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Case series

Updates in COVID-19 Related Lymphadenopathy - Frequent Deep Axillary Location and Possible Contralateral Involvement

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Abstract

Ipsilateral axillary lymphadenopathy related to COVID-19 vaccine was reported as a side effect and started to raise diagnostic dilemmas especially in oncology patients. Breast cancer patients are particularly prone to this benign pitfall that may result in unfortunate management changing or unnecessary biopsy, both causing additional emotional stress for the patients. We present three cases with axillary lymphadenopathy and one with axillary and bilateral supraclavicular lymphadenopathy, and focus on what haven't been reported yet: the deep and more superior location for the axillary lymphadenopathy and the possibility of contralateral lymphadenopathy secondary to COVID-19 vaccine. Their implication in breast cancer management will also be briefly discussed.

Keywords: ***contralateral lymphadenopathy, axillary lymphadenopathy, supraclavicular lymphadenopathy, COVID-19 vaccine, side effect***

Introduction

The European Medicines Agency issued authorization for four vaccines, Pfizer-BioNTech, Moderna, AstraZeneca and Johnson&Johnson COVID-19 vaccines, to help decrease the rate of infection and mortality due to coronavirus [1]. By now, in Romania more than 1 million people received one or two vaccine doses, and we started to notice challenging diagnostic imaging dilemmas related to them [2]. Ipsilateral axillary lymphadenopathy was reported as a side effect to Pfizer and Moderna vaccines, based on the clinical examination rather than using imaging. Thereby Pfizer reported "axillary swelling or tenderness" to be 0.3% (versus <0.1% in placebo group), while in the Moderna cohort, the axillary lymphadenopathy was detected in 11.6% and 16% of recipients following first and second dose of vaccine respectively [3,4].

At this time, several cases of benign unilateral axillary lymphadenopathy were reported, first reports made by breast imagers in patients undergoing screening ultrasound, breast MRI or mammography [5-7]. A diagnostic dilemma was raised, especially in oncology patients who undergo routine follow-up imaging procedures [8]. For breast cancer patients, the American Society of Breast Imaging suggested on educating patients that axillary swelling is normal response to vaccines and advised to specific BIRADS assessment category for screening patients [9]. However, there are no European or American guidelines addressed particularly to the management of breast cancer patients.

The purpose of this case series is to exhibit mammography and ultrasound (US) findings of COVID-19 vaccination induced lymphadenopathy, to highlight the location and to discuss its possible implications in the management and follow-up of breast cancer patients.

Case presentation

Case 1

50-year-old woman, with history of stage I - T2N0M0, left breast cancer, invasive ductal carcinoma "no special type" (CDI NST) grade 2, treated with breast conserving surgery in 2018. The patient presented for the annual screening evaluation. Ten days ago, she was a recipient for the first dose of Pfizer-BioNTech Covid-19 vaccine, in the left deltoid muscle. Clinical evaluation was inconspicuous. On mammography, both breasts were unremarkable; on the left axilla there was an enlarged lymph node, partially seen on the mediolateral-oblique (MLO) view. The subsequent left axillary US showed 4 enlarged lymph nodes, oval in shape, with smooth margins, displaying a centrally located hilum and hypoechoic cortex with a focal thickening up to 10mm. The remainder of the left breast was unremarkable. The contralateral axillary lymph nodes were used for the assessment

and showed a normal, non-enlarged lymph node with a uniformly hypoechoic cortex of 1.9mm. A BIRADS 3 score was attributed to the patient, and a short-time follow-up of 6 weeks was advised. The follow-up US showed a complete resolution of the left axillary lymphadenopathy, with normal lymph nodes visible (maximum cortical thickness of 2mm). **Fig 1**.

Fig 1: 50-years-old patient with treated left breast cancer (2018). Recipient of the first dose of Pfizer-BioNTech vaccine 10 days ago, in the left deltoid muscle. MLO views of the right (A) and left (B) breast, partially depicted an enlarged left axillary lymph node (arrow). Right axillary US (C) showed normal, non-enlarged lymph nodes with cortical thickness up to 1.9 mm. Left axillary US (D) displayed enlarged lymph nodes, with focal cortical thickness (arrow), and preserved hilum (*).

Case 2

46-year-old woman, with history of right breast cancer, CDI NST grade 3, stage IIIA - T2N2M0, with eight lymph nodes positive for malignancy that was treated with mastectomy and radiotherapy in 2016. The patient presented for a right axillary pain and right palpable lump. Five days ago, she was a recipient for the first dose of Pfizer-BioNTech Covid-19 vaccine, in the right deltoid muscle. For the reason that a diagnostic mammography was done 6 months prior, a targeted axillary US was now recommended. The right axillary US showed 3 enlarged lymph nodes, oval and round in shape, with indistinct margins, with a short-axis of 10mm, displaying a centrally located hilum and hypoechoic cortex with a maximum thickening up to 9.5mm. The Doppler mode highlighted the normal hilum vessels. The contralateral axillary lymph nodes were used for the assessment and showed normal, non-enlarged lymph nodes with a uniformly hypoechoic cortex up to 2mm. There was also multiple bilateral supraclavicular lymph nodes, oval and round in shape, with smooth margins and preserved hilum, with short axis up to 3mm. Secondary to the prior lymph node positive breast cancer, a relapse was now suspected, with a BIRADS 4B score attributed and an indication for biopsy. A core needle biopsy was performed in one of the axillary lymph node, and the subsequent histology revealed reactive lymphoid, follicular hyperplasia and diffuse paracortical hyperplasia, concluding towards a benign reactive lymphadenopathy. The patient returned to annual screening. **Fig 2**

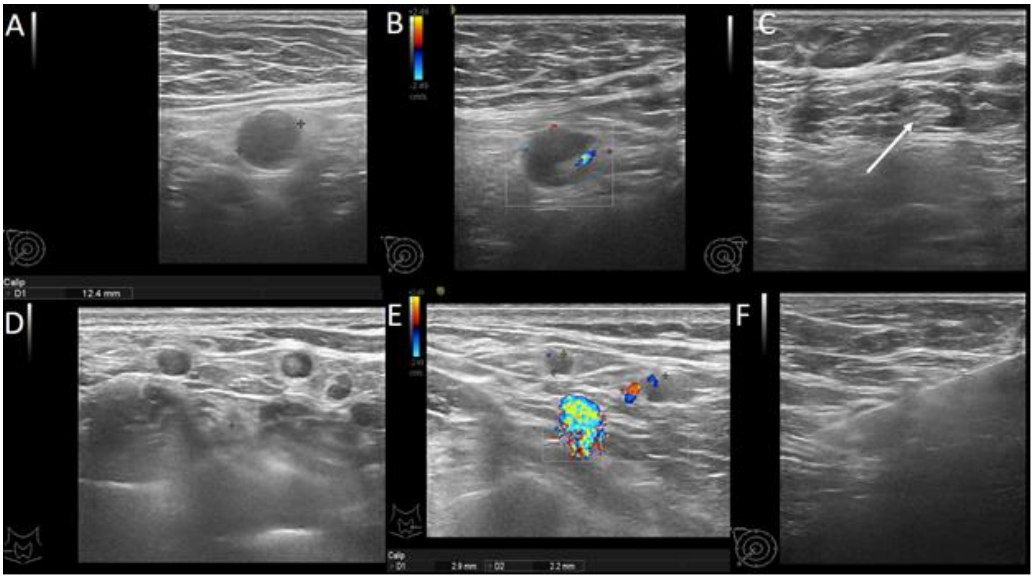

Fig 2: 46-years-old patient. First dose of Pfizer-BioNTech vaccine 5 days ago, in the right deltoid muscle. Right axillary US (A) showed suspicious lymph node, round, with indistinct margins, and short axis up to 12.4mm. The Doppler mode (B) highlighted hilum vascularity. Left axillary US (C) depicted normal, non-enlarged lymph node (arrow). Left (D) and right (E) supraclavicular US showed multiple round and oval lymph nodes, with short-axis up to 3mm. The core needle biopsy (F) was performed in one the right axillary lymph node.

Case 3

37-year-old woman, with family history of breast cancer (mother at 40 years old) was evaluated for a palpable right breast lump and palpable left axillary lump. The patient received the second dose of Pfizer-BioNTech Covid-19 vaccine, 2 days ago, in the right deltoid muscle. In the upper-outer quadrant of the right breast US showed an irregular, hypoechoic mass, with indistinct and spiculated margins, non-parallel to the skin, measuring 4 x 6 mm. The suspicious mass exhibited internal vascularity and a soft elastography appearance. The left axilla was clear from abnormal or suspicious lymph nodes. However, the right axillary US depicted 3 enlarged lymph nodes, with irregular shape, and partially indistinct margins, measuring up to 27 x 18 mm, with focal cortical thickness of 10.5mm. The hilum was preserved and displaced. The Doppler mode showed intense internal vascularity. The BIRADS 4b score was attributed and the patient underwent a core needle biopsy for the breast lesion. The histology revealed radial scar with intraductal epithelial hyperplasia (B3 lesion) for which she was scheduled for an US-guided vacuum biopsy. Regarding the axillary lymphadenopathy, a short-time follow-up was indicated, and after 6 weeks the symptoms subsided. **Fig 3**.

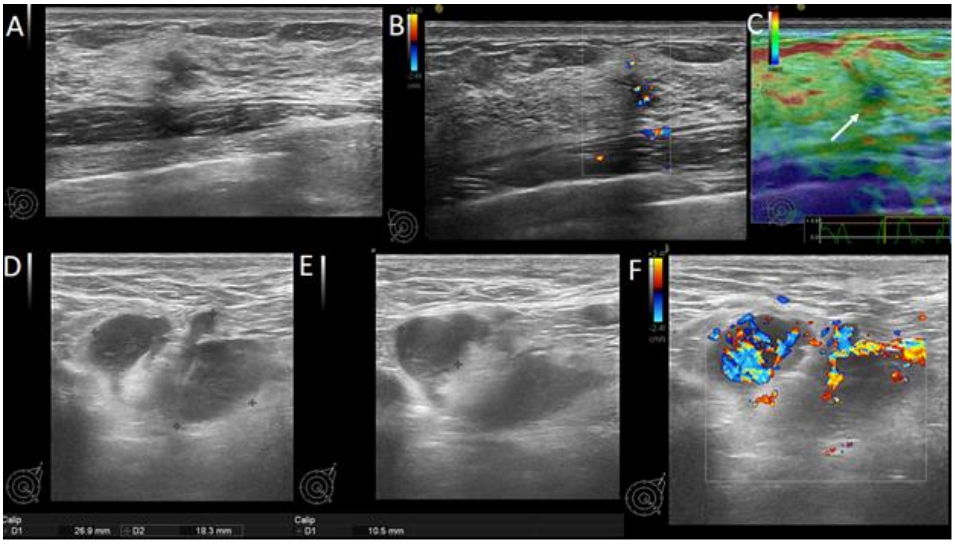

Fig 3: 37-years-old patient with family history of breast cancer. Second dose of Pfizer-BioNTech vaccine 2 days ago, in the left deltoid muscle. Right breast mass with indistinct and spiculated margins (A) internal vascularity (B) and soft elastography appearance (C, arrow). Left axillary US (A) showed enlarged lymph nodes, with irregular shape (D) and irregular cortical thickening (E), and intense vascularity (F), most probably related to the COVID-19 vaccine.

Case 4

42-year-old woman, with family history of breast cancer (sister at 35 years old), presented for an area of concern in the left breast. The patient was a recipient for the second dose of Pfizer-BioNTech Covid-19 vaccine, 7 days ago, in the left deltoid muscle. Clinical assessment and US of the left breast were unremarkable. The left axillary US showed 6 enlarged lymph nodes, oval in shape, with smooth margins, displaying a centrally located hilum and hypoechoic cortex with a maximum thickening of 4.5mm. The Doppler mode highlighted intense vascularity. The contralateral axillary lymph nodes were used for the assessment and showed normal, non-enlarged lymph nodes with a uniformly hypoechoic cortex up to 1.3mm. A BIRADS 3 score was attributed and a short-time follow-up of 6 weeks was indicated. The follow-up US depicted normal, non-enlarged axillary lymph nodes. **Fig 4**

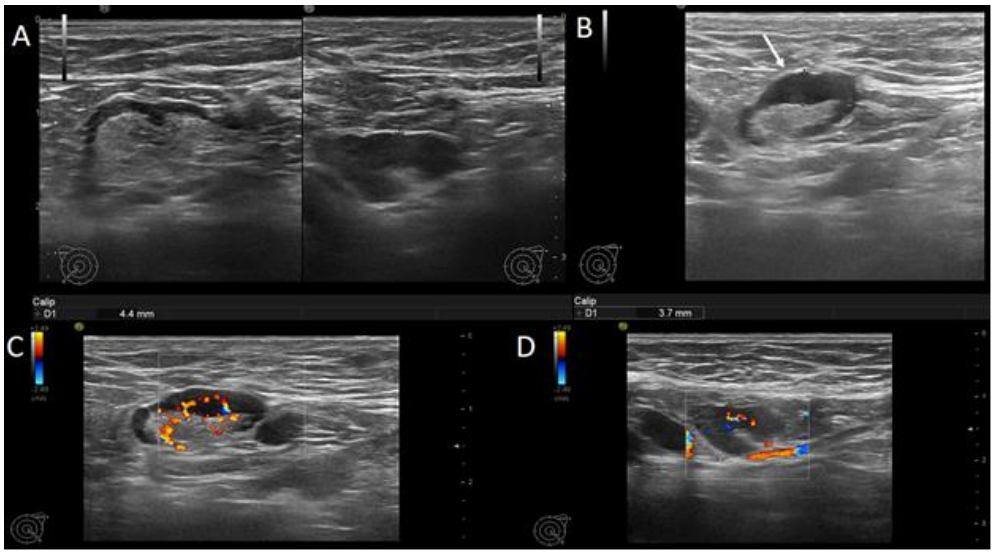

Fig 4: 42-years-old patient with family history of breast cancer. Second dose of Pfizer-BioNTech vaccine 7 days ago, in the left deltoid muscle. Comparative axillary US (A) showing normal cortical thickness on the right and uniformly thickened cortex on the left (arrow). Some of the lymph nodes displayed focal cortical thickness (B, *). Doppler mode highlighted intense vascularity of the left axillary lymph nodes (C, D).

Discussion

Breast imagers should take into account recent COVID-19 vaccination as a possible benign axillary lymphadenopathy, in particular for breast cancer patients. Furthermore, this finding is likely to become more prevalent with the rollout of the COVID-19 vaccines to the general population.

We have highlighted 4 cases of ipsilateral axillary lymphadenopathy and 1 case with associated bilateral supraclavicular lymphadenopathy, in patients that received the Pfizer-BioNTech COVID-19 vaccine. Two patients were treated previously for breast cancer, and two high-risk patients had positive family history for breast cancer. Principally, in breast cancer patients, it is vital to exclude malignancy by thoroughly examining the ipsilateral axilla, being also imperious to consider various benign etiologies for the axillary lymphadenopathy. The recent vaccination history in the ipsilateral upper extremity, is an uncommon differential diagnostic, well documented in the literature as occurring shortly after receiving the Bacille-Calmette-Guerin or seasonal influenza vaccines [10-12]. The Pfizer-BioNTech vaccine is known to cause ipsilateral "axillary swelling or tenderness".

In our case series, two out of four patients presented with symptoms of axillary pain or palpable axillary lump, while two were found to incidentally have unilateral axillary lymphadenopathy during follow-up or diagnostic imaging procedures. All four patients had positive history of recent (2 - 10 days) ipsilateral upper extremity vaccination with Pfizer-BioNTech COVID-19 vaccine. Additionally, the patients treated breast cancer received the COVID-19 vaccine prior the axillary assessment, on the same side as the breast cancer. This led to diagnostic challenges, in terms of differentiating the benign, vaccine-related lymphadenopathy from the malignant, breast cancer-related lymphadenopathy.

On US, all our patients presented with > 1 enlarged lymph nodes, with a visible hilum and variable thickened cortex (up to 10mm). Suspicious findings such as round or irregular shape and indistinct margins were also observed in two patients. On Doppler mode, the intense, inflammatory vascularity was demonstrated.

Regarding the management of breast cancer patients during COVID-19 pandemic, the European Society of Breast Imaging recommends prioritization of actions to be performed, and place imaging in women presenting with suspicious axillary findings in the high priority group (rapid appointment) and the systematic follow-up after breast cancer in the medium priority group (appointment within 3 months) [13,14]. There are no recommendation addressing the imaging or BIRADS category related to axillary or supraclavicular lymphadenopathy due to COVID-19 vaccines, which may have repercussion in the breast cancer patient's management.

The American Society of Breast Imaging advise that in patients who received a COVID-19 vaccination in the ipsilateral upper extremity within the preceding 4 weeks, to consider a short term follow-up exam in 4-12 weeks (BI-RADS category 3) following the second vaccine dose. If axillary lymphadenopathy persists after short term follow-up, then the lymph node sampling to exclude breast and non-breast malignancy needs to be considered 9. In our case, the patient number 2 had a personal history of breast cancer with positive lymph nodes and presented with suspicious axillary lymphadenopathy (round shape, indistinct margins) and multiple bilateral supraclavicular lymph nodes. Even if the size of supraclavicular nodes was less than 1 cm, the bilateral involvement of this node groups warrants heightened suspicion for clinically significant pathology, with up to 84% of the cases attributed to malignancy [15]. According to all the above mentioned rationale, a BIRADS 4b category and a core needle biopsy from the axillary node was performed. The histology concluded on a benign, most probably COVID-19 vaccine related lymphadenopathy.

Furthermore, we observed that all axillary lymphadenopathy were located superior and deep in the axilla compared to the common metastatic/recurrent breast cancer lymphadenopathy. This could be explain by the lymphatic drainage as the deltoid muscle which is the vaccine recipient, drains into the deltopectoral nodes and into the lateral axillary group that further drain in the apical axillary group, located deep and superior compared to the axillary base. In contrast, the majority of the breast is drained first in the anterior, posterior and central lymph nodes groups, with the highest frequency of metastatic lymph nodes found near the axillary tail [16]. To the best of our knowledge, this observation was not previously reported and may help in choosing the short-term follow-up or concluding as benign lymph nodes in a negative breast, in COVID-19 vaccine recipients. Moreover, we report the first case of contralateral supraclavicular lymph nodes related to COVID-19 vaccine that could represent a potential major imaging pitfall, which will probably be abundant in the next few months, as the world is entering a phase of massive immunization against COVID-19. **Fig 5**.

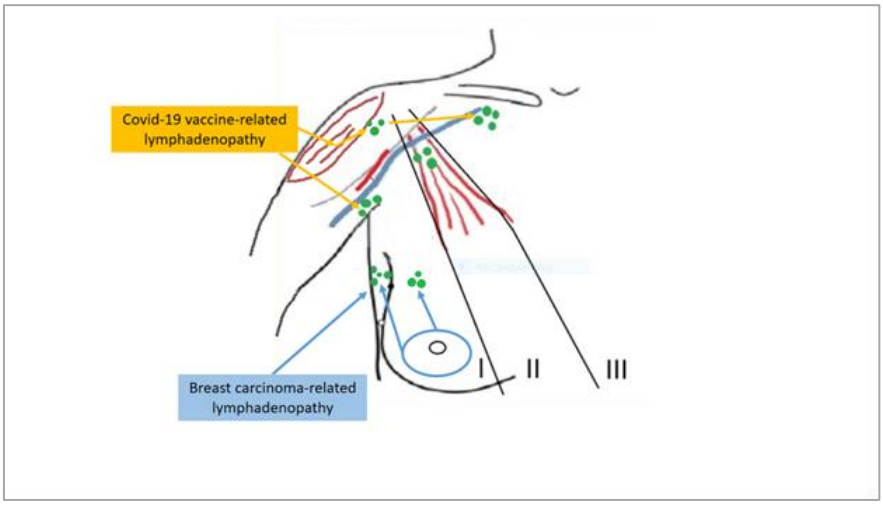

Fig 5: Upper extremity lymph node groups. Yellow route marks the deltoid muscle lymphatic drainage into deltopectoral nodes and lateral axillary group, while the blue route marks the majority of the breast lymphatic drainage and the lymph nodes located near axillary tail, as the more frequent site for breast cancer metastases. I,II,III – levels of lymphatic drainage.

Concluding

Our findings are vital, particularly for breast cancer patients that undergo imaging procedures. In this instance, the COVID-19 vaccine should be done in the opposite deltoid muscle, and/or the screening imaging modalities should be planned according to EUSOBI prioritizing guidelines, but preferably 6 weeks after the vaccine. Radiologists as well as oncologists, should be aware of this potential pitfall, related to COVID-19 vaccines, in order to preclude unnecessary changes in breast cancer patient's management or unnecessary biopsy. Deep and superior axillary lymphadenopathy with suspicious characteristics as well as contralateral supraclavicular lymphadenopathy may be found in COVID-19 vaccine recipients.

Ethics approval and consent to participate

The ethics committee waived the need for a written consent.
Personal data info was protected.

List of abbreviations

US - ultrasound
BIRADS - breast imaging reporting data system
COVID 19 - novel coronavirus 2019

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

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Authors' contributions

RP, AC and MD designed the study and written the paper. All authors read and approved the final manuscript."

References

[1] Treatments and vaccines for COVID-19, online article available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19 Accessed April 02, 2021.

[2] Official statement available online at: https://vaccinare-covid.gov.ro/comunicate-oficiale/ Accessed April 01, 2021

[3] Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events: Moderna COVID-19 Vaccine. US Center for Disease Control and Prevention Web site. https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html. Accessed February 06, 2021.

[4] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Perez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW, Jr., Hammitt LL, Tureci O, Nell H, Schaefer A, Unal S, Tresnan DB, Mather S, Dormitzer PR, Sahin U, Jansen KU, Gruber WC, Group CCT. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603-2615. doi: 10.1056/NEJMoa2034577 Crossref, Medline, Google Scholar

[5] Mehta N., Sales R.M., Babagbemi K. Unilateral axillary lymphadenopathy in the setting of COVID-19 vaccine. Clin Imaging. 2021;75:12–15.

[6] Edmonds CE, Zuckerman SP, Conant EF. Management of unilateral axillary lymphadenopathy detected on breast MRI in the era of coronavirus disease (COVID-19) vaccination. AJR Am J Roentgenol. In press.

[7] Ahn R.W., Mootz A.R., Brewington C.C., Ababa S. Axillary lymphadenopathy after mRNA COVID-19 vaccination. Radios Cardiothorac Imaging. 2021;3

[8] Özütemiz C, Krystosek LA, Church AL et al. Lymphadenopathy in COVID-19 vaccine recipients: diagnostic dilemma in oncology patients. Radiology. In press.

[9] Grimm L., Destounis, Dogan B. SBI recommendations for the management of axillary lymphadenopathy in patients with recent COVID-19 vaccination: Society of Breast Imaging Patient Care and Delivery Committee; 2021. https://www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-lymphadenopathy-post-COVID-vaccination.pdf

[10] Panagiotidis E., Exarhos D., Housianakou I., Bournazos A., Datseris I. FDG uptake in axillary lymph nodes after vaccination against pandemic (H1N1) Eur Radiol. 2010;20:1251–1253

[11] Shirone N., Shinkai T., Yamane T. Axillary lymph node accumulation on FDG PET/CT after influenza vaccination. Ann Nucl Med. 2012;26:248–252

[12] Williams G., Joyce R.M., Parker J.A. False-positive axillary lymph node on FDG-PET/ CT scan resulting from immunization. Clin Nucl Med. 2006;31:731–732

[13] Pediconi F., Mann R.M., Gilbert F.J. on behalf of the EUSOBI Executive Board. EUSOBI recommendations for breast imaging and cancer diagnosis during and after the COVID-19 pandemic. 2020. https://www.eusobi.org/content-eusobi/uploads/EUSOBI-Recommendations_Breast-Imaging-during-COVID.pdf Available at: Accessed September 9, 2020.

[14] Pediconi F., Galati F., Bernardi D. Breast imaging and cancer diagnosis during the COVID-19 pandemic: recommendations from the Italian College of Breast Radiologists by SIRM. Radiol Med. 2020;125(10):926–930. [PMC free article] [PubMed] [Google Scholar]

[15] Cunnane M, Cheung L, Moore A, di Palma S, McCombe A, Pitkin L. Level 5 Lymphadenopathy Warrants Heightened Suspicion for Clinically Significant Pathology. Head Neck Pathol. 2016 Dec;10(4):509-512. doi: 10.1007/s12105-016-0733-6

[16] Szuba A, Chachaj Z, Koba-Wszedybylb M, Hawro R, Jasinski R, Tarkowski R, Szewczyk K, Bebenek M, Forgacz J, Jodkowska A, Jedrzejuk D, Janczak D, Mrozinska M, Pilch U, Wozniewski M. Axillary lymph nodes and arm lymphatic drainage pathways are spared during routine complete axillary clearance in majority of women undergoing breast cancer surgery. Lymphology. 2011 Sep;44(3):103-12. PMID: 22165580.