PET/MRI in Axillary Staging

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Axillary surgery in breast cancer (BC) is no longer a therapeutic procedure but has become a purely staging procedure. The progressive improvement in imaging techniques has paved the way to the hypothesis that prognostic information on nodal status deriving from surgery could be obtained with an accurate diagnostic exam. Positron emission tomography/magnetic resonance imaging (PET/MRI) is a relatively new imaging tool and its role in breast cancer patients is still under investigation.

Keywords: breast cancer ; PET/MRI ; sentinel node biopsy

1. Introduction

Modern diagnostic imaging tools provide an accurate local and systemic staging in order to plan the primary treatment and to tailor the best surgical procedure. Whilst mammography, ultrasound (US) and magnetic resonance imaging (MRI) represent an excellent option to stage the T, staging the axilla with imaging is still challenging. To date, several studies have demonstrated the limitations of axillary ultrasound (Ax-US); these include the fact that it is an operator-dependent technique, its sensitivity ranges from 23% to 80% and also, it is unable to estimate the true axillary tumor burden [1][2]. Similarly, other tools such as standard breast MRI [3], Positron Emission Mammography (PEM) [4], PET/CT [5] are not accurate enough to predict axillary stage. On the one hand, two large meta-analyses have shown that Ax-US and selective needle biopsy correctly identifies around 50–55% of node-positive patients [2][6]. On the other hand, when considering the tumor burden, having abnormal nodes on Ax-US, mammogram and MRI often equates to having only 1–2 positive sentinel nodes that do not always change surgical plans [3][7][8]. However, the accuracy is not excellent and even when Ax-US identifies fewer than two abnormal nodes, patients are still more likely to have more than three positive nodes [9].

At first, axillary surgery had a curative intent and axillary dissection (AD) was always indicated; thereafter, SNB replaced AD and axillary surgery was more intended as a way to derive information on axillary status and plan adjuvant treatments. In fact, historical trials demonstrated no survival advantage in performing AD, and showed that it could cause more complications, long-term morbidities and, indeed, a worse quality of life [10][11][12][13]. Over time, AD has been progressively abandoned: IBCSG 23-01, ACOSOG Z0011 and AMAROS trials showed no survival advantage in completing AD in cT1-2 tumors with a positive sentinel node [12][13][14]. In parallel, primary systemic therapy (PST) has started to downstage positive axillae where AD was initially indicated and de-escalate final axillary surgery [15].

Considering this gradual switch in the role of axillary surgery from a therapeutic to a staging procedure, the role of imaging has strongly increased. Ideally, in the future, imaging might even replace surgery in the axillary staging of BC patients [16][17], while still providing reliable information to guide medical treatments. Today, systemic therapy is increasingly based on tumor biology rather than on nodal status, and gene expression signatures can also help decide on adjuvant treatment [18]. In this context, achievement of the most accurate preoperative imaging assessment of the axilla, in order to decide the most appropriate treatment for each patient, is an unmet need.

2. The Role of PET/MRI in Breast Cancer

PET/MRI is a relatively new imaging tool, and its field of application is still being studied. It was introduced in 2011 in the USA and UE, offering the potential to combine the specificity obtained by the functional imaging of PET with the superior sensitivity of MRI, and provide relevant information of higher diagnostic accuracy [19]. In particular, the fully integrated PET/MRI system provides a simultaneous imaging acquisition [20].

As regards BC, the application of PET/MRI was studied in four different settings: for preoperative staging at diagnosis, for follow-up staging, to predict the prognosis and the response to therapy (**Table 1**).

Table 1. Previous studies on PET/MRI in breast cancer patients divided according to the main objective of the exam into four groups: staging, follow-up, prognosis and response to therapy. (Nr.BC/Tot pts.: Number of breast cancer patients/total patients; NA: not available; WB: whole-body PET/MRI; B: breast PET/MRI).

Category Group	Reference	Total Number of Patients Nr. BC/tot. pts. (%)	Study Design	Patient Position	Type of Acquisition
STAGING	Catalano, O.A., 2013 [21]	35/134 (26.1%)	retrospective	supine	simultaneous
	Huellner, M.W., 2014 [22]	5/106 (4.8%)	prospective	supine	sequential
	Drzezga, A., 2012 [23]	3/32 (9.4%)	prospective	supine	simultaneous
	Appenzeller, P., 2013 [24]	7/63 (11.1%)	prospective	supine	sequential
	Wiesmuller, M., 2013 [25]	3/46 (6.5%)	prospective	supine	simultaneous
	Kirchner, J., 2018 [26]	38/38 (100%)	prospective	supine WB, prone B	simultaneous
	Botsikas, D., 2019 [27]	80/80 (100%)	prospective	supine WB, prone B	sequential
	Pace, L., 2014 [28]	36/36 (100%)	prospective	supine	simultaneous
	Kong, E., 2014 [29]	42/42 (100%)	prospective	supine WB, prone B	simultaneous
	Melsaether, A.N., 2016 [30]	51/51 (100%)	prospective	supine	simultaneous
	Van Nijnatten, T.J., 2018 [31]	12/12 (100%)	prospective	prone	simultaneous
	Taneja, S., 2014 [32]	36/36 (100%)	retrospective	supine WB, prone B	simultaneous
	Grueneisen, J., 2015 [33]	49/49 (100%)	prospective	prone	simultaneous
	Botsikas, D., 2016 [34]	58/58 (100%)	retrospective	supine WB, prone B	sequential
	Catalano, O.A., 2017 [35]	51/51 (100%)	retrospective	NA	simultaneous
	Goorts B., 2017 [36]	40/40 (100%)	prospective	prone	simultaneous
	Kirchner, J., 2020 [37]	56/56 (100%)	prospective	supine WB, prone B	simultaneous
	Bruckmann, N.M., 2020 [38]	104/104 (100%)	prospective	supine WB, prone B	simultaneous
	Bruckmann, N.M., 2021 [39]	154/154 (100%)	prospective	supine	simultaneous
FOLLOW-UP	Grueneisen, J., 2017 [40]	36/36 (100%)	prospective	supine	simultaneous
	Sawicki, L.M., 2016 [41]	21/21 (100%)	prospective	NA	simultaneous
	Pujara, A.C., 2016 [42]	35/35 (100%)	retrospective	prone	simultaneous
	Beiderwellen, K., 2013 [43]	10/70 (14%)	prospective	NA	simultaneous
	Chandarana, H., 2013 [44]	10/32 (31.2%)	prospective	NA	simultaneous
	Rauscher, I., 2014 [45]	4/40 (10%)	prospective	NA	simultaneous
	Catalano, O.A., 2015 [46]	109/109 (100%)	retrospective	NA	simultaneous
	Raad, R.A., 2016 [47]	15/208 (7.2%)	retrospective	NA	simultaneous
	Ishii S., 2016 [48]	33/123 (26.8%)	prospective	NA	simultaneous
	Kirchner, J., 2017 [49]	2/41 (5%)	prospective	NA	simultaneous
	Sonni, I., 2019 [50]	23/74 (31%)	prospective	NA	simultaneous
PROGNOSIS	Schiano, C., 2020 [51]	40/217 (18.4%)	retrospective	NA	simultaneous
	Margolis, N.E., 2016 [52]	12/12 (100%)	prospective	prone	simultaneous
	Catalano, O.A., 2017 [53]	21/21 (100%)	retrospective	supine WB, prone B	simultaneous
	Jena, A., 2017 [54]	69/69 (100%)	prospective	supine WB, prone B	simultaneous
	Jena, A., 2017 [55]	98//98 (100%)	prospective	prone	simultaneous
	Kong, E., 2018 [56]	46/46 (100%)	prospective	prone	simultaneous
	Incoronato, M., 2018 [57]	50/50 (100%)	prospective	prone	simultaneous
	Inglese, M., 2019 [58]	46/46 (100%)	prospective	prone	simultaneous
	Incoronato, M., 2019 [59]	77/155(49.7%)	prospective	supine WB, prone B	simultaneous
	Morawitz, J., 2021 [60]	56/56 (100%)	prospective	prone	simultaneous
	Murakami, W., 2020 [61]	55/55 (100%)	retrospective	supine WB, prone B	simultaneous
	Carmona-Bozo, J.C., 2021 [62]	32/32 (100%)	prospective	prone	simultaneous
RESPONSE	Jena, A., 2017 [63]	50/50 (100%)	prospective	supine WB, prone B	simultaneous
	Wang, J., 2017 [64]	14/14 (100%)	prospective	prone	simultaneous
	Romeo, V., 2017 [65]	4/4 (100%)	prospective	NA	simultaneous
	Cho, N., 2018 [66]	26/26 (100%)	prospective	supine WB, prone B	simultaneous
	Andreassen, M.M.S., 2020 [67]	24/24 (100%)	prospective	NA	simultaneous

On the one hand, the advantages of this hybrid diagnostic tool are a lower radiation dose when compared to PET/CT, better inter-observer agreement, a one-stage exam and more accurate detection of brain, bone and liver metastases. On the other hand, PET/MRI is still an expensive and time-consuming imaging method, which is not available everywhere; despite the attractiveness of performing a single exam when both PET and MR imaging are indicated, PET/MRI also exhibits other limitations (i.e., long duration, MR truncation, PET/MRI misregistration, etc.) [68].

To conclude, the role of PET/MRI in the BC setting is not yet well defined, although it shows good accuracy in BC local and systemic staging and could be considered in both monitoring and predicting the response to PST. However, the heterogeneity of the studies reported and the variability of the PET/MRI approach limit the comparison and the summation of data. Hence, current evidence is not sufficient to derive standard indications; ongoing and future research on PET/MRI could help clarify its role and establish whether it may represent a useful diagnostic and prognostic tool, or if it needs to be replaced or integrated with other conventional diagnostic tools.

3. PET/MRI in Axillary Staging: Current Evidence

Several studies have investigated the power of PET/MRI in staging the axilla; the results are encouraging but preliminary, due to the small sample size and inhomogeneous study population and design (**Table 2**).

Table 2. Previous studies on PET/MRI evaluating the axillary status in breast cancer (NA = not available, WB = whole body PET/MRI, B = breast PET/MRI).

Authors	Total Number of Patients	Study Design	Patient Position	Type of Acquisition	Axillary Node Detection Sensitivity	Axillary Node Detection Specificity
Kirchner, J., 2018 [26]	**38**	**prospective**	**supine WB, prone B**	**simultaneous**	**93%**	**95%**
Botsikas, D., 2019 [27]	**80**	**prospective**	**supine WB, prone B**	**sequential**	**0.85 (0.72–0.93)**	**0.89 (0.82–0.94)**
Melsaether, A.N., 2016 [30]	**51**	**prospective**	**supine**	**simultaneous**	**88–100% (CI 69, 97)**	**95% (CI 88, 98)**
Taneja, S., 2014 [32]	**36**	**retrospective**	**supine WB, prone B**	**simultaneous**	**60% on PET, 93.3% on MRI**	**91% on PET and MRI**
Grueneisen, J., 2015 [33]	**49**	**prospective**	**prone**	**simultaneous**	**78% (CI 52, 94)**	**90% (CI 74, 98)**
Botsikas, D., 2016 [34]	**58**	**retrospective**	**supine WB, prone B**	**sequential**	**79%**	**100%**

4. Conclusions

The modern battle for the breast surgical oncologist aims to achieve the least invasive but effective treatment and eventually find an imaging tool that is able to predict pathological results and spare women from future axillary surgery.

To date, the current evidence does not permit the avoidance of surgery, but PET/MRI might offer patients a one-stop-shop solution for local and systemic staging, and guide the surgical oncologist to de-escalate axillary surgery in selected patients. Results from prospective trials on PET/MRI are anticipated in the next five years and should help decide the potential applications of this cutting-edge imaging tool in BC treatment.

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