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The COVID-19 Vaccines Can Lead to False Positive Mammograms and Breast MRI. How Can we Decrease the Impact Caused by Post-Vaccination Lymphadenopathy in Breast Cancer and Oncology Patients?

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Abstract

There has been an increase in reporting clinical or radiological axillary lymphadenopathy after the coronavirus disease (COVID-19) vaccination. Cancer care is complex and multidisciplinary, which requires care events to be orchestrated promptly; radiology often serves a key role in diagnosis, post-diagnosis and is sometimes the patient's first step in cancer care initiation, especially in breast cancer. Radiologists are also a key role in other Multidisciplinary Teams (MDT) dealing with different departments. Therefore, identifying unnecessary management within the health system can generally enhance the patient's experience, reduce the pressure from providing extra health services, and reduce health costs.

Based on personal observation and previous literature, the author concludes that patients having breast cancer or recent breast cancer diagnosis in the pre- or peri-treatment setting could benefit from receiving a vaccination, if possible, in the anterolateral thigh or contralateral arm regardless if this vaccine is for influenza, HPV, etc. Whether this is applicable for the COVID-19 vaccine remains unanswered. This approach will potentially reduce the patient anxiety from having a recurrence or failure of treatment and decrease the strain of the health care system both functionally and economically. In addition, this approach can potentially reduce or eliminate cancellations, delays, and rescheduling of relevant imaging modalities. Also, the author suggests adding a history of vaccinations to all the imaging request forms; countries with digital health services can reap the benefit of generating extensive epidemiological data of post-vaccination lymphadenopathy. Thus, creating new base-evidence guidelines for managing reactive post-vaccination lymphadenopathy, and potentially avoiding duplicating unnecessary imaging and patient over-treatment.

Keywords

Digital Health, Health Cost, Patient's anxiety, PET/CT, Radiology

Introduction

The presence and advances in medical imaging have led to a more personalized medicine approach in treating patients by providing definitive diagnostic information, which subsequently led to longer lives of higher quality [1]. Most imaging services are already used for older patients. As the population is getting older, one would expect an increase in imaging demand due to a rise in cardiovascular diseases, cancer, degenerative diseases, etc. Cancer, for example, is a global burden. In 2018 there were an estimated 18 million cancer cases worldwide; 9.5 million cases were men and 8.5 million in women [2]. The top two cancers, lung and breast cancers, contributed 12.3% of the total number of new cases diagnosed in 2018 [2]. Breast cancer is the most commonly occurring cancer in women and the 2nd most common cancer overall [2]. Thus, cancer prevention is one of the most significant public health challenges of the 21st century [2].

The cost and the availability of different imaging modalities vary from one country to another and from one facility to another. However, regardless of this variation, imaging techniques are significant contributors to financial health costs; if used inadequately, this creates a financial burden for the health system and patients. For example, the total cost of performing different imaging services for patients coming through an emergency department in a teaching hospital stood at ≃$US 423 745 [3].

The presence of reactive post-vaccination in imaging can add unjustifiable costs to health care and expose individuals to unnecessary radiation doses. There is already overutilization of imaging in radiology for various reasons; therefore, adding additional unnecessary imaging could potentially overwhelm a system. Through this preliminary clinical observation, the author believes that reform in the guidelines in managing post-vaccination lymphadenopathy and research in this area is needed.

Both benign and malignant causes can lead to unilateral axillary lymphadenopathy. Lymphoma and breast cancer are among the common causes of malignancy, while inflammatory arthritides, benign reactive hyperplasia, and infectious etiologies are common benign causes [4]. Vaccination is also considered a rare cause of reactive lymphadenopathy, and it has been seen in various vaccinations, including influenza, Bacille Calmette-Guerin, smallpox, tetanus, diphtheria, and measles [4]. The transient inflammation of lymph nodes caused by vaccination may induce false-positive findings on FDG-positron emission tomography (PET) imaging [5]. The influence of non-adjuvant seasonal influenza vaccination on FDG-PET/CT imaging was investigated by [5], in which (4/5) 80% of patients with a history of influenza vaccination less than 7 days before imaging showed ipsilateral radiotracer accumulation in axillary lymph nodes [5]. Identifying the precise cutoff value is challenging, but FDG-PET performed within several days of vaccination has the possibility of false-positive inflammatory lymph nodes [5]. Generalized lymph node activation post-vaccination is a rare finding [6]. Still, a vaccine-related immune response should be considered even without evidence of tracer activity at the vaccination site when generalized FDG-avid lymphadenopathy is encountered [6].

10.2% of the Moderna mRNA COVID-19 vaccine recipients developed within 7 days of the 1st dose localized axillary swelling or tenderness ipsilateral to the vaccination arm (compared to 4.8% of placebo recipients) while 14.2% of the 2nd vaccine dose recipients developed axillary swelling or tenderness within 7 days (compared to 3.9% of placebo recipients) (**Fig-1**). Post-vaccination lymphadenopathy has also been reported with the Pfizer mRNA COVID-19 vaccine [4].

Breast MRI allows the complete visualization of levels I, II, and III axillary nodes while only a portion of the level I nodes may be visualized in mammography. This difference may explain the increase of identifying new axillary lymphadenopathy seen on Breast MRI compared to screening mammography [4]. There is currently heterogeneity in managing reactive post-COVID-19 vaccination lymphadenopathy; In the USA, for example, if it is an isolated unilateral axillary lymphadenopathy ipsilateral to the vaccination arm within 4 weeks of either vaccine dose, it will most likely be COVID-19 vaccine-related [4]. In these cases,

the lymphadenopathy is assessed as BIRADS 3 assessment (probably benign), and a recommend follow-up ultrasound is to be performed within 6-8 weeks following the 2nd vaccine dose. To minimize the likelihood of detecting reactive lymphadenopathy that necessitates follow-up imaging whenever clinically appropriate, screening MRI may either have scheduled before the 1st vaccine dose or 6-8 weeks after the 2nd vaccine dose [4].

Fig-1: A diagnostic mediolateral oblique mammogram of the left breast

The white arrows demonstrate prominent left axillary adenopathy and an intramammary lymph node [7]. The patient is a 37-year-old woman who developed a new, palpable left supraclavicular lymphadenopathy lump 5 days after her 1st dose of the Moderna COVID-19 vaccine in the left arm [7]. A Control mammogram after 2 weeks showed no change in the lymphadenopathy, and this patient was planned to take a new control in 3 months. No biopsy was taken [7].

A similar approach has also been done by [8], who reported that there had been an increase of requests for mammographies and axillary UL for patients presenting with painful and/swollen lymph nodes. These patients, when questioned, had painful and/swollen lymph nodes appearing after 1-25 days of ipsilateral deltoid administration of mRNA Pfizer-BioNTech COVID-19 vaccine. A similar approach has also been suggested by [9] for PET/CT scanning; PET/CT to be performed at least 2 weeks after vaccination. But if FDG PET/CT is not urgent and can be reasonably rescheduled, the ideal spacing of imaging is recommended 4-6 weeks after vaccination.

Especially for oncology patients, vaccine-induced lymphadenopathy may also create challenges in FDG PET/CT interpretation by confounding disease characterization and assessment of treatment response [9]. The mRNA vaccines may be more immunogenic than other traditional vaccine biotechnologies, potentially accounting for the lymphadenopathy observed on imaging [9]. Oncology patients with lymphomas, or malignancies that tend to involve the axillary, supraclavicular, or cervical lymph nodes, such as head and neck cancer, breast cancer, melanoma or sarcoma of the trunk or the upper limb, lung cancer especially upper lobe; as well as advanced-stage cancers; can create interpretive challenges in PET/CT scanning [9].

The Author's Personal Perspective

A cancer diagnosis can be associated with both psychological and physical stress [10]. Up to 52% of cancer survivors can experience variable degrees of levels of fear of cancer recurrence (FCR) [11]. Many breast cancer survivors experience high levels of FCR, depression, and anxiety [11]. The presence of palpable lymph nodes/lumps for the patient can cause stress of variable degrees and strains the health system (**Fig-2**) and (**Table-1 and Table-2**). There are different types of vaccines with varying routes of administration; examples are given in (**Table-3**). As stated previously, vaccination can lead to transient lymphadenopathy, which is a benign condition. The transient inflammation of lymph nodes caused by vaccination may induce false-positive findings on imaging, potentially adding extra unnecessary investigations, extra unnecessary hospital visits, etc (**Fig-2**).

Conclusion

Regardless of the reasons, several health systems globally were already stretched before the arrival of the COVID-19 pandemic. The pandemic has put or increased the pressure on the health systems and

stretched them beyond their capacity. Therefore, identifying areas where it is possible to decrease patient anxiety and/or the strain on the health system warrants and justifies the research. The transient inflammation of lymph nodes caused by vaccination may induce false-positive findings on imaging, potentially adding extra unnecessary investigations such as unnecessary biopsy and leading to patient over-treatment. These reactive post-vaccination positive findings become more challenging in oncology patients, especially in breast cancer. Oncologists and primary caregivers can counsel patients in regards to their vaccination.

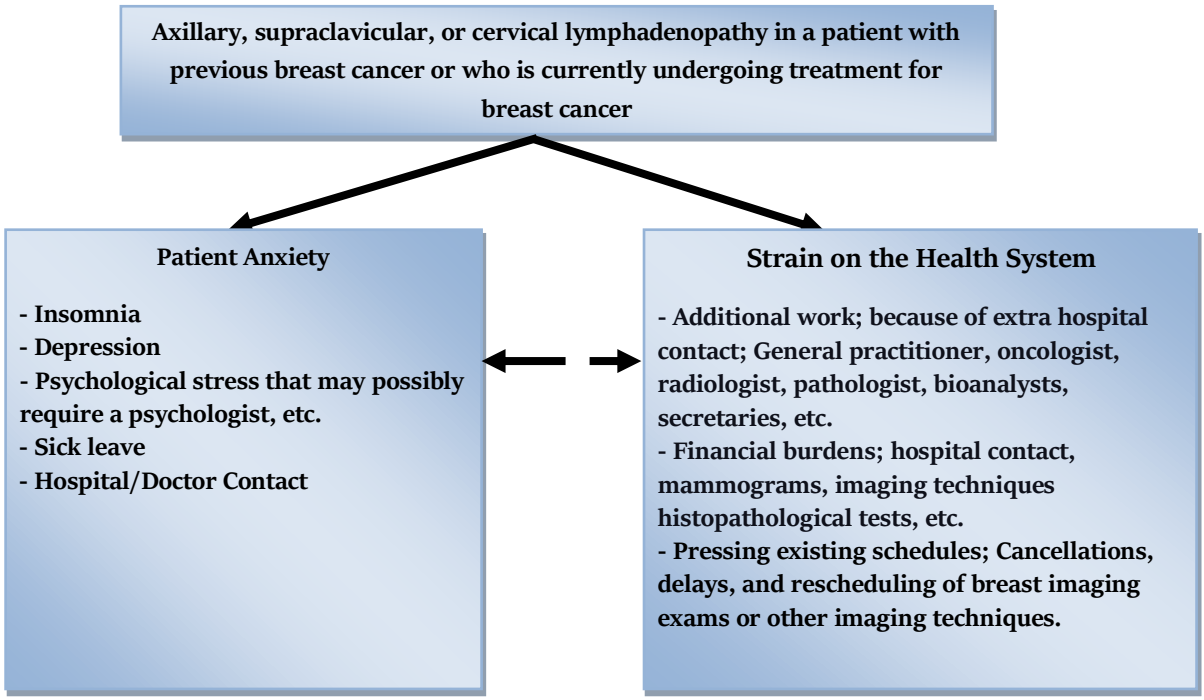

Fig-2:

The author's perspective on what impact axillary, supraclavicular, and cervical lymphadenopathy has on a patient with a/or previous breast cancer

Table-1: Examples of the financial costs for services in the health system in Denmark*

The Service	The Hypothetical Financial Cost in Danish Krone (*DKK*)
- A 10-minute consultation with a General Practitioner	146,79 DKK [14]
- A 30-minute consultation with a Specialist (Could be an neurologist, gastroenterologist, etc.)	1200-3200 DKK [15]
- A Clinical Mammography with a Breast Screening Ultrasound	2550 DKK [16]
- A Fine Needle Aspiration (FNA)	2350 DKK [16]
- A Core-Needle Biopsy	2350 DKK [16]

**The Danish welfare model promotes society-wide health and social equity through tax-financed services, including universal health care. Denmark has a universal tax-funded health care system with residency-based entitlement, which allows all to have free health care [12]. Private hospitals account for less than 1% of hospital beds in Denmark. If the public health system cannot adhere to government-mandated maximum waiting time guarantees, the patient is sent to private hospital services covered by the state. For the treatment of cancer or a suspicion of the presence of cancer, special rules have been laid down for maximum waiting times for hospital treatment of cancer patients. These rules apply to examinations, treatment, and post-treatment [13]. The waiting times are first considered when the patient has accepted (given consent to) a treatment offered at a hospital. However, it must take a maximum of 4 weeks from when the hospital ward receives the patient's referral for treatment until the patient has received treatment [13].*

Table-2: The hypothetical financial costs for the 5 patients, whom the author was involved in*

The Services that were provided for 5 patients, which the author was involved in	The Hypothetical Financial Cost (Based on Table-1)
- A 30-minute consultation with an Oncologist Specialist collegue (2 patients)	2 X (2600)= 5200 DKK
- A 30-minute consultation with a postgraduate medical doctor in clinical oncology residency program (3 patients)	3 X (439)= 1314 DKK
Contact with the breast clinic for cancer/Oncology department	**About 6514 DKK**
- A Clinical Mammography with a Breast Screening Ultrasound (5 patients)	5 X (2550)= 12750 DKK
- A Core-Needle Biopsy (2 patients)	2 X (2350)= 4700 DKK
The total hypothetical cost for the 5 patients	**23964 (≃ 24000) DKK (≃$US 4000)**

**The author saw 5 patients with palpable axillary lymphadenopathy in 6 weeks (March-April 2021). Retrospectively, this presentation was purely related to the COVID-19 vaccination.. Other colleagues in the Breast Cancer Clinic/Rigshospital have also encountered similar presentations following the COVID-19 vaccination. Still, the author does not have a registry of patients with this presentation seen by colleagues. These 5 observed patients had received COVID-19 vaccines; neither details on whether it was Moderna, Pfizer-BioNTech, or AstraZeneca were considered nor the details of the vaccine being the 1st or the 2nd shot at the time of presentation. Vaccination with AstraZeneca in Denmark was stopped around mid-March 2021. All 5 patients were sent to clinical mammography in what is called (National fast-track cancer pathway). Therefore, this course of management for these patients takes about 3-4 weeks. The author does not have access to the financial cost of each of these patients, but this is a rough estimation based on what is officially published from the referenced websites in Table-1. Also, the private sector prices don't necessarily correspond to what the private sector will receive from the government or what the health service will cost in the public sector because these patients might have received the clinical mammography only in the public sector. The economic costs of other expenses have not been included; calling the secretary etc. Also, according to the local system at the Breast Cancer Clinic/Rigshospital, every patient receiving a biopsy at the mamma radiology section must be seen again at the Breast Cancer Clinic to be informed of the biopsy's result. This extra visit to the clinic is not taken into consideration financially in this table. To report the current costs in US dollars, the cost in DKK was calculated based on the average price of dollars reported today by https://www.xe.com/currencyconverter/. The final cost in this table must be considered as a hypothetical and a crude estimation, which warrants more research to define the financial impacts.*

Table-3: Examples of vaccines and their route of administration*

The Name of the Vaccine	The Route of Administration	The Source of The information
1- The Moderna COVID-19 Vaccine	Intramuscular (IM) injection in the deltoid muscle	Centers for Disease Control and Prevention (CDC) (17)
2- Pfizer-BioNTech COVID-19 Vaccine	Intramuscular (IM) injection	Centers for Disease Control and Prevention (CDC)(18)
3- AstraZeneca COVID-19 Vaccine	Intramuscular (IM) into the deltoid muscle	The Canadian Ministry of Health(19)
4- Seasonal Influenza Vaccine	Intramuscular (IM) injection in the deltoid muscle or vastus lateralis muscle in the anterolateral thigh	Centers for Disease Control and Prevention (CDC) (20)
5- Human papillomavirus Vaccine	Intramuscular (IM) injection in the deltoid muscle or vastus lateralis muscle in the anterolateral thigh	Centers for Disease Control and Prevention (CDC) (21)

**These are an example of vaccines used in Denmark and several other countries. There are also other vaccines that can cause reactive lymphadenopathy and are approved in many countries globally, but these are beyond the scope of this manuscript. Therefore these vaccines have not been included in this table. Vaccination with AstraZeneca COVID-19 Vaccine was stopped around mid-March 2021 in Denmark.*

There are differences in immune responses among individuals, which can be genetically determined or due to factors related to the type of vaccination such as added adjuvant vaccine, live attenuated, etc. The COVID-19 vaccination using mRNA biotechnology is possibly more immunogenic than other vaccinations. An increase of reporting post- COVID-19 vaccination unilateral lymphadenopathy has increased awareness of the effects of reactive post-vaccination lymphadenopathy on the patients, especially cancer patients, the possible pressure on Radiology and Nuclear Medicine departments, and the health systems in general.

In the era of widespread COVID-19 vaccination, the author suggests a more institutional approach for oncology patients undergoing imaging after COVID-19 vaccination and other types of vaccination. The author agrees with previous suggestions that vaccination-related information should be added to the imaging request forms. The author suggests adding more detailed info of any vaccine in the requesting forms; influenza, HPV, Bacille Calmette-Guerin, COVID-19, type, site(s), date(s), and even mentions a 2nd or 3rd shot, etc. More data is needed to develop and establish practice guidelines. Intentionally designed studies to confirm these hypothetical assumptions in the preliminary observation by the author are warranted to optimize patient health care and decrease the pressure on the health system, especially with a population growing in age and complexity.

Quantitative data on how post-vaccine lymphadenopathy had affected the patients can be obtained and assessed using "Yes/No" questions. These questions can address if the patient had experienced FCR, anxiety symptoms, depressive symptoms, lack of sleep, sick leave, etc. Using tools as Fear of Progression Questionnaire-Short Form (FoP-Q-SF), General Anxiety Disorder Questionnaire (GAD-7), and Patient Health Questionnaire (PHQ-9) can be of use. Direct questions can also be added to the proposed questionnaire; ask whether these groups of patients would have preferred the anterolateral thigh approach for vaccination generally. Would the patient have reacted differently if more information regarding axillary, supraclavicular, and cervical lymphadenopathy was given to them before the vaccination? Also, asking for a patient's commentary on what would she/he suggest to tackle this issue could also be of great relevance and add more data for evidence-based guidelines.

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Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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