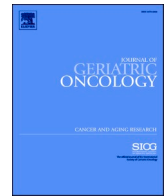




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Acceptance, efficacy, and safety of COVID-19 vaccination in older patients with cancer

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ARTICLE INFO

Keywords:

COVID-19
Aged
Vaccination
Drug-related side effects and adverse reactions
Medical oncology
Geriatric assessment

ABSTRACT

Purpose: The COVID-19 vaccination campaign began in December 2020, in France, and primarily targeted the oldest people. Our study aimed to determine the level of acceptance of vaccination in a population of older patients with cancer.

Methods: From January 2021, we offered vaccination with the BNT162b2 COVID-19 vaccine to all patients 70 years and older referred to our geriatric oncology center in Marseille University Hospital (AP-HM) for geriatric assessment before initiation of an oncological treatment. Objectives were to evaluate acceptance rate of COVID-19 vaccination and to assess vaccine safety, reactogenicity, and efficacy two months after the first dose.

Results: Between January 18, 2021 and May 7, 2021, 150 older patients with cancer were offered vaccination after a geriatric assessment. The majority were men (61.3%), with a mean age of 81 years. The two most frequent primary tumors were digestive (29.4%) and thoracic (18%). The vaccine acceptance rate was 82.6% and the complete vaccination rate (2 doses) reached 75.3%. Among the vaccinated patients, 15.9% reported mild side effects after the first dose and 23.4% after the second dose, mostly arm pain and fatigue. COVID-19 cases were observed in 5.1% of vaccinated patients compared with 16.7% in unvaccinated patients. Of the 22 vaccinated patients who agreed to have their serum tested, 15 had antibodies against the spike protein at day 21 after the first dose.

Conclusion: Our study showed a high acceptance rate of COVID-19 vaccination, with good tolerance in this frail population. These results highlight the benefits of organizing vaccination campaigns at the very beginning of oncological management in older patients.

Clinical trial registration: This study was registered May 23, 2019 in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03960593).

1. Introduction

Older frail people are more susceptible to severe forms of

Coronavirus 19 disease (COVID-19) than the rest of the population; the infection rate is higher and outcomes poorer, in particular for those with comorbidities such as hypertension, diabetes, cancer, or cardiological

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<https://doi.org/10.1016/j.jgo.2022.05.002>

Received 22 November 2021; Received in revised form 4 May 2022; Accepted 10 May 2022

Available online 16 May 2022

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Table 1
Characteristics of the population (n = 150 old patients with cancer).

Characteristics	Total population	
	N or Mean ± SD	% or [min-max]
Gender		
Women	58	38.7
Men	92	61.3
Age	81 ± 0.5	[70–94]
70–75	29	19.3
76–80	45	30.0
81–85	37	24.7
>85	39	26.0
Accommodation		
Home	133	88.6
Care facility	10	2.0
Nursing home	3	6.7
Other	4	2.7
Living alone	33	22.0
Caregiver present	127	84.7
Polypharmacy*	96	64.0
Cognitive impairment (n = 149)	65	43.6
Depression risk	50	33.3
Malnutrition	60	40.3
BMI (Kg/cm ²)	25.0 ± 0.4	[16.2–36.8]
Albumin (g/L)	38.7 ± 0.5	[25.0–65.0]
Functional status (n = 149)		
Independent	64	43.0
Dependent in ADL or IADL	31	20.8
Dependent in ADL and IADL	54	36.2
Mobility		
Impaired TUG	104	69.3
Impaired OLBT	135	90.0
Impaired gait speed	92	61.7
Falls in the 3 previous months	20	13.3
Handgrip strength impairment (n = 149)	58	38.9
G8 impairment	131	87.3
ECOG-PS (n = 149)		
0–1	65	43.6
2–4	84	56.4
Stage IV (n = 148)	56	37.8
Cancer type		
Digestive	44	29.4
Thoracic	27	18.0
Urological	20	13.3
Prostatic	15	10.0
Skin	14	9.3
Head and Neck	12	8.0
Breast and gynecological	12	8.0
Hematological	4	2.7
Other	2	1.3

BMI: Body Mass Index; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; TUG: Timed Up and Go test; OLBT: One Leg Balance Test; ECOG-PS: Eastern Cooperative Oncology Group-Performance status.

* at least 5 prescribed medications.

and respiratory diseases [1,2]. In patients with cancer, COVID-19 has negative consequences on treatment delays and increases the mortality rate [3–5]. In this context, the COVID-19 vaccination campaign that began in France on December 27, 2020, primarily targeted the oldest people and then patients being treated for cancer [6,7]. The European Society of Medical Oncology (ESMO), the International Society of Geriatric Oncology (SIOG), and the French-Speaking Society of Geriatric Oncology (SoFOG) rapidly recommended COVID-19 vaccination in patients and older patients treated for cancer [8–10]. The particular severity of COVID-19 in frail older patients and patients with cancer has led to the inclusion of these populations in clinical trials in which they are usually poorly represented [11].

In addition to its effectiveness, one of the other major challenges of vaccination is its acceptance by the population. The first data on vaccination in patients with cancer stated a low acceptance rate [12,13] and at best, a mild intention rate for the COVID-19 vaccine [14,15]. The very first data available on the intended acceptance of COVID-19 vaccination in French patients with cancer showed that only half of

patients intended to be vaccinated as soon as the vaccine was available [12]. Given the polemic surrounding COVID-19 vaccine, especially in the beginning of the vaccination campaign, and the observed worse outcomes in COVID-19 among older patients or patients with cancer, COVID-19 vaccination acceptance among older patients with cancer was and still is, crucial to limit adverse outcomes for this frail population.

However, the efficacy of vaccines in older patients is still unclear because of immunosenescence, including the reduction of both qualitative and quantitative aspects of the immune system available to respond to a vaccine [13,14]. A study on BNT162b2, a lipid nanoparticle-formulated, nucleoside-modified RNA COVID-19 vaccine, showed 95% efficacy seven days after the second dose in a population including 42% of older adults and 3.7% of adults with cancer [15]. In patients treated with anti-cancer agents, this vaccine could interfere with cancer treatment through a molecular phenomenon known as the permeation and retention effect [16]. Moreover, patients treated with immunotherapy could, in theory, display an exaggerated inflammatory immune response after vaccination. Despite this, vaccination appears to be the main tool to prevent severe outcomes and hospital admissions due to COVID-19.

From January 2021, we offered COVID-19 vaccination to all patients over 70 years old with cancer attending the geriatric oncology center for geriatric advice before initiation of oncological treatment. The main objective was to evaluate the acceptance of COVID-19 vaccination by older patients with cancer. The secondary objective concerned vaccine safety, reactogenicity, and efficacy in the two months following the first dose.

2. Materials and Methods

2.1. Study Design and Participants

This research is a study focused on vaccination prescription before oncological treatment, derived from the ongoing prospective observational cohort study “ChimioAge”, initiated in January 2017 at Marseille University Hospital (NCT03960593) [17]. The ChimioAge cohort aims to collect geriatric, oncological and drug prescriptions data of all consecutive patients aged 70 years or over with cancer, referred to our geriatric oncology center for geriatric advice before initiation of treatment. All patients benefit from a Comprehensive Geriatric Assessment (CGA) [18] and a Comprehensive Medication Reconciliation (CMR) [19–21].

From January 18, 2021, COVID-19 vaccination prescription was offered to all patients at the time of the CGA. Those who agreed received the BNT162b2 vaccine, which was administered intramuscularly in two doses 21 days apart, as part of the national vaccination campaign. Inclusion in the “vaccine survey” ended on May 7, 2021 (four months), when vaccination prescriptions were available in other centers (pharmacies or office of general practitioners or nurses) and when patients addressed for CGA were mostly vaccinated. Participants were followed up by telephone 60 days after receiving the first dose of the vaccine. Patients who were already vaccinated with a vaccine other than BNT162b2 were not eligible for the survey.

Geriatricians and pharmacists collected the data. Patients were included in the study after providing their written informed consent. The study protocol was approved by an Ethics Committee (CPP Ouest IV – Nantes registered under number 61/18.3).

2.2. Data Collection

The CGA, including assessment of autonomy, cognitive status, nutritional status, mobility, handgrip strength and polypharmacy (minimum of five prescribed medications) was assessed by both validated psychometric scales and clinical assessment, and has been previously detailed [17]. Information about demographic characteristics and lifestyle (age, gender, accommodations and presence of a caregiver)

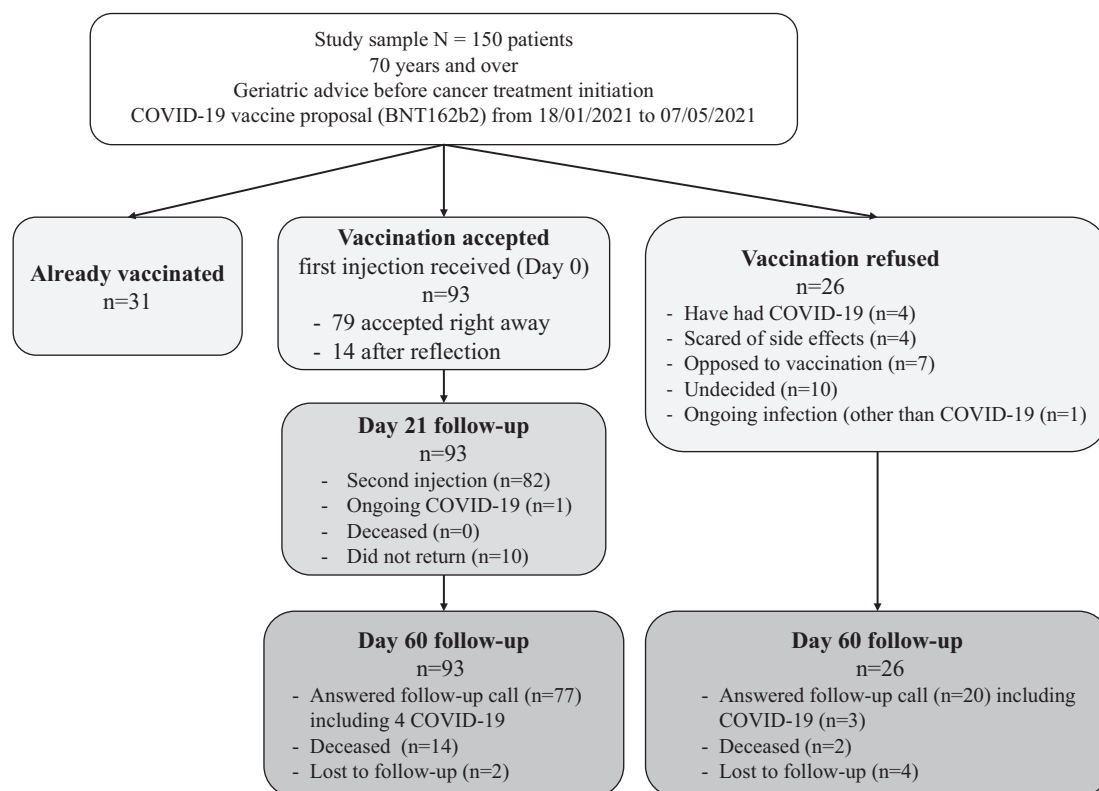


Fig. 1. Study flow chart.

were also collected. Cancer site and stage, treatment, hospitalizations, and death were obtained from the medical records. Among data directly related to CMR, only side effects of the vaccination collected during the CMR follow-up were analyzed.

2.3. Vaccine Uptake, Side Effects, and Efficacy

During the geriatric day hospitalization, patients received a CGA conducted by a geriatrician and a CMR conducted by a pharmacist. The CMR was usually conducted prior to the CGA and consisted of an in-depth interview with the patient about the current treatment and any self-medication or dietary supplements taken by the patient. During the vaccination campaign, the geriatricians and the pharmacists acted in synergy to explain the benefits and risks of COVID-19 vaccination. Vaccination was proposed at the end of the CGA, people who agreed received the first dose of the vaccine. Those who refused vaccination were asked about the reasons for not accepting or contraindications. A hospital pharmacist called all the patients included 60 days after administration of the first dose or refusal. The pharmacist collected reactivity and safety data from all the vaccinated patients 21 days after the first injection for the first vaccine dose (at the time of the second injection), and 60 days after the first injection for the second vaccine dose (last follow-up). Dates and reasons for hospitalizations, as well as COVID-19 infection dates, were collected from vaccinated and unvaccinated patients.

2.4. Laboratory Analyses

Among the vaccinated group, 22 patients agreed to have their serum samples tested for quantitative detection of anti-SARS-Cov-2 spike (S1) IgG antibodies (Euroimmun®, Luebeck, Germany) before the second vaccine dose. All samples with an ELISA ratio ≥ 0.7 , neutralizing

antibodies against SARS-Cov-2 were detected using a virus neutralization test (VNT100) [22]. Anti-S1IgG was expressed in standardized units (binding antibody units per mL) with a positive threshold of 35.2 BAU/mL.

2.5. Statistical Analysis

A descriptive analysis was performed for demographic, oncological, geriatric, and treatment characteristics of our population using head-counts and percentages for discrete data, as well as mean values plus or minus the standard error and the interval between the minimum and maximum values for continuous data. A comparative analysis of patients who accepted *versus* those who refused the vaccine was performed. The Chi-squared test was used to analyze discrete data whereas Student's *t*-test was used to analyze continuous variables. Concerning the serology testing, we compared the positive and negative serology results. All the statistical analyses were performed using SPSS software (version 17.0).

3. Results

Between January 18, 2021 and May 7, 2021, 150 older patients with cancer attending the day-care hospital for a CGA were offered vaccination against COVID-19 with the BNT162b2 vaccine and were included in the survey. The study sample consisted of 58 (38.7%) women and 92 (61.3%) men, with a mean age of 81 years (range 70–94). The most frequent primary tumors were digestive ($n = 44$; 29.4%) and thoracic cancers ($n = 27$; 18%). The socio-demographic, oncological, and geriatric characteristics of the patients are detailed in Table 1.

All patients were offered the BNT162b2 vaccine, and all were expected to have their cancer treatment within weeks of vaccination. Sixty two percent ($n = 93$) of the patients agreed to be vaccinated (79 patients (52.7%) accepted right away, fourteen patients (9.3%) initially refused

Table 2
Comparative analysis of geriatric and oncological characteristics between vaccinated and non-vaccinated patients – n = 146.

Characteristics	Vaccinated (n = 124)		Non-vaccinated (n = 22)		p-Value
	N or Mean ± SD	% or [min-max]	N or Mean ± SD	% or [min-max]	
Gender					
Women	47	37.9	9	40.9	0.815
Men	77	62.1	13	59.1	
Age	81 ± 0.5	[70–94]	81 ± 1.4	[70–94]	0.688
70–75	24	19.4	4	18.2	0.716
76–80	37	29.8	6	27.2	
81–85	32	25.8	4	18.2	
>85	31	25.0	8	36.4	
Accommodation					
Home	111	89.6	18	81.9	0.307
Care facility	7	5.6	3	13.6	
Nursing home	2	1.6	1	4.5	
Other	4	3.2	–	–	
Living alone	29	23.4	4	18.2	0.784
Caregiver present	104	83.9	19	86.4	1.000
Polypharmacy*	80	64.5	12	54.5	0.473
Cognitive impairment (n = 145)	53	43.1	9	40.9	1.000
Depression risk	42	33.9	5	22.7	0.336
Malnutrition	47	38.2	11	50.0	0.299
BMI (Kg/cm ²)	25.3 ± 0.4	[16.2–36.1]	23.3 ± 0.9	[17.1–36.8]	0.044
Albumin (g/L)	38.8 ± 0.5	[27.0–48.0]	38.1 ± 2.3	[25.0–65.0]	0.761
Functional status					
Independent	51	41.1	12	54.6	0.456
Dependent in ADL or IADL	28	22.6	3	13.6	
Dependent in ADL and IADL	45	36.3	7	31.8	
Mobility					
Impaired TUG	89	71.8	12	54.5	0.133
Impaired OLB ^T	112	90.3	20	90.9	1.000
Impaired gait speed (n = 145)	77	62.6	13	59.1	0.813
Falls in the past 3 months	17	13.7	2	9.1	0.739
Handgrip strength impairment (n = 145)	49	39.8	8	36.4	0.817
G8 impairment	108	87.1	19	86.4	1.000
ECOG-PS (n = 145)					
0–1	54	43.9	10	45.5	1.000
2–4	69	56.1	12	54.5	
Stage IV (n = 144)	47	38.2	6	27.3	0.470
Cancer type					
Digestive	35	28.2	8	36.4	0.512
Thoracic	22	17.7	4	18.2	
Urological	19	15.3	1	4.5	
Prostatic	11	8.9	3	13.7	
Skin	13	10.5	1	4.5	
Head and Neck	8	6.5	4	18.2	
Breast and gynecological	11	8.9	1	4.5	
Hematological	4	3.2	–	–	
Other	1	0.8	–	–	

BMI: Body Mass Index; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; TUG: Timed Up and Go test; OLB^T: One Leg Balance Test; ECOG-PS: Eastern Cooperative Oncology Group-Performance status.

* At least 5 prescribed medications.

but accepted upon reflection), 20.7% (n = 31) were already vaccinated, and 17.3% (n = 26) refused. Among those who refused, four were scared of the side effects of the vaccine, seven were against vaccination, ten were undecided at the time of the proposal, four had already been infected with COVID-19, and the last one had an ongoing infection but

Table 3
Descriptive analysis of COVID-19 vaccine (BNT162b2) patient-reported side effects.

Side effects (SE)*	After first injection (n = 82 respondents)†		After second injection (n = 77 respondents)‡	
	n	%	n	%
Absence of SE	69	84.0	59	76.6
Presence of SE	13	15.9	18	23.4
Local reactivity				
Arm pain	8	9.8	12	15.6
Rash	2	2.4	–	–
Systemic reactivity				
Fever	2	2.4	5	6.5
Asthenia	5	6.1	10	13.0
Headache	1	1.2	1	1.3
Other	–	–	1	0.7

* The 31 patients already vaccinated were excluded from this analysis.

† Information collected at the time of the second injection (day 21 after the first injection).

‡ Information collected at the end of follow-up (day 60 after the first injection).

not COVID-19 (Fig. 1). Patients who accepted vaccination and those who refused did not differ in terms of socio-demographic, oncological, and geriatric characteristics (Table 2).

A total of 82 patients out of the 93 who received the first dose returned for the second injection. Few of them (n = 13; 15.9%) reported mild side effects after the first vaccine injection, mostly arm pain at the injection site (Table 3). After the second injection, 23.4% of patients (n = 18) described side effects, mainly arm pain and fatigue. Taking into account those already vaccinated at the time of the study, the acceptance rate of the vaccine was 82.7% and the complete vaccination rate (two doses) reached 75.3%.

A total of eight COVID-19 cases were identified during follow-up: five (5.2%) cases in the vaccine group and three (18.8%) cases in the non-vaccinated group. Moreover, sixteen patients died during follow-up: fourteen in the vaccinated group and two in the non-vaccinated group. In the vaccinated group, one death was COVID-19-related (infection one week after the first vaccine injection, death 40 days later), and thirteen were cancer-related. In the non-vaccinated group, the causes of death were unknown for the two patients.

We analyzed responses to mRNA vaccination against COVID-19 among 22 patients, 21 days after the first dose of vaccine. We found specific antibodies to the SARS-CoV-2 spike protein in fifteen patients (68.2%). Neutralizing antibodies against SARS-CoV-2 were detected in three patients using VNT100.

The seven patients with a negative serology were more likely to be men, older, with metastatic cancer, and on multiple medications (Table 4).

4. Discussion

This single-center study reports acceptance of the COVID-19 vaccine by patients ≥70 years with cancer before initiation of oncological treatment. In our cohort, 82.7% of patients agreed to be vaccinated against COVID-19 and 75.3% received the two recommended BNT162b2 vaccine injections. Less than one in four vaccinated patients reported side effects, mainly injection site pain and fatigue. No serious side effects were reported.

Our results show a much higher acceptance rate of vaccination in the older population with cancer than expected given the results of opinion surveys carried out at the end of 2020 in France. A nationwide study showed that only 60% of the population aged over 65 years were considering vaccination against COVID-19 [23]. A cross-sectional survey on acceptance of COVID-19 vaccination among patients with cancer reported that only 53.7% intended to be vaccinated as soon as the vaccine was available. In the latter, the median age was 67 years and

Table 4

Comparative analysis of geriatric and oncological characteristics between vaccinated patients with positive versus negative serology, 21 days after first vaccine injection ($n = 22$).

Characteristics	Positive serology ($n = 15$)		Negative serology ($n = 7$)	
	N or Mean \pm SD	% or [min-max]	N or Mean \pm SD	% or [min-max]
Women	6	40.0	2	28.6
Age				
70–80	7	46.7	2	28.5
>80	8	53.3	5	71.4
Living at home	15	100	6	85.7
Living alone	2	13.3	3	42.9
Caregiver present	15	100	5	71.4
Polypharmacy*	6	40.0	6	85.7
Cognitive impairment	4	26.7	4	57.1
Malnutrition	5	33.3	2	28.6
BMI (Kg/cm ²)	24.3 \pm 1.3	[16.5–33.3]	24.7 \pm 1.5	[20.1–30.4]
Albumin (g/L)	41.1 \pm 1.1	[34.0–46.0]	37.1 \pm 1.7	[28.0–42.0]
Functional status				
Independent	7	46.7	4	57.1
Dependent in ADL or IADL	5	33.3	1	14.3
Dependent in ADL and IADL	3	20.0	2	28.6
Mobility				
Impaired TUG	12	80.0	5	71.4
Impaired OLB	13	86.7	7	100
Impaired gait speed	10	66.7	4	57.1
Falls	3	20.0	–	–
Handgrip strength impairment	4	26.7	1	14.3
G8 impairment	13	86.7	6	85.7
ECOG-PS				
0–1	8	53.3	4	57.1
2–4	7	46.7	3	42.9
Stage IV	4	26.7	3	50.0
Cancer type				
Digestive	1	6.6	3	43.0
Thoracic	4	26.7	–	–
Urological	4	26.7	2	28.5
Breast and gynecological	3	20.0	–	–
Other	3	20.0	2	28.5

BMI: Body Mass Index; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; TUG: Timed Up and Go test; OLB: One Leg Balance Test; ECOG-PS: Eastern Cooperative Oncology Group-Performance status; NA: Not Applicable.

* At least 5 prescribed medications.

47% of participants were undergoing active treatment against cancer [12]. However, the reported rate of vaccination refusal was similar to that observed in our study (17%) [12].

Moreover, the percentage of people vaccinated (75.3%) was also higher in our study than observed in the French older population at the same date: in France on May 20, 2021, only 54% of people ≥ 70 years had received full vaccination regardless of the vaccine type [24]. Vaccination was proposed by the geriatrician in the context of CGA, with time available to answer any questions the older patients and/or their caregivers had. In addition, and complementing the geriatrician's efforts, the pharmacists in charge of the CMR were also present to explain to the patients the benefits and risks of vaccination and reassured them on any fears they may have. The combination of geriatric and pharmacological assessment has certainly helped to improve the acceptance rate of the vaccine among hesitant older people, although it is impossible to distinguish the respective impact of the physician and the pharmacist on the older person's choice. In addition, patients did not have to wait for an appointment or come back later for their first injection, which was

easily accessible on the same day as the CGA. This convenience may have made a big difference for patients who often have limited mobility. We assume that both the time spent on correctly answering all the patients' questions and fears about the efficacy and side effects of the vaccine, as well as the pragmatic approach, were instrumental in increasing the acceptance rate. Of the remaining 26 patients who refused vaccination, five had reasonable reasons (were recently or currently infected with COVID-19). The last twenty-one patients were not vaccinated during the study (even after 60 days of follow-up).

According to our results, 16% and 23% of patients reported mild or moderate side effects after the first and second vaccine injections, respectively, as previously reported in adults aged over 70 years without cancer [25]. In contrast, the frequency of side effects in our study was lower than the 54% reported after the first dose in patients with cancer [26]; this discrepancy may be due to the fact that we proposed vaccination before cancer therapy was initiated, whereas it was done during the oncological treatment in Monin et al. [26]. Despite our cohort being too small to evaluate vaccine efficacy, the proportion of patients who had COVID-19 in the non-vaccinated group was three times higher than in the vaccinated group. In the study by Bernal et al., vaccination with one dose of BNT162b2 in 156,930 older adults was associated with a significant reduction in symptomatic COVID-19 and further protection against severe disease (43% reduced risk of emergency hospital admission and 51% reduced risk of death) [27]. Other studies showed poor efficacy of one dose of the BNT162b2 vaccine in older patients with cancer but a substantial serological response after two injections [12,26]. However, the correlation between the serological response to COVID-19 vaccination and clinical protection is still not fully documented [28].

The high frequency of digestive and lung cancers in our study is consistent with our usual activity but can also be explained by a kind of priority given to certain patients by oncologists, whether they are patients at risk because of pre-existing inflammatory lung disease or patients scheduled to receive immunotherapy. [29].

An important limitation of this study is the small number of quantitative detections of the anti-SARS-Cov-2 spike (S1) IgG antibodies made before the second vaccine dose and the lack of testing carried out after the second dose, which prevents us from drawing any conclusions regarding the effectiveness of the vaccine. Moreover, two vaccinated patients and four non-vaccinated patients were lost to follow-up at the end of the survey, and causes of death were unknown for the two non-vaccinated patients who died during the survey. The implementation of the study at the very beginning of the vaccination campaign and its termination after 60 days due to changes in national vaccination strategies may have also led to an overestimation of vaccine hesitancy in our study. Furthermore, we were not able to follow up on possible changes of mind in people who had refused vaccination, as the oncological follow-up of these patients was carried out in departments geographically distant from ours. In addition, it was a monocentric study including patients with all types of cancers and systemic treatments.

5. Conclusion

Our survey among older patients with cancer showed a high acceptance rate of COVID-19 vaccination in this population, probably linked to the choice of proposing vaccination in the context of the comprehensive geriatric assessment. COVID-19 vaccination carried out before initiation of cancer treatment was better tolerated than previously described and, of those who were fully vaccinated, only 5% were infected with COVID 19 and none developed severe forms. This suggests the possible benefit of not vaccinating at the same time as systemic cancer treatment when possible and organizing vaccination campaigns at the very beginning of oncological management. Larger studies to measure the durability and effectiveness of vaccine protection should be correlated with the BAU/VNT measurements before general rules can be implemented.

Author Contributions

Study concepts and design: AL. Couderc, L. Ninove, E. Nouguerede, D. Rey, M. Rebrouin, A. Daumas, P. Tomasini, L. Greillier, S. Salas, F. Duffaud, L. Dahan, M. Duluc, ME. Garcia, J. Pluvy, S. Chaleat, L. Farnault, G. Venton, T. Fourié, E. Nurtop, X. De Lamballerie, P. Villani, R. Charrel, F. Correard. **Study material or patients:** AL. Couderc, L. Ninove, P. Villani, R. Charrel, F. Correard. **Quality control of data and algorithms:** AL. Couderc, L. Ninove, P. Villani, R. Charrel, F. Correard. **Data analysis and interpretation:** AL. Couderc, L. Ninove, E. Nouguerede, D. Rey, P. Villani, R. Charrel, F. Correard. **Statistical analysis:** E. Nouguerede, D. Rey. **Manuscript preparation:** AL. Couderc, L. Ninove, E. Nouguerede, D. Rey, P. Villani, R. Charrel, F. Correard. **Manuscript editing:** AL. Couderc, L. Ninove, P. Villani, R. Charrel, F. Correard. **Manuscript review:** All authors read and approved the final manuscript.

Availability of Data and Materials

The data are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors have no conflicts of interest to declare about this work.

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