronin A, Keating NL, Taback N, Huskamp HA, Malin JL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. J Clin Oncol. 2012;30:4387-95.
25. Kierner KA, Hladschik-Kermer B, Gartner V, Watzke HH. Attitudes of patients with malignancies towards completion of advance directives. Support Care Cancer. 2010;18(3):367-72.
26. Martin RS, Hayes B, Grogorevic K, Lim WK. The effects of advance care planning interventions on nursing home residents: a systematic review. J Am Med Dir Assoc. 2016 Apr;17:284-93.
27. Hillman K. Dying safely. Int J Qual Health Care. 2010;22(5):339–40.
28. Wright AA, Keating NL, Balboni T, Matulonis UA, Block SD, Prigerson HG. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. J Clin Oncol. 2010 Oct;28(29):4457–64.

29. Miller RJ. Predicting survival in the advanced cancer patient. Henry Ford Hosp Med J. 1991;39:81-4.
30. Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. CA Cancer J Clin. 2005 May/Jun;55(3):164-77.
31. Kolva E, Rosenfeld B, Saracino R. Assessing the decision-making capacity of terminally Ill patients with cancer. Am J Geriatr Psychiatry. 2018 May;26(5):523-31.
32. Kwon SH, Im SH, Cho KW, Yoon SJ, Oh SY. Most advance directives written by patients with advanced cancer or their proxies request only minimally invasive treatments during end-of-life care. Am J Hosp Palliat Care. 2012;29(8):622-6.
33. Evans N, Bausewein C, Meñaca A, Andrew EV, Higginson IJ, Harding R, et al. A critical review of advance directives in Germany: attitudes, use and healthcare professionals' compliance. Patient Educ Couns. 2012 Jun;87(3):277-88.
34. Aw D, Hayhoe B, Smajdor A, Bowker LK, Conroy SP, Myint PK. Advance care planning and the older patient. QJM. 2012 Mar;105(3):225-30.
35. Cohen J, Pivodic L, Miccinesi G, Onwuteaka-Philipsen BD, Naylor WA, Wilson DM, et al. International study of the place of death of people with cancer: a population-level comparison of 14 countries across 4 continents using death certificate data. Br J Cancer. 2015 Nov;113(9):1397-404.
36. Jeurkar N, Farrington S, Craig TR, Slattery J, Harrold JK, Oldanie B, et al. Which hospice patients with cancer are able to die in the setting of their choice? Results of a retrospective cohort study. J Clin Oncol. 2012 Aug;30(22):2783-7.
37. Miles SH. Advanced directives to limit treatment: the need for portability. J Am Geriatr Soc. 1987 Jan;35(1):74-6.
38. Bomba PA, Kemp M, Black JS. POLST: an improvement over traditional advance directives. Cleve Clin J Med. 2012 Jul;79(7):457-64.
39. Schmidt TA, Zive D, Fromme EK, Cook JN, Tolle SW. Physician orders for life-sustaining treatment (POLST): lessons learned from analysis of the Oregon POLST Registry. Resuscitation. 2014 Apr;85(4):480-5.
40. Mahon MM. An advance directive in two questions. J Pain Symptom Manage. 2011 Mar;41:801-7.
41. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug;363(8):733–42.