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Clinical utility of tumour marker velocity of cancer antigen 15–3 (CA 15–3) and carcinoembryonic antigen (CEA) in breast cancer surveillance

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ABSTRACT

Background: Serum tumour markers, cancer antigen 15–3 (CA 15–3) and carcinoembryonic antigen (CEA) are not routinely recommended for detecting breast cancer recurrence and monitoring treatment. In this study, we aim to evaluate the diagnostic accuracy of absolute CA 15–3 and CEA levels and report on the clinical utility of tumour marker velocity in breast cancer surveillance.

Methods: 67 consecutive patients over a 15-year period (1998–2012) with available serial serum CA 15–3 and CEA measurements at recurrence were matched to a control group of patients. Tumour marker velocity was derived from the average change in consecutive tumour marker values over time, expressed in unit/year. Logistic regression analysis was performed to investigate the association between tumour characteristics, tumour marker velocity and disease recurrence.

Results: Using the Youden index values, the optimal cut-off values for absolute CA 15–3 and CEA corresponded to the normal assay reference range while tumour marker velocity values were derived to be 2.5U/mL/year and 1.2ng/mL/year respectively. CA 15–3 velocity > 2.5U/mL/year had the highest AUROC value of 0.85 than CEA velocity alone. When either tumour marker velocity exceeded threshold values, the sensitivity, specificity, negative predictive value and positive predictive value were 94.0%, 73.1%, 92.5%, and 77.8% respectively. In the multivariate logistic regression analysis, having both CA 15–3 and CEA velocity exceeding the cut-off values was shown to be a significant predictor for disease recurrence ($p = 0.01$).

Conclusion: These findings highlighted the clinical utility of serial tumour markers measurements and its velocity in breast cancer surveillance.

Background

The role of serum tumour marker in breast cancer surveillance remains controversial. Its routine use in follow-up strategies for asymptomatic women after treatment of breast cancer is excluded from major international guidelines such as ASCO, ESMO, or NCCN [1–4]. However, there have been several reported clinical utility of serial tumour marker measurements. The main applications are in prognosis and disease monitoring during treatment [5,6]. Although there is a lack of studies to demonstrate an association between early diagnosis of relapse and better outcome, many clinicians still rely on serial tumour marker measurement as a simple adjunctive test that could anticipate the diagnosis of recurrence with a lead time reported to be up to 9 months [7–9]. Of all the serum tumour markers in breast cancer, CA 15–3 and CEA have been the most used and recommended [9–12]. In a recent meta-analysis by Li of 36 studies with 12,993 subjects, it is shown that elevated CA 15–3 or CEA were associated with poor disease-free survival (DFS) and overall survival (OS) [13]. While some authors advocate for the tumour markers to be tested routinely, the extent of such recommendation is however, uncertain, and there are no guidelines for clinicians how to incorporate tumour marker measurement in breast cancer surveillance.

In this study, we investigate the diagnostic accuracy, clinical performance and the clinical utility of the rate of tumour marker

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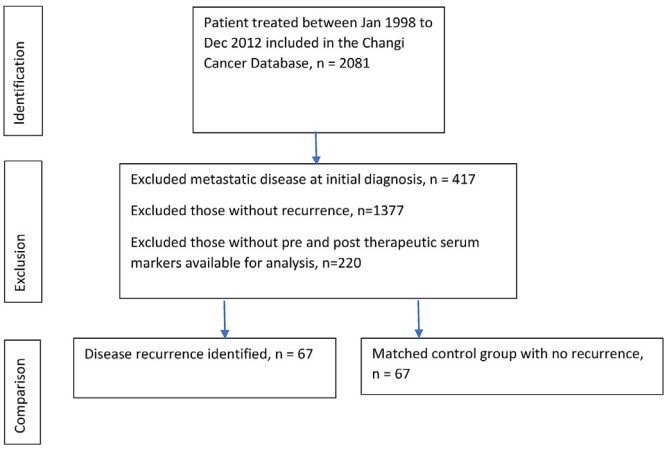

Fig. 1. Patient inclusion diagram.

change, also known as tumour marker velocity, in detecting disease recurrence for breast cancer surveillance. This concept is extrapolated from the use of prostate serum antigen in prostate cancer [14]. Since the introduction of PSA velocity in prostate cancer in 1992, it has become the focus of intense research activity and proposed to be predictive of disease recurrence under the European Association of Urology (EAU) guidelines, but no report of similar tumour marker dynamics has been explored in the field of breast cancer [15].

This case control study aims to illustrate the diagnostic accuracy of tumour markers and propose the clinical utility of derived values of tumour markers velocity to detect early disease recurrence during surveillance while adhering to the Reporting recommendations for tumour Marker prognostic studies (REMARK) [16].

Materials and methods

Clinical data extraction

Data was extracted from a prospectively collected hospital-based breast cancer registry of all patients treated at this institution. It includes patients' demographics, clinicopathological characteristics, treatment and follow up survival data. Clinical staging of breast cancer was classified by the TNM staging system according to the AJCC (American Joint Committee on Cancer Classification, 7th Edition). Data fields are entered by dedicated surgeon physicians and regularly updated upon conclusion of each clinic visit to minimise recall bias.

Study population and follow-up

Data of all female patients with unilateral non-metastatic invasive breast cancer at initial diagnosis between January 1998 and December 2012 at Changi General Hospital were retrieved from the database. We defined the case population by including patients with evidence of disease recurrence and available baseline and serial serum CA 15–3 and CEA measurements. A control group of patients with no evidence of disease recurrence were identified and matched in terms of demographic characteristics Fig. 1.

A case control study design was chosen due to the latency of disease recurrences encountered in breast cancer and to overcome limitations of a relatively small sample size. The study was reported according to the Reporting Recommendations for Tumour Marker Prognostic Studies criteria [16].

Consecutive tumour marker measurements before and after disease recurrence and patterns of recurrence were retrieved. Local recurrence was defined as recurrence within confines of ipsilateral breast, chest wall or regional lymph nodes while distant relapse was defined as recurrence of breast cancer occurring beyond these confines and categorised separately into bone, brain, lung, liver, distant nodes or multiple sites of disease.

Tumour marker assay analysis

Tumour markers CA 15–3 and CEA were captured at diagnosis and retrieved from the database. Laboratory assays were standardised throughout the study period using an automatic electrochemistry luminescence immunoassay system (Roche E170; Roche, Germany). The assay reference values of CA 15–3 and CEA were below 25U/mL and 5.0 ng/mL respectively, and the value was considered elevated or within normal limits for the marker if the level was above or below the cut-off value respectively.

Subsequent measurements of tumour markers were performed at regular intervals as part of routine follow-up according to the treating physicians' preference, usually at 3 to 6 monthly intervals. In cases of disease recurrence, tumour markers were repeated as part of staging investigations.

Tumour marker velocity was calculated by the change in consecutive tumour marker values over time, expressed in unit/year. In cases of disease recurrence, the value of tumour marker at recurrence was taken and the increment from the last recorded value before recurrence was used to calculate tumour marker velocity. In the control group, the last consecutive pair of tumour marker measurements was compared to obtain an average tumour marker velocity. Statistical analysis was performed to investigate the association between tumour characteristics, tumour marker velocity and disease recurrence.

The mathematical formula used to calculate tumour marker velocity; V is as follows

$$Vr = \frac{\mathrm{TM}a - \mathrm{TM}b}{t}$$

where V_r is the velocity in the recurrence group, TM_a is tumour marker level at recurrence, TM_b is tumour marker level before recurrence, t is the time interval between the two.

$$Vc = \frac{\mathrm{TM}l - \mathrm{TM}p}{t}$$

where V_c is the velocity in the control group, TM_l is the last known tumour marker level, and TM_p is the prior reading to that.

An illustration of calculation of tumour marker velocity is shown in examples below.

	CEA level at recurrence, TM_a	Last known CEA level before recurrence, TM_b	Time interval between the two reading, t	Tumour marker velocity, Vr
Patient with recurrence	10 ng/mL	5 ng/mL	6 months	10ng/mL/year
	Last known CEA level, TM_l	Prior CEA level, TM_p	Time interval between the two reading, t	Tumour marker velocity, V_c
Patient in control group	6 ng/mL	5 ng/mL	3 months	4ng/mL/year

Statistical analysis

Statistical analysis was performed with SPSS version 20, Chicago, Illinois. Chi-square test or Fisher's exact test were performed to determine the differences between groups for categorical variables. The optimal cut-off points for the tumour markers at time of recurrence were determined by Youden index values. Univariate and multivariate logistic regression analysis were performed to assess the relationship of patient clinicopathological characteristics and serum CA 15–3 and CEA values and velocity for the risk of disease recurrences. A p value < 0.05 was considered significant in all analysis. The independent variables related to recurrence were confirmed using univariate and multivariate analyses. All of the statistically significant variables in univariate analyses were incorporated into multivariate logistic regression analyses and variables with a P > 0.05 were eliminated.

The study was approved by the Singhealth Centralised Institutional Review Board committee. (Approval number 2015, 2059).

Results

Between January 1998 and December 2012, 2081 patients with breast cancer were treated in our institution. Of which, 1667 patients were non-metastatic at initial presentation. Subsequently, 287 patients (17%) developed disease recurrences. Of these, 220 without pre- and post-therapeutic serum tumour markers were excluded. Therefore, 67 cases with disease recurrence and available serial tumour marker measurements were identified. They were matched with a control group of 67 patients with no recurrence, in terms of demographic characteristics to study the association between tumour markers and risk of developing disease recurrence. The recurrence group had a median follow-up period of 57 months (range 13–146 months), and survival rate of 22.3%. The median disease-free interval for the recurrence group was 33 months (range 19–144). As for the control group, the median follow-up period was 29 months with a 92.5% survival rate.

Matched baseline demographics is shown in Table 1, while Table 2 outlines the clinicopathological characteristics of the two groups.

Elevated serum tumour marker levels as first indicator of disease recurrence, lead time, and pattern of recurrence

In the recurrence group, elevated levels of either one of the tumour markers above assay reference range were observed in 85% of the patients (n = 57). Mean CA 15-3 level was 160.7 IU/mL (range 7.7–2500 IU/mL) and mean CEA level was 39.1 ng/mL (range 1.2–696 ng/mL). 9 (13%) patients had isolated locoregional recurrence. Of the remaining 58 patients, 17 had bone metastasis (25%), 18 had liver (27%), 5 had lung (7%), and 18 had multiple sites of disease (27%).

In 23 patients (34%) with recurrence, elevated tumour marker was the first indicator of disease recurrence before clinical symptoms or detection by any other diagnostic methods. Among these 23 patients, elevated CA 15–3 was the first indicator of relapse in twelve patients, CEA in eight patients, and synchronous rise in both tumour markers were seen in three patients. Raised tumour markers prompted further cross-sectional imaging and detected recurrences with an average lead time of 4months (range between 1 and 12 months). Lead time was calculated based on the time interval between the first occurrence of raised tumour markers and date of diagnosis of disease relapse by clinical finding, radiological with or without pathological confirmation.

Computed tomography (CT) of the thorax, abdomen and pelvis detected the recurrences in majority of the cases (n = 18) while positive emission tomography-CT scan detected the recurrences in two patients, whose recurrence was not detected by conventional CT. Elevated tumour marker was associated more with distant recurrences (n = 20) than locoregional recurrences (n = 3).

In the control group, 4 patients had elevated tumour markers

Table 1
Baseline demographics between recurrence and non-recurrence group.

	All patient (n = 134)	Non-recurrence (n = 67)	Recurrence (n = 67)	p-value
Age, years				
Mean (SD)	55.6 (14.0)	57.9 (14.8)	53.2 (12.9)	P = 0.052
Ethnicity				
Chinese	88 (65.7)	45 (51.1)	43 (48.9)	P = 0.325
Malay	30 (22.4)	12 (40.0)	18 (60.0)	
Others	16 (11.9)	10 (62.5)	6 (37.5)	
Marital status				
Married	84 (64.1)	42 (50.0)	42 (50.0)	P = 0.759
Single	24 (18.3)	11 (45.8)	13 (54.2)	
Divorced/widowed	23 (17.6)	13 (56.5)	10 (43.5)	
Number of children				
Median (IQR)	2 (1, 3)	2 (1, 3)	2 (0, 3)	P = 0.169
Breastfeeding				
No	77 (61.1)	40 (51.9)	37 (48.1)	P = 0.584
Yes	49 (38.9)	23 (46.9)	26 (53.1)	
Age at menarche, years				
Mean (SD)	13.4 (1.8)	13.2 (1.8)	13.6 (1.8)	P = 0.182
Menopause status				
Pre-menopausal	57 (43.2)	27 (47.4)	30 (52.6)	P = 0.598
Post-menopausal	75 (56.8)	39 (52.0)	36 (48.0	
Family history				
No	112 (87.5)	57 (50.9)	56 (49.1)	P = 0.947
Yes	16 (12.5)	8 (50.0)	8 (50.0)	
Oral contraceptive				
No	104 (81.2)	55 (52.9)	49 (47.1)	P = 0.533
Yes	24 (18.8)	11 (45.8)	13 (54.2)	
Hormone replacement				
No	121 (95.3)	61 (50.4)	60 (49.6)	P = 0.437
Yes	6 (4.7)	4 (66.7)	2 (33.3)	

Table 2
Clinicopathological characteristics of study population.

Clinicopathological characteristics	Control	Recurrence	
Tumour status			
T1	25 (67.6)	12 (32.4)	P = 0.017
T2	34 (47.9)	37 (52.1)	
T ≥ 3	8 (33.3)	16 (66.7)	
Nodal status			
N0	40 (71.4)	16 (28.6)	P < 0.001
N1	16 (41.0)	23 (59.0)	
N2	6 (27.3)	16 (72.7)	
N3	5 (31.3)	11 (68.7)	
TNM Staging			
I	22 (68.8)	10 (31.2)	P = 0.001
II	30 (58.8)	21 (41.2)	
III	14 (28.6)	35 (71.4)	
Histological grade			
1	18 (81.8)	4 (18.2)	P = 0.004
2	15 (40.5)	22 (59.5)	
3	33 (45.2)	40 (54.8)	
Nottingham Prognostic Index			
Good	19 (76.0)	6 (24.0)	P = 0.003
Moderate	30 (53.6)	26 (46.4)	
Poor	17 (34.7)	32 (65.3)	
Vascular invasion			
No	34 (58.6)	24 (41.4)	p = 0.078
Yes	31 (43.1)	41 (56.9)	
Histology			
Ductal	56 (47.5)	62 (52.5)	P = 0.110
Others	11 (68.8)	5 (31.2)	
ER Status			
Negative	15 (53.6)	13 (46.4)	P = 0.638
Positive	51 (48.6)	54 (51.4)	
PR status			
Negative	19 (43.2)	25 (56.8)	P = 0.296
Positive	47 (52.8)	42 (47.2)	
Her2 status			
Negative	53 (60.2)	35 (39.8)	P = 0.054
Positive	12 (40.0)	18 (60.0)	

G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated.
T1: ≤ 2 (cm); T2: 2< but ≤5 (cm); T3: >5 (cm); T4: invasion of chest wall and skin.
N0: no regional lymph node metastasis; N1: metastasis involving 1–3 lymph nodes; N2: metastasis involving 4–9 lymph nodes; N3: metastasis involving ≥10 lymph nodes.
Nottingham Prognostic Index = (0.2xS)+N + G, where S is tumour size in centimetre, N is nodal status, G is histological grading, Good <3.4, Moderate 3.4<x < 5.4, Poor= >5.4.
ER: estrogen receptor.
PR: progesterone receptor.
Her2: human epidermal growth factor receptor 2.

above reference range despite no conclusive evidence of disease recurrence on CT and bone scan, translating into a false positive rate of 6%. 1 patient with raised CEA had findings of pancreatic intraductal papillary mucinous neoplasm and another had liver cysts, which are known possible causes of raised CEA. While no apparent cause was identified for the other 2 patients with raised CA 15–3, we note that their pre-therapeutic values were elevated which did not return to normal values, even after 2 years of treatment.

Cut-off value of CA 15–3 and CEA levels at recurrence and diagnostic accuracy of elevated tumour markers

Statistical analysis using Youden index values were performed to determine the optimal cut-off values of tumour markers at time of recurrence. The optimal cut-off values for CA 15–3 and CEA levels at time of recurrence were identified as 24.8U/ml and 4.3 ng/mL respectively. Using these new cut-off values, we divided patients into elevated and normal groups for further analysis of diagnostic accuracy. The results are presented in Table 3. Based on the area under receiver operating characteristic curve, both CA 15–3 and CEA have comparable discriminative ability and diagnostic accuracy in this study cohort.

Cut-off value and diagnostic accuracy of tumour marker velocity

Based on Youden index values, the optimal cut-off values for CA 15–3 velocity and CEA velocity were derived to be 2.5U/mL/year and 1.2ng/mL/year respectively. Due to acceptable AUROC values of both characteristics, we compared the discriminative ability of a combined criterion of having either tumour marker velocity raised above the cut-off values.

In terms of tumour marker velocity, using a single criteria of CA 15–3 velocity > 2.5U/mL/year alone had the highest discriminating ability with an AUROC value of 0.85 compared to CEA alone or a combined criterion of either tumour markers. CA 15–3 velocity > 2.5U/mL/year had highest positive predictive value of 83.1%, while in contrast, the combined criteria of having neither tumour marker velocity exceed the threshold, conferred the highest sensitivity and negative predictive value as shown in Table 4.

Finally, we correlated the association of cancer recurrence with tumour TNM staging, and previously validated Nottingham prognostic index against tumour marker velocity. Based on the ROC curve in Fig. 2, CA 15–3 velocity > 2.5U/ml/year remained the strongest discriminating criteria for cancer recurrence.

Using univariate analysis, patients with either CA 15–3 velocity >2.5U/mL/year or CEA velocity >1.2ng/mL/year was 43 times as likely to have cancer recurrence as compared to patient with & CA 15–3 velocity ≤ 2.5U/mL/year and CEA velocity ≤ 1.2ng/mL/year (OR: 42.9, 13.6, 134.9, p < 0.001). Multivariate logistic regression adjusting for tumour pathological characteristics showed that patients meeting the combined criteria of either CA15-3 or CEA tumour marker velocity (CA 15.3 velocity >2.5U/mL/year or CEA velocity >1.2 ng/mL/year) are at 73 times likely for cancer (OR: 73.4 95%CI (12.0, 334.6), p < 0.001) as shown in Table 5.

Discussion

CA 15–3 and CEA are complementary in their diagnostic characteristics

Previous studies have shown that CA 15–3 and CEA are the two most sensitive and commonly used tumour markers in breast cancer [12,17–19]. Our current study supports that both CA 15–3 and CEA have comparable discriminative ability for cases of disease recurrence with similar AUROC value at 0.84. The cut off values determined by the Youden index was close to the upper limit of the normal assay reference range and this observation was similar to other studies, which reported on their prognostic value for overall survival and disease-free survival [5,6,8,12]. Our study shows that the two tumour markers are complementary to each other. While CEA has a higher sensitivity of 75%, CA 15-3 has a higher specificity of 97%. The combination of the two tests yielded the highest diagnostic accuracy characteristics. Since tumour markers assessment is quick, relatively simple to perform, and have high positive predictive values, regular measurement of these two serum tumour markers could aid in early detection of disease recurrences. Further evaluation for locoregional or distant metastasis is justified if either of the absolute tumour marker value exceeds the normal reference range during surveillance.

Limitations in interpretations of persistently elevated tumour markers may be overcome by tumour marker velocity

We recognise the limitations of the tests' sensitivity and false

Table 3
Discriminative ability of absolute cut-off values of CA 15–3 and CEA levels at recurrence and diagnostic accuracy of elevated tumour markers.

	AUROC (95% CI)	Sensitivity	Specificity	NPV	PPV
Elevated CA 15–3 >24.8U/mL	0.84 (0.76, 0.91)	71.6	97.0	77.4	96.0
Elevated CEA >4.3 ng/mL	0.84 (0.76, 0.91)	75.0	92.5	80.5	90.0
Elevated CA 15–3 > 24.8U/mL or CEA >4.3 ng/mL	0.92 (0.86, 0.97)	93.9	89.6	93.8	89.9

Table 4
Diagnostic accuracy of raised CA 15–3 and CEA tumour marker velocity for cancer recurrence.

	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
CA 15–3 velocity >2.5 U/mL/year	0.85 (0.78, 0.91)	88.1	82.1	87.3	83.1
CEA velocity >1.2ng/mL/year	0.79 (0.71, 0.88)	73.8	85.1	78.1	81.8
Either CA 15–3 or CEA tumour marker velocity above threshold values	0.84 (0.76, 0.91)	94.0	73.1	92.5	77.8

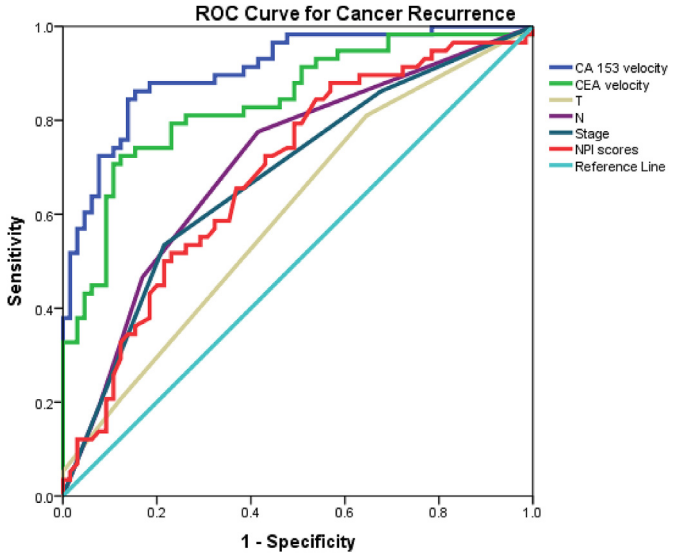

Fig. 2. Receiver operator characteristics curve for CA 15–3 and CEA tumour marker velocity exceeding threshold values of 1.2ng/mL/year and 2.5U/mL/year respectively against tumour status, nodal status, TNM staging and NPI scores.

positive rates, leading to some patients being subjected to unnecessary investigations. Hence our study attempts to refine the clinical utility of tumour markers by introducing the concept of tumour marker velocity, which is the rate of tumour marker change. Our study analysed the correlation of elevated tumour marker velocity with breast cancer disease recurrence. To our knowledge, this study is the first of its kind to identify a strong association between tumour marker velocity and breast cancer disease recurrence [12,13]. The authors postulate that the implications of such finding would be most relevant to help distinguish between clinically significant elevation from baseline variations of the tumour markers. The latter would otherwise not require further investigations. This phenomenon is often attributed to tumour biology or treatment effects. However, when serial tumour marker measurements continue to exceed the cut-off values, this study suggests that tumour marker velocity may aid in deciding between additional imaging investigations or observation. For the latter, trending the respective tumour markers at a shorter interval with appropriate clinical follow-up may be considered.

Proposed clinical utility and management algorithm

Based on our findings, we propose the following management algorithm in patients with elevated tumour markers. We suggest to first exclude locoregional recurrence and investigate for other causes associated with isolated raised CEA due to its lower specificity compared to CA 15–3. In the absence of locoregional recurrence and other causes of raised CEA, investigations to look for occult distant recurrences are recommended. If the workup remains negative for disease recurrence, the patient may be monitored more closely at 3 to 4 monthly intervals with clinical review and serial tumour markers measurement. The derived tumour marker velocity may then be used to guide the need to repeat radiological investigations to look for recurrences. When neither tumour markers velocity exceeds the threshold levels, the recurrence rate is low, and thus further investigations may be avoided. This is summarised in Fig. 3.

Given the average lead time of 4 months, subsequent surveillance is recommended at 3 to 4 monthly intervals, in order to identify early subclinical disease recurrence. The longest lead time observed in one of our patients was 12 months. Hence, we suggest that serial tumour marker measurements be done every 3 to 4 monthly, for at least 1 year. However, the current study is unable to

Table 5
Association between CA 15–3 velocity, CEA velocity, either CA 15–3 or CEA velocity and cancer recurrence after adjusting for tumour clinicopathological characteristics.

	Recurrence		Unadjusted		Adjusted	
	No (%)	Yes (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
CA 15–3 velocity						
<=2.5U/mL/year	55 (87.3)	8 (12.7)	REF	P<0.001		
>2.5U/mL/year	12 (16.9)	59 (83.1)	33.8 (12.9, 88.9)			
CEA velocity						
<=1.2ng/mL/year	57 (78.1)	16 (21.9)	REF	P<0.001		
>1.2ng/mL/year	10 (18.2)	45 (81.8)	16.0 (6.6, 38.7)			
Combined criteria either CA 15–3 or CEA velocity						
CA 15–3 $\leq$ 2.5 **&** CEA $\leq$ 1.2	49 (92.5)	4 (7.5)	REF	P < 0.001	REF	P < 0.001
CA 15–3 >2.5 **or** CEA >1.2	18 (22.2)	63 (77.8)	42.9 (13.6, 134.9)		73.4 (12.0, 448.6)	

address patients with persistently elevated tumour markers beyond the first year and without evidence of recurrence.

Clinical utility in early disease detection, providing reassurance and limitations

In our study cohort, 34% of the recurrences were detected based on raised tumour marker as the first indicator. This finding is similar to other studies, reporting a 40–60% detection rate of recurrence by raised tumour marker profile, with lead time up to 18 months prior to any clinical and/or radiological evidence of disease [18–20]. These disease recurrences would not have been diagnosed in otherwise asymptomatic patients, and hence not been treated with systemic therapy earlier. Given the advances in systemic treatment, and ongoing research trials targeting metastatic breast cancer, we postulate that the earlier detection might have a significant impact on patients' management and eventual prognosis [21,22]. However, this study was not designed to look at outcomes with early detection of recurrences.

The use of either absolute values or the combined criteria of having both tumour marker velocities below threshold values may be useful for its negative predictive value to reassure patients during surveillance when coupled with a comprehensive and unremarkable clinical review. The authors suggest obtaining a pre-therapeutic tumour marker measurement as baseline value and at regular intervals after completion of their primary therapy. This may be a useful adjunct but not to replace thorough clinical follow-up.

In this study, a handful of cases with raised tumour markers did not have disease recurrence (four patients in the control group). The authors recognise that the false positive rate of 6% may result in additional anxiety and cost from additional investigations. Therefore, it is suggested that patients be adequately informed about the limitations of routine measurements of tumour markers as part of

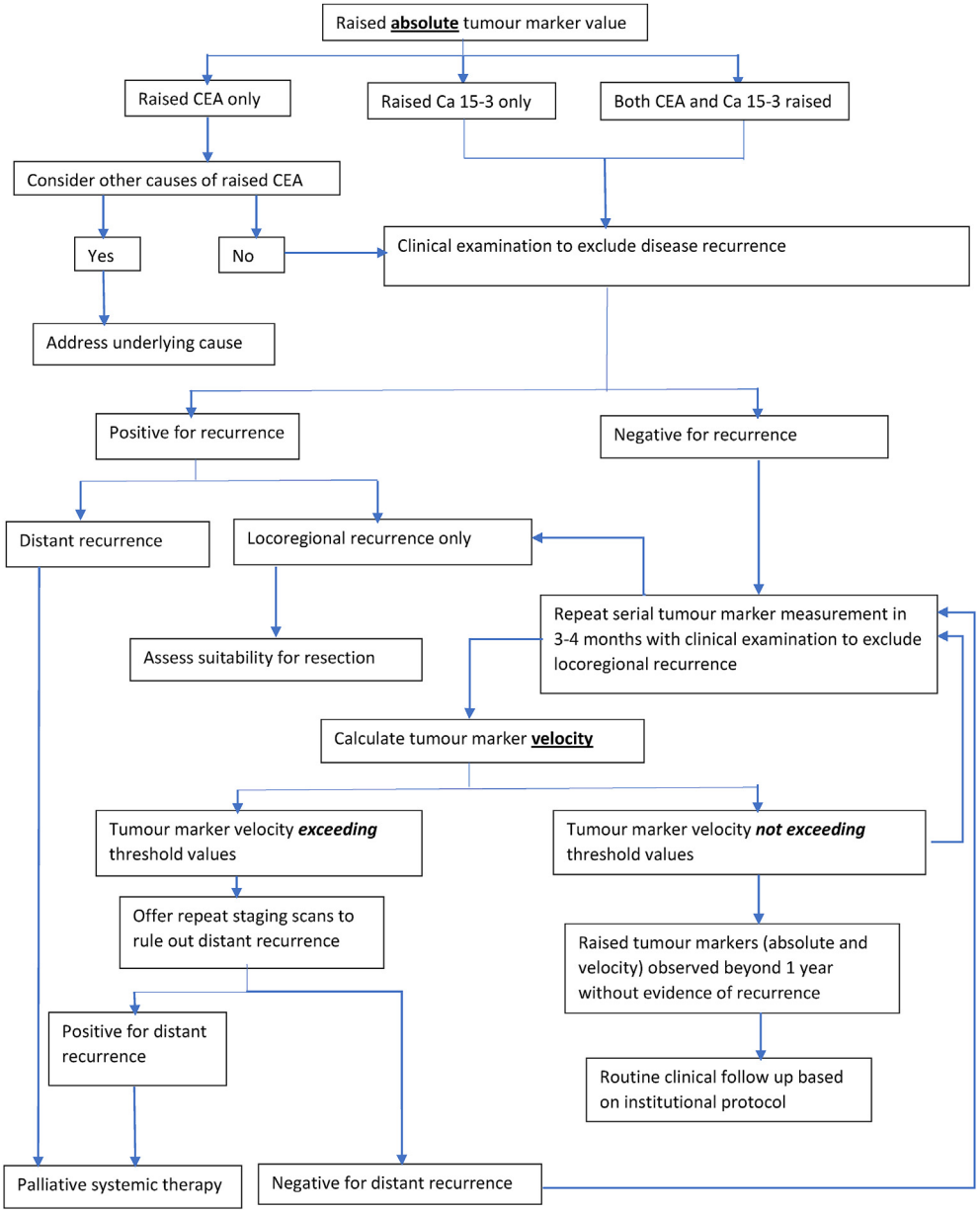

Fig. 3. Proposed management algorithm for raised tumour marker in breast cancer surveillance.

surveillance.

The authors recognise that this retrospective analysis is subjected to selection bias and has a relatively small sample size due to limited availability of serial tumour marker measurements for analysis. This is largely due to the inconsistent use of serial tumour marker measurements for surveillance due to lack of evidence of its usefulness. The limitations in sample size also translated into a large confidence interval despite statistically significant results. By using multivariate logistic regression analysis, the study adjusted for the effects of known confounding factors but effects of unknown confounding factors were not accounted for. Recognising these limitations, this study has nonetheless showed potential utility of CA 15–3 and CEA values and velocities in guiding clinicians in surveillance of patients with breast cancer.

Conclusion

Our study has found a strong association between tumour marker velocity and breast cancer recurrence. Tumour marker velocity may be a useful adjunct to absolute tumour marker values to distinguish between clinically significant elevated tumour markers from baseline variation. This can help to refine the clinical utility of serial CA 15–3 and CEA measurements in breast cancer surveillance.

Contribution

Study concepts: JX Hing, CW Mok, SM Tan. Study design: JX Hing, CW Mok, SM Tan. Data acquisition: All. Quality control of data and algorithms: All. Data analysis and interpretation: JX Hing, CW Mok, PT Tan, SM Tan. Statistical analysis: PT Tan, JX Hing, CW Mok. Manuscript preparation: JX Hing, CW Mok, PT Tan, SM Tan. Manuscript editing: JX Hing, CW Mok, SM Tan. Manuscript review: JX Hing, CW Mok, SM Tan.

Ethical approval for research

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Declaration of competing interest

There is no conflict of interest to disclose.

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The study was approved by the Singhealth Centralised Institutional Review Board committee. (approval number 2015, 2059).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.05.005.

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