Misinterpretation of raw data

Savaridas, Sarah

Published in:
British Journal of Radiology

DOI:
10.1259/bjr.20210741

Publication date:
2023

Document Version
Peer reviewed version

Dear Editor,

It was with great interest we read the article *The diagnostic performance of CESM and CE-MRI in evaluating the pathological response to neoadjuvant therapy in breast cancer: a systematic review and meta-analysis* recently published by BJR.(1) As the use of neoadjuvant chemotherapy (NAC) is available to more women, not only to downstage local disease but also assess chemosensitivity, the pressures on imaging services to monitor results inevitably increases. We agree with Tang *et al* that whilst MRI is considered the gold standard image-monitoring technique, it is an expensive and time-consuming, can be challenging to access and for some patients it is either contraindicated or poorly tolerated. Therefore, there is a pressing need to find alternative imaging techniques with similar accuracy.

In this article Tang *et al* review six papers which consider the accuracy of contrast enhanced spectral mammography (CESM), a relatively novel functional mammographic technique, in assessment of response to NAC. (2-7). They conclude that 'compared to CE-MRI, CESM has equal specificity, greater sensitivity and excellent performance, which may have a brighter prospect in evaluating the pathological response of breast cancer to NAC'.

Unfortunately, the authors did not appreciate that the studies included calculated diagnostic accuracy for differing objectives. Although the Forest plot included in the meta-analysis purports to show 'CESM sensitivity and specificity to predict pCR' only two papers actually calculated this (4, 5), two calculated the opposite – the diagnostic accuracy for detecting *residual disease* (2, 3) and two paper reported the accuracy for identifying 'responders' either defined as Miller-Payne grade 3-5, i.e. ≥ 30-90% reduction in tumour cells (7), or as 'all tumour responses'(6). The results of the meta-analysis, and conclusions drawn from it are therefore fundamentally flawed.

We concur with Tang *et al* that there is heterogeneity between studies, including in the definition of pCR. However, contrary to the assertion that all except ElSaid *et al* (6) defined pCR as the 'complete disappearance of invasive carcinoma and ductal carcinoma *in situ* (DCIS)', we assert that only two papers used this definition (4, 5). The feasibility study published by Barra *et al* (2) does not provide a definition and subsequent work published by this group defines it as the absence of invasive disease, yTP0/is.(3) Furthermore Moustafa *et al*(7) describe 'responders' as Miller-Payne grades III-V i.e. at least an estimated 30% reduction in tumour cells, which is not compatible with any pCR definition. Further heterogeneity may be due to timing of imaging, which was reported by two groups and ranged from 40 days to less than 10 days prior to surgery.(3, 7, 8) When reported, NACT regimes also varied both within and between studies, one study also included patients receiving neoadjuvant endocrine therapy (5).

Having reviewed the original papers in depth, it is possible to derive the raw results for five of the papers.(2-6) Whilst it is not possible to confidently derive raw results for pCR from the paper published by Moustafa *et al,*(7) it is possible to do so from subsequent work published by the same group.(8) Using this information, we have calculated the true diagnostic accuracy for detecting pCR for these six papers. Diagnostic accuracy results are displayed below (95% CI are showed in parenthesis).

Study	CESM	Pathology		Sensitivity (%) (95% CI)	Specificity	PPV	NPV	Prevalence
		pCR	Non-pCR					
Patel, 2018	CR	19	15	95.00 (75.13 – 99.87)	66.67 (51.05 – 80.00)	55.88 (45.29 – 65.96)	96.77 (81.45 – 99.51)	30.77 (19.91 – 43.45)
	Non-CR	1	30					
Barra, 2017	CR	2	1	100.00 (15.81 – 100)	83.33 (35.88 – 99.58)	66.67 (25.05 – 92.29)	100.00	25.00 (3.19 – 65.09)
	Non-CR	0	5					
Barra, 2018	CR	7	6	87.50 (47.35 – 99.68)	76.00 (54.87 – 90.64)	53.85 (35.64 – 71.08)	95.00 (74.99 – 99.18)	24.24 (11.09 – 42.26)
	Non-CR	1	19					
Iotti, 2017	CR	8	6	100.00 (68.75 – 93.98)	84.21 (68.75 – 93.98)	57.14 (39.02 – 73.54)	100.00	17.39 7.82 – 31.42
	Non-CR	0	32					
ElSaid, 2017	CR	5	0	83.33 (35.88 – 99.58)	100.00 (78.20 – 100.00)	100.00	93.75 (71.48 – 98.90)	28.57 (11.28 – 52.18)
	Non-CR	1	15					

Kamal, 2020	CR	20	1	95.24 (76.18 – 99.88)	98.33 (91.06 – 99.96)	95.24 (74.07 – 99.29)	98.33 89.70 – 99.75)	25.93 (16.82 – 36.86)
	Non-CR	1	59					

This work is highly topical and we are concerned that the erroneous results of this meta-analysis are being cited in further work and may be used to support a change in clinical practice. We therefore, invite Tang *et al* to reconsider the meta-analysis in light of the revised diagnostic accuracy figures provided above.

Yours Sincerely,

Dr Sarah Savaridas

1. Tang S, Xiang C, Yang Q. The diagnostic performance of CESM and CE-MRI in evaluating the pathological response to neoadjuvant therapy in breast cancer: a systematic review and meta-analysis. The British Journal of Radiology. 2020;93(1112):20200301.
2. Barra FR, de Souza FF, Camelo R, Ribeiro ACO, Farage L. Accuracy of contrast-enhanced spectral mammography for estimating residual tumor size after neoadjuvant chemotherapy in patients with breast cancer: a feasibility study. Radiol Bras. 2017;50(4):224-30.
3. Barra FR, Sobrinho AB, Barra RR, Magalhães MT, Aguiar LR, Albuquerque GFLd, et al. Contrast-Enhanced Mammography (CEM) for Detecting Residual Disease after Neoadjuvant Chemotherapy: A Comparison with Breast Magnetic Resonance Imaging (MRI). BioMed Research International. 2018;2018:1-9.
4. Iotti V, Ravaioli S, Vacondio R, Coriani C, Caffarri S, Sghedoni R, et al. Contrast-enhanced spectral mammography in neoadjuvant chemotherapy monitoring: a comparison with breast magnetic resonance imaging. Breast Cancer Res. 2017;19(1):106.
5. Patel BK, Hilal T, Covington M, Zhang N, Kosiorek HE, Lobbes M, et al. Contrast-Enhanced Spectral Mammography is Comparable to MRI in the Assessment of Residual Breast Cancer Following Neoadjuvant Systemic Therapy. Ann Surg Oncol. 2018;25(5):1350-6.
6. ElSaid NAE, Mahmoud HGM, Salama A, Nabil M, ElDesouky ED. Role of contrast enhanced spectral mammography in predicting pathological response of locally advanced breast cancer post neo-adjuvant chemotherapy. The Egyptian Journal of Radiology and Nuclear Medicine. 2017;48(2):519-27.
7. Moustafa AFI, Kamal RM, Gomaa MMM, Mostafa S, Mubarak R, El-Adawy M. Quantitative mathematical objective evaluation of contrast-enhanced spectral mammogram in the assessment of response to neoadjuvant chemotherapy and prediction of residual disease in breast cancer. Egyptian Journal of Radiology and Nuclear Medicine. 2019;50(1).
8. Kamal RM, Saad SM, Moustafa AFI, Gomaa MM, Mokhtar O, Gouda I, et al. Predicting response to neo-adjuvant chemotherapy and assessment of residual disease in breast cancer using contrast-enhanced spectral mammography: a combined qualitative and quantitative approach. Egyptian Journal of Radiology and Nuclear Medicine. 2020;51(1).