Is radiomic MRI a feasible alternative to OncotypeDX® recurrence score testing? A systematic review and meta-analysis

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Abstract

Background: OncotypeDX® recurrence score (RS) aids therapeutic decision-making in oestrogen-receptor-positive (ER+) breast cancer. Radiomics is an evolving field that aims to examine the relationship between radiological features and the underlying genomic landscape of disease processes. The aim of this study was to perform a systematic review of current evidence evaluating the comparability of radiomics and RS.

Methods: A systematic review was performed as per PRISMA guidelines. Studies comparing radiomic MRI tumour analyses and RS were identified. Sensitivity, specificity and area under curve (AUC) delineating low risk (RS less than 18) *versus* intermediate–high risk (equal to or greater than 18) and low–intermediate risk (RS less than 30) and high risk (RS greater than 30) were recorded. Log rate ratios (lnRR) and standard error were determined from AUC and 95 per cent confidence intervals.

Results: Nine studies including 1216 patients met inclusion criteria; the mean age at diagnosis was 52.9 years. Mean RS was 16 (range 0–75); 401 patients with RS less than 18, 287 patients with RS 18–30 and 100 patients with RS greater than 30. Radiomic analysis and RS were comparable for differentiating RS less than 18 *versus* RS 18 or greater (RR 0.93 (95 per cent c.i. 0.85 to 1.01); $P = 0.010$, heterogeneity (I^2)=0%) as well as RS less than 30 *versus* RS 30 or greater (RR 0.76 (95 per cent c.i. 0.70 to 0.83); $P < 0.001$, I^2=0%). MRI sensitivity and specificity for RS less than 18 *versus* 18 or greater was 0.89 (95 per cent c.i. 0.85 to 0.93) and 0.72 (95 per cent c.i. 0.66 to 0.78) respectively, and 0.79 (95 per cent c.i. 0.72 to 0.86) and 0.74 (95 per cent c.i. 0.68 to 0.80) for RS less than 30 *versus* 30 or greater.

Conclusion: Radiomic tumour analysis is comparable to RS in differentiating patients into clinically relevant subgroups. For patients requiring MRI, radiomics may complement and enhance RS for prognostication and therapeutic decision making in ER+ breast cancer.

Introduction

Breast cancer is a ubiquitous disease responsible for 11.6 per cent of new cancer diagnoses and is the second most common cause of cancer-related mortality, following lung carcinoma[1]. Historically, breast carcinoma was considered a homogeneous entity, with large-scale surgical resection and conventional cytotoxic chemotherapy prescription the cornerstone of controlling disease recurrence[2]. In the wake of the molecular era, heterogeneous biological properties have facilitated substratification of the disease into several distinct subtypes, with various multimodal treatment strategies being indicated, depending on the molecular and genetic processes driving tumorigenesis[3]. Although whole-genome sequencing is required to evaluate comprehensively intrinsic biological tumour characteristics, routine immunohistochemical appraisal of oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2/neu) has been rapidly incorporated into clinical practice, and reliably separates breast cancer into four molecularly diverse subtypes[3]. Luminal molecular subtypes, often perceived to carry favourable prognoses and to be indolent in

nature, are best treated with adjuvant endocrine hormonal therapy, and judicious systemic chemotherapy prescription[4,5].

In the era of personalized medicine, multiomic analyses are now the norm for oncological patient management[6,7]. Multigene molecular panels, such as the OncotypeDX® (Genomic Health Inc.®, Redwood City, California, US) 21-gene recurrence score (RS), have clearly segregated tumour types into those likely to benefit from systemic chemotherapy and those that would not[8]. However, despite validation and incorporation into European Society of Medical Oncology®, National Institute of Clinical Excellence®, American Society of Clinical Oncology® and National Comprehensive Cancer Network® guidelines[9–12], the assay carries several disadvantages, such as its cost and lengthy turnover time[13,14]. Radiomics is an evolving field that aims to examine the relationship between radiological features and the underlying genomic landscape of disease processes. This involves a radiologist acquiring imaging and performing segmentation, before quantitative analyses of medical imaging are performed using artificial intelligence software, with the aim of enhancing existing data available to clinicians through non-intuitive mathematical

evaluation of disease properties, many of which are imperceptible to the human eye[15,16]. In recent times, alternatives to RS testing have been proposed, such as the application of radiomic tumour analysis into clinical practice to aid therapeutic decision making and prognostication in certain cases. A recent hypothesis suggests that radiomics tumour analysis may have a role in augmenting multiomic cancer care, and studies evaluating the value of radiomics in comparing genomic and radiomic profiles of cancers may shed some light on to this proposition. Accordingly, the aim of the present systematic review and meta-analysis was to determine whether radiomic evaluation offers a feasible alternative to RS testing in substratifying patients diagnosed with early-stage, oestrogen-receptor-positive (ER+) breast cancer.

Methods

This systematic review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] and the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*[18]. As this is a systematic review of current literature, local institutional ethical approval was not required.

The study

population was patients diagnosed with ER+/human epidermal growth factor receptor-2 negative (HER2-) breast cancer with 0 to 3 metastatic lymph nodes who had undergone preoperative MRI, surgical resection, and subsequent RS testing on their resected breast cancer specimen.

Radiomic analyses were carried out using preoperative MRI of tumour tissue, and the discriminative ability of radiomic software was compared with the current standard RS testing for prognostication and therapeutic decision making in early ER+ breast cancer.

Primary outcomes included the evaluation of the clinical utility of breast MRI to stratify cancers into RS categories for the prediction of the likelihood of recurrence (indicated through recurrence score). Sensitivity, specificity and area under the curve (AUC) scores from receiver operating characteristic (ROC) curve analyses were also used to establish the reliability of MRI in determining RS. Secondary outcomes included correlating RS testing and MRI findings to determine their predictive value in delineating clinically actionable *versus* non-actionable RS groups (i.e., those indicated for combined adjuvant chemoendocrine therapy (actionable) *versus* adjuvant endocrine as monotherapy (non-actionable)).

Search strategy

An electronic search of the PubMed Medline, EMBASE and Scopus databases for relevant studies was performed on 30 November 2020. The search was performed for the following headings: (Breast Cancer) AND (Radiomics) AND (Biomarker). Included studies were limited to manuscripts published in the English language and studies were not restricted based on their year of publication. All duplicate studies were removed before titles were screened, and studies deemed appropriate had their abstracts and full texts reviewed. This search was performed by two independent reviewers.

Inclusion and exclusion criteria

Studies deemed appropriate for inclusion were those applying radiomic artificial intelligence computational algorithms and methods (machine-learning techniques, conventional neural networks and deep-learning techniques) in order to predict RS group from preoperative imaging. Studies relying upon subjective judgement of independent radiologists were excluded.

Studies meeting the following inclusion criteria were included: studies with patients with histologically confirmed ER+/HER2-breast cancer with 0 to 3 positive metastatic lymph nodes; studies in which RS testing had been performed on resected tumour specimens; studies in which breast MRI was performed before operation; studies detailing ROC curve analyses assessing the reliability of radiomic testing in differentiating RS groups (for example, RS 18 or less *versus* RS greater than 18, RS 29 or less *versus* RS greater than 30, etc.) or clinicopathological data with RS.

Studies meeting any of the following exclusion criteria were excluded from this study: studies detailing RS testing and other imaging modalities (for example, CT, ultrasound sonography imaging, mammographic imaging, etc.); review articles; studies including less than five patients or case reports; editorial articles; and conference abstracts.

Data extraction and quality assessment

The literature search was performed by two independent reviewers (M.G.D. and M.S.D) using the previously discussed predesigned search strategy. Duplicate studies were removed. Retrieved manuscripts were reviewed independently by both reviewers to ensure all inclusion criteria were met, before extracting the following data: first author name, year of publication, study design, country, level of evidence, study title, number of patients, RS data and AUC scores from ROC analyses. Data specific to AUC (expressed as rate ratios (RR), 95 per cent confidence intervals and *P* values) were directly extracted from tables and study text. Assessment of the quality of included radiomic studies was performed using the radiomics quality score, as outlined by Lambin and colleagues[19]. Where discrepancies in opinion occurred between the reviewers, a third reviewer was asked to arbitrate (M.R.B).

Statistical analysis

Data pertaining to RS testing and clinicopathological data were presented as proportions using descriptive statistics. Statistical analysis was performed according to the Cochrane guidelines[18]. Study-specific estimates of sensitivity and specificity were calculated from study data. Summary ROC analysis was used to illustrate the relationship between sensitivity and specificity of MRI radiomic analysis and RS testing, and to convey the diagnostic test performance of MRI and RS testing. In cases where sensitivity and specificity were not outlined by authors, estimated diagnostic test sensitivity and specificity were extracted from ROC analyses with most accurate sensitivity prioritized. AUC were expressed as RR and each corresponding confidence interval was retrieved directly for use in this meta-analysis, as described by Kester and colleagues[20]. Either fixed or random effects models were applied on the basis of whether significant heterogeneity ($I^2 > 50\%$) existed between studies included in any particular analysis. Symmetry of funnel plots were used to assess publication bias. Statistical heterogeneity was determined using I^2 statistics. Statistical significance was determined to be $P < 0.050$. Statistical analysis was performed using Review Manager (RevMan), version 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

The initial electronic search resulted in a total of 740 studies. Following removal of the 55 identified duplicate studies, the

remaining 685 titles were screened for relevance, of which 40 had their abstracts or full texts assessed for eligibility. Overall, nine clinical studies were included in this analysis, as depicted in *Fig. 1* [21–29].

Eight of these studies were from the US, while one study reported results from Korean patients[25]. Of the included studies, six used radiomic artificial intelligence, two used machine-learning techniques[23,26], and a single study used conventional neural networking to determine RS groups[22]. Individual studies included in this analysis are outlined in *Table 1*.

Clinical characteristics and OncotypeDX® recurrence score

Overall, 1216 patients were included in this study. The mean age at diagnosis was 52.9 (range 27–83) years. Four studies reported on menopausal status at the time of diagnosis; 50.8 per cent were postmenopausal (452 of 889 patients). Of 788 patients, the mean RS was 16 (range 0–75), with 401 patients (50.9 per cent) with RS less than 18, 287 (36.4 per cent) with RS 18–30, and 100 (12.7 per cent) with RS greater than 30 (*Table 1*).

RS was associated with histopathological tumour subtype, tumour grade, ER, PgR and HER2 expression (all $P < 0.001$ (χ^2 test)). In this analysis, 78.4 per cent of patients had node-negative disease (N0) and nodal status was not associated with RS ($P = 0.115$ (χ^2 test)), as illustrated in *Table S1*.

Comparability with MRI

Radiomic analysis of MRI images of resected tumour tissue was comparable for differentiating cancers with RS less than 18 and 18 or greater (RR 0.93 (95 per cent c.i. 0.85 to 1.01); $P = 0.010$, $I^2 = 0\%$), although less comprehensive in providing disparity between RS less than 30 and 30 or greater (RR 0.76 (95 per cent c.i. 0.70 to 0.83); $P < 0.001$, $I^2 = 0\%$) (*Fig. 2*). The sensitivity and specificity of MRI in delineating RS less than 18 *versus* 18 or greater was 0.89 (95 per cent c.i. 0.85 to 0.93) and 0.72 (95 per cent c.i. 0.66 to 0.78) respectively (*Fig. 3a; Table S2*). The sensitivity and specificity of MRI in delineating RS less than 30 *versus* 30 or greater was 0.79 (95 per cent c.i. 0.72 to 0.86) and 0.74 (95 per cent c.i. 0.68 to 0.80) respectively (*Fig. 3b; Table S2*). ROC curve for RS testing is outlined in *Fig. 3c*. No single radiomic biomarker that correlated directly with RS could be ascertained from more than one study.
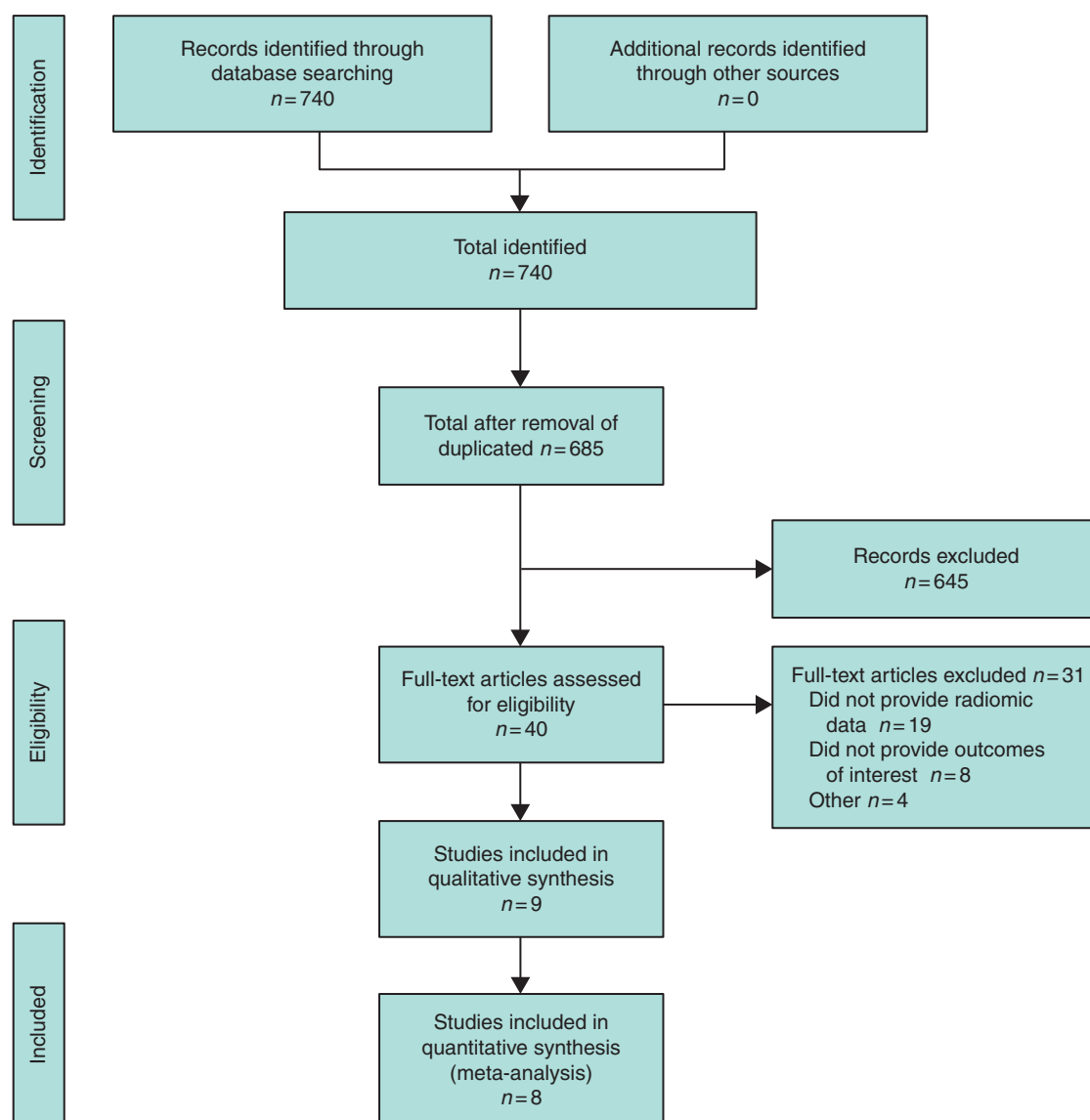

Fig. 1 PRISMA flow diagram detailing the systematic search process

Table 1 Details regarding the nine independent patient cohorts included in this systematic review

Author	Year	Study type (LOE)	Country	MRI scanner brand	n	Median age (years)	Mean RS (range)	n RS <18	n RS 18–30	n RS >30	RQS
Ashaf et al.[21]	2014	RC (III)	US	1.5T Lxecho®/Sontana®	56	55.6	N/R	27	19	10	17
Ha et al.[22]	2018	RC (III)	US	1.5T or 3 T Signa®	95	55.9	16 (1–75)	42	26	7	16
Jacobs et al.[23]	2020	RC (III)	US	3T Phillips®	31	53.0	N/R	21	9	1	17
Li et al.[24]	2016	RC (III)	US	1.5T GE®	134	53.6	N/R	77	40	17	18
Nam et al.[25]	2019	RC (III)	Korea	3T Phillips®	80	45.1	14 (3–39)	19	49	12	15
Saha et al.[26]	2018	RC (III)	US	1.5T or 3 T	84	54.0	16	25	32	27	18
Sutton et al.[27]	2016	RC (III)	US	1.5T or 3 T Signa®	67	50.3	16 (0–45)	45	19	3	19
Thakur et al.[28]	2019	RC (III)	US	3T Discovery®	261	53.2	15 (2–43)	145	93	23	16
Woodard et al.[29]	2018	RC (III)	US	N/R	408	53.5	18.9	N/R	N/R	N/R	15

LOE, level of evidence; *n*, number; RC, retrospective cohort; N/R, not reported; RS, OncotypeDX® recurrence score; RQS, radiomic quality score.
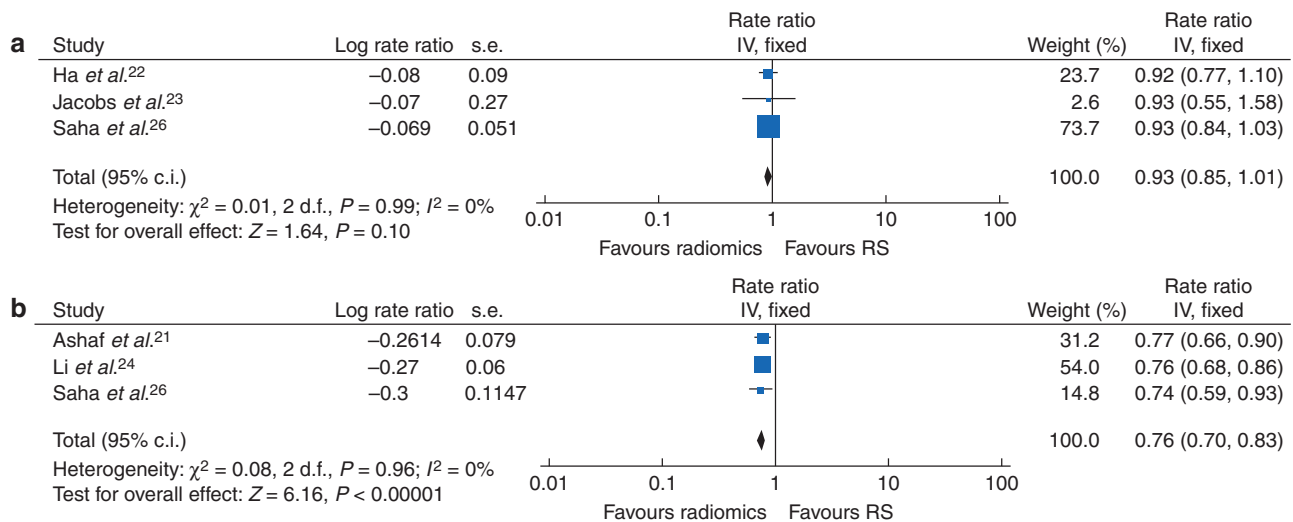

Fig. 2 Forest plots evaluating the comparability radiomic analysis of breast tumour MRI and OncotypeDX® recurrence score

a Differentiating tumours with recurrence score (RS) less than18 *versus* RS 18 or greater. **b** Differentiating tumours with RS less than 30 *versus* RS 30 or greater. s.e., standard error; IV, inverse variance.

Discussion

Contemporary oncological practice recognizes that each tumour has an idiosyncratic gene expression profile, enabling differentiation of cancers into diverse biological and molecular groups and profiles, even within the same molecular subtypes[30]. This provides a unique challenge and opportunity to the clinician, as the correct classification facilitates personalized medicine, with the identification of patients who respond to particular therapeutic strategies based on careful elucidation of their underlying host and tumour characteristics. RS testing, which has been incorporated into international guidelines following validation in prospective analyses[4,9–12], attempts to address this, and has facilitated the shift in the paradigm from pervasive conventional chemotherapy prescription to a more refined, personalized approach, within early-stage ER+ breast cancer. This systematic review and meta-analysis is the first appraising the feasibility of utilizing radiomic tumour analysis as a surrogate for RS, and incorporates data from 1216 breast cancers with corresponding MRI and genomic results. In the era of multiomic cancer care, radiomics offers the prospect of a novel, non-invasive modality for the personalization of treatment, as well as allowing for potential opportunities to augment or perhaps even replace current strategies in the future.

The most significant finding in this review is the data suggesting radiomic tumour analysis may provide a potential alternative to RS testing in discriminating early ER+ breast cancer with low risk of disease recurrence (RS less than 18) from tumours with intermediate–high risk of recurrence (RS 18 or greater) based on preoperative MRI, with a sensitivity of almost 90 per cent. For the physician, these findings have a number of potential implications for clinical practice: currently, combined chemoendocrine prescription is indicated in select cases following RS testing, however, this pooled analysis suggests certain patients may bypass postoperative tumour specimen genomic testing, proceeding directly to adjuvant endocrine therapy following curative oncological resection, provided they have had a preoperative MRI and their imaging is congruent with RS less than 18 on radiomic analysis. Although current management guidelines for early breast cancer do not include routine MRI staging to determine the extent of locoregional disease burden[31], cases such as invasive lobular carcinoma histological subtype, BRCA mutation carriers and equivocal mammographic imaging often rely on this modality to clarify diagnoses and to aid surgical planning[32,33]. In such cases, radiomic analyses may be implemented to guide therapeutic decision making, particularly as recent studies suggest as many as 60 per cent of cancers are RS less than 18[34,35]. Consequently, if the discriminative ability of radiomic analysis is
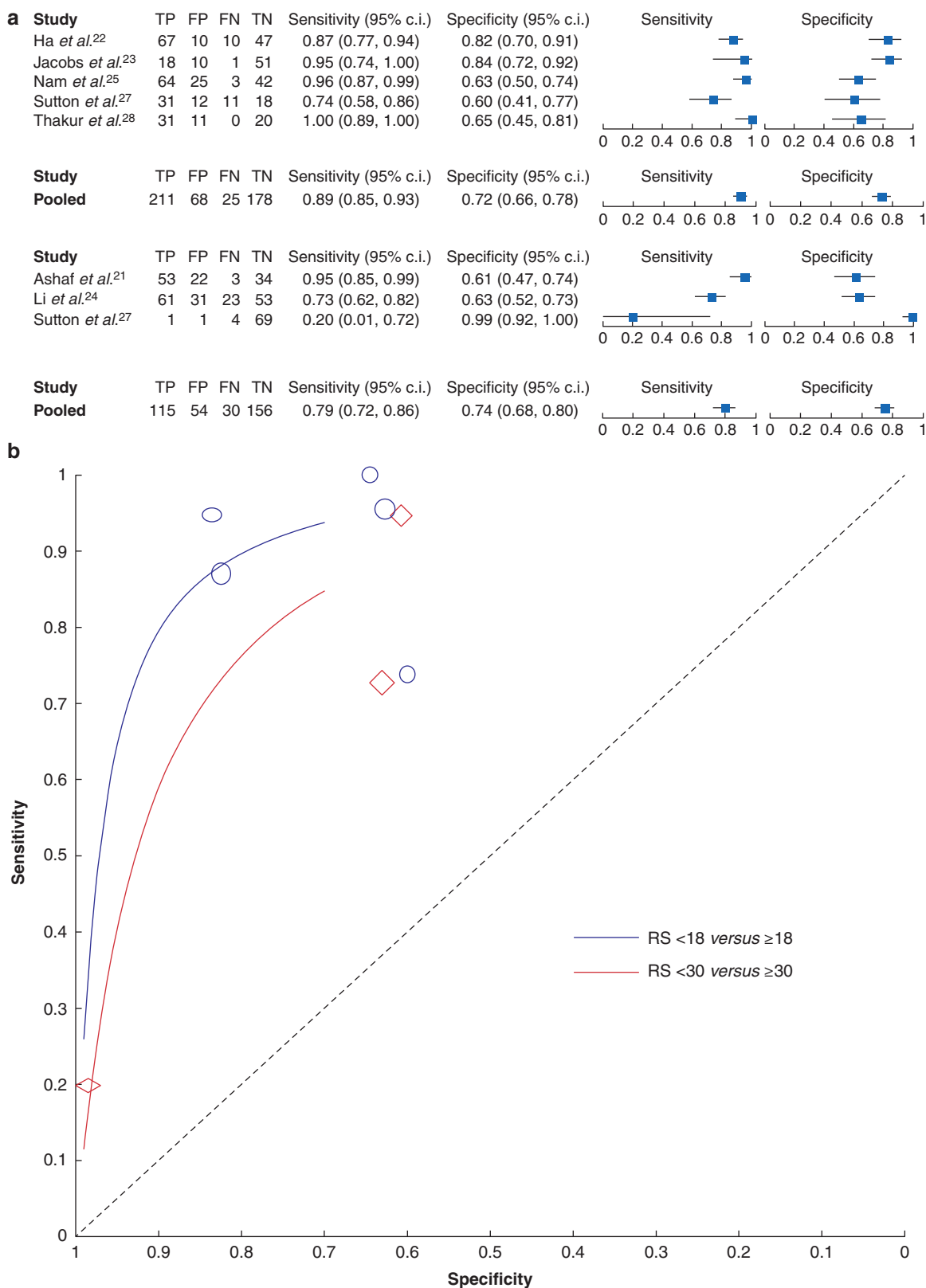
a

Study	TP	FP	FN	TN	Sensitivity (95% c.i.)	Specificity (95% c.i.)
Ha *et al.*[22]	67	10	10	47	0.87 (0.77, 0.94)	0.82 (0.70, 0.91)
Jacobs *et al.*[23]	18	10	1	51	0.95 (0.74, 1.00)	0.84 (0.72, 0.92)
Nam *et al.*[25]	64	25	3	42	0.96 (0.87, 0.99)	0.63 (0.50, 0.74)
Sutton *et al.*[27]	31	12	11	18	0.74 (0.58, 0.86)	0.60 (0.41, 0.77)
Thakur *et al.*[28]	31	11	0	20	1.00 (0.89, 1.00)	0.65 (0.45, 0.81)

Study	TP	FP	FN	TN	Sensitivity (95% c.i.)	Specificity (95% c.i.)
Pooled	211	68	25	178	0.89 (0.85, 0.93)	0.72 (0.66, 0.78)

Study	TP	FP	FN	TN	Sensitivity (95% c.i.)	Specificity (95% c.i.)
Ashaf *et al.*[21]	53	22	3	34	0.95 (0.85, 0.99)	0.61 (0.47, 0.74)
Li *et al.*[24]	61	31	23	53	0.73 (0.62, 0.82)	0.63 (0.52, 0.73)
Sutton *et al.*[27]	1	1	4	69	0.20 (0.01, 0.72)	0.99 (0.92, 1.00)

Study	TP	FP	FN	TN	Sensitivity (95% c.i.)	Specificity (95% c.i.)
Pooled	115	54	30	156	0.79 (0.72, 0.86)	0.74 (0.68, 0.80)

b

Fig. 3 The specificity and sensitivity of MRI for evaluating tumours for OncotypeDX® recurrence score

a Recurrence score (RS) less than 18 *versus* 18 or greater. **b** RS less than 30 *versus* greater than 30. **c** Receiver operating characteristic curve for RS less than 18 *versus* 18 or greater, and less than 30 *versus* 30 or greater. TP, true positive; FP, false positive; FN, false negative; TN, true negative.

proven in well conducted randomized trials, preoperative radiomic evaluation of all early ER+ breast cancers requiring MRI could complement or even replace RS testing with several clinical and economic implications.

Additionally, data from this pooled analysis supports radiomics in delineating cancers with RS greater than 30, with an implied sensitivity of almost 80 per cent, with similar specificity rates. Within the framework of early-stage ER+ disease, RS has emerged and successfully modulated cytotoxic chemotherapy prescription for the vast majority. However, differentiating those with RS greater than 30 is crucial, on account of the inherent indication for chemoendocrine therapy following substratification into this group, as proven through data published from the National Surgical Adjuvant Breast and Bowel (NSABP) projects[6]. However, it should be acknowledged that clinically relevant RS subgroups have been redefined by the work of Sparano and colleagues through the Trial Assigning Individualized Options for Treatment (*TAILORx*)[4]; the initial evidence for RS testing indicated scores greater than 30 to represent accurately those likely to benefit most from systemic treatment[6], adding validity to the results of this analysis. However, in modern oncological practice, RS greater than 25 is utilized as the cut-off in postmenopausal women, rendering the current analysis between the RS subgroups discussed somewhat at odds with current clinical practice. Albeit imperfect in the current form, non-invasive radiomic analysis remains an exciting prospect in oncology on a global scale. Buy-in from large international investment companies may be imperative to finance technological enhancement, and validate current concepts and principles prospectively, while refining machine-learning strategies through high-throughput image-based screening. If given the opportunity to be validated, it is plausible that radiomics has potential to become embedded into multidisciplinary discussion within clinical oncological practice, and to further personalize oncological patient care.

In recent times, there has been a move towards precision medicine in the field of oncology, with an emphasis placed on ensuring cost-effectiveness where possible. Moreover, in most European healthcare economies, the foundation for health and personal services for the majority of residents is funded through taxation of public funds . At present, the world's economy is subject to impending recession following the COVID-19 pandemic, and adaptations look imperative in ensuring cost-efficiency; RS testing is associated with a reported cost of approximately €3000[36], with turnaround times of up to several weeks, while the cost of conventional MRI scanning is often substantially less in certain healthcare economies[37,38]. Moreover, should radiomic neural networking become routine, its offers more cost- and time-effectiveness *versus* routine genomic analysis[39,40]. While data procured from MRI pertaining to macroscopic features (for example, tumour site, size, shape, degree of disease burden, etc.) are of course invaluable, features occult to the radiologist, such as grey-level co-occurrence matrix textural features, MR-derived entropy and surface-to-volume ratio, may serve patients by personalizing their medical care[41]. Furthermore, some clinicians may argue failure to extract such radiomic tumour data as routine, once MRI has been performed, is a disservice to prospective patients. From this viewpoint, it seems appropriate and rational that radiomic analyses are incorporated into the oncology paradigm, with substitution or supplementation of current biomarkers, to continue developing and adapting strategies of patient management in a cost-effective manner.

This systematic review has a number of inherent limitations. The field of radiomics involves a spectrum of artificial-intelligence techniques, including machine learning, conventional neural networks and deep-learning techniques. In this analysis, all of these methods are appraised under the umbrella term 'radiomics', despite variance in their reproducibility of data[42]. In this analysis, there was no single radiomic biomarker that correlated directly with RS that could be ascertained from more than one study, rendering sensitivity, specificity and rate ratios the most useful means of comparing radiomics and RS. Moreover, there is a limited number of patients in this analysis (1216 patients), and all included studies were of moderate levels of evidence, with none of the included studies being prospective in nature. Clinical cut-offs have been redefined following the publication of the results of the *TAILORx* trial[4], yet all studies included this analysis use traditionally accepted cut-offs. This shortcoming limits the relevance of the conclusions which can be drawn from this analysis and fails to support its implementation into clinical practice using traditional cut-offs (for example, in the setting of a premenopausal woman with RS less than 18, based on the results from the current analysis, radiomics would spare such a patient combined chemoendocrine therapy (predictive rate ratio of 0.93 in delineating RS less than 18 from 18 or greater (*Fig. 2a*)) indicating possible undertreatment). Difficulty ascertaining radiomic differences between RS less than 30 and greater than 30 is possibly due to a paucity of patients in the greater than 30 group being included in this analysis[21,24]. Furthermore, current indications for preoperative MRI only include scenarios such as invasive lobular carcinoma and BRCA-mutation carriers, reducing the value of implementing results of this analysis into current clinical practice models. Furthermore, the timely access to MRI in the preoperative period has not been evaluated in this review and may pose a real-world challenge to the clinical implementation of radiomics. In spite of these acknowledged limitations, this analysis supports the mantra that radiomic tumour analysis is imminent in personalizing cancer care for prospective patients.

Disclosure. The authors declare no conflicts of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

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