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RESEARCH ARTICLE

Perception and Experience of Oncologists regarding Vaccination of Cancer Patients on Active Treatment

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ABSTRACT

Background: The COVID-19 epidemic has wreaked havoc on individuals of all ages throughout the world. I In unprecedented time frame, its vaccination has been produced and made available to the general population. However, due to varying levels of its acceptance, vaccination did not gain widespread adoption. **Aim:** We aimed to measure the perception and experience of oncologists towards COVID-19 vaccination in cancer patients on active therapy. **Methods:** A cross-sectional survey with a self-administered questionnaire was circulated among oncology specialists in Egypt between September – and December 2021. **Results:** A total of 83 respondents participated of which 59% had more than 10 years of experience in the oncology field. The majority of the respondents 75 (90.4%) recommended giving the vaccine once available in case of hormonal treatment meanwhile the lowest percentage 32 (38.5%) was for anti CD20 monoclonal antibody, either as a single agent or combined with chemotherapy. Choices of 49 (59%), 46 (55%), and 43 (51.8%) to vaccinate patients on active treatment with cytotoxic chemotherapy, MoAb (except anti CD20), and immunotherapy respectively were reported. The inactivated COVID-19 virus vaccine was recommended by 39 (47%), followed by Vector vaccines in 20 (24.1%), 8 (9.6%) for the messenger RNA (mRNA) vaccines, while 16(19.3%) of them were undecided. Thirty-nine (47%) of the participants reported that patients on active treatment developed side effects from vaccination. The most conveyed side effects were fatigue in 34 (87%), fever or a local reaction each in 28 (71.8%), headache and myalgia equally in 19 (48.7%), and chills in 11 (28.2%), and myalgia in10 (25.6 %). **Conclusion:** Strategies to address the practicality of dealing with vaccination in cancer patients are needed. Emphasis on the installation of the latest data in caring for this population and increased awareness of the services provided is crucial. Surveys are a useful tool reflecting real-world practice.

Keywords: COVID-19, Cancer, Vaccination, Oncologists, survey.

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INTRODUCTION

Cancer patients are considered at high risk for complicated respiratory viral infections, and poor disease outcomes due to their immunosuppressed status. Furthermore, large cohort studies reported that cancer patients are at high risk for COVID-19-associated complications (Kuderer et al., 2020 and Sharma et al., 2021).

Vaccines result in less risk for symptomatic and severe COVID-19 in the patients enrolled in different studies, however, these studies were not powered enough to detect a signal for mortality protection from fatal COVID-19 and data in high-risk subgroups, such as patients with cancer (Al-Quteimat and Amer, 2020, and WHO, 2022).

As of January 2022, the WHO recommended that people who are more likely to get severe disease if infected (older persons and people with existing health conditions as cancer patients) are prioritized for vaccination. There is a need for vaccinating cancer patients to avoid excess morbidity and mortality during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Additionally, since immunosuppressed patients may be sources of prolonged viral shedding and development of variants, which highlight providing vaccinations to these vulnerable patients, may provide an additional societal benefit (Al-Quteimat and Amer, 2020, and WHO, 2022).

Cancer patients must be informed that although these vaccines are safe and effective in the general population, their effectiveness in immunosuppressed patients is emerging. The data on COVID-19 vaccine immunogenicity are mostly limited, early data has shown weak antibody responses in patients with solid tumors and hematologic malignancies, particularly patients on active treatment (Aydillo et al., 2020 and McCarthy et al., 2021). Recent data related to vaccination efficacy in cancer patients and ensuing recommendations are based on the expert opinion of international committees, which is constantly being modified accordingly (Monin et al., 2021).

Health care systems globally should exert additional efforts to take into consideration social vulnerability markers that have been demonstrated during this pandemic keeping in mind the inclusion of different racial/ethnic populations to establish true equity in the allocation of anti-COVID resources (Shroff et al., 2002 and Gayle et al., 2020). Based on the lack of data that recommend the vaccination in cancer patients and hesitation in the oncologist population in Egypt to recommend the COVID 19 vaccine, we conducted this descriptive cross-sectional survey study. It set out to develop and validate a tool to interpret vaccine acceptance and/or hesitancy to prescribe it to cancer patients by assessing the knowledge, attitude, practices, and best timing to administrate the COVID vaccine for cancer patients under active treatment among oncologists in Egypt.

METHODOLOGY

This cross-sectional study was conducted from September 19th, 2021, to December 19th, 2021, after approval from the Research and Ethics Committee, Faculty of Medicine at Helwan University, Egypt. The questionnaire was developed via expert group discussion and literature reviews guided by the “United Kingdom chemotherapy board Clinician Frequently Asked Questions (FAQs) and guidance on COVID-19 vaccine for patients receiving Systemic Anti-Cancer Therapy” (10) and validated with a focus group of 18 oncology consultants, and then set up through Survey Monkey platform as an online questionnaire (www.surveymonkey.com). The access link was shared through online platforms including emails, Facebook, and WhatsApp phone application.

The inclusion criteria for respondents’ eligibility included adults who are working as active oncologists in Egypt including medical oncologists, radiation oncologists, surgical oncologists, and clinical oncologists. The respondents were requested to take the survey without any time restrictions. The questionnaire consisted of 28 queries aiming to evaluate the knowledge and opinion of the participating oncologist. It was broadly divided into four sections. The first was the oncology specialist’s demographic features. The second section was subdivided into two components based on an initial response by the participants on advice to patients for vaccination whilst the different active treatments; if they opted to vaccinate during active treatment they were further queried to the second component of this section on the exact timing of vaccination within the therapy schedule, this is of course in case that form of therapy was cyclic and not in a continuously taken form. The active therapies included were cytotoxic chemotherapy (CTH), monoclonal antibodies (MoAb) with/without anti CD20, immunotherapy, TKIs (Tyrosine Kinase inhibitors). Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi), Cyclin-dependent kinase (CDK) inhibitors (CDK4/6i), hormonal treatment, radiation therapy alone (RTH), concurrent RTH with intravenous/or oral CTH.

The third set of questions sought the oncology specialists' observations in patients that had received their vaccinations whilst on active therapy, what vaccine was administered, the encountered side effects, the timing of the second dose and practical advice in cases of neutropenia or thrombocytopenia with certain recommended laboratory values (UK chemotherapy board, 2021) that may cause them to postpone vaccination for patients.

Lastly, the fourth set of the survey consisted of their personal outlook and preference to the type of vaccine, the efficacy obtained with vaccinating cancer patients on active therapy and if new fast track pathways are required to be established to navigate this process more smoothly for this special subset of patients.

Data analysis for responses was collected and descriptive statistics (frequencies, percentage) were calculated.

RESULTS

Demographic Results

A total of 83 respondents participated in this online survey, they were clinical oncologists mainly (37, 44.6 %) with more than 10 years experience in the oncology field (49, 59%) (Table 1).

Recommendation of COVID-19 Vaccination among cancer patients receiving different types of active treatment

The majority of the respondents 75 (90.4%) recommended giving the vaccine once available in case of hormonal treatment such as an antiestrogen, aromatase inhibitors or fulvestrant, meanwhile the lowest percentage 32 (38.5%) was for anti CD20 monoclonal antibody either as a single agent or combined with CTH, as 37 (44.6 %) of responders recommended to postpone the vaccine. With TKIs (Tyrosine Kinase inhibitors) as imatinib or sunitinib, 64 (77.2%) respondents opted for vaccination once available. PARPi as olaparib and CDK4/6i as ribociclib were equally picked by 61 specialists (73.5%).

Radiotherapy administration and vaccination were chosen by 63 (76%) participants and if combined as concurrent chemoradiotherapy (CCRT) with systemic chemotherapy (CTH) as cisplatin or carboplatin or oral chemotherapy e.g. capecitabine or temozolamide electing vaccine co-administration dropped slightly to 53 (63.9%) and 52 (62.7%) respectively. Almost similar choices of 49 (59%), 46 (55%), 43(51.8%) for vaccination in patients on active treatment with cytotoxic chemotherapy, MoAb (except anti CD20) either a single agent or combined with CTH and immunotherapy either as a single agent or combined with CTH respectively (Table 2) and (Figure 1). Further detailed questions on vaccination on the same day of the cycle for these previous therapies 30 (61%), 25(54.3%) and 18(42%) of the respondents recommended avoiding this on the same day of the cycle.

Recommendation of Specific Vaccination type (according to the availability in Egypt) to cancer patients

The majority of responders 39 (47%) recommended inactivated COVID-19 virus vaccine e.g., Sinopharm, followed by Vector vaccine e.g., AstraZeneca, Janssen & Johnson in 20 (24.1%). However, 8 (9.6%) responders recommended the messenger RNA (mRNA) vaccines e.g., Pfizer, Moderna and 16 (19.3%) of them were undecided to recommend any of the vaccines.

Recommendation for the improvement in local services and vaccine hubs in Egypt

Most of the responders 71 (85.6%) recommend that there could be an improvement in local services and vaccine hubs in Egypt to establish fast track pathways for referral and scheduled vaccination of cancer patients, 7 (8.4%) were satisfied with the current local services (Figure 2).

Vaccination types, side effects and proper timing of the second dose

Thirty-nine (47%) of the participants reported that their patients developed side effects when receiving the vaccination during active treatment. The most conveyed side effects were fatigue 34(87%), fever, local reaction by 28 (71.8%) of the participants, headache and myalgia 19 (48.7%), chills 11(28.2%), and arthralgia 10 (25.6 %). On the other hand, 44 (53%) of the participants reported that their patients didn’t develop any side effects after

receiving the vaccination during active treatment (Figure 3).

The participants indicated that the different vaccines received by these patients were inactivated COVID-19 virus vaccine e.g. Sinopharm in 15 (38.5%) and Vector vaccine e.g. AstraZeneca, Janssen & Johnson in 15 (38.5%), while 9 (23%) of them were not sure about the type of vaccine their patients received.

Concerning the timing of the second dose of the vaccine, 44 (53%) of the participants recommended receiving the second dose (for the vaccines that require a second dose) after 3-4 weeks, while 29 (35%) recommended 12 weeks. Interestingly, 10 (12%) of the participants were not sure about the proper timing to recommend the second dose for patients.

Platelets Count

Many of the participants 36 (43.4 %) recommended avoiding vaccination if the platelet count is $<20x10^9/L$, the same percentage stated that there is no consensus regarding low platelets count, while 11(13.2%) of participants were not sure about the proper decision in this case.

Neutrophils count

A majority of 55(66.3%) recommended avoiding the vaccination if neutrophils count $<1x10^9/L$, and 20 (24.1%) stated that there is no consensus regarding neutrophils count, whereas 8 (9.6%) of the responders were not sure what to recommend for their patients in this regard.

Vaccine efficacy was believed to be inadequate by 36 (43.4%) of the responders when given during systemic active CTH, while 30(36.1%) of the participants did not agree that it is less effective. Uncertainty was the option for 17(20.5%) of the participants concerning the adequacy of the vaccine in generating an immunoprotective response and active CTH coadministration.

DISCUSSION

The COVID-19 pandemic has profoundly altered the world as we once knew it. It has drastically impacted all aspects of daily life specially the health sector. When focusing on the most vulnerable groups, cancer patients lie in an unenviable position with a competing risk of death from an untreated malignancy against developing a life-threatening complication from SARS-CoV-2 as a result of the immunocompromised state the patient may experience; if not due to cancer itself but as a result of the antineoplastic treatment given (Lewis et al., 2020 and Yu, 2020).

Therefore it has increasingly been recognized that protecting this at-risk group, with prioritization to those on active therapy is fundamental and is endorsed by expert regulatory authorities (UK chemotherapy board, 2021, National Comprehensive Cancer Network, 2022, British Columbia Cancer Agency, 2021, European Society for Medical Oncology, 2022). However, little is known about Covid-19 vaccination interaction with cancer therapies as few trials included patients on active treatment. Typically live-attenuated vaccines are contraindicated in patients under immunosuppressive (Rubin et al., 2014, and Lopez et al., 2017) therapy but the currently approved vaccines are not of this category (Brisse et al., 2020).

Many caring for cancer patients in the oncology departments requested guidance in the practical issues of vaccination with different agents therefore it was of interest to collect the practice of a group of professionals 59% having more than 10 years experience in the field and 63% dealing with more than 50 patients per month.

Current recommendations endorse the administration of the vaccine whenever possible, preferably prior to the initiation of chemotherapy (but not on the same day)(UK chemotherapy board, 2021). Contrary to most respondents in the current survey was not unanimous in that circumstance, perhaps only closely so in the case of hormonal therapy with 90.4% agreeing to administer without delay.

Pertaining to anti-CD20 monoclonal antibodies usage various societies have advocated polar views concerning the resultant efficacy of the vaccine either to be given immediately or to be postponed for 6 months after the anti-CD20.

Table 1. Physicians (Respondents) Biography (n =83)

Characteristic	Parameter	Study Population; n (%)
Gender	Male	44 (53%)
	Female	39 (47%)
Oncology Specialty	Clinical	37 (44.6 %)
	Medical	25 (30.1 %)
	Radiation	7 (8.4%)
	Surgical	10 (12%)
	Hematology	4 (4.9 %)
Years of experience in the oncology field	0-5	14 (17%)
	5-10	20 (24%)
	>10	49 (59%)
Institute	Ministry of health	13 (15.8%)
	University Hospital	54 (65 %)
	Private Hospital	8 (9.6 %)
	Other	8(9.6%)
Number of reviewed patients per month	10 – 20	13 (15.7%)
	20-50	18(21.7%)
	> 50	52(62.6%)

Table 2. Physicians' response according to the type of active treatment (n=83)

Physician Response	Yes*	NO**	I am not sure
Cytotoxic CTH	49 (59%)	24 (29%)	10 (12%)
MoAb (except anti CD20) (+/-CTH)	46 (55%)	28 (34%)	9 (11%)
MoAb anti CD20 (+/-CTH)	32 (38.5%)	37 (44.6%)	14 (16.9%)
Immunotherapy (+/-CTH)	43 (51.8%)	32 (38.6%)	8 (9.6%)
TKIs	64 (77.2%)	10 (12%)	9 (10.8%)
PARPi	61 (73.5%)	6 (7.2%)	16 (19.3%)
CDK4/6i	61 (73.5%)	9 (10.8%)	13 (15.7%)
Hormonal treatment	75 (90.4%)	3 (3.6%)	5 (6%)
RTH alone	63 (76%)	14 (16.8%)	6(7.2%)
CCRT (systemic)	53(63.9%)	24 (28.9%)	6 (7.2%)
CCRT(oral)	52 (62.7%)	28 (33.7%)	3 (3.6%)

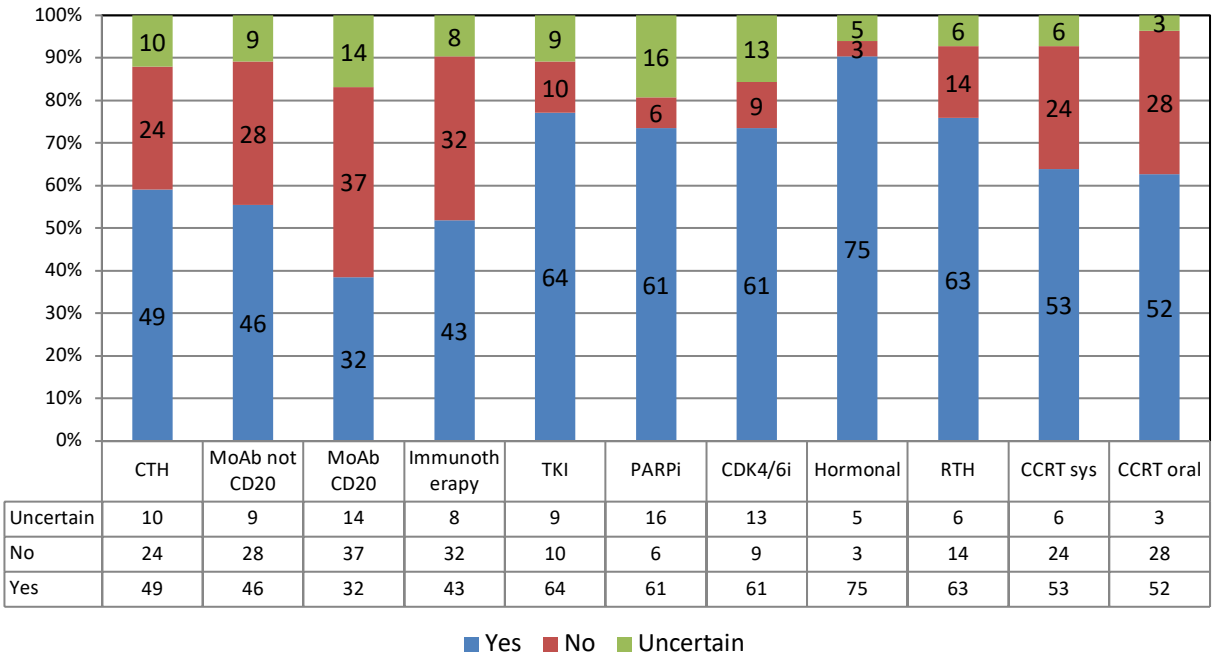
* Vaccine should be given once available during active treatment
** Postpone the vaccine till the end of treatment

(10) Thirty-two (38.5%) respondents agreed to administer the anti- CD20 monoclonal antibody either as a single agent or combined with chemotherapy whilst 37 (44.6 %) of responders recommended to postpone the vaccine, again reflecting the mixed views about the proper timing in this instance.

Various studies have revealed lower seroconversion rates for patients with haematological malignancies, generally where these monoclonal antibodies are incorporated into therapy, compared to patients with solid malignancies explaining the hesitancy to vaccinate in the current surveyed oncology cohort (Shepherd et al., 2021, Thakkar et al., 2021, Addeo et al., 2021, Ehmsen et al., 2021). As a result of the lower seroconversion rate, Shepherd et al. advocated prioritization of patients with hematologic malignancy for supplementary booster vaccination, whereas solid cancer patients can be prioritized by age.

One study found that after full mRNA vaccination in cancer patients seroconversion was 66% (215/323) versus 93% (197/210) in haematological and solid malignancies respectively. Furthermore, the rate of seroconversion varied according to the subtype of hematological malignancy being highest in diffuse large B-cell lymphoma (85%; 29/34) and lowest in mantle cell lymphoma (11%; 1/9) (Ehmsen et al., 2021).

Thakkar et al. observed a significantly lower seroconversion rate with hematologic malignancies; predominantly recipients of highly immunosuppressive therapies such as



	CTH	MoAb not CD20	MoAb CD20	Immunotherapy	TKI	PARPi	CDK4/6i	Hormonal	RTH	CCRT sys	CCRT oral
Uncertain	10	9	14	8	9	16	13	5	6	6	3
No	24	28	37	32	10	6	9	3	14	24	28
Yes	49	46	32	43	64	61	61	75	63	53	52

Figure 1. Physicians' response to vaccination according to the type of active treatment (n=83)

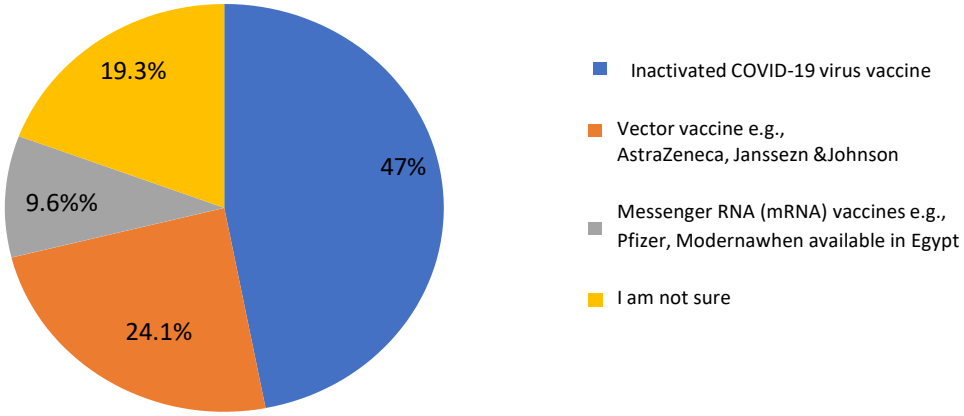


Figure 2. Recommended Type of Vaccine according to availability in Egypt

anti-CD20 therapies (70%) and stem cell transplantation (73%). Higher rates were reported for hormonal therapies (100%) and immune checkpoint inhibitor therapy (97%) post-vaccination. One study even stated that none of the patients obtained an antibody response if the anti-CD-20 antibody was taken 6 months before vaccination (Addeo et al., 2021).

Generally an “as soon as possible” has been frankly stated for vaccination of cancer patients on active treatment once eligible, perhaps even to administer the vaccination between treatment cycles, when therapy immunosuppression is lowest.

Yet if recovery of marrow function is not expected and in those receiving continuous treatment with targeted agents, vaccination should be given when available (National Comprehensive Cancer Network, 2022). The UK Chemotherapy board did advise to not administer the vaccine on the same day of the cytotoxic chemotherapy but in the current survey, only 30 (61%) selected this. (UK chemotherapy board, 2021) Concerning radiotherapy and vaccination, the approach remains consistent, but the Canadian guidance added a preference to give vaccination before the commencement of radiation if a delay will not compromise survival outcomes.

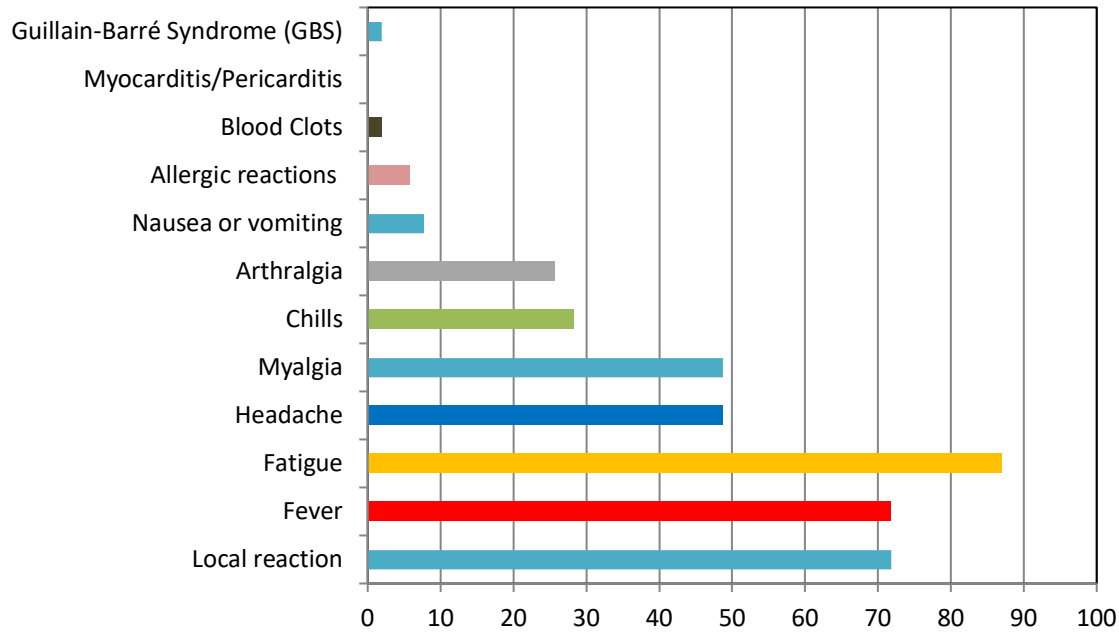


Figure 3. Reported vaccine side effects in percentages

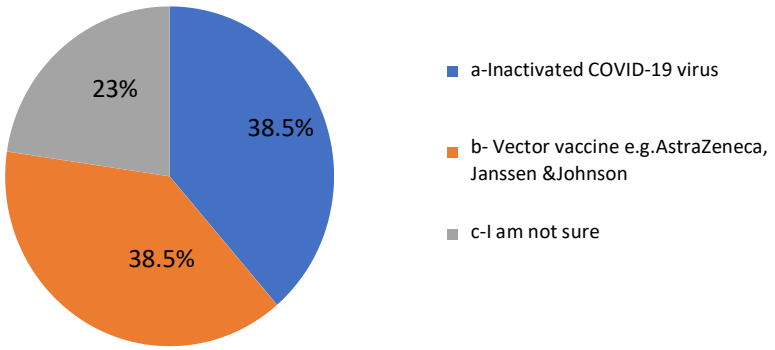


Figure 4. Type of vaccine received by the patients who reported side effects

They further advocated vaccination as early as possible in the course of radiotherapy, and if vaccination was done with the 2 doses during or in the proximity of the course then a third dose was advised (British Columbia Cancer Agency, 2021). A small percentage ranging from 14 (for RTH only) to 28% (for CCRT with oral CTH) advised postponing vaccination in the current sample, underscoring the need to establish clear pathways to support the most recent updates. This has been the general long-standing notion to not interact with the possible adverse events secondary to antineoplastic agents and ideally vaccine administration should occur when the patient is in a clinically stable state (European Society for Medical Oncology, 2022, and Rubin et al., 2014).

FDA-approved or EUA vaccines are preferred by the NCCN advisory committee (National Comprehensive Cancer Network, 2022), especially mRNA vaccines (Pfizer/BioNTech [BNT162b2/Comirnaty®] or Moderna [mRNA1273]) over the Janssen/Johnson & Johnson [Ad26.COV2.S Adenovirus vector] vaccine as recommended by the Centers for Disease Control- Advisory Committee on Immunization Practices (ACIP).

By the end of 2021 the WHO, approved eight COVID-19 vaccines, including two mRNA vaccines (mRNA-1273/Spikevax and BNT162b2/Comirnaty), three non-replicant viral vector-based [Ad26.COV2.S and two formulations of ChAdOx1 nCoV-13 (AZD1222/Vaxzevria and Covidshield)] and

three inactivated viral vaccines (Sinopharm-BBB, CoronaVac and Bharat Biotech Covaxin) (WHO, 2022).

Thus physician's choice of vaccine is understandable being mainly the inactivated COVID-19 virus vaccine e.g., Sinopharm, then the Vector vaccine e.g., AstraZeneca, Janssen & Johnson in this study and this is mainly a reflection of the available vaccines at the time of the survey as the others, though available now, were not at that time.

Available vaccines so far agree with the expected side effects reported in the current survey and have demonstrated a favorable safety profile in the general population, with the expectant post-vaccination arm soreness, fatigue, fever, and headache, with other side effects that may be encountered (Polack et al., 2020, Baden et al., 2021, Food and Drug Administration, 2021). When giving the vaccine the British guidelines (UK chemotherapy board, 2021) acknowledged the lack of consensus on thrombocytopenia (<20 x 10^9/L) and neutropenia (<1 x 10^9/L; without growth factor support) as a limitation to not administer. The values they stated were asked in the survey with 36 of the respondents (43.4 %) for thrombocytopenia and 55 (66.3%) for neutropenia choosing to forego vaccination till laboratory values were recovered. When questioned about vaccine efficacy during active therapy slightly more were skeptical (43.4%), 36.1% saw it as efficient, whilst the remaining respondents were unsure. Clearly, this is a work in progress as many trials have addressed and tested for seroconversion in cancer patients documenting its occurrence with variable degrees (Shepherd et al., 2021, Addeo et al., 2021, Ehmsen et al., 2021).

Perhaps unrelated to the current survey but having undeniable influence is hesitancy amongst immunocompromised patients to receive the COVID-19 vaccine. This has been linked to various sociodemographic factors in addition to a genuine fear of side effects and safety concerns with these novel protectants (Williamson, et al., 2020).

The dispersion of knowledge is the only way to counteract this hesitancy on the patient's part including the medical professionals dealing with these cases to further educate, understand and reassure this vulnerable subset of patients on

the necessity of receiving immunization against SARS-CoV-2. Therefore, this survey represents an essential measure of physicians' knowledge and perspectives concerning vaccination in these patients that may need improvement as they are one of the cornerstones offering guidance in this matter. Advocating the ESMO society message to vaccinate, monitor and educate is essential (Garassino et al, 2021).

Limitations of the present study are in part due to its cross-sectional nature revealing but a snapshot of practice and views at the time the survey was distributed, as more vaccines are currently available with even new recommendations on further third dosing, providing fast track pathways for a vaccination with walk-in stations, rapid scheduling within 24 hours and increasing vaccination hubs to facilitate the service for the population. Also, the somewhat limited sample size may not be adequately representative of the total oncology professionals' attitude and stance regarding this matter. Notwithstanding this last drawback, it is always useful to gain insights about how healthcare providers implement therapy and advise their patients making this report the first published in this setting; of course, this is to the best of our knowledge as previous literature was mostly patient-centric.

To conclude, clearly more awareness and knowledge need to be fulfilled in many aspects concerning oncology patients' management in these trying times of the COVID pandemic, and the current survey merely revealed its presence. Reports from advisory committees are in a perpetual state of updating trying to provide the best guidance in this immunocompromised special population based on the latest data at hand. The different views expressed by respondents when compared to current recommendations highlight a pressing need for informative programs with a special emphasis on a national or international registry for cancer patients receiving these vaccines in all stages of the disease to better fully appreciate the impact and outcome they produce. By actively engaging the oncology specialists to process the vast amount of novel data, whilst continually

encouraging a cognizant attitude may cancer patients be rightfully served.

CONFLICT OF INTEREST

The authors declare that no conflict of interest to disclose.

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