A Probabilistic Cross Sectional Imaging Atlas of Healthy Axillary and Paraclavicular Lymph Nodes in Breast Cancer Patients

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Research Article

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Abstract

BACKGROUND

The aim of the present study was to generate an atlas of lymphatic drainage in breast cancer patients to be used in cross sectional diagnostic and therapeutic imaging.

METHODS

The distribution of healthy lymph nodes is investigated as a surrogate for lymphatic drainage in cross sectional imaging. 2094 healthy LN were contoured contralateral to the primary tumor site on PET-CT datasets of 153 breast cancer patients. Using rigid and non-rigid registration techniques 1939 LN were transferred to a “standard patient” CT data set. Thus, a healthy lymph node atlas was generated. The location of the healthy LN was compared to the RTOG and ESTRO clinical target volumes radiotherapy contouring recommendations.

RESULTS

The mean volume of healthy LN was 0.17cm$^3$±0.28cm$^3$ and the mean diameter was 0.77cm±0.36cm. Most LN were in level I (69.20%), supraclavicular (14.80%) and level II (10.50%). The remaining LN were in the internal mammary (2.70%), intraglandular (1.80%) and level III (1.00%). The ESTRO guideline encompassed the healthy LN in 35.00% completely, in 31.10% partly and in 33.90% not at all. The RTOG encompassed 48.00% of the healthy LN completely, 28.80% in part and 23.20% not at all.

CONCLUSION

Our study lead to the most comprehensive 3D-imaging atlas of healthy LN in cross sectional imaging. The results can be used to generate a strategy to further reduce the rate of lymphedema by irradiation. Further, the atlas can be used to determine the probability of a visible LN in a specific location to be healthy.

Introduction

With 14% of cancer deaths and 23% of cancer cases, breast cancer belongs to the most common cancer in women worldwide [1]. The lymphatic drainage of the breast plays an important role in the metastases of breast cancer but also has an impact on late toxicities of treatment - such as lymphedema [2]. Recent published studies changed the treatment paradigm in breast cancer. Radiotherapy can be performed with an equivalent oncological outcome and lower rates of lymphedema than axillary lymph node dissection (ALND) [2]. ALND can be safely replaced by sentinel lymph node radiotherapy if the patients are irradiated with high tangents after surgery [3,4]. Both, the EORTC 22922/10925 and the MA.20 trial, showed higher rate of disease-free survival and distant disease-free survival using additional regional nodal irradiation in breast cancer patients [5,6]. Thus, irradiation of the lymphatic drainage is essential in high risk breast cancer patients. Nonetheless, the study protocols of the EORTC and the MA.20 trials were designed in the 1990’s and patients underwent “simple” radiotherapy with a high not intended dose to the axilla due to the 2D radiotherapy techniques. The same is true for the data of Giuliano et al.[3,4]. Nowadays treatment planning is CT based and radiation dose is often highly conformal to the irradiated volume as defined by the Radiation Therapy and Oncology Group (RTOG) (available PDF file: https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx; 04.04.2019) or by the European Society for Radiotherapy and Oncology (ESTRO) in 2015 [5]. Unfortunately, these contouring recommendations are significantly different from each other. As a result of all these factors, the decision whether, how and which of the levels of the axillary lymph nodes should be treated becomes even more complex and an exact knowledge of the axillary CT milieus becomes imperative. Several studies on the pathological lymph nodes are available [7–9]. None is available on healthy lymph nodes.

The aim of this study is to generate a “3D-healthy lymph node atlas” in order to:

1. describe the “cold spots” and “hot spots” of healthy LN and therefore improve the accuracy of diagnostic prediction of lymph node metastases in cross sectional imaging by providing a map with probabilities of healthy – and thus implicitly pathological – LN,
2. understand how much of the healthy lymphatic drainage is included in modern radiation therapy fields and ultimately allow a prediction of the risk of lymphedema.

Methods And Materials

Few cross sectional diagnostic imaging provide an infallible result in detection of pathological vs. healthy lymph nodes. FDG PET/CT has a higher specificity (92%) and sensitivity (58%) than CT for pathological nodes and can be used as a pre-test for the selection of ALND or SLN biopsy as a treatment option [10]. So, it was the chosen imaging technique in our study. Figure 1 depicts a CONSORT diagram of this retrospective study.

All visible healthy LN were contoured contralateral to the axilla with the PET positive lymph nodes in each of the corresponding 153 CT datasets of the FDG/PET-CT (Eclipse 13.0, Varian Medical Systems, Palo Alto, CA). A total of 2094 healthy LN were each contoured in the axillary levels I-III, supraclavicular (ESTRO: level IV), in the internal mammary region and intraglandular. There were no constrains on size of the LN. All lymph nodes were contoured by the same investigator (LE) and the contouring was verified by two experienced radiation oncologists independently (KJB and MND). Using rigid and non-rigid image registration techniques 1939 healthy LN were transferred successfully to a standard patient’s CT dataset. All transferred LN
were again verified by two experienced radiation oncologists independently (KJB and MND) with regard to dimension and localization on the standard dataset. 155 LN were too small for transfer or were incorrectly transferred (i.e. on the wrong anatomical location as compared to the original dataset – transferred for e.g. within bones or within muscles) and were therefore excluded. The “standard” dataset is the CT of a 50-years old patient with a BMI of 26.6, a bust girth of 85 cm and a cup size B [7]. The method of transferring LN using rigid and non-rigid image registrations has already been established in a previous study [7]. Summing up the binary masks of the LN a “3D-healthy lymph node atlas” with information on quantity (“hotspots” and “cold spots”) as well as quality (dimensions) of LN was created. Further, the CTVs according to ESTRO and RTOG were contoured on the standard CT dataset.

In self-written MATLAB scripts the overlapping (OL) of the ESTRO/RTOG lymph node levels and the healthy lymph node localizations were calculated. An OL of < 5% means outside, an OL between 5–95% partly outside and an OL of > 95% within the ESTRO/RTOG guideline borders (Table 1). We present mean ± standard deviation and average (range).

Table 1

| Lymph Node Region | Overall Location of Healthy LN | Location within the ESTRO CTV | Location within the RTOG CTV |
|-------------------|--------------------------------|-------------------------------|-------------------------------|
|                   | Absolute (n)                  | Relative (%)                  | inside | partly outside | outside | inside | partly outside | outside |
| level I            | 1342                          | 69,20%                        | 521    | 38,80%        | 463     | 34,50% | 358          | 26,70%  |
| level II           | 204                           | 10,50%                        | 115    | 56,40%        | 72      | 35,30% | 17           | 8,30%   |
| level III          | 20                            | 1,00%                         | 8      | 40,00%        | 10      | 50,00% | 2            | 10,00%  |
| level IV/ supraclavicular | 287                  | 14,80%                        | 27     | 9,40%         | 50      | 17,40% | 210          | 73,20%  |
| internal mammary   | 52                            | 2,70%                         | 6      | 11,50%        | 8       | 15,40% | 38           | 73,10%  |
| intraglandular     | 34                            | 1,80%                         | 1      | 2,90%         | 0       | 0,00%  | 33           | 97,10%  |
| TOTAL              | 1939                          | 100%                          | 678    | 35,00%        | 603     | 31,10% | 658          | 33,90%  |

For each contoured LN a classification of inside the CTV, partly outside the CTV and outside the CTV was performed. Inside meaning that > 95% of the specific LN was within the CTV; partly outside: 5–95% of the LN volume was within the CTV and outside representing overlap of less than < 5% of the LN volume with the CTV. Herein we present how many LN were considered within the ESTRO/RTOG CTV, partly outside or outside the CTV.

Results

We detected 1939 healthy LN with a median of 12 healthy LN per patient (range 1 – 37). The mean diameter was 0.77 ± 0.36 cm, the mean volume was 0.17 ± 0.28 cm³. Table 1 summarizes the overall location of the healthy LN.

Most healthy LN occurred in level I, followed by the supraclavicular level and level II. A highly unusual location for healthy LN is the axillary level III - with only 20 LN out of the 1939 contoured LN localized within this level.

Table 1 also depicts the distribution of healthy LN within the ESTRO and RTOG CTVs. Almost 61.20% of the healthy lymphatic drainage will be outside or partly outside if the actual axilla (level I) is delineated according to the ESTRO CTV. On the other hand, the treated volume outside or partly outside the RTOG CTV will be only 45.00% for level I. Therefore, a treatment according to the CTV of the ESTRO irradiates a considerably lower proportion of the physiological lymphatic drainage than the CTV of the RTOG.

Figure 2 depicts the color-coded delineation of healthy LN (n = 1 – 16) in several axial slices of the CT-template. To visualize these results the boundaries of the ESTRO CTV and the “3D-healthy lymph node atlas” are depicted together on the standard patient (Fig. 3). Figure 4 depicts the RTOG contouring recommendation and the healthy LN cold and hot spots.

Discussion

This is the largest published 3D cross sectional imaging dataset on the occurrence of healthy LN within the lymphatic drainage system of breast cancer patients. Our results indicate that LN are highly unlikely to be seen in CT imaging in LIII and thus this information should be taken into account during assessment of diagnostic imaging of breast cancer patients. Further we could show that different contouring recommendations are likely to result in different coverages of the healthy lymphatics and might have an impact on lymphedema risk.

With surgery and radiotherapy being the two pillars of local therapy in breast cancer, an inclusive definition of the same regions is imperative [11–13]. The most difficult question of lymphatics in breast cancer, is how to translate surgical information into cross sectional imaging information (such as CT, used in radiotherapy).
First of all, surgical studies are not always congruent with each other. As one of the first, Berg et al. investigated the localization and the positivity of axillary LN removed during radical mastectomies in 324 cases and related them to the primary tumor. He defined level I inferior and lateral, level II behind and level III medial and superior to the m. pectoralis minor muscle. Most LN were in level I (45%), then in level II (35%) and level III (20%) regardless of pathologic or healthy [14]. More recent studies with different surgical axillary approaches have shown a slightly different outcome. In 227 patients Clough et al. showed that the SLN localization in the axilla - using dye or nanocolloid tracer - was 214 (94.2%) in Berg's level I and 13 (5.8%) in level II. While 51 patients have positive SLN, the remaining were negative (176 patients) [15]. In the study of Smith et al. 7370 LN were examined. The median was 18 per specimen. 1698 LN were positive and 5311 were negative. LN were classified according to a proximal (the part below the lower border of the m.pectoralis minor), a middle (between the upper and the lower border) and a distal level (above the upper border). 1177 negative LN were in the proximal level, 2477 in the middle level and 1657 in the distal level. The positive and negative LN combined were mostly located in the middle level (2968 LN of 7009, 42.3%) [16].

Secondly, the surgical information provided by all the SLN and ALND studies is very difficult to be translated into imaging. The definition of the limit of level I of Berg et al. is roughly comparable to the definition of level I by RTOG/ESTRO. Berg's level II, the nodes behind the muscle, is approximately level II of RTOG/ESTRO. Level III by Berg et al. (superior and medial to the muscle) could be level III of the ESTRO/RTOG — but it is not apparent how far Berg's level III extends cranially. Further, Berg's postulated boundaries are quite vague to be translated into cross sectional imaging: modifying the arm position results in a different coverage of the LN levels in 3D imaging [17]. Similarly, Smith et al. describes only caudal and cranial limits of the levels without all other dimensions. In cross sectional imaging however, a three dimensional description is needed, with a definition also of the lateral, medial, anterior, posterior borders. These "lacking" surgical margins are intrinsically determined by the surgeon's view on the surgical situs, but are elementary for cross sectional imaging [17].

Some educational reviews are available on CT diagnostic imaging and axillary levels. Lengelé et al. postulates the axilla to be limited ventral by the m.pectoralis minor and major, backwards by muscles like the m.latissimus dorsi, lateral there are the muscles of the arm and medial there is the m.serratus anterior [18]. The base is the lower boundary of the major muscle and m.latissimus dorsi, upwards and medially the clavicula and the first rib are the limits. The axilla is divided in level III using the inferolateral and superomedial edges of the m.pectoralis minor and the inferior border of the m.pectoralis major as limitations. Again, drawbacks for the use of this information for treatment planning is that the position of the clavicula is highly dependent on the patient position and there is no clear anatomical correlation between the clavicular position and the location of the lymphatics.

Nonetheless, the atlas presented herein could help in closing the previously described knowledge gap in diagnostic imaging [10]. We could demonstrate, that healthy LN are highly unlikely to be found in level III in cross sectional imaging (only 1% of the 1939 contoured LN were found herein). This result can be taken into account in assessing breast cancer staging CTs with visible LN in level III.

Both, the ESTRO and the RTOG tried to provide a more specific definition of axillary levels for radiotherapy treatment planning in breast cancer taking vessels into account. However, the two definitions are significantly different. The ESTRO level I is limited medial by level II and the thoracic wall, cranial the axillary vein is still included and the humeral head is omitted, lateral there is a line between m.pectoralis major and m.deltoides, the 4–5 rib is the caudal border, ventral the m.pectoralis minor and major and dorsal the limit is up to the thoraco-dorsal vessels and to a line between m.latissimus dorsi and the intercostal muscles [5]. RTOG's level I is determined medial by the lateral border of the m.pectoralis minor, cranial the axillary vessels cross the lateral m.pectoralis minor, lateral the boundary is the medial site of the m.latissimus dorsi, the insertion into the ribs of the m.pectoralis major is the caudal border, ventral there is the anterior surface of the m.pectoralis major and m.latissimus dorsi and dorsal it is the anterior surface of the m.subscapularis [19].

Several studies are available on the coverage of pathological LN by these two atlases. None is available on the coverage of the healthy lymphatics. This is highly important as several large studies showed an important oncological effect of regional lymph node irradiation (RLNR) of lymphatics in breast cancer. For e.g. the AMAROS trial compared irradiation for regional control to ALND in cN0 patients with positive SLN. For regional control both options were acceptable. In ALND lymphedema occurs more frequently [2]. A more recent study, underlined these findings [20], with the 5-year cumulative incidence rates of lymphedem being 30.1%, 24.9%, 10.7%, and 8.0% for ALND + RLNR, ALND alone, SLNB + RLNR, and SLNB alone, respectively. Nonetheless, in the AMAROS study the radiotherapy technique was mostly 2D [21] and in the screening study [20], LNs were contoured according to RTOG or RADCMP atlases.

Modern radiotherapy is 3D based, with steep gradients to not irradiated tissues. Thus, a precise knowledge of the lymphatics (i.e. with LN used as surrogates for the region of the lymphatic drainage) and their coverage by different atlases is imperative.

We could demonstrate in our study, that treating lymphatics according to one of the two atlases — ESTRO or RTOG — translate in different coverage of the healthy lymph nodes. Hypothetically, treating patients with RLNR, but contouring according to ESTRO or to RTOG, might results in different lymph edema risk for these patients. If we consider our data, surgery of level I and level II (i.e. ALND) will remove 79.70% of the visible LN - i.e. a large part of the lymphatic drainage. RLNR irradiation of Level II, III, IV and IMA (as recommended after EORTC 22922/10925 and the MA.20 ) will spare a significant part of the healthy lymphatics (which will be outside/partly outside) the treatment field: 61.2% according to ESTRO CTV and 45 % according to RTOG CTV. This knowledge enables a better understanding of the lymphedema risk and can be used to generate a strategy to further reduce the rate of lymphedema.

A limitation of our study is the single institutional character of the database and the use of PET-CT data. Nonetheless, as all healthy LN were contoured contralateral to the PET-CT positive axilla, we tried to minimize the shortcoming of cross sectional imaging in healthy vs. pathological LN detection.
Conclusion

This study represents the largest atlas of physiological lymph node distribution in breast cancer. The provided images depict "hotspots" - i.e. areas in which healthy LN accumulate within the lymphatic drainage system - and "cold spots" - i.e. regions where healthy LN are rarely to be found. This information is useful in the interpretation of radiological imaging (i.e. LN are rarely visible in level III). The atlas can be used to determine the probability of a visible node in a specific location to be healthy. The contouring guidelines for radiation therapy encompass different percentages of the lymphatics in breast cancer and thus might have a different impact on the lymphedema.

Declarations

Statements

Acknowledgments – not applicable

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Statement of Ethics

All patients gave their informed consent for the CT imaging and treatment planning. The study is conducted according to the ethical principles that have their origin in the Declaration of Helsinki. The current version of the Declaration will be observed. The recommendations of Good Clinical Practice, valid since 17.1.1997, are taken into account where applicable. The study was approved by the local ethics committee of the Technical University Munich (553/19 S).

Conflict of Interest Statement

CSE:

Advisory Boards/Advisor: BMS, Astra Zeneca, Roche, Novocure, Daiichi Sankyo, Icotec

Speakers Honoraria: BMS, Astra Zeneca, Roche, Novocure, Daiichi Sankyo, Icotec, Brainlab, varian, Accuray, Zeiss Meditec, Dr. Sennewald, Elekta, Merck Darmstadt, Medac

All other authors declare no conflicts of interest.

Author Contributions

Conceived and designed the experiments: MND. Performed the experiments: LE; KJB; MD. Reviewed the experiments: MND, KJB. Provided the infrastructure: SEC. Analyzed the data: LE, KJB, MD, MND. Wrote the paper: LE, MND. All authors read and approved the final manuscript.

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