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Determinants of cancer treatment and mortality in older cancer patients using a multi-state model: Results from a population-based study (the INCAPAC study)

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ABSTRACT

Introduction: Several studies have reported disparities in the care management and survival of older cancer patients. The aim of our study was to identify determinants of treatment administration in this population of cancer patients aged over 65 years taking into account competing risks of death.

Methods: The INCAPAC study is a population-based study. Four cancer registries and three prospective cohort studies on older subjects (age ≥65 years) from Gironde, a French department, were merged to identify older cancer patients. We used a non-parametric multi-state model including three states (cancer, treatment and all-cause death). This model allowed studying determinants of treatment administration (all treatments including curative, symptomatic and palliative treatments) and mortality considering that patients can move from cancer state to death state, either directly or through the treatment phase. Studied variables were demographic and socioeconomic-, cancer-, health-, and geriatric-related.

Results: A total of 450 patients were included in the analyses. They were mainly aged 85 and over, men and educated. Among included patients, 372 (83%) received cancer treatment. In the final multivariate model, dementia was associated with a lower likelihood of receiving cancer treatment (HR = 0.68, 95% CI = 0.47–0.99). In treated patients, age, sex, comorbidities, dependency and stage at diagnosis were associated to all-cause mortality, and in untreated patients, diagnosis of dementia and stage at diagnosis were associated to mortality.

Conclusion: Further studies are necessary to understand the impact of geriatric impairments on treatment administration and to develop clinical practice guidelines.

1. Introduction

With 14.1 million new cases and 8.2 million deaths in 2012, cancer is a major cause of morbidity and mortality worldwide [1]. More than half of all cancer cases and deaths occur in people aged 65 and over, and this trend is likely to increase in the coming years, mainly due to the ageing population [2].

Some studies have reported disparities in terms of care management and survival between the older adults and their younger counterparts. These studies highlighted that older patients are diagnosed at a later

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Table 1
Sources, recording time and details of studied variables, the INCAPAC study.

Variable	Source	Recording time	Reporting way	Details
Age	Cancer registries	Diagnosis of cancer	Physician	65–79 years 80–84 years 85 years and over
Sex	Cancer registries	Diagnosis of cancer	Physician	Female Male
Living alone	Cohort studies	Pre-diagnosis visit	Self-reported	Yes No
Education	Cohort studies	Inclusion visit	Self-reported	Primary school or less Higher than primary school
Advanced stage of cancer	Cancer registries	Diagnosis of cancer	Physician	Yes No
Number of daily drugs	Cohort studies	Pre-diagnosis visit	Self-reported + inspection of drug packages and prescription forms	0–6 > 6
Hierarchical dependency	Cohort studies	Pre-diagnosis visit	Self-reported + evaluation by a neuropsychologist	Autonomy or low dependency Moderate or high dependency
Dementia	Cohort studies	Pre-diagnosis visit	Physician	Yes No

stage, are less likely to receive either adjuvant or any treatment at all and have a poorer survival [3]. Among older patients, some studies also reported disparities in care (e.g. treatment, treatment delay) and survival based on age [4–7], race [5,7–10], socioeconomic status [4,6,7], area of residence [11] or presence of comorbidities [4,5,7,8]. Advanced stage at diagnosis has also been associated with poorer survival, a shorter delay to treatment and a lower likelihood of undergoing surgery or of receiving adjuvant chemotherapy [4–7,9,11]. Moreover, some studies showed that older cancer patients with dementia received less specific cancer treatment [12–16].

Ageing population represents a challenge to healthcare systems particularly in cancer care [17]. The scarcity of data from clinical trials and the lack of guidelines may contribute to undertreatment of older cancer patients [18]. Possible reasons of undertreatment include concerns regarding toxicity, morbidity, lack of access to care and physician and patient preferences [19,20]. Therefore, understanding which older cancer patients do not receive treatment is an important question to address adequate interventions.

Although numerous population-based studies have observed disparities in care management and survival among older cancer patients, most of them used data from cancer registries or administrative databases. Thus, few of them used individual information to measure socioeconomic status, and some disregarded specific geriatric impairments (cognitive status, functional status, etc). Lastly, most studies examining the determinants of treatment administration did not take into account the competing risk of death, especially high in the older population [21]. A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest.

In order to understand which older cancer patients receive treatment, we conducted this population-based study in French older cancer patients (INCAPAC) to identify determinants of treatment administration accounting for competing risk of death. This study also aimed at identifying determinants of all-cause mortality in this population.

2. Patients and methods

2.1. Study population and data

The INCAPAC study is a population-based study. The French department of Gironde (1.5 million inhabitants) is covered by four cancer registries: three site-specific (mesothelioma, central nervous system, and hematological malignancies registries) and a general population-based (recording all other tumors) registries. Gironde registries are part of the French National Public Health agency and the National Cancer Institute. In addition, three cohort studies enrolling subjects aged 65 years and over were initiated in Gironde: the PAQUID (1998) [22], the 3-City (1999) [23], and the AMI (2007) studies [24]. A major interest of these cohorts is to collect a large amount of individual data on the included participants. Using number of alive subjects in cohorts, cancer incidence and mortality rate in older adults, we estimated the sample size at 620 older cancer patients.

We merged data from the cancer registries and the cohorts to identify older cancer patients. Data were merged matching on last name, first name, date of birth, postcode and place of residence. We included subjects i) aged 65 years and over from the PAQUID, the 3-City or the AMI study; ii) alive on January 1st 2005 (common start date of tumor recording); iii) resident in Gironde; and iv) with a validated cancer diagnosis recorded in one of the cancer registries from January 1st 2005 to December 31st 2014. We included all invasive malignant tumors (including skin tumors) and benign tumors of the central nervous system. For patients with multiple tumors, only one was considered: i) the first one diagnosed if there were several tumors with a minimum of a 6 months interval between their diagnosis, ii) the one with the worse prognosis if there were several tumors diagnosed within less than 6 months.

In order to not consider data about patients' characteristics that was too old, those with a delay between the last completed cohort follow-up visit before the cancer diagnosis and the diagnosis of cancer equal or superior to 6 years were excluded.

2.2. Outcomes

The primary outcome was first treatment administration defined as any cancer treatment (versus no treatment) including curative, palliative and symptomatic treatments. This information was registered by registries and qualified as unknown when no information was available about treatment receipt. All-cause mortality was the secondary outcome and was measured from the date of diagnosis. Patients were censored at time of death or at time of last contact with alive status from registries.

2.3. Studied variables

We identified the cancer pre-diagnosis visit in each cohort, which was the last completed follow-up visit before the cancer diagnosis. Studied variables were extracted from cohorts (face-to-face interviews) and registries (medical records) at different times (Table 1). We considered demographic and socioeconomic (age at diagnosis, sex, living alone, education), cancer-related (stage at diagnosis), health-related (number of daily drugs), and geriatric-specific (hierarchical dependency, diagnosis of dementia) characteristics. In our sample with a large range of cancer locations, advanced stage was determined from the presence of metastases in solid tumors (except for central nervous system tumors where grade was used) and medical expertise (AM,PS) for hematological malignancies. The number of daily drugs was used as

a proxy of comorbidities [25]. Hierarchical dependency was determined from Activities of Daily Life (ADL) [26,27], Instrumental Activities of Daily Life (IADL) [28] and the Rosow and Breslau scale [29]. A patient was considered as presenting moderate or high dependency if he/she was classified as dependent on IADL and/or ADL. Dementia was actively screened for in cohort studies, with a two-step diagnosis: a cognitive evaluation made by a neuropsychologist through a series of psychometric tests, followed by an examination by a senior neurologist for participants suspected of having dementia. Finally, the diagnosis was validated by an independent committee of neurologists and geriatricians, based on DSM-IV (Diagnostic and Statistical Manuel of mental disorders – Fourth edition) criteria [30]. All types of dementia were considered. Dependency is part of the dementia process, as the diagnosis of dementia requires both the presence of cognitive decline and a repercussion on ADL. However, dependency can also be due to other causes, such as physical causes. Studying both dementia and dependency allows to assess different geriatric impairments.

Besides individual data, we also considered the number of general practitioners per 100,000 inhabitants as first quartile versus others (≤79.5 versus > 79.5). These data were provided by a dedicated national institution (Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques).

2.4. Statistical analyses

The population was described according to patient, tumor and care-management characteristics.

In order to take the competing-risk of death into account, we used a non-parametric multi-state model that included the following three states: 0) cancer; 1) treatment; 2) all-cause death (Fig. 1) [31]. All individuals started in state 0 and could eventually end up in the absorbing state 2, visiting or not the intermediate state 1. For each transition, the model allowed evaluating the impact of risk factors in the transition, providing the hazard ratio (HR): risk of receiving treatment, risk of death in patients who received treatment, risk of death in patients who did not receive treatment. The choice of variables in the initial multivariate model was performed based on the literature and variables were then selected using a stepwise procedure (final model). Because of their recurrence in the literature, age, sex and stage at diagnosis were retained in the final model irrespective of their significance. As few variables involved missing data and as they accounted for less than 5%, observations with missing data were not considered in the statistical analyses. Therefore, analyses were case-completed.

As some patients had a null delay between the diagnosis and the treatment administration (e.g. histological diagnosis during surgery), we modified the delay to one day to include them in the analysis. Additionally, we performed a sensitivity analysis after excluding these patients.

Analyses were performed using SAS® 9.3 and the MState R package [32].

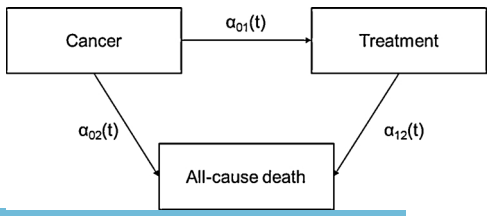

Fig. 1. Multi-state model. α_{01}, α_{12} and α_{02} are the intensity functions, the INCAPAC study.

3. Results

3.1. Sample characteristics

The study initially included 486 patients and 450 were included in the main analysis (Fig. 2). Patients' characteristics are presented in Table 2. Stage at diagnosis of patients with unknown treatment (n = 36, 7.4%) differed significantly from that of other patients ($p < 0.001$) and the former were more likely to have skin, prostate or liver cancer (data not shown).

After the cancer diagnosis, 372 (83%) patients received treatment. The median time between diagnosis and treatment initiation was 10 days (Q3 = 41, max = 906). The median follow-up after cancer diagnosis was 1.1 year (Q3 = 2.8, max = 8.4) and 240 (53%) patients died during follow-up. One year after the cancer diagnosis, the probabilities of being alive were 10.3% without treatment (cancer) and 54.2% having been treated for cancer at least once after diagnosis (treatment). The probability of being dead with or without receiving cancer treatment at least once (death) was 35.5% (Fig. 3). Four years after the cancer diagnosis, the probabilities were 3.1%, 30.7% and 66.2%, respectively.

Patients with a null delay were more likely diagnosed at an unknown stage ($p < 0.05$) and with skin or bladder cancer ($p < 0.05$) (data not shown) and were not significantly different concerning other characteristics.

3.2. Determinants of treatment administration and all-cause mortality (Table 3)

In the final multivariate multi-state model, age, sex and advanced stage at diagnosis were not associated with treatment administration. However, patients with dementia were less likely to receive treatment (HR = 0.68, 95% CI 0.47–0.99). Other factors initially considered (education, living alone, number of daily drugs, dependency, number of general practitioners) were not associated with treatment administration.

Untreated and treated patients diagnosed with an advanced stage had a higher mortality risk (HR = 7.73, 95% CI 3.92–15.24 and HR = 4.24, 95% CI 2.97-6.05, respectively). Results were similar for patients with unknown stage at diagnosis. Moreover, among untreated patients, those with dementia had a higher mortality risk (HR = 2.78, 95% CI 1.25-6.18) and among treated patients, the oldest (HR = 1.95, 95% CI 1.31-2.92), men (women HR = 0.55, 95% CI 0.39–0.78), those taking more than 6 daily drugs (HR = 1.67, 95% CI 1.22–2.28) and those presenting moderate or high dependency (HR = 1.73, 95% CI 1.22–2.44) had a higher mortality risk ().

3.3. Sensitivity analyses

After removing patients with a null delay between diagnosis and treatment (n = 300), the association between treatment administration and dementia was close to significance (HR = 0.62, 95% CI 0.36–1.08). Mortality results were similar to those from the main analysis.

4. Discussion

The main analyses showed that dementia preceding cancer diagnosis was significantly associated with a lower likelihood of receiving treatment. Stage at diagnosis was associated with all-cause mortality in untreated and treated patients. Dementia was associated with higher mortality risk in untreated patients only. Sex, number of daily drugs and dependency were associated with mortality in treated patients. In any analyses, living alone and education level were not retained. To our knowledge, this is the first population-based study that uses multi-state analyses.

Our results regarding treatment administration and older cancer

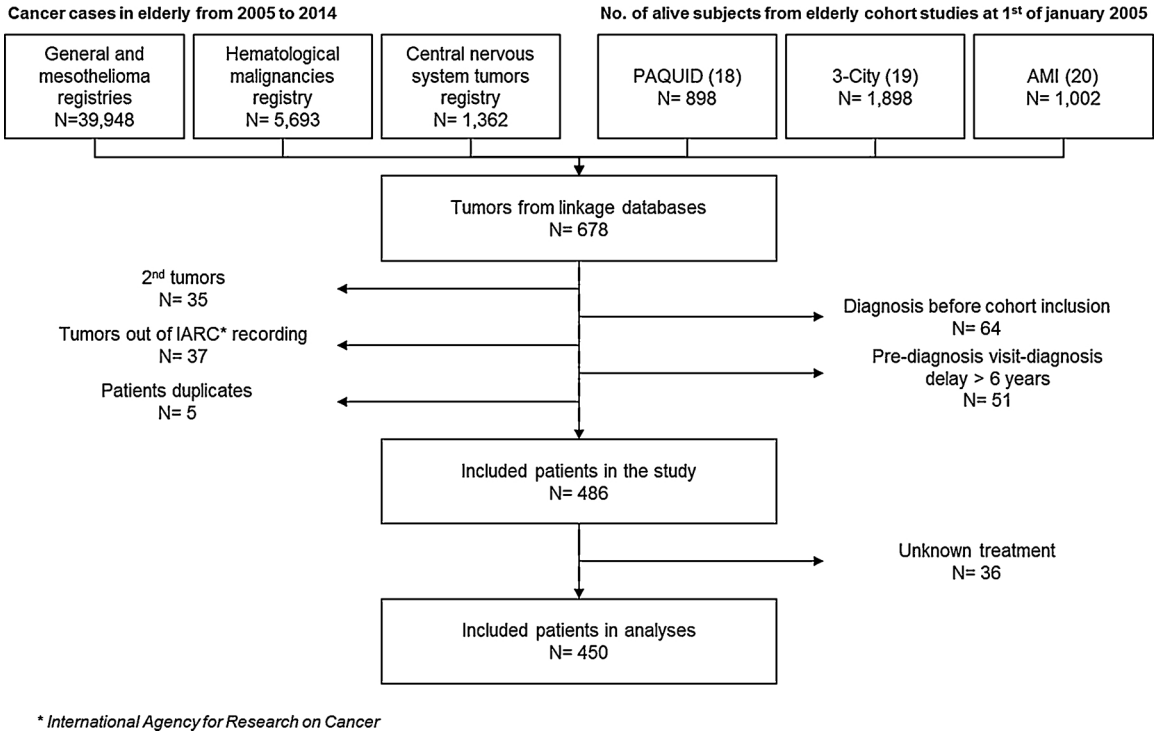

Fig. 2. Flow-chart of the INCAPAC study.

Table 2
Patient characteristics in the INCAPAC study (n = 450).

	N	(%)
Age at cancer diagnosis		
65–79	130	(28.9)
80–84	148	(32.9)
85+	172	(38.2)
Sex		
Men	246	(54.7)
Women	204	(45.3)
Education		
Primary school or less	214	(47.6)
Higher than primary school	236	(52.4)
Living alone (pre-diagnosis visit)		
No	275	(61.1)
Yes	175	(38.9)
Number of daily drugs (pre-diagnosis visit) (n = 447)		
≤6	269	(60.2)
> 6	178	(39.8)
Hierarchical dependency (pre-diagnosis visit) (n = 429)		
Autonomy or low dependency	296	(69.0)
Moderate or high dependency	133	(31.0)
Dementia (pre-diagnosis visit) (n = 448)		
No	391	(87.3)
Yes	57	(12.7)
Number of general practitioners per 100,000 inhabitants in place of residence at diagnosis		
≤79.5	119	(26.4)
> 79.5	331	(73.6)
Advanced stage at diagnosis		
No	283	(62.9)
Yes	117	(26.0)
Unknown	50	(11.1)
Cancer site		
Colon-rectum	77	(17.1)
Skin other than melanoma	60	(13.3)
Hematological malignancies	59	(13.1)
Prostate	49	(10.9)
Breast	35	(7.8)
Other	170	(37.8)

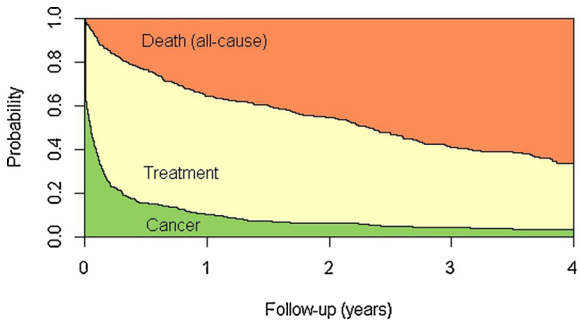

Fig. 3. Stacked probabilities of being in a given state at each follow-up time, estimated by the Aalen-Johansen estimator in the INCAPAC study (n = 450 patients).

patients with dementia are consistent with previous studies [12–16]. These findings may be explained by patient and care provider (first medical contact) characteristics. Firstly, patients with dementia face impaired communication skills that may lead to difficulties in grasping the healthcare system and in communicating with care providers [33]. Secondly, cognitive impairment may limit the way that medical physicians recommend treatments because of lower adherence due to impaired ability, side effects due to addition of treatments and poor prognosis [33–35]. Physicians' ethical point of view could explain that some older cancer patients with dementia did not receive treatment as decision to not refer patients to specialist oncologist (Delva BMC Cancer 2011). At last, patients' and relatives' preferences regarding treatment may also have an impact and explain our results (Puts Cancer Treat Rev 2015). Nevertheless, the impact of dementia on treatment administration in older cancer patients remains poorly studied. Our results using the multistate model revealed that advanced stage, age and comorbidities at diagnosis were not associated to treatment administration but associated with mortality.

Our results in treated patients emphasize that comorbidities and advanced stage at diagnosis were associated with higher mortality, which is consistent with previous reports [36–38]. Dependency

Table 3
Determinants of treatment administration and all-cause mortality in untreated and treated French older cancer patients, multi-state model, 2005–2014 (n = 425), the INCAPAC study.

	Treatment administration[a]			All-cause mortality in untreated patients[a]			All-cause mortality in treated patients[a]		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age at cancer diagnosis			0.571			0.335			**< 0.001**
65–79	1.00	–		1.00	–		1.00	–	
80–84	0.86	[0.65-1.14]		0.85	[0.36-1.99]		0.93	[0.62-1.41]	
85+	0.91	[0.68-1.20]		1.43	[0.58-3.51]		1.95	[1.31-2.92]	
Sex			0.779			0.873			**< 0.001**
Men	1.00	–		1.00	–		1.00	–	
Women	0.97	[0.78-1.21]		0.95	[0.54-1.70]		0.55	[0.39-0.78]	
Advanced stage at diagnosis			0.145			**< 0.001**			**< 0.001**
No	1.00	–		1.00	–		1.00	–	
Yes	0.78	[0.60-1.02]		7.73	[3.92-15.24]		4.24	[2.97-6.05]	
Unknown	0.83	[0.57-1.21]		5.05	[2.21-11.54]		2.33	[1.47-3.69]	
Number of daily drugs (pre-diagnosis visit)									**0.002**
≤6							1.00	–	
> 6							1.67	[1.22-2.28]	
Hierarchical dependency (pre-diagnosis visit)						0.285			**0.002**
Autonomy or low dependency				1.00	–		1.00	–	
Moderate or high dependency				1.50	[0.71-3.13]		1.73	[1.22-2.44]	
Dementia (pre-diagnosis visit)			**0.046**			**0.012**			
No	1.00	–		1.00	–				
Yes	0.68	[0.47-0.99]		2.78	[1.25-6.18]				

[a] Adjusted analyses on cohort studies.

(moderate or high) was also associated with higher mortality risk in this population. Association between functional limitations and mortality has been reported in few studies [39,40].

This study has some limitations. First, we cannot extrapolate our results by cancer site since our objective was to identify general factors in these older patients and we chose to evaluate treatment administration (all type versus not). Moreover our sample size was too small for subgroup analyses. Second, some variables such as diagnosis of dementia and hierarchical dependency were assessed at the cancer pre-diagnosis visit which could be up to 6 years before cancer diagnosis (median = 1.3 IQR = 1.4). However, this delay was mainly less than 3 years and allowed collecting information before the cancer could have any effect of the variables (pre diagnosis symptoms or diagnosis). Third, we cannot eliminate other potential factors and probably missed interesting data such as social vulnerability [41]. However, collecting these data may not be easy and in the present study their definition was not standardized among all the cohort studies.

On the other hand, the use of linked databases among cancer registries and cohorts represents the main strength of the present study. The use of data from cancer registries provided exhaustive, objective and validated cancer cases. Indeed, none of them were excluded regarding specific characteristics such as place of care (e.g. hospital type), comorbidities or frailty like in some other studies (e.g. hospital cohort studies, clinical trials). The sex distribution in our sample was similar to that reported in French older cancer patients [42]. Secondly, cohorts allowed obtaining individual socioeconomic data and provided geriatric-specific data about dependency and dementia. In this study, dementia was actively screened and validated by tests and medical experts and its prevalence was close to prevalence of dementia in Europe [43,44]. However, included older subjects in the three cohorts may be not representative to French older people.

In conclusion, our population-based study provided results on the association between cognitive impairment and the treatment administration in older cancer patients. Similar studies with geriatric-specific data that measure geriatric syndromes or frailty are needed, as well as an evaluation of the results in order to improve cancer care for older cancer patients.

Authorship contribution

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.

Conception and design

A Galvin, C Helmer, G Coureau, B Amadeo, A Monnereau, I Baldi, F Delva, S Mathoulin-Pélissier.

Acquisition of data

A Galvin, C Helmer, G Coureau, B Amadeo, F Delva, S Mathoulin-Pélissier

Analysis of data

A Galvin, P Joly, C Sabathé

Interpretation of data

A Galvin, C Helmer, G Coureau, B Amadeo, P Joly, C Sabathé, M Rainfray, P Soubeyran, F Delva, S Mathoulin-Pélissier

Drafting the article or revising it critically for important intellectual content

A Galvin, C Helmer, G Coureau, B Amadeo, P Joly, C Sabathé, A Monnereau, I Baldi, M Rainfray, P Soubeyran, F Delva, S Mathoulin-Pélissier

Final approval of the version to be published

A Galvin, C Helmer, G Coureau, B Amadeo, P Joly, C Sabathé, A Monnereau, I Baldi, M Rainfray, P Soubeyran, F Delva, S Mathoulin-Pélissier

Conflict of interest statement

The authors have no conflicts of interest to disclosure.

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