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Acute tolerance of Moderna mRNA-1273 vaccine against COVID-19 in patients with cancer treated with radiotherapy

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Although the published data about the safety of the vaccines in patients with cancer are scarce,[1] the National Comprehensive Cancer Network recommends that patients with cancer should be prioritised for COVID-19 vaccination[2] because their risk of infection, severe illness, and death due to COVID-19 are higher than for the general population.[3] Moreover, the public health burden of COVID-19 might be lessened via the vaccination of patients with cancer because, as immunocompromised individuals, they might be a source of prolonged viral shedding and could contribute to the onset of viral variants.[4] On March 10, 2021, the Italian Health Ministry stated that selected patients with cancer had maximum priority to receive vacciantion. The selected categories were patients with active advanced disease, patients receiving immunosuppressive treatment, and patients who had finished their cancer treatment in the past 6 months.[5] Consequently, patients treated with radiotherapy were also prioritised.

To our knowledge, no data are available regarding the tolerance of vaccination in patients who have received radiotherapy in the past 6 months. Because radiotherapy might affect the immune system by both suppressing and enhancing the immune response, the safety of the COVID-19 vaccines might be different in this specific setting. Moreover, the American Society for Radiation Oncology encourages patients with cancer who are receiving radiotherapy to consult with their oncologist about the timing for vaccination.[7] Therefore, data on the tolerability of COVID-19 vaccines in this population might be of interest to radiation oncologists because there is a paucity of data to help in patient counselling. Thus, we decided to assess tolerance to the Moderna mRNA-1273 vaccine (elasomeran) among patients treated with radiotherapy at our centre (Radiation Oncology Unit, Santa Maria Annunziata Hospital, Department of Oncology, Azienda USL Toscana Centro, Florence, Italy). The pivotal study[6] of the Moderna mRNA-1273 vaccine did not include individuals with cancer.

The Moderna mRNA-1273 vaccine was offered to patients who had been treated with radiotherapy in the 6 months before recruitment. Patients treated with systemic treatment (chemotherapy, immunotherapy, or targeted therapy) in the past 6 months were excluded because their vaccination was offered in the Oncology Unit. Patients were scheduled to receive two doses of vaccine, 28 days apart. Patients who were previously infected with SARS-CoV-2 were excluded if the infection occurred in the 3 months before the first dose. If the patient had been infected 3–6 months before the first dose, only the first dose was administered. A cohort of emergency medical services workers from the Operative Emergency Service team at Azienda USL Toscana Centro who received two doses of the Moderna mRNA-1273 vaccine against COVID-19 in the same time period as the patients with cancer were surveyed as a reference group of healthy volunteers. This group was chosen post hoc for comparison of safety and tolerance. A sample

	First dose		Second dose	
	Radiotherapy cohort (n=153)	Reference cohort (n=185)	Radiotherapy cohort (n=152)*	Reference cohort (n=185)
Grade 2 adverse events	7 (5%)	8 (4%)	39 (26%)	78 (42%)
Pain at injection site	4 (3%)	6 (3%)	9 (6%)	9 (5%)
Redness at injection site	0	0	1 (1%)	0
Swelling at injection site	0	0	1 (1%)	4 (2%)
Fatigue	2 (1%)	0	11 (7%)	13 (7%)
Headache	1 (1%)	0	4 (2%)	8 (4%)
Fever	0	0	2 (1%)	22 (12%)
Chills	0	0	1 (1%)	4 (2%)
Nausea	0	0	0	1 (1%)
Vomiting	0	0	0	1 (1%)
New or worsening muscle pain	0	1 (1%)	8 (5%)	11 (6%)
New or worsening joint pain	0	1 (1%)	2 (1%)	5 (3%)
Grade 3 adverse events	1 (1%)	1 (1%)	6 (4%)	19 (10%)
Pain at injection site	0	1 (1%)	0	0
Redness at injection site	1 (1%)	0	1 (1%)	0
Fatigue	0	0	0	4 (2%)
Fever	0	0	5 (3%)	10 (5%)
Chills	0	0	0	1 (1%)
New or worsening muscle pain	0	0	0	2 (1%)
New or worsening joint pain	0	0	0	2 (1%)
Grade 4 adverse events	0	0	6 (4%)	10 (5%)
Fever	0	0	6 (4%)	10 (5%)

Data are n (%) and adverse events are graded according to US Centers for Disease Control and Prevention vaccine adverse event reporting system. Grade 1 events are not shown for ease of readability. *One participant only received the first dose of vaccine due to previous SARS-CoV-2 infection.

Table 1: **Early adverse events (up to 7 days) after first and second doses of Moderna mRNA-1273 vaccine in the radiotherapy and reference cohorts**

size for the reference cohort of at least 177 patients was defined on the basis of the maximum proportion of adverse events within 28 days of vaccination in the patients in the radiotherapy cohort. We assessed the safety of the two injections of Moderna mRNA-1273 vaccine and report early adverse events (ie, local and systemic side-effects up to 7 days after each dose) and late adverse events (ie, local and systemic side-effects up to 28 days after each dose). Participants were followed up by telephone 7 days after each dose for the collection of data regarding early adverse reactions. Participants were also followed up by telephone 12–14 days and 28 days after each vaccine dose to investigate late events. Side-effects were graded according to the US Centers for Disease Control and Prevention (CDC) vaccine adverse event reporting system.[8] The hypothesis of a worse tolerance in patients who have had or are undergoing radiotherapy would have been confirmed if a proportion lower than 1·0% in the reference group had grade 3 adverse events up to 28 days after the first dose (one-sided α value of 0·05). Adverse events rates and use of antipyretic medications in the two groups (radiotherapy cohort *vs* reference cohort) were compared using a two-proportion Z test.

Patients were recruited to participate between March 28 and 31, 2021. The initial cohort of patients with cancer who had been treated with radiotherapy in the past 6 months included 435 patients, of whom 282 were excluded (111 were vaccinated in the oncology unit, 148 were already vaccinated because they belonged to other prioritised groups, 11 refused vaccination, six because of recent SARS-CoV-2 infection, and six because of poor general conditions due to terminal cancer), leaving 153 patients in the experimental cohort (appendix). The cohort comprised 98 (64%) women and 55 (36%) men, with a median age of 72 years (range 33–85). Between April 5 and 8, 2021, the first doses of the vaccine were administered and between May 3 and 6, 2021, the second doses were administered. One patient received only the first dose of vaccine because of previous SARS-CoV-2 infection 4 months before the scheduled first dose. The most frequent primary tumours were breast (75 [49%] patients) and prostate (42 [27%]) cancers. 96 (62%) patients had received postoperative radiotherapy, whereas 33 (22%) patients had received definitive radiotherapy, 14 (9%) patients had received stereotactic ablative radiotherapy, and ten (6%) patients had received palliative radiotherapy. Radiotherapy was ongoing in 41 (27%) patients, whereas it was completed in the previous 3 months for 43 (28%) patients or previous 6 months for 69 (45%) patients. Tumour and treatment characteristics are described in the appendix. Notably, five (3%) patients had previously had severe drug allergic reactions.

	First dose		Second dose	
	Radiotherapy cohort (n=153)	Reference cohort (n=185)	Radiotherapy cohort (n=152)*	Reference cohort (n=185)
Grade 2 adverse events	0	1 (1%)	1 (1%)	3 (2%)
Itching at injection site	0	1 (1%)	0	0
Allergic dermatitis	0	0	1 (1%)	0
Headache	0	0	0	1 (1%)
Abdominal pain	0	0	0	1 (1%)
Paraesthesia	0	0	0	1 (1%)
Grade 3 adverse events	6 (4%)	4 (2%)	0	1 (1%)
Pain at injection site	2 (1%)	0	0	0
Redness at injection site	2 (1%)	1 (1%)	0	0
Swelling at injection site	2 (1%)	0	0	0
Axillary lymphadenopathy	0	2 (1%)	0	1 (1%)
Low blood pressure	0	1 (1%)	0	0

Data are n (%) and adverse events are graded according to US Centers for Disease Control and Prevention vaccine adverse event reporting system. Grade 1 events are not shown for ease of readability. *One participant only received the first dose of vaccine due to previous SARS-CoV-2 infection.

Table 2: **Late adverse events (up to 28 days) after first and second doses of Moderna mRNA-1273 vaccine in the radiotherapy and reference cohorts**

51 (33%) patients receiving radiotherapy had no adverse events after the first dose of vaccine and 57 (38%) had no adverse events after the second dose. 30 (20%) patients receiving radiotherapy had no adverse events after either the first or second vaccine dose. Grade 1 adverse events occurred in 88 (58%) of 153 patients after the first dose and 63 (41%) of 152 patients after the second dose, and grade 2 or higher adverse events occurred in 14 (9%) patients after the first dose and 52 (34%) patients after the second dose (tables 1, 2). After the first dose the maximum grade of early adverse event was grade 3 (one [1%] patient), whereas after the second dose the maximum grade of early adverse event was grade 4 (six [4%]). For late adverse events, after the first dose the maximum grade of reported events was grade 3, which were injection site reactions in six (4%) patients, and after the second dose the maximum grade of adverse event was grade 2, which occurred in one (1%) patient who had a generalised

See Online for appendix

allergic dermatitis in the trunk and in the legs that completely recovered after use of steroids and antihistamine medications. Use of antipyretic or pain medication increased significantly between the first (eight [5%] patients) and the second dose (32 [21%]; two-proportions *Z* test p<0·0001). Notably, all five patients who had previously had severe allergic reactions had adverse events of grade 2 or lower.

Between June 10 and 16, 2021, 185 healthy volunteers who had received two doses of the Moderna mRNA-1273 vaccine in the period between March 1 and May 10, 2021, were recruited. The volunteers had recorded their adverse events after each dose, and in June they were interviewed to grade these events according to the CDC vaccine adverse event reporting system. 46 (25%) of 185 controls had no adverse events after their first dose of vaccine and 47 (25%) had no side-effects after the second dose. 16 (35%) of 46 patients with no adverse events after the first dose had no adverse events after the second dose. Grade 1 adverse events occurred in 130 (72%) volunteers after the first dose and in 75 (41%) volunteers after the second dose. Similar to the radiotherapy group, the maximum grade of early adverse events was grade 3 (pain at injection site; one [1%] volunteer) after the first dose and grade 4 (fever in ten [5%] volunteers) after the second dose (table 1). Four (2%) individuals in the reference cohort had late grade 3 adverse events after the first dose and one (1%) after the second dose (table 2). Use of antipyretic or pain medication increased significantly between the first (six [3%] of 185 controls) and the second dose (64 [35%]; two-proportions *Z* test p<0·0001).

We found that tolerance to the Moderna mRNA-1273 vaccine was not worse in patients who have undergone or are having radiotherapy than in healthy controls both for early adverse events (one-sided p=0·46 after first dose and p=1·00 after second dose for grade 2 adverse events; p=0·45 after first dose and p=0·99 after second dose for grade 3 adverse events; and p=0·73 after second dose for grade 4 toxicity) and late adverse effects (p=0·82 after first dose and p=0·72 after second dose for grade 2 adverse events; p=0·17 after first dose and p=0·82 after second dose for grade 3 adverse events). In summary, our data, although based on a small number of patients and limited by the observational nature of the study, showed that the safety profile of the Moderna mRNA-1273 vaccine does not raise any specific concerns in patients with cancer who received radiotherapy in the past 6 months.

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silvia.scoccianti@uslcentro.toscana.it

Radiation Oncology Unit (SS, CDP, BGL, LP, PA, RB, SF), Medical Oncology Unit ((MP, MSP, LF), and Direzione Sanitaria (AB) Santa Maria Annunziata Hospital, Department of Oncology, Azienda USL Toscana Centro, Florence, 50012, Italy; Institute for Cancer Research, Prevention and Clinical Network, Cancer Risk Factors and Life-Style Epidemiology Unit, Florence, Italy (SC); Medical Physics Unit, Santa Maria Annunziata Hospital, Azienda USL Toscana Centro, Firenze, Italy (SR); Medical Oncology Unit, San Giuseppe Hospital, Empoli and Breast Unit Firenze, Department of Oncology, Azienda USL Toscana Centro, Florence, Italy (FM); Public Health and Preventive Medicine Residency, University of Florence, Florence, Italy (FF)

1 Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. *Lancet Oncol* 2021; **22:** 581–83.

2 Recommendations of the NCCN COVID-19 Vaccination Advisory Committee, version 3.0. https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v3-0.pdf?sfvrsn=b483da2b_60 (accessed Aug 5, 2021).

3 Italian Health Ministry. Approvazione del Piano strategico nazionale dei vaccini per la prevenzione delle infezioni da SARS-CoV-2 costituito dal documento recante «Elementi di preparazione della strategia vaccinale», di cui al decreto 2 gennaio 2021 nonche' dal documento recante «Raccomandazioni ad interim sui gruppi target della vaccinazione anti SARS-CoV-2/COVID-19» del 10 marzo 2021. (21A01802). Italian Government, March 10, 2021. https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=79430&completo=true (accessed Aug 5, 2021; in Italian).

4 Aydillo T, Gonzalez-Reiche AS, Aslam S, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. *N Engl J Med* 2020; **383:** 2586–88.

5 Yang L, Chai P, Yu J, Fan X. Effects of cancer on patients with COVID-19: a systematic review and meta-analysis of 63,019 participants. *Cancer Biol Med* 2021; **18:** 298–307.

6 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384:** 403–16.

7 American Society for Radiation Oncology. COVID-19 clinical guidance. Arlington, VA: American Society for Radiation Oncology, Jan 26, 2021. https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance (accessed June 1, 2021).

8 US Centers for Disease Control and Prevention. Local reactions, systemic reactions, adverse events, and serious adverse events: Moderna COVID-19 vaccine. Atlanta, GA; US Centers for Disease Control and prevention, Dec 20, 2020. https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html (accessed June 3, 2021).