MRI and intraoperative pathology to predict nipple-areola complex (NAC) involvement in patients undergoing NAC-sparing mastectomy

Prediction of occult nipple-areola complex (NAC) involvement in breast cancer patients undergoing NAC-sparing mastectomy

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Abstract

Background: Nipple-areola sparing mastectomy (NSM) with immediate implant reconstruction is an option for patients with non-locally advanced breast cancer. The prediction of occult tumour involvement of the nipple-areola complex (NAC) may help select candidates to NSM.

Patients and methods: We prospectively recorded clinical and pathological data, magnetic resonance imaging (MRI) results and intraoperative pathological assessments of the subareolar (SD) and proximal nipple ducts (ND) of 112 consecutive breast cancer patients scheduled for NSM. All parameters were correlated with final pathological NAC assessment by univariate and multivariate analysis.

Results:

Thirty-one patients (27.7%) had tumour involvement of the NAC. At univariate analysis, age (p=0.001), post-menopausal status (0.003), tumour central location (p=0.03), tumour-NAC distance measured by MRI (p=0.000) and intraoperative pathologic assessment (SD + ND) (p= 0.000) were significantly correlated with NAC involvement. At multivariate analysis, only MRI tumour-NAC distance (p = 0.008) and menopausal status (p= 0.039) among all preoperative variables retained statistical significance. The sensitivity and specificity of MRI tumour-NAC distance were 32.2% and 88.6% and those of intraoperative pathologic assessment were 46.7% and 100%, respectively. Sensitivity, specificity and accuracy of the double assessment (MRI plus intraoperative pathology) were 50.0%, 96.2% and 84.1%, respectively.

Conclusion

Intraoperative pathologic assessment and tumour-NAC distance measured by MRI are the most important predictors of occult NAC involvement in breast cancer patients. A negative pathological assessment and a tumour-NAC distance ≥ 5 mm allow optimal discrimination between NAC positive and NAC negative cases and may serve as a guide for the optimal planning of oncological and reconstructive surgery.

Introduction

The most important evolution of breast cancer surgery after the introduction of sentinel node dissection is likely represented by the progressive reduction of the amount of breast skin that is removed during mastectomy. The shift towards more conservative types of mastectomy began with the introduction of implant-based immediate reconstruction in the early 1990s (1). The term skin-sparing mastectomy (SSM) was originally introduced to describe the removal of breast and nipple-areola complex (NAC) as well as the previous biopsy scars through a pre-planned incision with the preservation the remaining skin envelope of the breast (2). Further refinements of SSM combined with immediate breast reconstruction allowed superior cosmetic outcomes and rapidly made it the preferred option for early breast cancer patients undergoing mastectomy (3). This change of practice occurred all over the world despite the lack of randomized studies proving the oncological safety of SSM. Indeed, several observational studies and a metanalysis (4,5) suggest that SSM is not significantly different from total mastectomy in terms local recurrence rates and most scientific societies have endorsed SSM for early breast cancer patients (6).

Although NAC involvement has been reported to occur in up to 58% of breast cancer patients (7), recent data suggest that it is actually less frequent (8). Therefore, a new type of mastectomy with the preservation of the NAC, named “NAC sparing mastectomy” (NSM), has been proposed as a possible alternative in selected breast cancer patients undergoing immediate reconstruction (9,10) or in BRCA1/2 mutation carriers opting for prophylactic surgery (11,12). Several institutions have now adopted NAC sparing mastectomy in breast cancer patients and early follow up data on oncological safety and postoperative complications are reassuring (13).

In patients who are candidates to NSM, preoperative assessment of the NAC helps optimal surgical planning, while intraoperative awareness of NAC infiltration allows the conversion to a SSM, avoiding the need of a second delayed surgery to remove the NAC. The likelihood of NAC involvement has been associated with several tumour characteristics

such as retroareolar location, distance from the NAC, size, multifocality/multicentricity, grade, lympho-vascular invasion, extensive intraductal component, and lymph-nodal status (14-17). We recently showed that tumour-NAC distance measured by magnetic resonance imaging (MRI) of the breast is the key preoperative predictor of NAC involvement in a series of total mastectomies performed at our Institution (18). Furthermore, intra-operative evaluation of the retro-areolar tissue is very sensitive for detecting cancer cells in the sub-areolar tissue with a false negative rate as low as 11.8% (19).

In the current study, we prospectively assessed the relative contribution and usefulness of breast MRI and intraoperative pathological assessment of the NAC for the prediction of NAC involvement and surgical planning in a consecutive series of NSM.

Patients and Methods

Since January 2010 to January 2012 we enrolled all patients candidates to NAC sparing mastectomy into a protocol approved by the Institutional Review Board that included preoperative MRI and intra-operative assessment of NAC status. Potential candidates to NAC sparing mastectomy were all patients affected by invasive or in situ ductal carcinoma without evident clinical tumour involvement of the NAC and/or the skin, not amenable to breast conserving surgery and willing to undergo immediate implant-based reconstruction. Exclusion criteria were patients with locally advanced tumours not undergoing or not responding to preoperative chemotherapy, inflammatory breast cancer and Paget's disease of the nipple. Patients with bilateral malignancy could be included, but not those undergoing prophylactic mastectomy or mastectomy performed for non-malignant lesions and lobular carcinoma in situ of the breast. All patients signed a written informed consent. All clinical (age, menopausal status, tumour location, nodal involvement), radiological (tumour - NAC distance, tumour largest diameter and multifocality) and pathological (tumour size, histology grade and immuno-histochemical profile, multifocality/multicenticity, in situ component, nodal involvement) data were recorded in a prospectively maintained institutional database.

MRI examinations were acquired with a 1.5T equipment and dedicated phased-array 8-channel coil (HDx Signa Excite, GE HealthCare Milwaukee, WI, USA), following the recommended technical requirements (20). In particular, the dynamic study was performed by a 3D Vibrant sequence (slice thickness 2.6 mm; matrix 416x416; temporal resolution 90 seconds) acquired before and 5 times after iintravenous contrast agent administration (0.1mmol/kg of Gadobenate Dimeglumine, Bracco Imaging, Milan, Italy) at a flow rate of 2 ml/s. Multiplanar reconstructions (MPR) obtained from subtracted images (1^{st} and 5^{th} post-contrast series – pre-contrast acquisition) were used to assess prospectively the diameter of the lesion, which was defined as the maximum extent of suspicious enhancement. In the case of bifocal, multifocal or multicentric lesions, these were considered as a single mass and the reference measure reflected the whole area occupied in the breast. A conventional measure of the larger tumour foci was also recorded in this group. MRI Tumour NAC-distance was measured by electronic calipers, on both axial and sagittal Maximum Intensity Projection (MIP) images. Both these measurements, as well as the minimum distance between the base of the NAC and the nearest margin of the lesion (18) were evaluated to predict the likelihood of NAC involvement.

During NAC sparing mastectomy, the maximum amount of breast tissue was excised while raising the NAC as a full-thickness skin flap. A 1 cm-thick disc of tissue containing the ducts just beneath the areola (subareolar ducts or SD) was biopsied and orientated. A second biopsy was taken by sampling the ducts contained in the central portion of the proximal nipple (proximal nipple ducts o ND). Both biopsies were sent for frozen section. NAC involvement was defined by the presence of invasive ductal/lobular carcinoma and/or ductal carcinoma in situ/ductal intraepithelial neoplasia (DIN1c – DIN3), but not of lobular carcinoma in situ/lobular intraepithelial neoplasia (LIN1-LIN3). Only if either of the samples revealed malignancy at intra-operative or definitive histology the NAC was removed respectively at the time of mastectomy or as a second surgery under local anaesthesia.

The quantitative variables were compared with the Pearson chi-square test or Fisher's exact test. Qualitative variables were compared using the analysis of variance. The

normality of variables was tested by the Kolmogorov–Smirnov procedure. Variables not normally distributed were analysed using the non-parametric Mann–Whitney U test. Univariate and multivariate analyses using logistic regression models were undertaken to predict involvement of the NAC (yes/no) on the basis of clinical characteristics, MRI findings, intra-operative and postoperative pathological findings. Variables included tumour histologic type, multifocality/multicentricity, node positivity, lymphovascular invasion, grade, hormone receptor status, HER-2/neu expression, proliferation markers (Ki-67), in situ component, and extensive intraductal component (defined as ≥ 25 % of tumour cells in ducts). A Receiving operating characteristics (ROC) curve was constructed and the best cut-off point was searched for optimal balance between sensitivity and specificity of tumour-NAC distance for the sagittal, axial, minimum and mean distances from the NAC. A p value of ≤0.05 was considered statistically significant. All statistical analyses were performed by SPSS for Windows.

Results

Twenty-seven per cent of the patients had NAC pathological involvement (31/112). At univariate analysis, older age (p = 0.001), postmenopausal status (p = 0.003) central tumour location (p = 0.03), nodal involvement (p = 0.002), low Ki-67 expression (p = 0.006), MRI tumour–NAC mean distance (p = 0.000) and intra-operative pathological assessment (p = 0.000), were all significantly associated with NAC involvement at definitive pathology. Tumour involvement was most frequent in SD than ND (43.3% vs 20%), and ND were the only positive ducts in one patient (Table 1).

A multivariate analysis including all variables obtainable pre-operatively (menopausal status, clinical nodal status, central tumour location, tumour-NAC distance at MRI, histological type, grading and immuno-histochemical profile) revealed that only MRI tumour-NAC distance (p = 0.008) and menopausal status (p= 0.039) provided independent information on the likelihood of NAC involvement at definitive histology.

A Receiver Operating Characteristic (ROC) curve was constructed for sagittal, axial, minimum and mean tumour – NAC distances (Figure 1). Overall, the diagnostic performance of axial tumour-NAC distance (Area Under the Curve = 0.716) was slightly superior to either the sagittal or minimum distance measurements.

Different cut-offs of the tumour-NAC distance for the prediction of NAC-involvement at MRI were tested (Table 2). If the cut-off of tumour-NAC distance by MRI was set at 10 mm, all diagnostic parameters of the combined assessment of the NAC (MRI plus intraoperative pathology) were superior to MRI alone, whereas only sensitivity (53.6% vs. 46.7%) was improved by the combined assessment as compared to intraoperative pathology alone. Similarly, if the a cut-off was lowered at 5 mm, all diagnostic parameters were superior for the combined assessment as compared to MRI alone except for the negative predictive value (84.4% vs. 87.6%), whereas only sensitivity (50.0% vs 46.7%) was superior for the combined assessment as compared to intraoperative pathology alone (Table 3).

Discussion

The rates of tumour NAC involvement in the literature are inconsistent (14-21) likely due to different pathological protocols for NAC evaluation and variable accuracy of clinical and pathological data collection. For example, a recent systematic review of the literature showed that only 6.4% of the nipple cores of 2477 NAC sparing mastectomies were involved with tumour (13). This is less than half of the rate (14.2%) of NAC involvement shown in a study of 2323 consecutive total mastectomy specimens with grossly unremarkable nipples evaluated at final pathology by sagittal sections through the entire nipple and sub-areolar tissue (8). Such a difference in the rate of NAC involvement in two large retrospectives studies likely reflects a selection bias towards tumours of less advanced stage, and/or not involving the central quadrant of the breast, or pre-neoplastic lesions in patients submitted to NAC sparing mastectomy as compared to total mastectomy

(13).

Conversely, in our current consecutive series of NAC sparing mastectomies, 28.2% of the patients had a positive NAC, exactly two-fold the rate that we detected in a previous series of total mastectomies performed at our institution (14%) (18). Of note, both of our series were constituted only by breast cancer patients and included advanced and centrally located tumours. The higher figure of NAC involvement in the current series may be due to a pathological protocol specifically aimed at assessing tumour infiltration of SD and ND, whereas the protocol of our previous retrospective study relied on a standard pathological assessment of the NAC (18). Indeed, other studies of NAC sparing mastectomy with similar criteria of pathological assessment show NAC involvement rates comparable to our current study (19).

In order to facilitate surgical planning, other groups have explored the relationship of several preoperative clinical and radiological parameters with the likelihood of NAC involvement (Table 4). Unfortunately, clinical criteria alone or in combination with mammography (MX) and/or ultrasound scan (US) are associated with variable and limited accuracy. For example, Stolier et al in a series of 58 breast cancer patients submitted to total mastectomy reported that clinical and radiological criteria had a sensitivity of 46.2% and a specificity of 55.6% and they found no added benefit from the inclusion of such criteria to intra-operative histological assessment of the NAC.

Data on preoperative assessment of the NAC by MRI are more encouraging (18,19). In our previous retrospective study (18), by setting the cut-off of the tumour-NAC distance at 10 mm, MRI outperformed MX in the prediction of NAC involvement with a sensitivity of 100% vs. 71% and a specificity of 66% vs. 63% respectively. Moon et al. (21) in a retrospective analysis of 51 breast cancers reported that NAC enhancement at MRI had a sensitivity of 93.8% and a specificity of 85.7%. In the current prospective study, axial tumour - NAC distance at MRI with a cut-off set at 10 mm had lower sensitivity (53.6% vs 100%), but higher specificity (88.6% vs. 66.0%) as compared to our retrospective study (18), and its

overall accuracy was slightly increased by setting the cut-off at 5 mm (78.5% vs. 75.8%). To the best of our knowledge, the only similar prospective study reported a sensitivity of 28% and a specificity of 100% for the initial MRI report, while a blinded re-review of all MRI scans looking specifically for NAC involvement increased sensitivity to 56% and lowered specificity to 95% (19).

Our study confirms the crucial role of intra-operative pathological assessment of the NAC whose diagnostic performance was as good as that of the combined assessment (MRI + pathological), except for a lower sensitivity. Although many authors examine only the SD to decide whether the NAC can be preserved or not, Steen et al reported that 23% (4/17) of the cases with positive nipple biopsy had negative SD and positive ND (19). Accordingly, we found that 1 out of 14 (7.1%) NAC-positive cases at intra-operative assessment had only ND involvement. Therefore, we confirm that double intra-operative assessment of SD and ND increases the sensitivity of pathological intraoperative assessment and we believe that it should be performed to guide the management of the NAC.

We found that axial tumour-NAC distance at MRI is the most accurate parameter to foresee the likelihood of NAC involvement preoperatively and can improve the sensitivity of pathological intraoperative assessment. Preoperative assessment of the NAC is important as it may help select the best surgical strategy and inform the patients about the likelihood that the NAC could be removed. Indeed, if the NAC is preserved, one-stage breast reconstruction with immediate placement of the prosthesis can be planned in selected cases. Conversely, if the NAC has to be sacrificed, a two-stage reconstruction with the placement of a skin expander is generally preferable (22,23). Furthermore, It is well known that exhaustive preoperative information may significantly influence the choices of breast cancer patients on their favourite type of surgery (24) and reduce their feelings of regret and dissatisfaction with the operation (25).

In conclusion, our study suggests that MRI may offer valuable information on the likelihood that the NAC can be preserved, although the surgical management is essentially guided the

intra-operative pathological examination of both SD and ND. If MRI and intraoperative pathology do not suggest tumour involvement, the NAC can be preserved in almost 85% of the cases. Therefore, this combined assessment appears a reliable guide for patient information, surgical planning and intra-operative management of the NAC during mastectomy.

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Table 1. Univariate analysis of tumour characteristics associated with involvement of NAC

Factor	Histopathologic NAC involvement (final pathology)		P
	No	**Yes**	
	81 (72.3%)	**31 (27.7%)**	
Clinical (preoperative)			
Age (mean)	46 y	53 y	0.001
Premenopausal status	60 (71.4%)	14 (42.4%)	0.003
Received neoadjuvant therapy	6 (7.1%)	1 (3%)	NS
Tumour central location	1 (1.3%)	3 (10%)	0.03
Nodal involvement (clinical and/or cytological)	25 (29.8%)	16 (48.5%)	NS
Radiological (preoperative)			
Tumour size on MRI (mean)	28.4 mm	28.7 mm	NS
Distance of tumour from NAC on MRI (mean)[&]	33.6 mm	19.3 mm	0.000
Multifocal or multicentric disease on MRI	41 (72.9%)	20 (87.0%)	NS
Pathological (intraoperative)			
Subareolar nipple ducts (SD) involvement	0 (0%)	13 (43.3%)	0.000
Proximal nipple ducts (ND) involvement	0 (0%)	6 (20%)	0.000
SD and/or ND involvement	0 (0%)	14 (46.7%)	0.000
Pathological (definitive)			
Path T2 or greater	31 (37.3%)	16 (48.5%)	NS
Aggregate size of lesion (only invasive component) (mean)	17.0 mm	20.9 mm	NS
Histologic intraductal cancer	15 (18.5%)	4 (12.9%)	NS
Histologic infiltrating lobular cancer	11(13.1%)	4 (12.1%)	NS
Multifocal or multicentric disease	25 (29.8%)	10 (30.3%)	NS
Nodal involvement	29 (38.2%)	20 (62.5%)	0.02
Lymphovascular invasion: positive	35 (47.9%)	18 (62.1%)	NS
Grade: high	43 (57.3%)	13 (40.6%)	NS
ER: positive^	63 (79.7%)	28 (87.5%)	NS
PR: positive^	56 (70.9%)	25 (75.8%)	NS
HER-2/neu: positive°	13 (20%)	3 (10.3%)	NS
Ki-67: high*	54 (87.1%)	18 (62.1%)	0.006
In situ component: present	34 (40.5%)	17 (51.5%)	NS

*NAC nipple–areolar complex, MRI magnetic resonance imaging, [&]A mean of sagittal, axial and minimum distances was used *G3; ER estrogen receptor, PR progesterone receptor; ^positive ≥ 1% of stained cells; *high: >20%, of stained cells; ° positive: 3+ or amplified*

Table 2: Diagnostic performance of different measurements of tumour-NAC distance by MRI

	Sagittal			Axial			Minimum distance		
Cut-off (mm)	**≤5**	**≤10**	**≤20**	**≤5**	**≤10**	**≤20**	**≤5**	**≤10**	**≤20**
Sens (%)	32.2	38.7	58	32.2	38.7	58.0	32.2	38.7	58.0
Spec (%)	88.0	85.0	79	88.6	85.8	75.3	88.6	85.0	74.6
PPV (%)	76.9	48.0	42,8	76.9	60.0	40.9	76.9	48.0	39.1
NPV (%)	78.7	78.1	81,4	87.6	80.2	80.2	78.7	78.1	80.3
Acc (%)	78.5	77.6	67	78.5	75.8	65.1	78.5	71.4	63.4

NAC: nipple-areola complex; MRI: magnetic resonance; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: accuracy

Table 3. Diagnostic performance of preoperative MRI assessment, intraoperative pathological assessment and combined assessment on the prediction of NAC involvement

Variable	Sens (%)	Spec (%)	PPV (%)	NPV (%)	ACC (%)
Positive intraoperative histology^	46.7	100	100	84.0	86.0
MRI suspicious for NAC involvement (< 5 mm)*	32.2	88.6	76.9	87.6	78.5
MRI suspicious for NAC involvement (< 10 mm)*	38.7	85.8	60.0	80.2	75.8
MRI suspicious for NAC Involvement (< 5 mm)* or positive intraoperative histology	50.0	96.2	82.3	84.4	84.1
MRI suspicious for NAC Involvement (< 10 mm)* or positive intraoperative histology	53.6	88.6	62.5	84.3	79.4

^*Subareolar and/or proximal nipple ducts; *Axial tumour-NAC distance ; MRI magnetic resonance imaging, NAC nipple–areolar complex; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; ACC: accuracy*

Table 4. Studies on the prediction of NAC involvement by clinical (C), radiological (R) and intraoperative pathological (IP) assessment

Author	Nr. Pts.	NAC involved∞ (%)	Method of prediction	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Schecter (14)	31	42	R^	92	77	-	93
Loewen (16)	116	10	R^	82	62	20	97
D'Alonzo (18)	39	14	R§	100	66	39	100
Billar (15)	392	16	C	61	86	45	92
	37		R°	38	96	62	89
	37		C+R	48	97	69	93
Steen (19)	77	23	C	61	92	69	89
	77		R§	56	95	77	88
	77		C+R§	67	86	60	89
Stolier (17)	40	42.5	C+R^	46.2	55.6	-	-
	57		IP*	88.2	100	-	-
	40		C+ R^+ IP*	92.3	55.6	-	-
Current study	112		R§#	32.2	88.6	76.9	78.5
			IP	46.7	100	100	86.0
			R§+ IP*	50.0	96.2	82.3	84.4

*NAC: nipple areola complex; Pts.: patients; Sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value; ∞at definitive pathology; * subareolar ducts (SD) and proximal nipple ducts (ND) assessment; °MX/US/MRI; ^MX; §MRI; #cut off: 5 mm*

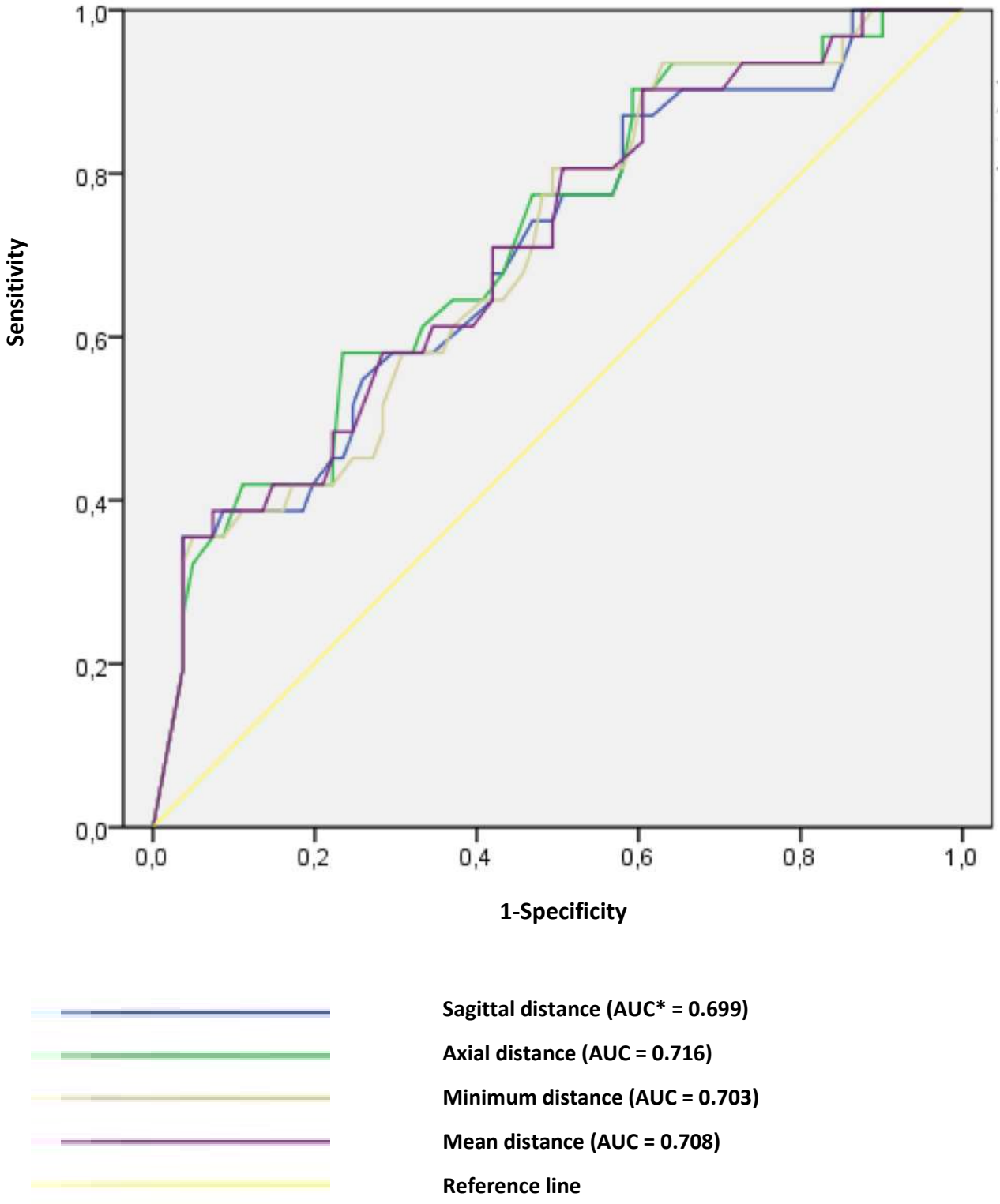

Figure 1: Receiver Operating Characteristic (ROC) Curve for the performance of Sagittal, Axial, Minimum and Mean Tumour – Nipple Areola Complex (NAC) distance at MRI to discriminate NAC involvement at definitive pathology.
***AUC: Area Under the Curve**