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▶ **To cite this version:**

HAL Id: hal-02473157
https://amu.hal.science/hal-02473157

Submitted on 10 Feb 2020

Recurrent major depressive disorder's impact on end-of-life care of cancer: a nationwide study.

Running title: Recurrent major depressive disorder and end-of-life care

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Category: Original Report.

Word count. Abstract = 277; Manuscript =2709.

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Abstract

Objective. We still don't know if recurrent major depressive disorder (RMDD) may impact the quality of the end-of-life (EOL) cancer care in France. To tackle this knowledge gap, we explored EOL care in RMDD subjects who died from cancer compared to subjects without psychiatric disorder in a 4-year nationwide cohort study.

Design. Nationwide cohort study.

Setting. National hospital database, France.

Participants. All patients aged ≥15 years who died from cancer in hospital: 4070 RMDD subjects and 222,477 controls, 2013-2016, France.

Main outcome measures. Palliative care in the last 31 days of life and high-intensity EOL care including chemotherapy in the last 14 days of life, artificial nutrition, tracheal intubation, mechanical ventilation, gastrostomy, cardiopulmonary resuscitation, dialysis, transfusion, surgery, endoscopy, imaging, intensive care unit and emergency department admission in the last 31 days of life. Multivariate generalized mixed models with log-normal distribution was used to compare RMDD subjects and controls.

Results. Compared to the controls, the RMDD subjects died 3 years younger, had more comorbidities, more thoracic cancers, less metastases and longer time from cancer diagnosis to death. After matching and adjustment, subjects with RMDD were found to receive more palliative care and less high-intensity EOL care, had fewer iterative admissions to acute care unit, and died less often in the intensive care unit and emergency department.

Conclusions. RMDD subjects were more likely to receive palliative care associated with less high-intensity EOL care. Yet the interpretation may be discussed, resulting from either patients'/families' wishes or difficulties for providers in offering personalized care to RMDD.

Keywords. High intensity end-of-life care, palliative care, cancer, recurrent major depressive disorder, health services research.

Introduction

A good-quality EOL care includes (1) early referral to palliative care unit; (2) high-intensity care cessation resulting in low rates of emergency department (ED) visits, intensive care unit (ICU) stays, overuse of chemotherapy and all potentially life-prolonging interventions near death (Earle et al., 2008; Ho et al., 2011; Revon-Rivière et al., 2019; Wright et al., 2008). This good-quality EOL care may be specifically impacted by Recurrent major depressive disorder (RMDD) factors such as increased suicidal ideation, lack of motivation, treatment refusal, memory and attention impairments, irritability, impaired autonomy, increased treatment side-effects and poor social support.

A study published in 2016 has suggested that both pre- and post-cancer depression may impact end-of-life (EOL) cancer care (Doan et al., 2016). This study was based on the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which includes one third of the Medicare healthcare users. The participants were aged 66 years or older, diagnosed with cancer from 2004 to 2011 and died of cancer within 3 years. The authors concluded that both pre- and post-cancer depression subjects received less high-intensity care and were more often referred to palliative care. Another American study on the same database confirmed these results on small-cell lung cancer in patients aged>67 (McDermott et al., 2018).

These results deserve replication in a non-US country to determine if the association between major depression and lower EOL high-intensity care was specific of the US care system. Moreover, the populations included in the SEERS database was not exhaustive, the studies were limited to elderly patients and depression was defined in the 12 previous months, including also isolated depressive episodes. Depression was defined as the occurrence of one diagnosis among brief and prolonged depression (F309.0, International

Classification of Diseases, ninth revision (ICD-9)) or bipolar and psychotic depressions (F296 & F298, ICD-9) or non-specified depression (WHO, 1978). These results could have been explained by the inclusion of bipolar and psychotic patients and it remains unclear if "pure" depression may impact EOL care as well. Bipolar, psychotic are very different from non-bipolar and non-psychotic depression in its prognosis, treatment response (Fond et al., 2018; Sienaert et al., 2013) and thus may have different impact on EOL care. Moreover, the authors did not exclude dementia, which can be increased in depression and may impact EOL care.

Recurrent major depressive disorder (RMDD) is a severe lifetime/chronic recurrent form of depression defined in the 10th ICD version with the F33* code (WHO, 2004). It is classically defined by at least 3 major depressive episodes, which predicts a high risk of relapse and indicate a life-long antidepressant treatment. RMDD is classically included in the "severe mental disorders" alongside with bipolar disorders and schizophrenia due to its prevalence, its high costs and severe consequences on functioning (König et al., 2019).

In summary, acute episodes of pre-cancer depression (including bipolar and psychotic depression) in the 12 to 36 months have been associated with lower high-intensity care in EOL American cancer patients, but it is unclear if a RMDD history of chronic depression may impact EOL care as well. It remains also unclear if mixed forms of depression (bipolar or psychotic) or dementia may explain these results. Our hypothesis was that RMDD had the same impact (even higher) on the EOL cancer care than pre-cancer acute depression.

To tackle this knowledge gap, we explored EOL care of RMDD patients who died from cancer compared to subjects without severe psychiatric disorder in a 4-year French nationwide cohort.

Methods

Study design and data source

This is a population-based cohort study of all patients aged ≥15 years who died from cancer in the hospital in France between January 1, 2013, and December 31, 2016. The study was based on the French national hospital database (Programme de Médicalisation des Systèmes d'Information (PMSI)), in which administrative and medical information is systematically collected for acute (PMSI-MCO) and psychiatric (PMSI-PSY) care. This information is anonymized and can be reused for research purposes (Revon-Rivière et al., 2019; Rochoy et al., 2019). The PMSI is based on diagnosis-related groups, and all diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10) (Boudemaghe and Belhadj, 2017). Patients were identified using the algorithm developed by the French National Institute of Cancer (INCA) specifically designed to identify cancer-related treatment in the French national hospital database(INCA, 2013). EOL patients were identified using the following criteria: i) in their last 3 months of life, ii) diagnosed with solid cancer in a metastatic stage or with brain or liver cancer (regardless of the stage of the disease, as these tumors are rarely metastatic and usually lethal at local regional stages) (Rochigneux et al., 2017), and/or (iii) received palliative care (authorization of a palliative unit or bed care or the ICD-10 code for palliative care [Z515]). Data from patients who died in the community or in nursing homes are not available in the PMSI. As dementia may be a confounding factor and given that RMDD is associated with an increased risk of dementia, patients with a diagnosis of dementia were excluded (ICD codes: F00*, F01*, F02*, F03*, F051*, G30*, G311*).

From this selection, we defined 3 populations:

1) Cases: The RMDD patients were defined by a specific ICD code for recurrent major depressive disorder (F33*) in the PMSI-MCO database and/or in the PMSI–PSY database during the 3 previous years before death after exclusion of F20*/F22*/F25* (schizophrenia), F30*/F31* (bipolar disorder), F603* (borderline personality disorder) diagnoses. These diagnoses are associated with specific severity, treatment and relapsing characteristics; they have thus been excluded to homogenize the cases group. F32* (isolated depressive episodes) have not been included in the case group to avoid any confusion between RMDD and post-cancer/ EOL depression that have different impact on EOL care (McDermott et al., 2018).

2) Controls: The controls were patients from the PMSI-MCO database without psychiatric conditions according to the specific ICD codes (chapter F*) and without admission in psychiatry (PMSI–PSY).

3) Matched controls: Cases and controls were matched using a 1:4 ratio according to 3 criteria: age at death (+/- 2 years), sex and primary cancer location (15 modalities).

Outcome measures

Different outcomes were assessed:

- Palliative care: palliative care in the last 31 days, palliative care in the last 3 days of life, and the time (days) between the first palliative care and death.

- High-intensity EOL care based on previously defined criteria (Earle et al., 2008, 2005, 2004, 2003):

1) intrahospital chemotherapy in the last 14 days of life and artificial nutrition (enteral or parenteral nutrition), tracheal intubation, mechanical ventilation, gastrostomy onset or change, cardiopulmonary resuscitation, dialysis, blood transfusion, surgery, imaging and endoscopy in the last 31 days of life.

2) at least 1 ED admission, 1 ICU admission, 1 air extraction chamber (sterile chamber) admission, more than 1 admission and length of stay (LOS) in the acute care unit in the last 31 days of life and death in the ICU/ED.

Appendix Table A1 lists the specific codes used for each outcome.

Potential confounding factors

Six sociodemographic, clinical or hospital characteristics were considered as potential confounders for EOL care for cancer and were included in our analyses. These factors were determined according to the variables available in the PMSI database that may have impacted the EOL care of patients:

- Social deprivation assessed by an index validated on French data and based on the postal code of the domicile (Rey et al., 2009). The FDep09 index involves four socioeconomic ecological variables: percentage of high-school graduates, median household income, percentage of blue-collar workers and the unemployment rate. The FDep09 index was categorized according to quartiles, from the least (Q1) to the most deprived area (Q4).

- year of death (as the EOL practice may have evolved throughout time as mentioned in the rationale);

- time from cancer diagnosis to death;

- comorbidities assessed using the Charlson modified Comorbidity Index (Quan et al., 2005) (computed from ICD-10 codes recorded as primary or secondary diagnoses over the course of the last 3 months of life, excluding dementia and the 2 items referring to cancer, i.e., metastatic solid tumor and malignancy);

- metastasis (ICD-10 codes C78 and C79) (as a metastasis diagnosis may accelerate palliative care admission);

- hospital category (at last hospitalization before death).

Statistical analysis

The analyses were conducted in 2 steps.

First, comparisons between cases and controls (unmatched populations) were performed for sociodemographic, clinical and hospital data: Chi-square tests or Student's t tests according to the nature of the variable (step 1).

Second, comparisons between cases and (1:4) matched-controls were performed using univariate conditional logistic regressions for binary outcome measures and univariate generalized mixed models with log-normal distribution for quantitative outcomes (time (days) between the first palliative care and death; length of stay in the acute care unit in the last 31 days of life). Then, we performed as many multivariate analyses as outcomes to analyze the association between the groups (cases/ matched-controls) and each outcome. Six confounding factors were included in the models: social deprivation (4 categories/quartiles from the most favored (Q1) to the most deprived area (Q4)), year of death (4 categories: 2013 to 2016), time between cancer diagnosis and death (days), metastases (yes/no), Charlson modified comorbidity index (3 categories: 0, 1 or 2, >=3 comorbidities) and hospital category (2 categories: cancer specialty vs. nonspecialty centers). These analyses were performed with a multivariable generalized linear model (logistic for qualitative outcomes; log-normal for quantitative ones) with the matched cluster as a random intercept using the PROC GLIMMIX in SAS (step 2).

The statistical analysis was performed with SAS 9.4 (SAS Institute). Statistical significance was defined as $p < 0.05$.

Results

Overall, 3,361,043 patients with cancer were identified in France between 2013 and 2016. Among them, 398,913 deaths were identified during this period, and 226,547 were finally included in this study after removing dementia and psychiatric diagnoses other than RMDD (Flow chart Figure 1). A total of 4070 patients were defined as RMDD patients (cases) and compared to 222,477 controls (step 1). A total of 4064 RMDD patients were then matched with their 16,256 controls (6 RMDD patients were excluded in the matching process due to the absence of matched controls) (step 2).

Comparison between cases and controls

Compared to controls, RMDD patients were found (Table 1) to die younger (mean age at death 68.7+/-12.8 years for RMDD vs. 71.8+/-12.7 for controls) and to be less deprived; to have a longer time between cancer diagnosis and death; to have more thoracic, respiratory system, bone, central nervous system and male genitalia cancers and less metastases; to have higher comorbidities, including more renal disease, rheumatologic arthritis disease, peripheral vascular disease, hemiplegia or paraplegia, mild liver disease, AIDS/HIV, diabetes with or without complications, cerebrovascular disease, chronic pulmonary disease, congestive heart failure and more myocardial infarction; to have more cancer specialty center care for the last hospitalization.

Comparison between cases and matched controls

After matching, RMDD subjects were found to have more peptic ulcer disease than their controls in addition to the above-mentioned differences (except the match criteria) (Table 2) In the multivariate analysis, RMDD patients were found (Table 3) to have more palliative care in the last 31 days of life and in the last 3 days of life and a longer length of palliative care follow-up before death; to have less chemotherapy in the last 14 days of life, dialysis,

blood transfusion, surgery and imaging, but more artificial nutrition in the last 31 days of life; to be less likely to be admitted to an acute care unit with longer LOS in the last 31 days of life and to have fewer deaths in the ICU/ED.

Discussion

RMDD was associated with a 3-year earlier death, more comorbidities, more thoracic central cancer, less metastases; less deprivation and more cancer specialty center care than controls. After matching and adjustment, RMDD patients received more palliative care, less chemotherapy, dialysis, blood transfusion, surgery, imaging, more artificial nutrition and died less in the ICU/ED than controls. These RMDD characteristics are consistent with those of American studies (Doan et al., 2016; McDermott et al., 2018) who included patients with acute depression during the 12 to 24 months prior to cancer diagnosis, without excluding dementia, bipolar disorders and psychotic depression.

RMDD was associated with a 3-year earlier death consistently with higher level of comorbidities in RMDD(Walker et al., 2015). RMDD comorbidities may negatively influence the prognosis of cancer by increased complexity of treatment and necessity of close collaboration with primary care providers already known as insufficient(Shaw et al., 2019). This insufficient collaboration points out the need for the development of integrated care before cancer occurrence and during cancer care for RMDD patients.

We have also found that RMDD patients had a longer time between cancer diagnosis and death (median 426 vs. 327 days). This result is not consistent with previous studies suggesting that patients with severe mental illness may have a shorter time between diagnosis and death (Doan et al., 2016; Irwin et al., 2014; McDermott et al., 2018). This discrepancy may be due to specific factors of depression. Depression is related to several

dimensions of abnormal illness behavior (e.g., hypochondriasis, irritability, denial, disease conviction)(Grassi et al., 1989). Depressed patients may be more anxious on their health and may seek more care and counseling compared to subject without depression, with higher fear of progression (Dinkel et al., 2014). Contrary to bipolar disorders or schizophrenia, they may receive a better follow-up for their psychiatric and somatic conditions due to less hostility(Lahera et al., 2015).

RMDD patients died more frequently of tobacco-related cancers consistently with increased tobacco smoking, decreased tobacco cessation and increased lung cancer risk and in RMDD(Fond et al., 2013; Jia et al., 2017; Stubbs et al., 2018). RMDD should thus benefit from personalized smoking cessation programs.

RMDD was associated with less metastases and longer time between cancer diagnosis and death. This suggests a difference in cancer stages at first contact with oncology team(Montagna et al., 2019). RMDD subjects may receive a more careful somatic follow-up alongside with their psychiatric follow-up. Depression is also known as a potential predictive factor for unknown somatic illnesses including cancer. Some depressive symptoms like fatigue and weight loss may also orientate for a better screening of cancer and thus an earlier care. RMDD subjects may also have hypochondriac thoughts that may lead them to receive more screening exams.

RMDD patients died more in specialized centers, suggesting a lack of contact with cancer non-specialty centers previously described in France (Jego et al., 2019). Unexpectedly, RMDD patients were less deprived while RMDD have been extensively associated with deprivation (Patel and Kleinman, 2003). Deprived RMDD patients may die earlier from other causes (including cardiovascular diseases, addictions and self-attempt), lower access to EOL care and lack of social support(Irwin et al., 2019).

Globally, RMDD seem to receive a "better quality" EOL care, *i.e.,* more palliative and less high-intensive care (Earle et al., 2008, 2005, 2004, 2003). These results confirmed those found in elderly patients with small-cell lung cancer (McDermott et al., 2018) and those on Medicare system (Doan et al., 2016). Yet, our data does not discriminate a better consideration of RMDD patients' wishes from a greater difficulty in delivering care. This greater difficulty may come from three levels of care barriers:

(1) On the provider level, treating physicians may be more prone to switch to palliative care in RMDD patients who may express a wish of withdraw curative treatments due to higher side effects. There is no evidence for this hypothesis in the literature to date. This may also explain our lower rates of chemotherapy, blood transfusion and dialysis.

(2) On the patient level, the lower rates of high-intensity care may be due to increased desire to hastened death(Rosenfeld et al., 2014; Villavicencio-Chávez et al., 2014) associated with increased hopelessness, suicidal ideation, lack of motivation, majored fatigue and increased risk of fall in RMDD(Zhang et al., 2018). The higher rates of artificial nutrition in RMDD patients may be due to higher rates of malnutrition caused by depressive anorexia(Zhang et al., 2019).

(3) On the health system level, palliative care units have been designed to manage complicated situations including RMDD issues (lack of social support/isolation, homelessness and impaired autonomy)(Kleiboer et al., 2011), which may explain our longer RMDD length of palliative follow-up.

These three levels of barriers should thus be captured with qualitative approaches and raise questions on the future organization on the EOL care of subjects with RMDD. In the present study, the RMDD subjects were already diagnosed before cancer onset. The differences in EOL care are thus not a matter of undiagnosed depression. Yet we don't know

if RMDD subjects received correct psychiatric follow-up due to the absence of data on resistant depression status, outpatient consultations and treatments, which is a limit of the present work. To exceed this limit, we excluded isolated major depressive episodes diagnoses from the database to avoid any confusion between recurrent pre-cancer depression and post-cancer and EOL depression. Our RMDD group is thus probably followed-up and treated in psychiatry due to the severe impact of RMDD in daily functioning.

Yet we still don't know how psychiatric and cancer care should be articulated to exceed the three-level barriers. It may thus call for the creation of a model of psychiatric oncology care based on better integration of psychiatry, oncology and EOL care.

Limitations. Only deaths at hospital were analyzed here. The whole cancer care of RMDD should be explored to determine if these results are limited to EOL care. Stages of cancer, psychiatric symptomatology (number of depressive episodes, severity, hospitalizations, age at RMDD onset) and psychotropic drugs were not available. Patients dying outside hospital were not included; yet only 3% died at home and 13% in nursing homes in 2013 (Poulalhon et al., 2018). Recurrent major depressive disorder diagnosis was defined on a 3-year basis (vs. only 1 year for Doan et al.), which strengthens our group definition. Despite its importance, post-cancer depression has not been explored in the present study given that our database was a hospital database. Most of the acute depressive episodes are treated outside the hospital, which may have biased our analyses. Future studies should include ambulatory data to address this question such as the French reimbursement ambulatory database (Système National des Données de Santé/SNDS).

Strengths. This study has explored a 4-year national database of >220,000 deaths from cancer with a validated method of patient selection (Rochigneux et al., 2017). This study is the first replication of Doan et al. results, which suggests that the impact of RMDD

on EOL is not due to the USA healthcare system while Doan et al. study has included only a one-third subsample of medicare database(Doan et al., 2016). Doan et al. limited their results to patients aged >66 while almost one third of our subjects were aged less than 60 years. The case and control groups have been strongly homogenized by excluding other forms of depressions (bipolar, schizophrenic, borderline and isolated depressive episodes including post-cancer and EOL depressive episodes). Our selection focused on people at the end of life requiring palliative care (see flowchart and inclusion criteria) and thus avoid including patients for whom death was not expected (and thus justified more high intensity care).

Conclusion

RMDD patients may benefit from a better EOL care than their controls without psychiatric disorders. Yet the interpretation may be discussed, resulting from either patients'/families' wishes or difficulties for providers in offering personalized care to RMDD.

Conflicts of interest

None declared.

Availability of Data and Materials

The PMSI database can be only accessed by employees of the French public hospitals according to the Commision Nationale de l'Informatique et des Libertés (CNIL) and is available at the following URL: https://epmsi.atih.sante.fr/welcomeEpmsi.do

Authors' contribution.

GF and LB wrote the first draft of the manuscript. VP and VO carried out the selection process and the statistical analyses. All authors have reviewed the final manuscript.

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