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Original Research

Survival and risk of COVID-19 after SARS-COV-2 vaccination in a series of 2391 cancer patients



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Abstract Background: Patients with cancer are at high risk of severe or lethal COVID-19. The impact of SARS-COV-2 vaccination on the risk of developing COVID-19 was investigated in an exhaustive series of patients from a comprehensive cancer center.

Methods: This is a study of the exhaustive population of 2391 cancer patients who were prescribed SARS-COV-2 vaccination until 09/21. Patient characteristics, documented SARS-COV-2 infection with RT-PCR, and survival were collected. The primary endpoint was the rate of COVID-19 after vaccination. Secondary endpoints included risk factors to develop COVID-19 after vaccination, with a comparison with the cohort of vaccinated health care workers (HCW), and risk factors for death.

Results: From January to September 2021, among 2391 patients with cancer under active treatment in whom a SARS-COV-2 vaccine was prescribed, 659 (28%), 1498 (63%) and 139 (6%) received 1, 2, and 3 doses, respectively. Ninety five patients received a single dose of

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vaccine after a previous COVID-19. Two thousand two hundred eighty five health care workers (HCW) received one ($N = 17$, 0.7%), 2–3 ($N = 2026$, 88.7%) vaccine doses and one dose after COVID-19 ($N = 242$, 10.6%). With a median follow-up of 142 and 199 days for patients and HCW, respectively. Thirty nine (1.6%) patients and 35 (1.5%) HCW developed COVID-19 after vaccination. Six of 39 cancer patients and no HCW died because of COVID-19 within 50 days after diagnosis. Independent risk factors for COVID-19 in vaccinated patients were age, single dose of vaccine without previous COVID-19 and anti-CD20 treatment in the last three months. Independent risk factors for death included metastatic disease, gender, cancer type, but also documented COVID-19 before vaccination.

Conclusions: Patients receiving two or more doses of COVID-19 vaccine have reduced risk of COVID-19. The risk of death of vaccinated cancer patients presenting COVID-19 remains high. COVID-19 before vaccination is associated with an increased overall risk of death.

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1. Introduction

Cancer patients are at high risk of death from COVID-19, with a 28-day mortality rate after documented SARS-COV-2 infection with RT-PCR ranging from 10 to 38% [1–9].

This increased risk of death is observed in all cancer types, of all stages [1–9], but has been reported to be higher in patients with associated comorbidities, with advanced lung cancer, in patients with hematological malignancies, in particular those treated with anti-CD20 Ab, in patients with lymphopenia, and a biological inflammation profile with CRP increase in particular [4–14].

This increased risk of death is considered to result from immunodepression and inflammation associated with cancer as well as from cytotoxic and immunomodulating treatments, resulting in defective B and T cell response against SARS-COV-2 [10–14]. Lymphopenia is consistently associated with a worse outcome after COVID-19 infection in cancer patients [4,6–8].

Vaccination with mRNA based or recombinant virus vaccines have been shown to reduce the risk of documented SARS-COV-2 infection with long lasting protection in the general population [15–18]. The protective effect of SARS-COV-2 vaccines have also been demonstrated in cancer patients in relatively small sized series [19–22], although cancer patients develop less efficient antiviral immune response after vaccination [23–26]. In a series of 1503 patients reported from our center, we reported on a higher incidence of COVID-19 in patients who received only one vaccine dose [21]. The impaired immune response observed in general in frail patients prompted researchers to investigate additional strategies for immunization. An additional vaccination boost has been proposed in transplanted patients with encouraging results [26–30]. Heterologous versus homologous boosts were also tested and reported to yield similar antibody response in patients without cancers [27]. A single dose of vaccine has been found to be

efficient in patients who recovered from symptomatic COVID-19 infection [31].

Whether these strategies are efficient in cancer patients is still unclear. To address these questions, we analyzed the real-life efficacy of the vaccination program proposed for cancer patients in the comprehensive cancer Center Leon Berard (CLB). All patients were proposed for two doses of vaccines, homologous or heterologous depending on vaccine availability at that time, and a third dose after four months. Patients with a previous documented symptomatic COVID-19 infection were proposed for a single dose of vaccine in line with national recommendations.

We present here the clinical efficacy of SARS-COV-2 vaccination in this population of 2391 cancer patients receiving active cancer treatment in the Centre Leon Berard, and an analysis of the risk of documented SARS-COV-2 infections and death.

2. Material and methods

2.1. Study design and objectives

This is a retrospective study of the exhaustive series of patients with a prescribed and documented COVID-19 vaccination in the CLB until September 30, 2021. Data were collected until October 31, 2021.

The primary objective of the study was to describe the incidence of documented COVID-19 in cancer patients after vaccination against SARS-COV-2 in the exhaustive population of 2391 cancer patients in whom vaccination was prescribed on the site until September 2021. Patients who received one, two, or three doses of homologous or heterologous COVID-19 vaccines were compared, as well as patients who received a single dose of vaccine after a documented and symptomatic COVID-19 infection, as described [28]. The other objectives were the comparison of vaccine efficacy in patients versus health care workers

(HCW) of the same center, the identification of predictive risk factors for the development of a documented COVID-19 after vaccination, the mortality of COVID-19 in cancer patients after SARS-COV-2 vaccination, and the overall risk of death in the different groups.

2.2. Patients

All cancer patients in whom vaccination was prescribed within the Comprehensive Cancer Center of Lyon (Centre Leon Berard, CLB) from January 1 to September 30, 2021 were included. Only patients who have agreed to have their personal data analyzed internally for academic research were analyzed, in agreement with the national and European laws. The study was approved by the institutional review board of the Centre Leon Berard on March 2021. The inclusion criteria were: a histological diagnostic of cancer, a documented vaccination using one of the four available vaccine options in the observation period prescribed by physicians in the center, i.e., the BNT162, the mRNA-1273, the Chadox1, the Ad26.Cov2s vaccines [15–18], ongoing or active cancer treatment, a consultation in the center during the same observation period.

2.3. Vaccination

The national policy in France for doses and type of vaccination varied over time. From April 2021 it was recommended to reserve the AstraZeneca vaccine to patients aged above 55. However, the majority of patients received mRNA vaccines. Overall, the Pfizer, Moderna, Astra-Zeneca, and Johnson vaccines were used as first dose in 1914 (80%), 395 (16.5%), 67 (2.8%), and 15(0.6%) patients, respectively, with no significant difference of distribution between those aged under or above 60. Patients with a previous documented symptomatic COVID-19 infection were proposed for a single dose of vaccine in national recommendations.

2.4. Extracting electronic patient records (EPR) with the consore tool

The information on vaccination and patient characteristics were collected from the electronic patient records (EPR) with the CONSORE tool as previously described [32], see also <https://www.sword-group.com/en/news/projet-consore>). ConSoRe is a new data analytics solution aggregating diverse forms of structured and unstructured data extracted from EPR and structuring cancer management for all patients. It uses natural language processing to search aggregated data and perform advanced data mining. This tool enables the collection of clinical information integrated to the electronic patient record; these were subsequently validated manually if inconsistent data were collected.

The EPR of all patients consulting the institution from January 2021 to October 2021 were screened. The EPR system of the CLBs includes a standard set of data (e.g., tumors characteristics, treatments, vaccines, deaths) as well as information present only in unstructured data sources. The extracted relevant structured data was integrated in Excel files.

2.5. Health care workers (HCW)

The cumulative incidence of COVID-19 in the 2285 vaccinated health care workers of the same institute was calculated from the date of the first vaccine dose, and analyzed according to the number of doses. Only dates of vaccination and of COVID-19 diagnosis (when relevant) available in the Occupational Medicine Department (OMD), were analyzed. The project was presented to the ethics Committee of the Centre Leon Berard and to the representative instances of workers of the hospital (Comite Social & Economique, CSE). HCW were all contacted and had the option to opt-out. Three opted out. Conversely, six HCW whom data were not declared at the OMD department (fellows, recent hiring) requested to participate.

2.6. Data

The following data were collected for cancer patients: demographic characteristics (age, weight, body mass index, gender, tobacco ...), cancer characteristics (histotypes, primary site, stage), previous cancer treatments in the last months, dates and types of vaccines, patient outcome (date of documented SARS-COV-2 infection, survival, last news). Only dates of vaccinations, dates of documented RT-PCR + for SARS-COV-2 were analyzed for HCW. Only RT-PCR + documented SARS-COV-2 infections were retained as events.

2.7. Statistical analysis

The distribution of clinical characteristics was analyzed using Chi-squared test, Fisher exact test, Mann–Whitney U test. Survival was plotted from the date of the first dose (or for some analyses, from subsequent doses) of vaccine to the date of documented SARS-COV-2 using RT-PCR test, to the date of death or to the date of last news if alive at the time of the analysis (November 2021). Survival of cancer patients diagnosed with COVID-19 after the date of vaccination was plotted from the date of the positive SARS-COV-2 RT-PCR to the date of death or last news. Cumulative risk of death was plotted according to the inverse Kaplan–Meier method, and groups were compared using the logrank test. A landmark analysis 21 days after the first vaccine dose was performed to limit the biases related to the infections occurring in the first days after the first dose of vaccine. Independent risk factors for documented COVID-19 infection, or death

were evaluated using Cox proportional hazard model in univariate and then multivariate analysis for parameters with significant statistical value in univariate analysis. Backwards selection procedure was used to determine the final model by removing non-significant variables ($p > 0.05$) one at a time. All statistical analyses will be performed using SPSS 23.0 software SPSS (IBM, Paris, France).

3. Results

3.1. Patients

From January 4 to September 30, 2021, 2391 cancer patients without previous documented COVID-19 were prescribed COVID-19 vaccination in the center, including 95 patients with a previously documented SARS-COV-2 infection and who received a single vaccine dose per national recommendations. For the remaining patients, 659 (28%), 1498 (63%), and 139 (6%) cancer patients received 1, 2, or 3 injections of COVID-19 vaccine at a median interval of 28 days (range 13–80) between dose 1 and 2, and 96 days (range 41–202) between dose 2 and 3, respectively. Nineteen hundred fourteen (80.1%), 395 (16.5%), 67 (2.8%), 15 (0.6%) received BNT162b2, mRNA-1273, Chadox1 and Ad26.cov2.S vaccines as first doses depending on availability [15–18]. 31 of 2391 (1.6%) patients received a heterologous vaccine for dose 2. Table 1 describes the clinical characteristics of the patients according to the number of vaccines doses received. A significantly larger proportion of female patients, of smokers, of patients with hematological malignancies, receiving anti-CD20 received 2 or 3 doses of vaccines (Table 1). In the

same hospital, 2285 health care workers (HCW) were vaccinated for COVID-19, with one ($N = 259$, 11.3%) or 2–3 doses ($N = 2026$, 88.7%). In France, vaccination is mandatory by law for all active HCW.

3.2. Cumulative incidence of documented COVID-19

We first compared the incidence of COVID-19 after a first vaccine dose in cancer patient to that observed in the population of the 2285 health care workers of the hospital. Median follow-up for the 2 populations is 142 days (range: 1–253) and 199 days (range 3–288) respectively. Respectively 39 of 2391 (1.6%) patients versus 35 of 2285 (1.5%) HCW presented a RT-PCR documented COVID-19 infection: the cumulative incidence of post vaccination COVID-19 was numerically higher, not significantly in the patient population (Logrank = 3.11, $p = 0.07$; Fig. 1A). The difference was not significant either when considering only populations who received 2 to 3 vaccine doses or vaccinated with a single dose after a documented COVID-19 (not shown).

Thirty nine of the 2391 cancer patients presented a documented SARS-COV-2 infection at a median of 27 days after the first vaccine dose. COVID-19 was documented in 28/659 (4%), 11/1498 (0.7%), and 0/139 (0%) who received one, two and three doses of vaccines respectively, and in 0/95 (0%) in those receiving the single vaccine dose after a documented COVID-19 ($p < 0.0001$, Table 1). Fig. 1B shows the cumulative risk of SARS-COV-2 infection in the same 4 subgroups from the first dose of vaccine (logrank = 55.0, $p < 0.0001$), from the last dose of vaccine (Fig. 1C, logrank = 41.6, $p < 0.001$). With a landmark analysis of 21 days after the first vaccine dose to limit the biases

Table 1
Patient characteristics and outcome according to vaccination status

	All ^a	Vaccination doses ^b				p-value
		1	2	3	One dose post COVID-19	
All	2391 (100%)	659 (28%)	1498 (63%)	139 (6%)	95 (4%)	
Gender						
Female	1236 (52%)	355 (29%)	773 (63%)	48 (4.5%)	52 (4.2%)	0.03
Age						
Median (SD)	65 (13)	62,6 (15)	60,9 (14)	64,7 (12)	58,9 (15)	0.001
>60	1401 (59%)	391 (28%)	863 (62%)	97 (7%)	50 (4%)	0.02
BMI>30	314 (13%)	88 (28%)	185 (59%)	22 (7%)	19 (6%)	0.13
Smoking	1078 (45%)	252 (23%)	719 (67%)	83 (8%)	24 (2%)	0.000
Haematological cancers	517 (22%)	136 (26%)	306 (59%)	51 (10%)	24 (5%)	0.000
Breast Ca	446 (19%)	130 (29%)	285 (64%)	11 (3%)	20 (5%)	0.009
Lung Ca	284 (12%)	72 (25%)	179 (63%)	26 (9%)	7 (2%)	0.04
Prostate Ca	126 (5%)	53 (42%)	67 (53%)	5 (4%)	1 (1%)	0.001
Anti-CD20 Ab	69 (3%)	12 (17%)	41 (59%)	14 (20%)	2 (3%)	0.000
Metastases	1214 (51%)	319 (26%)	782 (64%)	68 (6%)	45 (4%)	0.34
PCR + COVID-19^c	39 (2%)	28 (4%)	11 (0.7%)	0 (0%)	0 (0%)	0.000

^a % of the whole population.

^b % of the subgroup.

^c % of the whole group of vaccination doses.

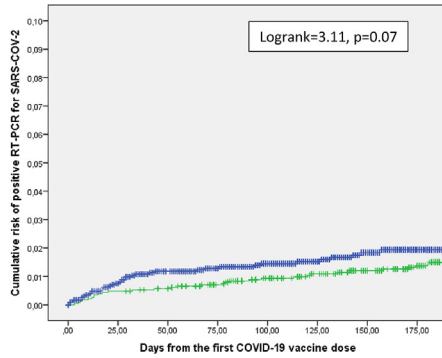
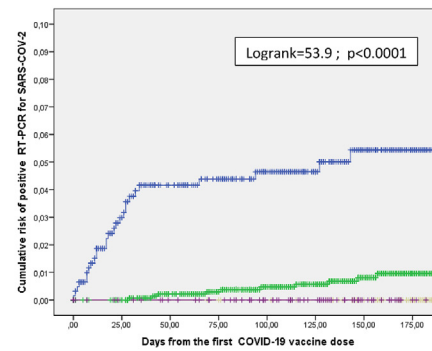
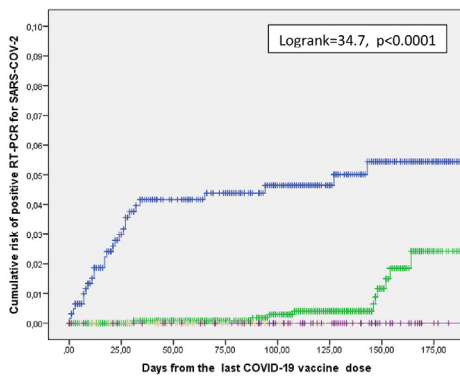
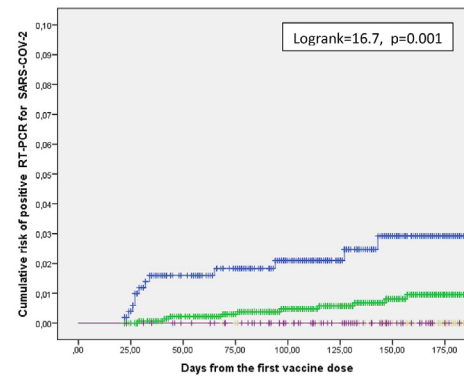
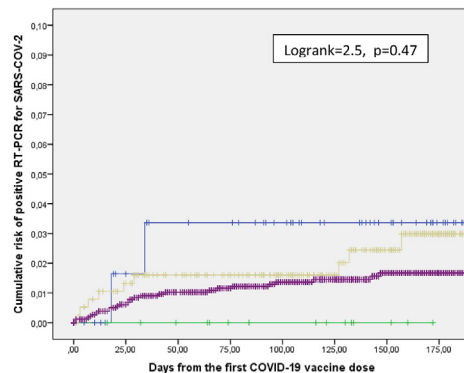
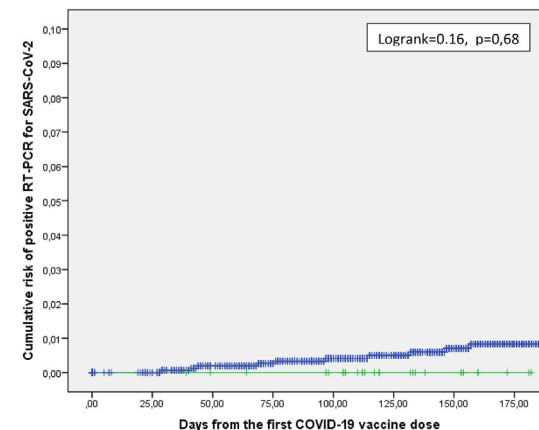
A: Cancer patients and Health Care Workers**B: COVID-19 in cancer patients after the first dose of SARS-COV-2 vaccine per number of vaccine doses****C: COVID-19 after the last dose of dose of SARS-COV-2 vaccine per number of vaccine doses****D: COVID-19 in cancer patients after the first dose of SARS-COV-2 vaccine per number of vaccine doses (landmark analysis at 21 days)****E: COVID-19 according to the type of vaccine given for the first dose****F: COVID-19 in patients receiving homologous or heterologous vaccines**

Fig. 1. Cumulative incidence of RT-PCR + documented COVID-19 after SARS-COV-2 vaccine. **A:** Incidence of documented COVID-19 from the first vaccination dose in health care workers (green) vs cancer patients (blue) (logrank = 3.11, $p = 0.07$). **B:** Since the first dose of SARS-COV-2 vaccine according to the number of vaccine doses. In blue: patients having received one dose of SARS-COV-2 vaccine (28 events/659); in green patients having received 2 doses of SARS-COV-2 vaccine (11 events/1498); in brown patients having received 3 doses of SARS-COV-2 vaccine (0 events/139); in purple: patients having received 1 dose of SARS-COV-2 vaccine after a previously documented COVID-19 (0 events/95) (Logrank = 53.9, $p < 0.0001$); **C:** Since the last dose of dose of SARS-COV-2 vaccine (blue: 1 dose; green: 2 doses; brown: 3 doses; purple 1 dose after a documented COVID-19; logrank = 34.7, $p < 0.0001$). **D:** COVID-19 in cancer patients after the first dose of SARS-COV-2 vaccine per number of vaccine doses (landmark analysis at 21 days) (blue: 1 dose; green: 2 doses; brown: 3 doses; purple 1 dose after a documented COVID-19; logrank = 16.7, $p = 0.001$); **E:** Since the first dose of the different vaccine types: Chadox1 (blue), BNT162b2 (green) mRNA-1273 (brown); Ad26.cov2.S (green); logrank = 2.5, $p = 0.47$). **F:** Incidence of documented COVID-19 from the first vaccination dose patients receiving homologous or heterologous vaccines (31/2391 (1.6%) patients) (logrank = 0.16, $p = 0.68$). Curves are plotted from the date of the first SARS-COV-2 vaccination dose (**A,B,D,E,F**) or from the date of the last SARS-COV-2 vaccination dose (**C**). Median follow-up 142 days for patients, 199 days for HCW.

related to the infections occurring in the days after the first dose of vaccine, the incidence of COVID-19 was 13/515 (2.5%), 11/1446 (0.7%), 0/139 (0%) and 0/89 (0%) in the same 4 subgroups (logrank = 16.7; $p = 0.001$) (Fig. 1D). In the group of HCW, a single vaccine dose was also associated with an increased risk of post vaccination COVID-19 (not shown). In cancer patients, no significant difference was observed between the four vaccines products used for the first dose (Fig. 1E, logrank = 2.5, $p = 0.47$). No significant differences were observed for patients vaccinated twice or more with homologous or heterologous vaccines (Fig. 1F, logrank = 0.16, $p = 0.68$).

A multivariate analysis was conducted to determine independent risk factors for developing a documented COVID-19 after a first vaccination. Cancer histotype, primary site, stage, age, gender, anti-CD20 treatment, number of vaccine doses (1 vs 2 vs 3), comorbidities (obesity, smoking) were tested in univariate analysis. Significant risk factors in univariate analysis i.e. age, anti-CD20, number of vaccine doses > 1 and smoking were included as covariates in the multivariate model. Age younger than 60, treatment with anti-CD20 in the last 3 months, and a single vaccine dose were independently associated with increased risk of COVID-19 (Table 2). Of note, there was a significantly larger proportion of patients aged above 60 who had received 3 vaccine doses (97/1304 [6.9%] versus 42/948 [4.2%], $p = 0.006$). The same 3 parameters were retained by the model when the multivariate analysis was conducted with a landmark analysis of 21 days (not shown). In patients who received 2 or 3 vaccines or a single dose after a documented Covid-19, younger age (< 60) and treatment with anti-CD-20 in the last three months were retained as independent risk factors (not shown).

3.3. Survival

The survival of the 39 cancer patients with documented COVID-19 after vaccination was then explored. Fig. 2A shows the survival of vaccinated cancer patients from the date of documented SARS-COV-2 infection. With six deaths due to COVID-19, the cumulative death-rate at day 50 post-infection (date of positive PCR) was 17.6% (Fig. 2A). All six patients are considered to have died from COVID-19 as the primary cause in the context of a solid tumor ($N = 4$) or lymphoid hemopathy ($N = 2$) in advanced stage. No significant difference was observed between patients who received one and > 1 dose of vaccine (not shown). No death is reported in the 35 HCW with documented COVID-19 post vaccination (0/35 vs 6/39, $p = 0.015$).

There were respectively 43/616 (5.5%), 95/1403 (6.3%), 7/132 (5.0%), 9/86 (9.5%) reported deaths in patients who had received 1, 2, 3, and 1 dose of vaccine post COVID-19, respectively. We investigated the overall survival from the first vaccination dose for

patients who developed or not COVID-19 infection. Cumulative risk of death was numerically higher in the group of patients who were diagnosed with COVID-19 after vaccination (Fig. 2B). In Fig. 2B, the blue curve indicates the cumulative risk of death in patients in whom no diagnosis of COVID-19 was made: in this group, 148/2352 (6.3%) patients died at a median time of 109 days (range 1–201) all from cancer or treatment related causes, compared to 6 the 39 (15.4%) patients diagnosed COVID-19 after vaccination.

Finally, we investigated the risk factors for any cause of death in this vaccinated cancer patient population in a multivariate Cox model. Cancer histotype, tumor site, metastatic stage, age, gender, anti-CD20 treatment in the last three months, number of vaccine doses, comorbidities (obesity, smoking) were tested in univariate analysis. Significant risk factors in univariate analysis i.e., metastatic stage, male gender, hematological malignancies, previous COVID-19 infection prior to vaccination were introduced as covariates in the model. Metastatic disease at vaccination, hematological malignancies, male gender, but also previous COVID-19 before vaccination was independent adverse risk factors for death (Table 2). Documented COVID-19 before vaccination was associated with an hazard ratio for death of all causes of 2.187 (Table 2).

4. Discussion

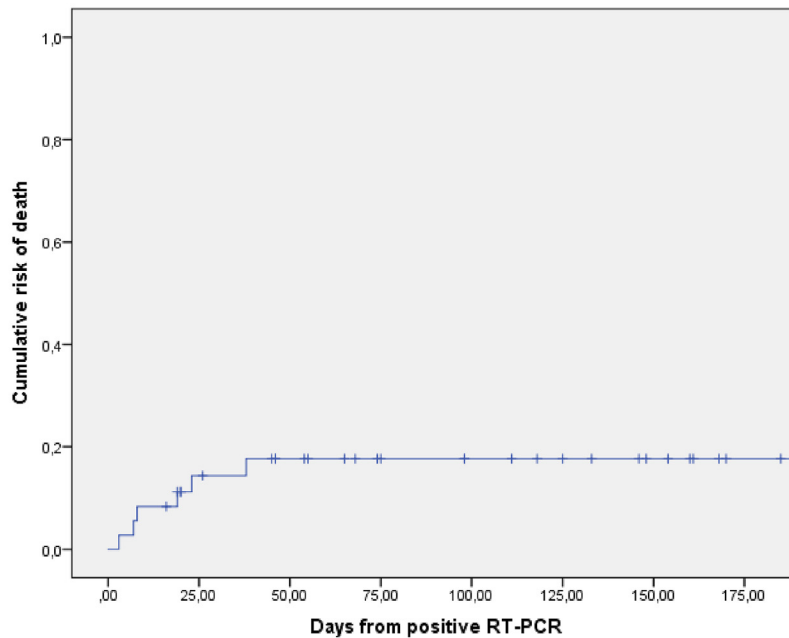
This series describes the efficacy of COVID-19 vaccine program in a real-life population of 2391 cancer patients treated in a comprehensive cancer center. It shows the efficacy of the full vaccination program in a large cohort of cancer patients, and also indicates that COVID-19 remains a significant risk factor for death of cancer patients even in the six months following vaccination. Pre-vaccination COVID-19 was also identified as an independent risk factor for death in this population.

With a median follow-up of 142 days, this analysis confirms the favorable impact of a complete vaccination program in cancer patients. It shows that the magnitude of protection conferred by a complete vaccine program is not significantly different in cancer patients and HCW

Table 2
Multivariate analysis of risk factors of post vaccine COVID-19 or death after the first vaccine dose

	Beta	SE	HR	p-value
Risk factors for COVID-19				
Only one vaccine dose	2,235	,360	9,34	,000
Anti-CD20 treatment	1,422	,607	4,143	,019
Age \geq 60	-,706	,325	0,494	,030
Risk factors for death				
Metastatic disease	1,547	,254	4,696	,000
COVID-19 before 1st vaccine dose	,782	,346	2,187	,024
Hematological malignancy	,648	,271	1,912	,017
Male gender	,451	,167	1,570	,007

A: Risk of death of COVID-19 diagnosed after vaccination



B. Risk of death from all causes in vaccinated patients who developed or not COVID-19

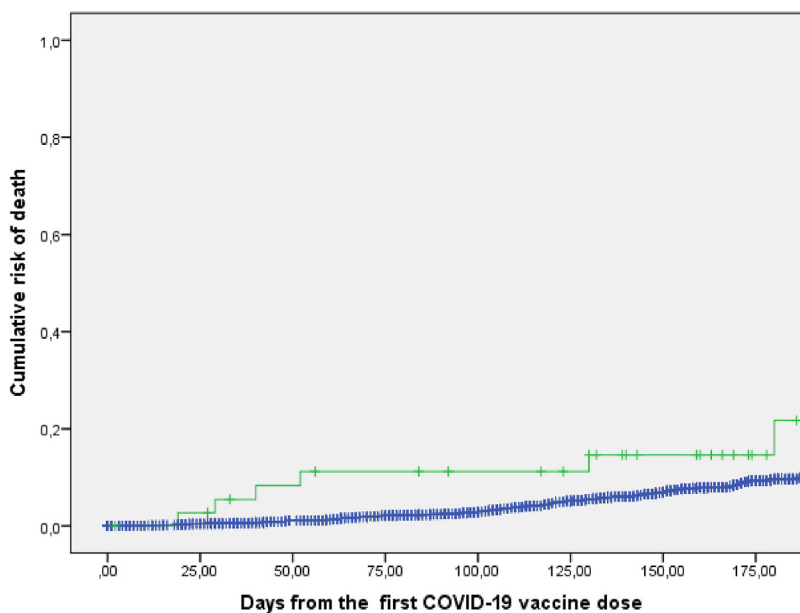


Fig. 2. **Mortality of COVID-19 diagnosed after vaccination.** A: Time (days) from the positive SARS-COV-2 RT-PCR + post vaccine to the date of death or the date of last news. B: Cumulative risk of death from the first day of vaccination in patients who developed COVID-19 (green) or did not develop (blue) a documented COVID-19 after first vaccination dose.

working in the same hospital regarding the risk of COVID-19 post vaccination, even though a slightly higher cumulative incidence of COVID-19 is observed post vaccination in cancer patients. In the present study.

There were no documented COVID-19 in patients who received three doses, nor in patients vaccinated once after a documented COVID-19 as per the national recommendations. For the group of patients vaccinated with 3

doses, the follow-up post last vaccine dose is obviously shorter than that of patients vaccinated twice, limiting the significance of the absence of any documented COVID-19 in this subgroup. Most COVID-19 were diagnosed at a short term after the vaccines, with a median of 27 days post first vaccine dose. A landmark analysis after 21 days confirms actually the increased risk of COVID-19 in patients receiving one dose versus others, in the patient population, as well as in the population of HCW.

The analysis of risk factors to develop COVID-19 after vaccination in this large series identified age < 60, anti-CD-20 treatment and single vaccine dose as parameters associated with an increased risk. While the negative impact of anti-CD20 [22–25] and of a single dose of COVID-19 vaccine is documented [19–21], the observation of younger age being associated with an increased risk of post vaccination COVID-19 is surprising. It may reflect less rigorous protective measures post vaccination in young patients with good clinical condition or other not yet reported epidemiological specificities of this population. The significantly larger proportion of patients aged above 60 who had received 3 vaccine doses is also likely to contribute to these observations. Of note, there were no significant difference in the types of vaccine given to patients aged < 60 and ≥60 (data not shown).

High mortality was however observed for cancer patients presenting with a COVID-19 after vaccination, with a 17.6% cumulative risk of death at day 50. Indeed, 6 of the 39 cancer patients died in the 50 days post documented RT-PCR. Conversely, none of the 35 HCW presenting with documented COVID-19 died, with one requiring a short hospitalization. In cancer patients, COVID-19 after vaccination remains a disease with a high risk of death in cancer patients. It is therefore essential to maintain precautions (masks, social distancing) in hospitalization and during all steps of cancer patient management. Third vaccination dose may also be recommended, since none of the 139 patients who received a third dose so far presented a COVID-19 after vaccination with the limit of the short follow-up discussed above. It is also important to note that no COVID-19 was observed either in patients who received a single vaccine dose after a documented episode of COVID-19 before vaccination.

Several parameters were found independently correlated with the risk of death from any cause in this population of vaccinated cancer patients. As expected, the presence of a metastatic disease was independently associated with a higher risk of death, but others such as male gender and hematological malignancy were not necessarily expected. For hematological cancer, this may reflect the aggressive natural history of these diseases as compared to the other neoplasia, but also most likely the frequent use of anti-CD20 for B cell malignancies. Though anti-CD20 treatment was not found correlated to overall survival, it is identified as an independent risk

factor for post vaccination COVID-19, which are associated with a high mortality as discussed above.

Surprisingly, a documented previous COVID-19 infection before the single vaccine dose was also associated with an increased risk of death in this series. The medical explanation of this observation remains unclear, but similar findings were recently reported for cancer patient series with a previously documented COVID-19 [33]. Cancer patients remain fragile for a long period of time after COVID-19, and therefore remain at higher risk of complications or death, in particular patients with long lasting symptoms [33]. In the present study, documented COVID-19 before the first vaccine dose was associated with a hazard ratio for death of all causes above 2, while none of these patients presented a COVID-19 after vaccination. While the description of the possible causes of increased mortality remain unclear, one can hypothesize the delays to cancer treatment [34], adapted treatment, poor PS or increased risk of DVT/PE may all have contributed to this observation. Death rate after documented COVID-19 was high confirming the importance to maintain protective measures in cancer patients after vaccination.

The results presented in this study are consistent with previous reports showing the importance of a full vaccination program [19–22]. It is consistent with the reports of the value of a third vaccine both in terms of clinical efficacy and immunological response [26–30,35,36]. It further indicates the severity of the rare post-vaccination COVID-19 in cancer patients, with a mortality rate of post-vaccination COVID-19, which is not different from that of non-vaccinated patients [1–9]. The immunosuppression associated with cancer, and cancer treatments, are correlated to a less efficient immune response in other studies, with baseline lymphopenia, and inadequate Ab response or T-cell response now well documented for these patients [1–9,23–26]. The present report indicates that cancer patients remain at high risk of death when presenting a documented COVID-19 and should persist on protective measures, within and outside the hospital.

This study has several limitations. It focuses on patients in whom vaccination was prescribed in the center and does not take in account patients vaccinated outside the center. This is not a randomized study testing the value of the number of vaccine doses, which would be needed to demonstrate the impact of the number of vaccine doses, in particular the third dose, in the population of cancer patients [26]. For the survival analyses, not all information of comorbidities were collected, for example, cardiovascular disease or diabetes. The CONSOLE tool has limitations for the collection of information on follow-up and require manual verification when data are missing or inconsistent [32]. As a descriptive real-life study, vaccinations were proposed and applied to patients at different time of the disease course, explaining heterogeneous outcomes. The vaccine

products applied were variable according to supplies with sometimes heterologous second vaccines, though is a limited proportion of patients. Finally, the follow-up remains relatively limited and will need to be updated in the years to come.

Nevertheless, this real-life series of 2391 patients provides important and reassuring information of the protection conferred by vaccines in cancer patients. This analysis indicates however the remaining severity of COVID-19 in cancer patients after vaccination, in marked contrast with HCW of the same hospital. It also indicates that protective measures should be maintained in cancer patients, including consideration of additional third vaccine doses as suggested for immunosuppressed patients [26–30], in particular young patients, and those recently treated with anti-CD20. The observation that a documented COVID-19, prior to vaccination is associated with an increased risk of death in the period after vaccination is of concern, and suggest a long term impact of COVID-19 of the natural history of neoplastic diseases.

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Author contribution

Conceptualization: JYB, PH, MLS. Methodology: PH, BF, M-LS, SC, DP, J-YB. Software: PH, SC, DP, JYB. Data curation: PH, DF, MLS, SA, NC, OT, TB, IRC, BR, MLF, VA, ASM, PZ, JYB. Writing- Original draft preparation: JYB. Investigation: PH, DF, MLS, SA, NC, OT, TB, IRC, BR, MLF, VA, ASM, PZ, JYB. Supervision: JYB, BF, MLS. Software, Validation: PH, DP, SC. Writing- Reviewing and Editing: all authors.

Conflict of interest statement

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