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Assessment of the impact of comorbidity on the survival of cancer patients treated by palliative care teams

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ABSTRACT

Objective: The usefulness of the age-adjusted Charlson Comorbidity Index (ACCI) as a gauge of the impact of comorbidity on survival is known in the geriatric population. In palliative care, there is little research studying the correlation between comorbidity and survival in the advanced stages of oncological disease. The aim of our study was to explore the impact of comorbidity, measured with the ACCI, on survival in our patients. Our hypothesis was that higher ACCI scores would be associated with lower survival rates after the first visit.

Method: We conducted a prospective observational study over one year. Patients were attended by palliative home care teams. The main variables were: survival from metastatic disease after the first visit and ACCI score on the first visit. We also employed a descriptive analysis and a Kaplan–Meier survival analysis, including different ranges of ACCI scores.

Results: The final sample included 66 subjects. The standard patient was a 76-year-old man with lung cancer who had received chemotherapy. The overall average ACCI score was 10.45. Significant differences were found between the different locations of metastatic disease (greater survivals in breast, ovary, and prostate; $p = 0.005$) and some treatments (hormone and radiotherapy; $p = 0.001$ for each), but not from the first visit. We found lower survival rates among lung cancer patients with higher comorbidity (ACCI $\geq 11, p = 0.047$), with no differences on other primary locations or overall values.

Significance of results: The data show that comorbidity measured by the ACCI may be an interesting prognostic factor during the late stages of disease, as we have found in lung cancer. More research is certainly needed.

KEYWORDS: Comorbidity, Survival analysis, Prognosis, Advanced cancer, Palliative care

INTRODUCTION

The main aim of palliative care is to ensure a patient's quality of life and manage all the aspects related to good symptom control. However, the question of survival and its related factors is also relevant (Temel et al., 2010), especially where the management of prognosis information is concerned. Regarding the latter, we believe there is a need for better knowledge of matters relating to comorbidity and its impact on survival during the final stages of life.

The association between morbidity and mortality in geriatric populations (Guralnick et al., 1996) and during the initial stages of oncological disease has been widely studied (Ouellette et al., 2004; Singh et al., 1997; Birim et al., 2005; Smith et al., 2011; Koppie et al., 2008; Santos-Arrontes et al., 2008; Tetsche et al., 2008; Albertsen et al., 2011; Fernandez-

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Ruiz et al., 2009). The usefulness of the Charlson Comorbidity Index (CCI) as a gauge of the impact of comorbidity on survival in geriatric populations is well known (Charlson et al., 1987; Guitérrez-Misis et al., 2012). Its usefulness as an aid in decision making in non-oncological diseases such as terminal kidney disease (Yong et al., 2009; Beddhu et al., 2000) and COPD (Blinderman et al., 2009) is also well documented. The correlation between the severity of comorbidity, measured with the CCI, and various outcomes related to survival has been studied in patients with colorectal cancer (Ouellete et al., 2004), head and neck cancer (Singh et al., 1997), non-small-cell lung cancer (Birim et al., 2005; Smith et al., 2011), bladder cancer (Koppie et al., 2008), renal clear-cell cancer in localized stages (Santos-Arrontes et al., 2008), ovarian cancer (Tetsche et al., 2008), prostate cancer (Albertsen et al., 2011) and extrahepatic cholangiocarcinoma (Fernandez-Ruiz et al., 2009). The CCI is mainly employed as a decision-making aid (Smith et al., 2011). In oncological diseases, the impact of comorbidity on survival is well established (Piccirillo et al., 2004). This impact is more noticeable in patients with tumors with a longer natural history than in those with more aggressive forms of cancer (Legler et al., 2011; Read et al., 2004).

In the field of palliative care, comorbidity has been studied as a response-modulating factor in the control of symptoms (Currow et al., 2007), and has been used in multiple studies as a control variable (Yong et al., 2009). The few existing studies in advanced oncological disease seem to indicate that comorbidity is not correlated with survival (Santos-Arrontes et al., 2008; Gettman et al., 2003). However, these data were gathered in a population with single tumor locations (i.e., renal clear-cell carcinoma). Furthermore, this research sought to assess comorbidity from initial diagnosis rather than during the final stages of the disease.

The objective of our study was to explore the impact of comorbidity, measured with the age-adjusted Charlson Comorbidity Index (ACCI), on survival in patients treated by a palliative care team (PCT) who have solid primary tumors in different locations, under the hypothesis that higher ACCI scores would also be associated with lower survival during the later stages of the disease.

METHODS

A prospective observational study was carried out. All individuals who consecutively entered the home care program as new patients during the study period were included. The calculated sample size ranged from 57 to 95. The inclusion criteria were as follows: every new patient over 18 who received a first visit from a palliative home care team (PHCT) with a score of less than 6 points on the Palliative Prognostic Index (life expectancy of more than 3 weeks) (Morita et al., 1999); all patients who agreed to be part of the study by informed consent; and all patients who died before follow-up. With the aim of obtaining a sufficient sample for each of the tumor locations, the oncological criteria were defined as consisting of:

- solid primary neoplasm with anatomo-pathological diagnosis in one of the locations with higher prevalence and mortality in Navarre (Navarre Institute of Public Health, 2007; Navarre Health System, 2008): lung, colorectal, breast, prostate, stomach, and ovary
- metastatic disease—defined by the evidence of progression, either loco-regional or distant—that impeded a healing approach.

We registered all new patients who entered the home care program since the initial date of the study until there were 100 patients in the sample or the date of final follow-up arrived (always staying within the range of the calculated sample size). The linkage between the number assigned to each patient and the number of the medical history in our computer program was recorded in a separate document with the aim of "blinding" subsequent statistical analysis. Data on patients excluded from the study were collected and classified according to the exclusion criteria and subsequently presented in a flowchart.

The main variables were: survival since diagnosis of metastatic disease (in days), survival since the first visit (in days), and ACCI score (Charlson et al., 1987) on the first visit. Other sociodemographic and health variables collected were: sex, age, location of primary tumor, anatomo-pathological strain, received treatment (chemotherapy, radiotherapy, hormone therapy or surgery), and Palliative Performance Scale (PPS) score.

The information sources consulted were our software application and the computerized medical histories of the Navarre Health Service, including both hospital and primary care facilities, in order to make ACCI scores more reliable.

We analyzed the data using SPSS (v. 19) software, carrying out a descriptive analysis. Kaplan–Meier survival analysis was performed to assess the relationship between survival and comorbidity. To assess survival in each of the comorbidity groups, a separate analysis was carried out for different ranges of comorbidity on the ACCI, in order to see whether there was a significant cutoff point.

The study and the informed consent form were approved by the ethics committee of the Hospital San Juan de Dios in Pamplona.

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RESULTS

The data collection period ran from May 2, 2011 to June 30, 2012. In total, 269 patients were analyzed (Figure 1), of which 171 were men (63.5%) and 98 women (36.5%). Some 25% (16) of the final sample of 66 patients was female and 75% (50) male. At the time of final follow-up, 66 patients died, and those were the final sample. The average age was 76.

The tumor locations for the total study population are shown in Table 1. The overall average ACCI score (Figure 2) was 10.45 ($SD = 1.94$). Table 2 shows the received treatments, chemotherapy being the most common (65.2%).

The mean and median survivals are shown in Table 3 (see Figure 3: survival, time elapsed since first visit). A sufficient sample was obtained for this analysis only in cases of lung, colorectal, prostate, and stomach cancer (but not for ovarian and breast tumors). As to the Kaplan–Meier curves for survival, significant differences in survival since metastatic disease diagnosis were found between the different tumor locations, with greater survival in breast, ovary, and prostate tumors (log rank = 16.92, $p = 0.005$). However, we did not find differences in survival since the first visit (log rank = 4,047, $p = 0.5$).

We found a higher survival rate from metastatic disease in those who had received hormone therapy or radiotherapy, with statistically significant differences ($p = 0$, 001 for both). However, we did not find these differences in survival, since the first visit or according to primary tumor location.

We also analyzed differences in survival according to ACCI score and different breakpoints and found shorter survival in lung cancer patients with statistically significant ($p = 0.047$) higher comorbidity (ACCI $\geq$ 11; see Figure 4, Table 4), with no differences in other primary tumor locations or overall values.

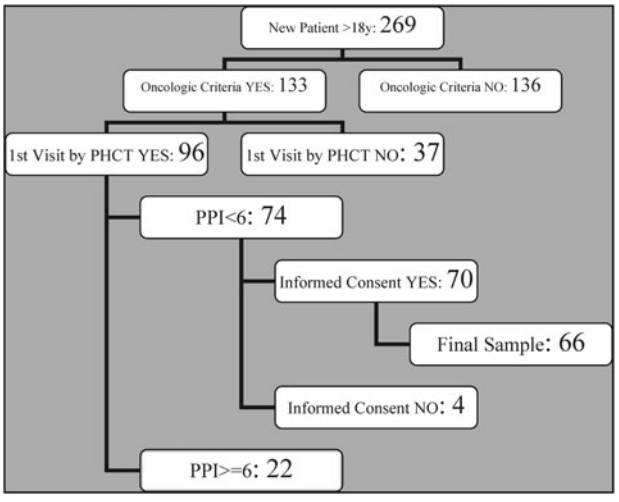

Fig. 1. Flowchart.

DISCUSSION

We believe that ours is the first study to perform a specific assessment of the correlation between comorbidity and survival exclusively during the final stages of oncological disease in a population served by palliative care teams (PCTs). Our data show that comorbidity is a prognostic factor with statistically significant weight, at least in the late stages of lung cancer in patients attended by a PCT.

When considering survival in lung cancer, it is mandatory to take into account the work of Temel and colleagues on non-small-cell lung cancer and early palliative care (Temel et al., 2010). That research group demonstrated a positive impact of early introduction of a specific PCT on quality of life and symptom control in their population. They also showed a possible positive effect upon survival in this group, compared to those in standard care. However, they did recognize the limitations of this conclusion, as survival was not a main aim of their research. In our study, we registered tumor locations instead of strains, so our sample does not allow a strict sub-assessment of a group similar to the one used by the Temel group. In addition, we believe that our patients, as we shall explain below, were included in our home care program at a much later stage than those in Temel's sample, which means such a comparison would be inappropriate. Aside from that, Temel and associates did not find it necessary to register comorbidity, whereas it was the main variable in our study. Therefore, we believe that,

Table 1. *Primary location (included in the study)*

Lung	45 (22 included)
Colorectal	35 (18)
Prostate	23 (11)
Pancreas	22
Stomach	21 (9)
Head and neck:	17
Brain	16
Breast	11 (4)
Bladder	9
Liver or bile ducts	8 each one
Kidney or soft tissues	7 each one
Primary unknown	6
Utero, lymphoma, leukemia, or melanoma	4 each one
Ovary (2 included), AMS or esophagus	3 each one
Mesothelioma, myeloma, small intestine, or myelodisplastic syndromes	2 each one
Cervix	1

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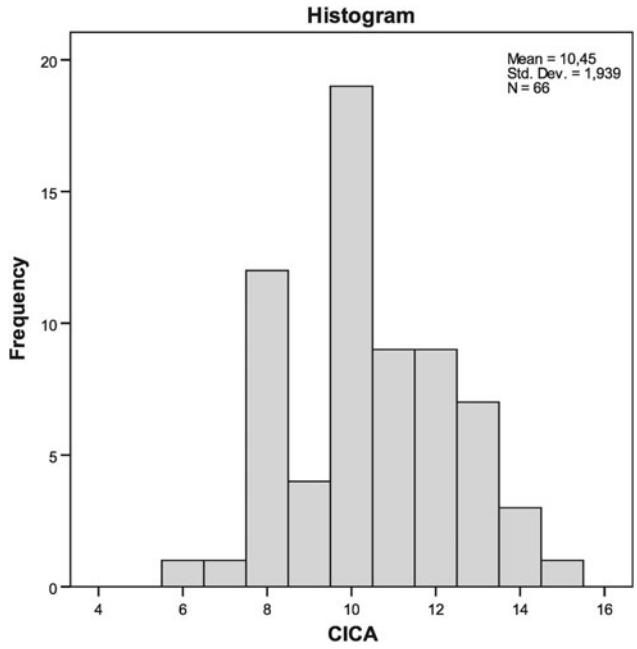

Fig. 2. Charlson Index distribution.

although both Temel's and our studies present data on survival in lung cancer patients, any potential comparison between the two would require more detailed analysis.

According to the literature reviewed (Gomez-Baptiste et al., 2001; Trujillo et al., 2007; Molina et al., 2008; Pita et al., 2009; Alonso-Babarro et al., 2011), data from a sample cared for by a PHCT are similar to the epidemiological data from the general population. In our study, sociodemographic variables confirmed this information with regard to sex and age, but not so with regard to tumor location. Our sample shows a sex distribution similar to that of other studies (59.4–68% of men in the literature vs. 63.5% in our study) (Gomez-Baptiste et al., 2001; Trujillo et al., 2007; Molina et al., 2008; Alonso-Babarro et al., 2011). Our age distribution (mean and median around 75 years) is also comparable to the ranges found in the literature (average of 66.7–73.3; Trujillo et al., 2007; Molina et al., 2008; Pita et al., 2009; Alonso-Babarro et al., 2011; or 76% over 60 years, Gomez-Baptiste et al., 2001).

Survival from metastatic disease matches ranges reported in the literature (Molina et al., 2008; Alonso-Babarro et al., 2011), which, in our opinion,

Table 2. *Oncological treatments (only sample)*

Chemotherapy	65.2%
Hormone therapy	22.7%
Surgery	31.8%
Radiotherapy	39.4%

Table 3. *Mean and median survival (days)*

Survival	Mean (*SE*)	Median (*SE*)
From metastatic disease (SMD)	545.92 (74.31)	272 (57.38)
From first visit (S1V)	66.39 (7.4)	41 (8.63)

indicates a similarity between both populations. Median survival since the first visit (equivalent to time in the program) was 41 days, similar to previously reported data (Alonso-Babarro et al., 2011).

Although our ACCI global average score (10.45 points) seems to indicate that our sample is comparable to those employed in other studies in terms of comorbidity, most of the research we know of utilizes the general CCI, which is not adjusted for age. Furthermore, other studies carried out to date tend to include their patients from the time of diagnosis or, in some cases, since the beginning of active therapy. Therefore, we have found no studies with which to establish a direct comparison of our results.

The data in the literature on the subject of received treatments (surgery 35%, chemotherapy 31.52%, radiotherapy 21.19%, hormone therapy 7.61%) (Molina et al., 2008) match ours only regarding surgery (31.8%), as our sample presented higher percentages of CT (65.2%), RT (39.4%), and HT (22.7%). We believe that this can be explained by the current trend to extend cancer treatment (especially chemotherapy). In addition, the increase of the radiotherapy spectrum in recent years may also have had an impact on these results. However, it is our view that these matters exceed the purpose of our study.

Tumor location is also an important aspect of our study. Our data are consistent with those reflected

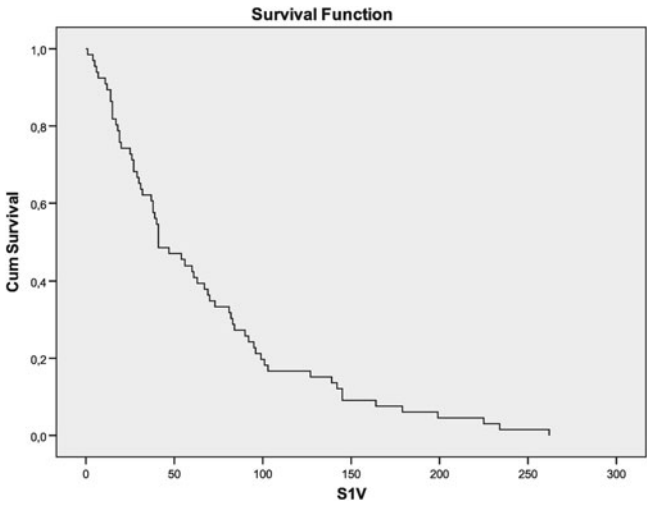

Fig. 3. Survival from first visit.

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in the literature (Gomez-Baptiste et al., 2001; Trujillo et al., 2007; Molina et al., 2008; Alonso-Babarro et al., 2011), with great similarity in some cases (Pita et al., 2009). However, our findings differ from previous studies in terms of correlation with the epidemiological findings in our local area (Hauser et al., 2006). The higher prevalence of breast and ovarian cancer in Navarre (Navarre Health System, 2008), together with the associated high mortality rates (Navarre Institute of Public Health. 2007), are not reflected in the population covered by our service. In turn, pancreatic cancer, head and neck cancer, and CNS tumors all feature at higher rates in our work than in the epidemiological data. This discrepancy was already identified by Viguria and Rocafort (1999) with data from the same service. However, in that case, patients were mostly hospitalized and the palliative care program was in its early stages of implementation.

We believe that this highlights several important issues. Our first inclusion criterion was based on prevalence and mortality due to cancer in Navarre. In view of the aforementioned results, it is clear that this criterion was not suitable, since it resulted in exclusion of 50% of the population we serve. This would make our results less applicable to the entire population, restricting the results mainly to the four examined locations (lung, colorectal, prostate, and stomach). However, we believe this factor does not alter the validity of our results.

A second matter to review has to do with the referral criteria. Both the time of the first visit and the location of the tumor in our patients are dependent variables based on referral criteria external to our service (which are not modifiable). We believe that this fact surely affects data on survival since the first visit (not since diagnosis of metastatic disease), as well as the differences in the epidemiological data. This leads us to suspect that other factors are involved, which may include the greater symptomatic impact of certain tumor locations compared to others, the presence of symptoms that are more disturbing than others, the aesthetic impact, and the greater impact on caregivers of certain tumors compared to others. However, it is clear that these questions have little to do with the main objectives of our study.

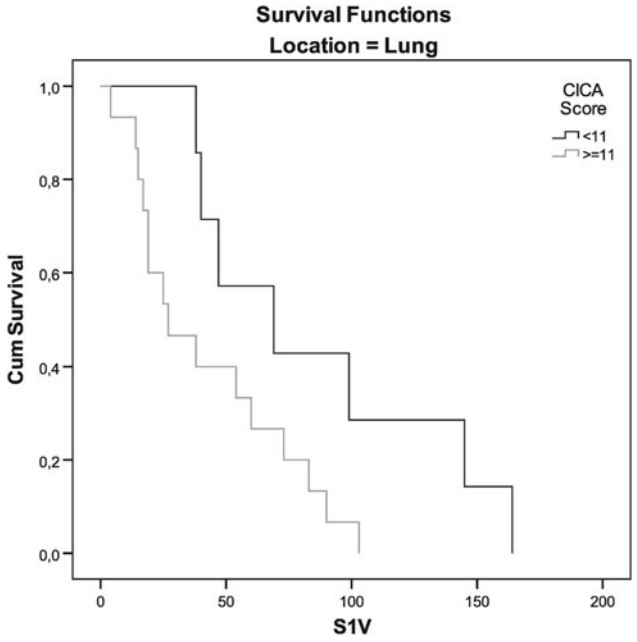

Fig. 4. Survival of lung cancer patients from first visit (ACCI cutoff = 11).

Our findings on improved survival from metastatic disease in patients treated with hormone therapy or radiotherapy are interesting. We believe that no conclusion can be drawn due to the many factors not analyzed (because they were not primary objectives of our study). However, these results are congruent with the established evidence on these treatments. They also showed no differences in survival since the first visit, even when analyzing different primary locations. This concerns the natural history of each tumor, especially survival during the final stages of the disease in a population such as ours, with a median survival of less than two months. There are studies that claim that the relevance of location for prognosis varies at different stages of the disease (Hauser et al., 2006). Location, treatment, and comorbidity seemed to have considerable weight at the beginning, which disappeared toward the end stages. Our results are consistent with this hypothesis. In the stages where we take care of patients, there are no differences in survival related to the various tumor locations analyzed or treatments received since the first visit. However, comorbidity measured with the ACCI shows a correlation with survival in lung cancer, with a cutoff point at 11. We did not find any other results with statistically significant differences, whether overall or in other tumor locations. This could be due to our small sample size. Despite this, we believe that this result suggests that the ACCI could be a better prognostic factor than location or treatments received for patients from the time they are admitted to a palliative care program.

Table 4. *Lung cancer and survival from first visit, ACCI breakpoint = 11*

ACCI Score	Mean (*SE*)	Median (*SE*)
<11	86 (19.5)	69 (28.8)
≥11	42.7 (8.25)	27 (12.23)

Log rank = 3.94, $p = 0.047$.

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Some authors employed CCI score ranges instead of total scores when assessing the impact of comorbidity. Santos-Arrontes and colleagues (2008) found significant differences in survival in patients with located (but not advanced) stages of clear-cell renal carcinoma and CCI scores equal to or less than 2. They employed these results to recommend an expected attitude toward patients with CCI scores higher than 2, apparently because survival in these cases seemed more influenced by comorbidity than by aggressive surgical treatment. Other investigators found an ACCI cutoff point at 5 or higher associated with a relative risk of 1.1 for overall survival for each point of the ACCI (Smith et al., 2011). Our data differ from these two studies in terms of the lower impact of comorbidity during these stages. We found differences in survival between the groups with less and more comorbidity, using several cutoff points and different primary locations, with the aforementioned exception of lung cancer.

We have acknowledged some possible limitations of our study. The selection of locations and the arbitrary referral criteria of our service have been discussed. To this we must add the possibility of low statistical power due to small sample size. Nevertheless, our sample size was within the range of our calculations prior to the study. We also believe it would have been useful to collect PPI and PPS data from the general population, because these are independent factors with forecasting potential. This would help us increase the homogeneity of our sample. Finally, we believe there are uncontrolled variables in both samples that could explain the different survival figures for the radiotherapy and hormone therapy groups.

In conclusion, we believe that the results of our study support the initial hypothesis that comorbidity, measured with the ACCI at the first visit with a palliative home care team, may be an interesting prognostic factor during the late stages of the disease, as we have found in lung cancer. We contend that this is the first study of its kind in this population, and that further work with larger samples is needed to further this line of inquiry.

DISCLOSURES

The authors state that they have no potential conflicts of interest to declare.

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