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Tumour volume analysis applied to imaging and histological examinations in breast cancer

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ABSTRACT

Purpose: Response Evaluation Criteria in Solid Tumours (RECIST) determines partial response (PR) and progressive disease (PD) as a 30 % reduction and 20 % increase in the longest diameter (LD), respectively. Tumour volume analysis (TVA) utilises three diameters to calculate response parameters.

Patients and methods: We conducted a pilot investigation of patients who underwent neoadjuvant breast cancer treatment and evaluation using RECIST with LD measurements and TVA with three diametric measurements, using the parameters PR (>30 % tumour regression), PD (>20 % tumour growth), and intermediate stable disease (SD). According to TVA, RECIST miscategorised 7 of 28 patients (25 %). We evaluated 145 patients who underwent baseline breast magnetic resonance imaging (MRI), neoadjuvant chemotherapy, presurgical MRI, and surgery and calculated LD and volume from all MRI examinations.

Results: Of the 173 patients, 157 had measurable disease at baseline and treatment completion, and 32 were miscategorised (20.4 %). The number of patients with a PR increased from 123 to 150 after TVA. The sensitivity of RECIST-measured responses (95 % confidence interval: 97–100 %) was 100 % for TVA. This altered the staging, as 32 of 157 (20.4 %) patients were allocated to another response group, with fewer cases of SD: 26 patients moved from SD to PR and 6 patients from SD to PD.

Conclusion: Measuring a solid mass using LD is fundamentally flawed, as the lesser axes considerably affect the volume, leading to inaccurate response categorisation, with implications for patient management. TVA is a novel method that increases accuracy of tumour size measurement and response to therapy.

1. Introduction

The purpose of this study is to propose a new method of tumour response evaluation of neoadjuvant therapy (NACT).Tumour Volume Analysis (TVA) uses three diameter volume estimation of a cancer rather than the longest diameter (LD).Superior accuracy is achieved with TVA, which may alter response categories to treatment, and so change clinical management in some patients.

Previous methods of measuring solid tumours were the World Health Organization (WHO) guidelines and the Tumour Node Metastasis (TNM) system.

The current standard method is the Response Evaluation Criteria in Solid Tumours (RECIST), introduced in 2000. This method incorporates percentage changes in the LD to indicate partial response (PR), stable disease (SD), and progressive disease (PD) [1].

Tumour size measurement can be standardised by applying the diameter from the RECIST response percentages to volume measurements. The maximum dimensions of lesions measured along three planes, axial, coronal, and sagittal, should be considered. All measurements should be performed by one operator and verified by another. Validation can be achieved as required, with inter- and intra-observer measurements in a subset showing a high Kappa agreement value [2].

We previously conducted a pilot study [3] based on the NEOCENT trial findings [4]. The proportion of patients who responded to

Abbreviations: CR, complete response; CRT, complete response time; LD, longest diameter; ICHT, Imperial College Healthcare Trust; NACT, neoadjuvant chemotherapy; NPV, negative predictive value; pCR, pathology complete response; PD, progressive disease; PPV, positive predictive value; PR, partial response; RCB, residual cancer burden; rCR, radiology complete response; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; TDT, tumour doubling time; TuVol, logo for tumour volume; TVA, tumour volume analysis.

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treatment (achieved tumour regression) did not differ significantly between neoadjuvant chemotherapy (NACT) and endocrine treatment groups, although endocrine treatment was preferred because of its simplicity of delivery. The median percentage of tumour regression in partial responders (>30 % reduction) was compared using LD and volume in both groups.

The NEOCENT trial revealed a response of −44 % by diameter and −81 % by volume ($p < 0.0001$) [3]. PR is defined as a 30 % reduction in the sum of unidimensional tumour measurements correlated with PR to therapy. Studies have proposed PR calculation based on the percentage reduction in tumour volume [5].

TNM staging and RECIST use the single LD method; however, RECIST uses the following additional percentage changes to measure treatment response: PR (−30 %), PD (+20 %), and intermediate SD [1]. The measurement of a solid tumour using a single diameter does not consider the lesser axes, which reduces the volume unless the mass is a true sphere. This explains why RECIST overestimates tumour size and underestimates the treatment benefit [6].

Furthermore, RECIST estimates that a 30 % reduction in LD is correlated with a 50 % reduction in volume [1]. A 30 % reduction in the diameter of a sphere corresponds to a 65 % decrease in volume, and a 20 % reduction in the diameter of a sphere corresponds to a 49 % decrease in volume. Progressive Disease with +20 % diameter equals 73 % increase in volume. Stable Disease with +10 % diameter equals 33 % increase in volume and Stable Disease with +15 % diameter equals 52 % increase in volume [7]. The lesser axes dictate the shape and volume of the mass (Fig. 1). Fig. 1 depicts the permutations of a mass with an LD of 3 cm; the other diameters are 3, 2, and 1 cm, and three axial measurements ensure maximum accuracy [8].

The volume of a sphere is calculated using formula $4/3\ \pi r^3$, which translates into an eight-fold increase in volume when the diameter doubles and by $8 \times 8 = 64$ when the diameter doubles again. Thus, RECIST is inherently inaccurate, and an improved method for measuring tumour size and assessing treatment response is required.

2. Methods

2.1. Study population

This retrospective case series included 173 female patients who underwent neoadjuvant treatment (NACT or endocrine treatment) for breast cancer before surgery at three centres: the University of California San Francisco (USA) with other USA sites, Imperial College Healthcare Trust (ICHT; UK) with other UK sites, and Asan Medical Centre (Korea). All patients underwent serial imaging with three tumour diameter measurements at baseline and the end of treatment.

2.1.1. Inclusion criteria

Women with histologically proven invasive breast cancer who consented to receive NACT followed by appropriate breast surgery were included in this study. The demographics of the study population trended towards menopausal age and above. The ethnicities were diverse and included white, black, Indian, South Korean, and other oriental populations.

2.1.2. Exclusion criteria

Men, non-adult females, and patients who did not consent to receive treatments were excluded from the study. No exclusions were made on account of other medical conditions, provided the patient could tolerate chemotherapy and breast surgery.

2.2. Pilot study

A pilot study was conducted with 28 eligible patients from NEOCENT, a randomised trial that included postmenopausal women aged <70 years with Estrogen Receptor ER-positive breast cancer (tumour size >2 cm). The downstaging effects of letrozole and NACT were compared before surgery. Twelve patients were randomised to chemotherapy FE100C with 6 × 3 weekly cycles, and 16 patients were randomised to receive letrozole 2.5 mg orally for 18–23 weeks. Handheld ultrasonographic measurements were also obtained. Ultrasound was used for the Pilot and this study taking core biopsies with local anaesthetic,it also established that the lesion was solid and not cystic. It is recognised that ultrasound is not now used in the assessment of lesion size or as a method of measurement. NEOCENT data was collected up to 2011.

2.3. ACRIN 6657

ACRIN 6657, which was conducted at the University of California, San Francisco, investigated 105 patients aged 26–68 years with ≥3 cm, stage 2 or 3 breast cancer, and who were selected to undergo NACT with an anthracycline-based drug with or without taxanes. The first author was provided with magnetic resonance imaging (MRI) data for 221 patients. In total, 105 patients with mass-like lesions and three measured diameters were eligible for the analysis. We excluded 116 patients with non-mass-like lesions who underwent a single LD measurement.

2.4. ICHT

Forty patients aged 28–75 years eligible for NACT based on tumour size, lymph node involvement, or other indications were recruited from the ICHT. Patients with locally advanced or inflammatory cancers were

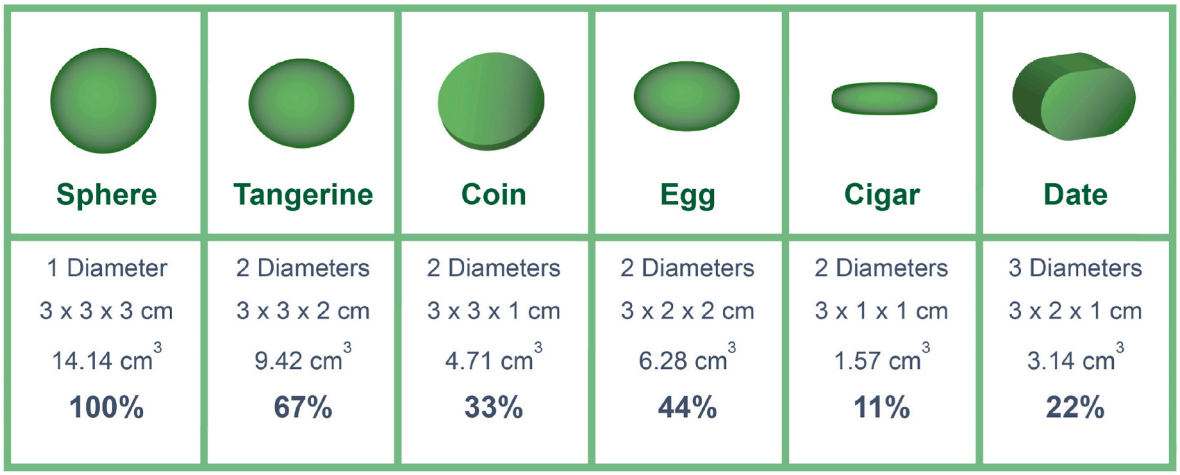

Fig. 1. Diameter permutations of a mass with the longest diameter as 3 cm and the other diameters as 3, 2, or 1 cm.

excluded from the study. Serial MRI scans and LD and three-dimensional (3D) measurements were recorded to compare RECIST with TVA. Chemotherapeutic agents (doxorubicin, cyclophosphamide, paclitaxel, carboplatin, trastuzumab, or docetaxel) were dependent on stage, immunotype, and patient fitness. All patients underwent surgical excision of the residual mass followed by histopathological examination and measurements.

TVA methodology entails the measurement of a solid mass using three diameters to compare differences in the calculated volumes in cubic centimetres and as percentages [6–8]. The formula for calculating the volume of a sphere is modified to allow for three different radii, a, b, and c, whose diameters were 2a, 2b, and 2c, respectively, and the volume is calculated using the formula: $4/3\ \pi\ a \times b \times c$. The features are three baseline diametric measurements of a solid for volume calculation, which can be compared with those of the treated tumour in cubic centimetres and percentages. These percentage changes can also be compared with the LD in RECIST for reference. Other novel features tumour doubling time (TDT) and complete response time (CRT)) were also measured. In both cases, the baseline volume calculation was followed by the measurement of the post-treatment or subsequent volume. The interval (days) between two volumes was used to obtain the results (days) [8]. CRT can be applied to serial measurements during chemotherapy to assess the treatment response. TDT identified two cases of primary endocrine resistance to letrozole in the pilot study [3].

The following formula allows for exponential growth in the measurement of TDT and CRT.

$$TDT = \frac{D \times (\log 2)}{\log\left(1 + \frac{r}{100}\right)}$$

where TDT = tumour doubling time.

D = Days of interval between volume measurements

r = rate of growth.

$$\frac{r}{100} = \frac{(vol\,2 - vol\,1)}{vol\,1} \times 100$$

The TVA algorithm can be applied to ultrasound imaging, MRI, computed tomography, and positron emission tomography. The primary outcome of this study was the correlation between the sensitivity and specificity of clinical response to therapy using volumetric and RECIST assessments, respectively. It also established that volumetric measurement of a solid mass is significantly more accurate than diametric measurement, to stratify patients into the correct response group. $P < 0.0001$.

Although the superior accuracy of volumetric measurements is self-evident (Fig. 1), RECIST is the standard method for assessing treatment response, owing to the complicated mathematical calculations required for volume estimation. This issue is resolved by the TuVol algorithm, which requires only linear measurements. To ensure standardisation and accuracy, the same cutoffs used in the RECIST assessment (30 % reduction and 20 % increase in LD were designated as PR and PD, respectively, and SD was designated as the intermediate between PR and PD) were applied to the three-diameter TVA measurements. Volumetric measurements are more sensitive than LD measurements; thus, they can help re-stratify some patients with SD predominantly into the PR group and others into the PD category.

3. Results

3.1. Pilot study of the NEOCENT trial

Of the 28 patients from the NEOCENT pilot study, 15 exhibited PR with a >30 % reduction in diameter, and 20 demonstrated a >30 % reduction in volume (NACT group, n = 8; endocrine group, n = 12; Table 1). Four patients in the pilot study did not exhibit tumour regression (chemotherapy group, n = 2; endocrine group, n = 2). The two endocrine therapy-treated tumours underwent a 104 % and 36.3 % enlargement, i.e., PD (>20 % increase in volume), although the diametric measurements showed an SD of −2.5 % and −2.9 %, respectively. TVA revealed PD, which was not identified by RECIST and could alter clinical management. These two patients appeared to have primary endocrine resistance to letrozole. Furthermore, 7 of 28 patients (25 %) were miscategorised: 5 patients with SD to PR and 2 patients with SD to PD were allocated to the incorrect group [3].

3.2. CRT and TDT

Baseline and final volumes were calculated from three diametric measurements and a known interval (days) between imaging [8]. The 20 patients with treatment response demonstrated CRT ranging between −23 and −250 days. The two tumours that were enlarged according to TVA alone had a TDT of +135 and + 337 days, respectively, and had increased by more than 20 % in volume but were designated as SD by diametric assessment. Five more patients were designated as having SD by diametric assessment but regressed by > -30 % according to volumetric assessment.

3.3. ACRIN 6657 (University of California, San Francisco) and ICHT studies

Table 2 summarises the data of the 145 patients with diametric and volumetric percentage changes with respect to both RECIST and TVA. Only 75 of the 105 patients with ACRIN achieved PR (30 % reduction) according to RECIST, while 92 showed PR by volume. Twenty-eight patients had SD according to RECIST, but only eight patients had SD according to TVA. PD >+20 % was observed in only two patients according to RECIST but in five patients according to TVA. Thus, similar to the pilot study, the ACRIN and ICHT cohort studies revealed that TVA identified PD cases that RECIST overlooked.

In patient 1085 SF, RECIST showed a PD of +31.8 %, but TVA, with smaller lesser axes, showed a PR of −81.8 %

3.4. Combined analysis of the data presented in Tables 1 and 2

A total of 173 patients were analysed, of whom 16 showed a complete response (CR), and 157 had measurable disease on both baseline and presurgical imaging. Of the 157 patients, 32 were allocated to the incorrect response group, 26 to the PR group, and 6 to the PD group (20.4 %). These results altered the staging because patients categorised as having achieved PR rather than SD demonstrated unrecognised treatment benefits. Six patients with PD were assessed for cessation or switching to their current therapeutic regimen.

The advantage of TVA over RECIST is its enhanced accuracy in placing patients into the correct response category, which resulted in fewer patients in the SD group. Table 1 shows that seven of 28 (25 %) patients were moved to another category: two patients with SD to PD and five with SD to PR. Of the 145 patients, 25 (17.2 %) were moved to another category SD to PD, four patients; SD to PR, 21 patients; (Table 2).

Comparison of responders with −30 % PR on RECIST and those with −30 % PR on TVA.

The sensitivity of all RECIST responses, i.e., the proportion of true-positive responses using TVA, was 100 % (95 % CI: 97–100 %). The specificity of all RECIST non-responses, i.e., the proportion of non-responses in the TVA method (true negatives), was 46 % (95 % CI: 31.8–60.7 %). Supplementary material Appendix A1.

Comparison of responders with −30 % PR on RECIST and those with −50 % volume on RECIST.

The sensitivity of all RECIST responses, i.e., the proportion of responders in the volume method (true positives), was 99.2 % (95 % CI: 95.6–100 %). The specificity of all RECIST non-responses, i.e., the proportion of non-responders in the volume method (true negatives), was

Table 1
Data of 28 patients from the NEOCENT pilot study
Chemotherapy (12) and Endocrine therapy (16) showed diametric and volumetric percentage changes in both RECIST and TVA terms.

Columns 2, 3, 4 > -30% LD response correlated with > -50% Volume
Columns 5, 6, 7 > -30% Volume response correlated with > -30% LD
Column 3 sorted by RECIST > -30%
Column 7 sorted by TVA > -30%

PARTIAL RESPONSE PR > -30%	STABLE DISEASE SD < -30% regression < +20% progression	PROGRESSIVE DISEASE PD > +20%

PARTIAL RESPONSE PR LD > -30%	VOLUME RESPONSE Vol > -50%

Column 3 Diameter: PR = 15, SD = 13, Total = 28
Column 4 Volume correlated with Diameter: PR = 17, Intermediate = 4, SD = 5, PD = 2, Total = 28

Column 7 Volume: PR = 20, SD = 6, PD = 2, Total = 28
Column 6 Diameter correlated with Volume: PR = 15, SD = 13, Total = 28

Treatment	Patient	LD > -30%	Vol > -50%	Patient	RECIST %	TVA %	CRT/TDT days
Ct	19	-77	-98	19	-77	-98	-23
En	24	-64	-87	8	-39	-95	-33
En	28	-63	-95	12	-32	-90	-33
Ct	10	-48	-84	24	-64	-87	-33
Ct	14	-44	-87	28	-63	-95	-38
En	1	-44	-84	14	-44	-87	-51
Ct	21	-44	-81	10	-48	-84	-53
En	13	-44	-81	1	-44	-84	-54
En	16	-41	-65	26	-26	-84	-56
En	8	-39	-95	21	-44	-81	-57

62 % (95 % CI: 47.2–75.3 %). Supplementary material Appendix B1.

A comparison of a group with −30 % RECIST PR with a TVA PR of −30 % and a group with a RECIST volume of −50 % revealed true-positive sensitivities of 100 % and 99.2 %, respectively, the primary end point. The correlation between the true-negative specificity of the two groups was lower, at −46 % and −62 %, respectively, which may be because more patients were designated as having a response of TVA -30 % than those with a response of RECIST < -30 %.

3.5. Residual cancer burden (RCB)

Table 3 demonstrates that in 16 of 40 cases (40 %) disease was detected in both MRI and RCB, while in 13 cases (32.5 %) no disease was identified by either method. No concordance was observed in the remaining 11 cases (27.5 %).

The presurgical MRI scans of 40 ICHT patients were analysed, in addition to the diameter and volume of the RCB. The RCB was measured from the LD of the histological specimen, and the volume calculated using the radius (half the diameter),which resulted in a larger volume, unless the mass was spherical.

Table 4 compares MRI,LD and volume with RCB,LD and volume which are expressed as percentages.

Fourteen patients had measurable disease in both the MRI and RCB. Two further patients (18,26) with MRI disease, had only scant isolated cancer cells in the residual cancer site. In the first eight patients (4,16,25,36,20,12,6,22) the RCB volume percentage is smaller than suggested by the MRI. In the last six patients (15,5,34,29,14,39) the RCB volume is larger than suggested by the MRI.

In approximately 60 % (actual 57 %) of patients the RCB volume was smaller than that estimated by the MRI diameters.

In approximately 40 % (actual 43 %) of patients the RCB volume was larger than that estimated by the MRI diameters.

The only Histologic Medullary type carcinoma occurred in patient 39 with a RCB 3978.3 % greater than the MRI estimate.

A scatterplot (Supplementary Material Fig. 2) shows Spearman's rho (0.99) for the RCB,LD and RCB measured volume ($p < 0.0001$),and another scatterplot (Supplementary Material Fig. 3) shows Spearman's rho (0.98) for the MRI,LD and MRI measured volume ($p < 0.0001$)

The median age of the 40 patients from the ICHT cohort was 47.5 years (range: 28–75 years), and the mean age ± standard deviation was

En	23	-38	-64	13	-44	-81	-58
Ct	5	-36	-72	5	-36	-72	-73
En	12	-32	-90	20	-31	-73	-80
En	27	-32	-74	27	-32	-74	-89
En	20	-31	-73	23	-38	-64	-89
Ct	18	-28	-45	16	-41	-65	-90
Ct	15	-27	-27	6	-21	-64	-92
Ct	26	-26	-84	18	-28	-45	-168
En	3	-25	-40	3	-25	-40	-250
En	4	-25	-9	7	-14	-36	-196
En	6	-21	-64	25	-6	-29	-282
Ct	7	-14	-36	15	-27	-27	-305
En	25	-6	-29	2	+5.5	-29	-317
En	11	-2.9	+36.3	4	-25	-9	-1005
En	17	-2.5	+104	9	0	0	-
Ct	9	0	0	17	-2.5	+104	+135
Ct	2	+5.5	-29	11	-2.9	+36.3	+337
Ct	22	+13.6	+14.1	22	+13.6	+14.1	+728

Median and IQR for cases.
Median percent regression with PR > -30 %.
Diameter RECIST; N = 15, Median -44 % IQR (-48 to -36).
Volume TVA; N = 20, Median -81 % IQR (-87 to -64.5).
$p \leq 0.0001$.
Wilcoxon signed rank test.

50.1 ± 12.6 years. Of the 40 patients, 20 each underwent mastectomy and 20 wide local excision of the marked tumour bed. Moreover, 12 showed ER-positive and HER2-positive phenotypes, whereas 11 had ER-negative and HER2-negative phenotypes. Ten patients showed ER-negative and HER2-positive phenotypes, 6 showed ER-positive and HER2-negative phenotypes, and 1 exhibited ER-positive and HER2-borderline phenotypes. Histopathological results indicated 36 cases of ductal carcinoma, 2 of lobular carcinoma, 1 of ductal carcinoma with lobular carcinoma, and 1 of medullary carcinoma.

4. Discussion

Unlike this study, previous studies have measured the functioning tumour volume and enhancing tumour volume. The Functional tumour volume was measured by semiautomated computer analysis of gadolinium contrast enhanced signal ratio method [9]. Tumour sphericity is related to a higher incidence of pCR if the tumour is a well-circumscribed and well-defined single mass, i.e., morphological pattern 1 [10–12]. A meaningful tumour response was observed after NACT in 81 % of patients, especially in Human Epidermal Receptor HER 2+ and triple-negative cases [13]. MRI is the standard imaging modality for baseline and preoperative residual disease assessment, although tumour morphology, enhancement kinetics, and diffusion-weighted imaging are also used to measure early, intermediate, and post-NACT responses [14]. A study that measured residual disease after NACT in 382 patients concluded that RCB was related to several histological features combined, including the size and cellularity of the primary tumour and the number of positive nodes. Four RCB categories were described based on clinical response, viz. responder 0 or responder 1 (pCR or minimal residual disease), and non-responder II or non-responder III (where III represents a poor prognosis, which was observed in 13 % of patients) [15].

Studies have shown that ultrasound measurement of tumour volume provides a more sensitive assessment of tumour response than diametric [4] and MRI measurements [16], raising the issue of tumour measurement accuracy by diameter or volume [17]. Studies investigating the ability of LD and RECIST to measure tumour volumes concluded that RECIST could not identify the largest mass, as observed in 9 % of cases [18]. The diameter/radius of a sphere is mathematically connected to its volume. A PR with a 30 % diameter reduction invariably results in a 65 % decrease in volume. Similarly, a PD with a 20 % increase in diameter is associated with a 73 % increase in volume [7].

The measurement of residual tumour diameter of the surgical specimen is considered the gold standard and can be used for correlation with MRI or ultrasound results [19]. The correlation coefficients of MRI residual tumour size with the histological specimen showed good overall accuracy in 17 of 35 studies. Although MRI was better than the alternative methods, it was associated with over- and underestimation of

Table 2
Data of 145 patients from the University of California at San Francisco (SF, n = 105) and Imperial College Healthcare Trust (IC, n = 40) that showed diametric and volumetric percentage changes in both RECIST and TVA terms.

Columns 1, 2, 3 > -30% LD response correlated with > -50% Volume
Columns 4, 5, 6 > -30% Volume response correlated with > -30% LD
Column 2 sorted by RECIST > -30% Column 6 sorted by TVA > -30%

PARTIAL RESPONSE PR	STABLE DISEASE SD	PROGRESSIVE DISEASE PD
> -30%	< -30% regression < +20% progression	> +20% progression

PARTIAL RESPONSE PR	VOLUME RESPONSE
LD > -30%	Vol > -50%

Column 2 Diameter: CR = 16, PR = 92, SD = 35, PD = 2 Total = 145
Column 3 Volume correlated with Diameter: CR = 16, PR = 110, Intermediate = 4, SD = 10, PD = 5,
Total = 145
Column 6 Volume: CR = 16, PR = 114, SD = 10, PD = 5, Total 145
Column 5 Diameter correlated with Volume: CR = 16, PR = 92, SD = 35, PD = 2, Total = 145

Patient	LD > -30%	Vol > -50%	Patient	RECIST %	TVA %
2 IC	-100	-100	2 IC	-100	-100
3 IC	-100	-100	3 IC	-100	-100
7 IC	-100	-100	7 IC	-100	-100
8 IC	-100	-100	8 IC	-100	-100
10 IC	-100	-100	10 IC	-100	-100
17 IC	-100	-100	17 IC	-100	-100
19 IC	-100	-100	19 IC	-100	-100
21 IC	-100	-100	21 IC	-100	-100
23 IC	-100	-100	23 IC	-100	-100
27 IC	-100	-100	27 IC	-100	-100
28 IC	-100	-100	28 IC	-100	-100

31 IC	-100	-100	31 IC	-100	-100
33 IC	-100	-100	33 IC	-100	-100
35 IC	-100	-100	35 IC	-100	-100
37 IC	-100	-100	37 IC	-100	-100
40 IC	-100	-100	40 IC	-100	-100
9 IC	-94.6	-99.98	9 IC	-94.6	-99.98
1010 SF	-93.3	-99.9	1010 SF	-93.3	-99.9
1064 SF	-93.2	-99.9	1043 SF	-90.4	-99.9
1165 SF	-92	-99.9	1064 SF	-93.2	-99.9
1043 SF	-90.4	-99.9	1071 SF	-87.7	-99.9
1229 SF	-89.2	-99.9	1165 SF	-92	-99.9
1233 SF	-88.4	-99.9	1229 SF	-89.2	-99.9
1071 SF	-87.7	-99.9	1233 SF	-88.4	-99.9
1206 SF	-86.6	-99.5	1147 SF	-84.1	-99.7
1147 SF	-84.1	-99.7	1097 SF	-82	-99.6
1180 SF	-84	-99.5	1180 SF	-84	-99.5
1097 SF	-82	-99.6	1206 SF	-86.6	-99.5
30 IC	-78.7	-96.9	24 IC	-64.7	-99.1
1157 SF	-75.7	-98.5	32 IC	-73.6	-98.8
1172 SF	-75.6	-98.4	1184 SF	-67.5	-98.6
1191 SF	-75.6	-97.4	1157 SF	-75.7	-98.5
1029 SF	-74	-97.9	1172 SF	-75.6	-98.4
32 IC	-73.6	-98.8	1009 SF	-63.8	-98.2
22 IC	-73	-95.6	1029 SF	-74	-97.9

29 IC	-71.8	-97.9	29 IC	-71.8	-97.9
1005 SF	-71.8	-97.8	1005 SF	-71.8	-97.8
34 IC	-70.97	-95.87	12 IC	-61.2	-97.6
1077 SF	-70.5	-96.7	1191 SF	-75.6	-97.4
1210 SF	-69	-95.5	1011 SF	-60.9	-97.2
1184 SF	-67.5	-98.6	30 IC	-78.7	-96.9
24 IC	-64.7	-99.1	1077 SF	-70.5	-96.7
1009 SF	-63.8	-98.2	18 IC	-60.7	-96.5
1086 SF	-63.7	-86	1158 SF	-60.7	-96.4
15 IC	-62.7	-88.7	1138 SF	-33.8	-96.1
12 IC	-61.2	-97.6	34 IC	-70.97	-95.87
1011 SF	-60.9	-97.2	4 IC	-60	-95.8
1144 SF	-60.8	-95	22 IC	-73	-95.6
18 IC	-60.7	-96.5	1210 SF	-69	-95.5
1158 SF	-60.7	-96.4	1204 SF	-60	-95.1
1209 SF	-60.7	-93.4	1144 SF	-60.8	-95
4 IC	-60	-95.8	1164 SF	-57.1	-94.4
1204 SF	-60	-95.1	16 IC	-16.6	-94.2
1060 SF	-58.7	-87.6	1136 SF	-46.3	-94
1110 SF	-58.3	-92.6	1155 SF	-57.8	-93.8
1007 SF	-58	-92.2	1209 SF	-60.7	-93.4
1155 SF	-57.8	-93.8	39 IC	-51.8	-93.4
1134 SF	-57.8	-89.7	1110 SF	-58.3	-92.6
1164 SF	-57.1	-94.4	1146 SF	-56.5	-92.5

1225 SF	-57	-92.5	1225 SF	-57	-92.5
1146 SF	-56.5	-92.5	1007 SF	-58	-92.2
1205 SF	-56	-89.9	1017 SF	-53	-91.9
1004 SF	-55	-89.9	1226 SF	-41.1	-91.5
1135 SF	-53.5	-90.9	1100 SF	-52.7	-91
1017 SF	-53	-91.9	1135 SF	-53.5	-90.9
1033 SF	-53	-83	1201 SF	-52.8	-90.7
1201 SF	-52.8	-90.7	1168 SF	-25	-90.4
1100 SF	-52.7	-91	1123 SF	-43.5	-90.2
1150 SF	-52.3	-87.2	1004 SF	-55	-89.9
1237 SF	-52	-85.7	1205 SF	-56	-89.9
39 IC	-51.8	-93.4	1134 SF	-57.8	-89.7
14 IC	-51.3	-88.3	1223 SF	-37	-89.6
1160 SF	-50.6	-60.2	1047 SF	-47.8	-89.5
1187 SF	-50	-87.2	1002 SF	-44.8	-89.2
1114 SF	-50	-67.9	1090 SF	-18.7	-88.8
1132 SF	-50	-67.6	15 IC	-62.7	-88.7
1154 SF	-48.6	-82.4	1041 SF	-41.1	-88.6
1018 SF	-48	-80.5	14 IC	-51.3	-88.3
1047 SF	-47.8	-89.5	1060 SF	-58.7	-87.6
1128 SF	-47.8	-87.4	1128 SF	-47.8	-87.4
1109 SF	-46.6	-63.7	1039 SF	-40	-87.3
1136 SF	-46.3	-94	1150 SF	-52.3	-87.2
1188 SF	-45	-81.6	1187 SF	-50	-87.2

1002 SF	-44.8	-89.2	1086 SF	-63.7	-86
1123 SF	-43.5	-90.2	1237 SF	-52	-85.7
11 IC	-41.6	-80.6	38 IC	-35.2	-84.9
1082 SF	-41.2	-78.9	1096 SF	-38.6	-84.6
1226 SF	-41.1	-91.5	1033 SF	-53	-83
1041 SF	-41.1	-88.6	1154 SF	-48.6	-82.4
1039 SF	-40	-87.3	1203 SF	-29.5	-82.3
1106 SF	-40	-74.7	1085 SF	31.8	-81.8
1096 SF	-38.6	-84.6	1169 SF	-30	-81.8
1008 SF	-38	-62.17	1188 SF	-45	-81.6
1223 SF	-37	-89.6	11 IC	-41.6	-80.6
1053 SF	-37	-74.6	1018 SF	-48	-80.5
38 IC	-35.2	-84.9	1003 SF	-34	-80.5
1183 SF	-35	-54.8	1103 SF	-34.6	-79.2
1103 SF	-34.6	-79.2	1019 SF	-33.9	-78.9
1003 SF	-34	-80.5	1082 SF	-41.2	-78.9
1019 SF	-33.9	-78.9	1127 SF	-31.5	-76.2
1138 SF	-33.8	-96.1	1106 SF	-40	-74.7
25 IC	-33	-62.3	1053 SF	-37	-74.6
1065 SF	-31.7	-69.9	1095 SF	-28.9	-74
1127 SF	-31.5	-76.2	1091 SF	-20.8	-72.6
36 IC	-31.3	-70.1	36 IC	-31.3	-70.1
1117 SF	-30.5	-47.9	1031 SF	-20.9	-70
1169 SF	-30	-81.8	1065 SF	-31.7	-69.9

1055 SF	-30	-66.9	26 IC	-29	-69.4
1203 SF	-29.5	-82.3	1114 SF	-50	-67.9
26 IC	-29	-69.4	1 IC	-17.2	-67.8
1095 SF	-28.9	-74	1132 SF	-50	-67.6
1078 SF	-28.2	-65.6	1055 SF	-30	-66.9
1040 SF	-27.5	-54.9	1078 SF	-28.2	-65.6
1159 SF	-27.5	-44.5	1109 SF	-46.6	-63.7
1168 SF	-25	-90.4	25 IC	-33	-62.3
1069 SF	-22.5	-62	1008 SF	-38	-62.17
1070 SF	-21	-55.5	1069 SF	-22.5	-62
1031 SF	-20.9	-70	1160 SF	-50.6	-60.2
1091 SF	-20.8	-72.6	13 IC	-19.7	-58.7
1072 SF	-20	-51.7	1070 SF	-21	-55.5
13 IC	-19.7	-58.7	1040 SF	-27.5	-54.9
1090 SF	-18.7	-88.8	1183 SF	-35	-54.8
1179 SF	-18	27.4	1072 SF	-20	-51.7
6 IC	-17.4	-51.2	6 IC	-17.4	-51.2
1 IC	-17.2	-67.8	1124 SF	-15.7	-49.2
16 IC	-16.6	-94.2	1117 SF	-30.5	-47.9
1107 SF	-16.6	-36.5	1193 SF	-5.5	-45.6
1124 SF	-15.7	-49.2	1159 SF	-27.5	-44.5
5 IC	-15.3	-10	1025 SF	-10.6	-37.8
1044 SF	-12.9	13.2	1107 SF	-16.6	-36.5
1025 SF	-10.6	-37.8	1174 SF	-9	-28.1

1214 SF	-9.5	54.6	1197 SF	0	-23.4
1174 SF	-9	-28.1	20 IC	-5.2	-21.48
1066 SF	-9	-18.8	1046 SF	-6.9	-18.8
1046 SF	-6.9	-18.8	1066 SF	-9	-18.8
1193 SF	-5.5	-45.6	1230 SF	0	-13.8
1073 SF	-5.5	-11.3	1073 SF	-5.5	-11.3
20 IC	-5.2	-21.48	5 IC	-15.3	-10
1197 SF	0	-23.4	1200 SF	17.6	-5.8
1230 SF	0	-13.8	1044 SF	-12.9	13.2
1175 SF	12	404	1179 SF	-18	27.4
1199 SF	12.6	35.6	1199 SF	12.6	35.6
1200 SF	17.6	-5.8	1214 SF	-9.5	54.6
1085 SF	31.8	-81.8	1116 SF	139.1	139.1
1116 SF	139.1	139.1	1175 SF	12	404

Correlated by Diameter column 2 with Diameter:> - 30 %: CR = 16, PR = 92, SD = 35, PD = 2, Total 145.
Correlated by Diameter with Volume > −50 %: CR = 16, PR = 110, Intermediate = 4,SD = 10, PD = 5, Total 145.
Correlated by Volume column 6 with Diameter > - 30 %: CR = 16, PR = 92, SD = 35, PD = 2, Total 145.
Correlated by Volume > −30 %: CR = 16, PR = 114, SD = 10, PD = 5, Total 145.

Table 3
Radiological and histological findings in terms of MRI and RCB.

	No. of patients		Proportion of patients
MRI and RCB rCR and pCR	16	Disease present in both	40 %
	13	No disease present in either	32.5 %
MRI+ and RCB-	8	Disease on MRI, but no RCB	20 %
RCB+ and MRI-	3	RCB, but not on MRI	7.5 %

residual disease after NACT [20], akin to our study.

Factors influencing residual tumour size as diagnosed by MRI were investigated, and their accuracy depended on tumour phenotype, MRI morphology, and biomarkers. The mean between MRI and histology tumour size was ±1.0 (range: 1–14; [21].

MRI with volumetric imaging of the functional tumour volume was conducted after NACT and was more accurate than pCR in predicting relapse-free survival, which can be identified after one cycle of chemotherapy [14]. The surgical specimens can indicate pCR as the endpoint. Two other systems, RCB, and revised American Joint Cancer Cases, can be used for tumour staging in cases where some cancer cells have been identified [22]. One study generated a nomogram comprising 359 women in the first cohort and 351 in the validation cohort, all of whom had undergone NACT and surgery. Assessment by MRI to predict pCR requires hormone receptor, Ki-67, and MRI variables such as small tumour size, low signal intensity, and no enhancement from the tumour bed [23].

Volumetric assessment has been considered in the revised RECIST 1.1 guidelines, but the lack of standardisation and availability has encumbered this approach [24]. Volume measurements are preferable to unidimensional imaging if validation can be established [2]. The cost and availability of any software are factors responsible for two-dimensional measurements in clinical practice.

Additionally, the final clinical outcome, a single-maximal two-dimensional measurement versus a 3D measurement derived from three orthogonal measurements, proved the latter to be more accurate. Study limitations relate to data collection from MRI measurement and observer interpretation. Tumour mass is measured by 3 diameters, not segmented.

5. Conclusions

Based on the findings of this study, we recommend the integration of TVA with conventional RECIST guidelines as a more accurate method of measuring tumour size and evaluating treatment response. Suitable software additions to ultrasound, CT, MRI and PET would enhance tumour measurements and clinical information.

Ethics

This retrospective case study was conducted following the principles of the Declaration of Helsinki.

Informed consent was obtained from all patients. Ethical approval was not required.

Audit Service evaluation was registered number 597.

Table 4
Imperial College Healthcare Trust cohort: MRI, LD, and TVA versus the residual cancer burden.

RCB = Residual Cancer Burden pCR = pathology Complete Response
ITC = Isolated Tumour Cells rCR = radiology Complete Response

MRI Measurement		Difference Percentage		Residual Cancer Burden RCB Measurement		
Number	MRI LD	Difference %	Residual CB LD	Residual CB Vol	Difference %	MRI TVA
4	14	-95.7	0.6	0.000113	-100.0	0.59
16	25	-99.08	2.3	0.0064	-99.1	0.654
25	67	-73.1	18	3.05	-95.9	75.42
36	35	-57.1	15	1.76	-88.1	14.84
20	18	-36.1	11.5	0.79	-62.4	2.12
12	12	-58.3	5	0.065	-61.7	0.17
6	19	-26.3	14	1.43	-49.4	2.83
22	7	-21.4	5.5	0.087	-20.7	0.109
1	24	0	pCR	pCR	0.0	2.348
2	rCR	0	pCR	pCR	0.0	rCR
3	rCR	0	pCR	pCR	0.0	rCR
7	rCR	0	pCR	pCR	0.0	rCR
8	rCR	0	pCR	pCR	0.0	rCR
9	3	0	pCR	pCR	0.0	0.005
10	rCR	0	pCR	pCR	0.0	rCR
11	70	0	pCR	pCR	0.0	69.93

13	61	0	pCR	pCR	0.0	52.3
17	rCR	0	pCR	pCR	0.0	rCR
18	20	0	ITC	ITC	0.0	1.15
19	rCR	0	4	0.03	0.0	rCR
21	rCR	0	pCR	pCR	0.0	rCR
23	rCR	0	pCR	pCR	0.0	rCR
24	12	0	pCR	pCR	0.0	0.125
26	71	0	ITC	ITC	0.0	78.06
27	rCR	0	pCR	pCR	0.0	rCR
28	rCR	0	26	9.2	0.0	rCR
30	10	0	pCR	pCR	0.0	0.753
31	rCR	0	pCR	pCR	0.0	rCR
32	10	0	pCR	pCR	0.0	0.252
33	rCR	0	14	14	0.0	rCR
35	rCR	0	pCR	pCR	0.0	rCR
37	rCR	0	pCR	pCR	0.0	rCR
38	11	0	pCR	pCR	0.0	0.283
40	rCR	0	pCR	pCR	0.0	rCR
15	19	-15.79	16	2.14	22.5	1.75
5	22	-18	18	3.05	47.3	2.07
34	9	33.3	12	0.90	57.8	0.38
29	9	5.5	9.5	0.45	79.2	0.254
14	36	-30.55	25	8.18	93.8	4.22
39	13	177	36	24.4	3978.3	0.59

Data statement

The data presented in this study can be obtained from the corresponding author upon reasonable request.

Author contributions

Angus B. Gordon: conceptualisation, methodology, software, validation, investigation, resources, data curation, writing–original draft, visualisation, and project administration. Adrian Lim: Methodology, Validation, Data curation, writing, review and editing, and supervision. Alexander Sheeka: Data curation, writing, review, and editing. Suzy Cleator: Data curation, writing, reviewing, and editing. Daniel Leff: Supervision.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109578.

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Scroll Down For Supplementary Material

Supplementary Material

Figures 2 and 3.

Appendices A1 and B1

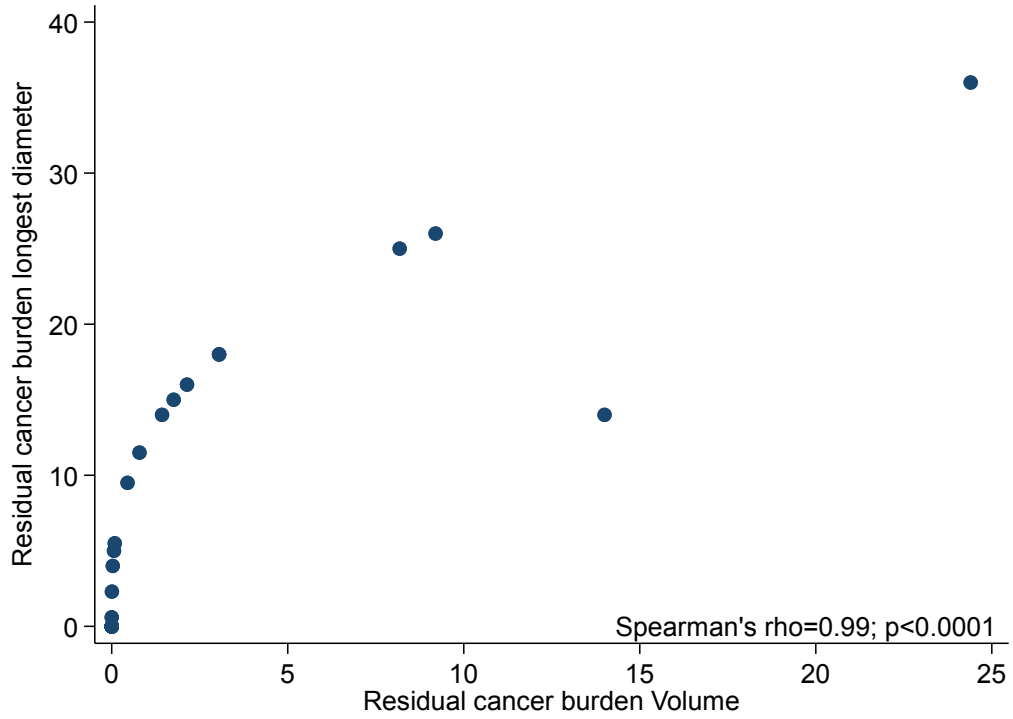

Figure 2. Relationship between residual cancer burden longest diameter and residual cancer burden volume

Wilcoxon signed rank test. (p<000.1)

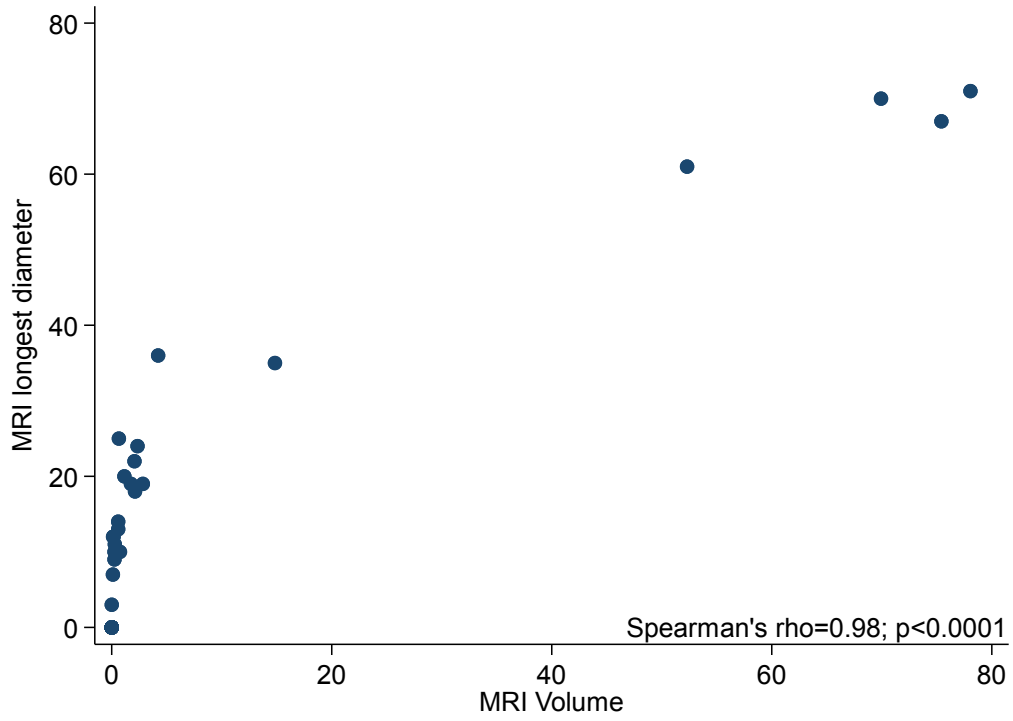

Figure 3. Relationship between MRI LD and MRI volume

MRI: magnetic resonance imaging, LD: longest diameter

Wilcoxon signed rank test (p<0.0001)

APPENDICES

Appendix A1 and Appendix B1

Results from Tables 1 and 2 statistical analysis of 173 patients

A1. Comparison of 30% RECIST with 30% PR on TVA

		Total volume analysis		
		Response	No response	Total
RECIST response (Gold standard)	Response	123	0	123
	No response	27	23	50
	Total	150	23	173

RECIST : n = 123 responders, Median = -57.1% (IQR: -75.7 to 43.5)

TVA : n = 150 responders, Median = -89.7% (IQR: - 97.8 to 74.6)

Wilcoxon sign rank test p<0.0001

Sensitivity: of all the RECIST responses what proportion will be the responses in the volume TVA method (True Positives)?. = 100% (95% CI: 97.0%-100%)

Specificity: of all the RECIST non responders what proportion will be non responders in the volume TVA method (True Negatives)? = 46% (95% CI: 31.8% to 60.7%)

Positive Predictive Value (PPV) = What proportion of TVA responders are truly responders
via RECIST? = 82% (95% CI: 74.9% to 87.8%)

Negative Predictive Value (NPV) = What proportion of TVA non responders are truly non responders
via RECIST? = 100% (95% CI: 85.2% to 100%)

Appendix B1 Comparison of -30% PR on RECIST with -50% volume on RECIST.

		Volume test		Total
		Response	No response	
RECIST response (Gold standard)	Response	122	1	123
	No response	19	31	50
	Total	141	32	173

LD 30: n = 122 responders, Median = -57.1% (IQR: -75.7 to -43.5)

Vol 50: n = 141 responders, Median = -90.2% (IQR: -97.9 to -80.5)

Wilcoxon signed rank test p<0.0001

Sensitivity: of all the RECIST responses, what proportion will be be responses in the Volume TVA method (True Positives)? = 99.2% (95.% CI: 95.6% to 100%)

Specificity: of all the RECIST non responders, what proportion will be non responders in the TVA method (True Negatives)? = 62% (95% CI:47.2% to 75.3%)

Positive Predictive Value (PPV) = What proportion of TVA responders are truly responders by RECIST? = 86.5% (95% CI: 79.8% to 91.7%)

Negative Predictive Value (NPV) = What proportion of TVA non responders are truly non responders by RECIST? = 96.9% (95% CI: 83.8% to 99.9%)