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Published in:
Radiation Protection Dosimetry

DOI:
10.1093/rpd/ncv417

2016

Document Version:
Peer reviewed version (aka post-print)

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Growth rates of primary breast cancers

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ABSTRACT

This study aimed to investigate the growth rate of 31 consecutive invasive breast cancers based on volume measures on at least two serial mammograms and its relation to histopathological findings. The average tumour volume doubling time in all invasive breast cancer subtypes was 282 days (range 46-749 days). Grade III breast cancers had a significantly shorter average tumour volume doubling time of 105 days (range 46-157 days) compared to grade I & II tumours (average of 296 days, range 147-531 days and average of 353 days, range 139-749 days, respectively) (p = 0.002). Multiple linear regression identified that tumour volume doubling time was positively associated with patient age, histological grade and progesterone receptor expression, and inversely associated with axillary lymph node involvement, HER2 and Ki-67 expression ($p < 0.001$). In conclusion, tumour volume doubling time as estimated on serial mammography may provide important prognostic information relevant for clinical decision-making.

INTRODUCTION

Mammographic images contain potentially useful prognostic information on the growth rate of malignant breast tumours, information that is rarely used in treatment planning. This is particularly true for patients participating in mammography screening programmes that imply repeated examinations at regular intervals, but also applicable to symptomatic patients provided earlier mammograms are available. From such an image bank it is possible to estimate the tumour volume doubling time (t_D), i.e. the time it takes for a tumour to increase its volume two-fold. One way to estimate the t_D is to measure the tumour diameter at diagnosis and on the preceding mammogram assuming that the volume-doubling time is constant and the tumour approximately spherical in shape[1]. Some tumours can retrospectively be tracked on numerous serial mammograms, generating growth curves, which can be described by either exponential, logistic or Gompertz functions[2-4].

Several studies have estimated the volume doubling time of breast cancers based on mammograms[1,2,5-11], however, few have correlated t_D with histopathological characteristics[2,7,9-11]. To the best of the authors' knowledge, only one study based on ultrasound has correlated t_D with tumour characteristics such as the oestrogen receptor (ER), the progesterone receptor (PR), the human epidermal growth factor receptor 2 (HER2) and Ki-67 expression[12].

The purpose of this study was to estimate the growth rates of breast cancers based on information from mammograms and its relation to mammographic and pathological tumour characteristics.

MATERIALS AND METHODS

Patient population

One-hundred-eleven consecutive biopsy-proven breast cancers were diagnosed at Skåne University Hospital, Malmö from August 1st to December 31st 2014. All the patients' medical journals and mammograms were retrospectively reviewed. The Regional Ethical Review Board at Lund University approved the study (Dnr 2015/105).

The exclusion criteria were as follows: no invasive tumour i.e. patient only presenting with ductal carcinoma *in situ* (DCIS) (n = 16); invasive tumour less than 5 mm on diagnosis (n = 5); no previous mammogram or more than three years to prior mammogram (i.e. more than two screening rounds apart) (n = 41); not a measureable tumour extent due to following reasons: no visible tumour; too dense breast to delineate tumour border; multifocality and/or pronounced *in situ* component (n = 18); leaving 31 eligible cases for tumour growth rate estimation.

Growth rate estimation

One experienced radiologist (I.A.) and one medical physicist (D.F.) measured in consensus the largest tumour diameter on each mammogram using a calibrated built-in software tool (Syngo Mammoreport; Siemens, Erlangen, Germany) (Figure 1). Caution was exercised to measure reproducibly, consistently and always in the same projection between the serial mammograms. The choice of projection was based on

where the tumour mass was most clearly discerned. In cases of spiculated lesions the nucleus of the tumour was measured[13].

Twenty-three patients had one prior mammogram. Of these, twenty were discovered at regular screening and three were interval cancers. The growth rate, expressed as $t_{D,}$ was estimated from measurements based on the assumption of constant exponential tumour growth:

$$t_D = \frac{\ln 2\,(t_1 - t_2)}{3\,(\ln d_1 - \ln d_2)}$$

where d_1 and d_2 are the tumour diameters at times t_1 and t_2, respectively.

Eight patients had more than one prior serial mammogram where the tumour could be measured retrospectively, which made it possible to construct growth curves. Two functions were used to model tumour growth: the exponential growth function and the Gompertz growth function. Exponential growth has the form:

$$V(t) = c * e^{k*t}$$

where *c* is the start volume, *k* is the growth rate, *t* is the time and assuming a spherical tumour shape, *V(t)* can be calculated from the tumour diameter, *d(t)*, by:

$$V(t) = \frac{4\pi}{3}\left(\frac{d(t)}{2}\right)^3$$

Gompertz growth has the form:

$$V(t) = a * e^{-b*e^{-k*t}}$$

where a is an asymptote, *b* sets the displacement along the time axis, *k* is the growth rate and *t* is the time.

In order to calculate tumour growth rates in patients without visible abnormality on the previous screening mammogram, an initial 5-mm tumour size was assigned if the diagnosed tumour was located in fatty area and a 10-mm initial tumour size was assigned if the diagnosed tumour was located in dense area[5,14]. These assigned sizes represent the maximum size of a tumour that could potentially have been missed at the time of screening. However, in this study it was only done for the three interval cancer cases.

Pathological characteristics

Information on tumour histology, staging, and prognostic factors was retrieved from pathology reports (Skåne University Hospital, Malmö, Sweden). All patients underwent primary surgery according to regional guidelines including mastectomy or breast-conserving surgery as well as sentinel node biopsy. In patients with metastatic sentinel node, axillary clearance was performed. Axillary node involvement was classified as positive in the presence of micro- and macrometastases, as negative in the presence of only isolated tumour cells or no node involvement, or not applicable (N/A). The histological subtype of breast cancers was classified according to WHO guidelines[15]. All tumours were graded according to the Nottingham (Elston/Ellis) grading system[16]. Vascular invasion was determined by immunohistochemistry (IHC) using antibodies against CD34 and CD31 (BD Pharmingen) to detect blood vessels and podoplanin/D2-40 (Signet antibodies) to detect lymphatic vessels. ER- and PR positivity was evaluated by IHC with monoclonal antibodies (Ventana/Roche) with a cutoff for positivity set to > 10 % according to current Swedish clinical guidelines. HER2 status was determined by fluorescence in situ hybridization according to international standards[17]. Ki-67 expression was measured with the

antibody MIB1 (DAKO) and the cutoff for positivity was set to > 20 % positively stained tumour cells.

Statistical analysis

The growth curve fitting of exponential- and Gompertz functions was done in MATLAB (version r2014b, Mathworks, Natick, MA, USA) by iteratively minimizing the root mean square error (RMSE) for the corresponding model fits. Data were analysed using the SPSS software (version 22; IBM Corp., Armonk, NY, USA). Independent samples t-test was performed with regards to t_D. One-way analysis of variance (ANOVA) was used to determine whether there was a statistically significant difference in t_D stratified according to the histological grades of the tumours.

Multivariate analysis using backward stepwise ($p > 0.1$) multiple linear regression was performed with t_D as dependent variable and the following possible independent variables: patient age, mammographic and histopathological characteristics such as tumour size at diagnosis, histological tumour type, vascular invasion, tumour stage, axillary lymph node involvement, histological grade, oestrogen receptor, progesterone receptor, HER2 and Ki-67 expression. *P* values of < 0.05 were considered statistically significant.

RESULTS

Descriptive data of the 31 patients can be seen in Table 1. The estimated average t_D of all cancers was 282 ± 167 days (range 46-749 days) (Figure 2). Lobular carcinomas had significantly longer average t_D compared to ductal types: 431 days (range 229-

749) days) *vs*. 236 days (range 46-531 days), respectively ($p = 0.007$). Grade III breast cancers had a significantly shorter average t_D of 105 days (range 46-157 days) compared to grade I & II tumours (average of 296 days, range 147-531 days and average of 353 days, range 139-749 days, respectively) ($p = 0.002$). Patients with axillary lymph node involvement had significantly shorter t_D compared to lymph node negative patients: 146 days (range 46-326) days) *vs*. 334 days (range 123-749 days), respectively ($p = 0.005$).

Exponential and Gompertz growth functions were applied to data for those cases (n = 8) that had more than two measurable tumour diameters (Figure 3). The average normalized RMSE was slightly lower, although not significantly ($p > 0.05$), for the Gompertz fit, (RMSE = 0.035), compared to the exponential fit (RMSE = 0.062), indicating that the current stage of tumour growth was better modelled by the Gompertz function for the eight cases in this study.

The three interval cancers had significantly shorter t_D of 96 days compared to the average t_D of 302 days for the remaining cases ($p < 0.039$) (Figure 4).

Multiple linear regression identified that t_D was positively associated with patient age, histological grade and PR expression, and inversely associated with axillary lymph node involvement, HER2 and Ki-67 expression ($p < 0.0001$). There was a strong correlation between the predictors tumour stage and axillary lymph node involvement ($r = 0.919$, $p < 0.0001$). Because of this multicolinearity, tumour stage was excluded in the regression model. Ki-67 expression was the strongest univariate variable explaining t_D ($R^2 = 0.43$, $p < 0.0001$).

DISCUSSION

In this study it was found that the growth rate of primary breast cancers vary by a factor as much as 20 from very fast growing to slow growing tumours (Figure 2). The Ki-67 protein, which increases as the cells prepare to divide into new cells, was found to be the strongest univariate predictor of growth rate. This seems rational as the growth rate of breast cancer is the net result of cell reproduction rate and growth inhibiting factors on the other side[18].

The estimated average t_D of 282 days in this study was in the range of other reported studies (105-327 days)[1-3,6-12]. Previous reporting of tumour growth and histopathological findings are inconsistent and some of these studies use outdated histopathological measures making a direct comparison difficult. Nevertheless, patient age[8,9,11], axillary lymph node involvement[2,7] and advanced TNM stage[11,12] have been shown to correlate with t_D. Kusama et al. and Kuroshi et al. both found that tumour volume doubling time correlated with survival[9,11]. In this study, younger patients with grade III tumours, axillary lymph node involvement and advanced TNM stage, were estimated to have the shortest t_D. In addition, this is the first mammographic study to the best of the authors' knowledge, which has associated tumour characteristics such as PR, HER2 status and Ki-67 expression with t_D. Ryu et al. have shown that t_D, assessed by ultrasound, is associated with molecular breast cancer subtype, with ER-positive tumours showing the slowest growth, HER2-positive tumours with intermediate growth and triple negative tumours showing the fastest growth[12]. Additionally, in univariate analysis, ER-, PR status and Ki-67

expression were significantly associated with t_D, however, patient age, histological grade, HER2 status and axillary lymph node involvement were not[12].

The assumption of an exponential growth curve with constant doubling times proved to give a good estimate of breast cancer growths as it did not differ significantly from the Gompertzian model. It could be hypothesized that tumours visible during early imaging phase (< 35 mm) have growth rates mostly governed by the cell reproduction rate of the given tumour cells. This results in an exponential growth with constant doubling times and as a consequence the fit of the S-shaped Gompertzian function found a local RMSE minimum that accurately modelled the exponential early growth rate phase excluding the late growth rate phase when growth velocity is likely to decrease with the increasing burden on the tumour (by factors such as limited nutrition etc.). This was true for all but, notably, one smaller tumour in the late decelerating growth rate phase where it can be seen that the Gompertz function has a distinct S-shape, modelling growth in a manner which is notably different from the exponential approximation (Figure 3). One problem with the modelled Gompertzian function was that no upper limit constraint (parameter a) was set, representing a bounded growth. Future work will involve a generalized logistic function with a upper limit constraint describing the average maximum achievable tumour volume[3,19,20].

Consecutive cancer patients at Skåne University Hospital in Malmö during August and December 2014 were included in this study, thus minimizing selection bias. The main limitation in this study was the small sample size due to the large exclusion of women with no prior mammograms (n = 41). Additionally, women with not

measurable tumours (n = 18) could likely comprise faster growing tumours biasing the average t_D towards slower-growing tumours.

The method of estimating the tumour growth rate based on mammograms is subject to various sources of error. An assumption was made that radiologically conspicuous densities were retrospectively defined as carcinomas, even though histologically a carcinoma was proven only on diagnosis. Factors such as positioning and breast compression differ between mammograms of the same breast; however, these errors can be minimized if it is possible to construct growth curves. Regarding those cases when the tumour cannot be precisely defined, i.e. when a discrepancy between mammographic and pathologic size occur; it is not necessary to obtain a correct mammographic size, it is sufficient that the deviations from correct measurement are reproducible and consistent with each mammogram when calculating the tumour growth rate based on exponential growth[2]. Also, the measured diameter was used to estimate t_D based on a spherical tumour shape, but a better approximation might have been to assume an ellipsoid shape, however, the average difference between calculated growth rates of the two shape assumptions is small and varies only by a couple of days[7]. It is also worth mentioning that in order to calculate tumour growth rates for patients without visible abnormality on the previous screening mammogram, an initial tumour size can be assigned depending on the location of the tumour. By setting a fixed upper size limit (5 mm and 10 mm, respectively) it is possible that the t_D may have been slightly underestimated in these cases as the tumours could well be smaller. Although applicable for all cases, this was only applied to the patients presenting interval cancer and not for the serial mammography cases, where the term not measureable was used if the tumour was not visible.

The ability to correlate static pathological tumour characteristics and dynamic radiological observations in terms of growth rates may add prognostic value to current prognostic markers[21]. Furthermore, the growth rate of tumours is an important variable input in many models dealing with the planning and evaluation of screening programmes[20], thus, a reliable t_D is necessary to estimate benefits and harms from related terms such as length bias and lead time[22,23]. Because of the wide span of t_D, the very fast growing cancers will only rarely be observed with the intervals used in current breast cancer screening programmes and the very slow growing cancers could be subjected to overdiagnosis, resulting in overtreatment.

Online websites for calculating chest nodules volume doubling times can be found on the internet based on the same equations as described in this work, which should make it easy to implement, when possible, the calculation of t_D in the clinical mammography routine work. It could also be a useful metric when tracking tumours during neoadjuvant therapy. The information gained could for instance state that a tumour is still increasing in size but at a decreased growth rate.

It is also worth mentioning that “early” detection during screening is a somewhat misleading word. By extrapolating from the exponential growth function it takes about 30 tumour volume doubling times for a 10 μm tumour cell to reach a tumour size of 10 mm, i.e. on average 30 x 282 ≈ 23 years, assuming constant doubling time, before it is detectable on a mammogram.

In conclusion, it was observed that the growth rate of breast cancers vary from very fast growing to slow growing tumours and that the growth rate was associated with patient age, histological grade, PR expression, axillary lymph node involvement, HER2 and Ki-67 expression. Ultimately, t_D could be incorporated in the multivariate biomarker panel that guides clinical treatment strategies today.

FUNDING

This work was supported by Governmental funding of clinical research within the National Health Service [2014/413 to D.F.].

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Table 1. Selected patient- and tumour characteristics of the 31 patients.

Age (years)*	62 ± 12 (42-87)
Tumour size at diagnosis (mm)*	19.5 ± 13.4 (7-80)
Characteristics	No. (%)
Histological type	
Ductal	23 (74)
Lobular	7 (23)
Other	1 (3)
Histological grade	
I	8 (26)
II	16 (52)
III	7 (22)
Axillary lymph involvement	
Positive	7 (23)
Negative	23 (74)
N/A	1 (3)
Oestrogen receptor†	
Positive	23 (74)

Negative	8 (26)
Progesterone receptor[†]	
Positive	21 (68)
Negative	10 (32)
HER2 receptor	
Positive	4 (13)
Negative	27 (87)
Ki-67 expression[†]	
High	21 (68)
Low	10 (32)

[*]Mean value, standard deviation and range.

[†]Dichotomized values. Oestrogen and progesterone cutoff value at 10% and Ki-67 at 20%.

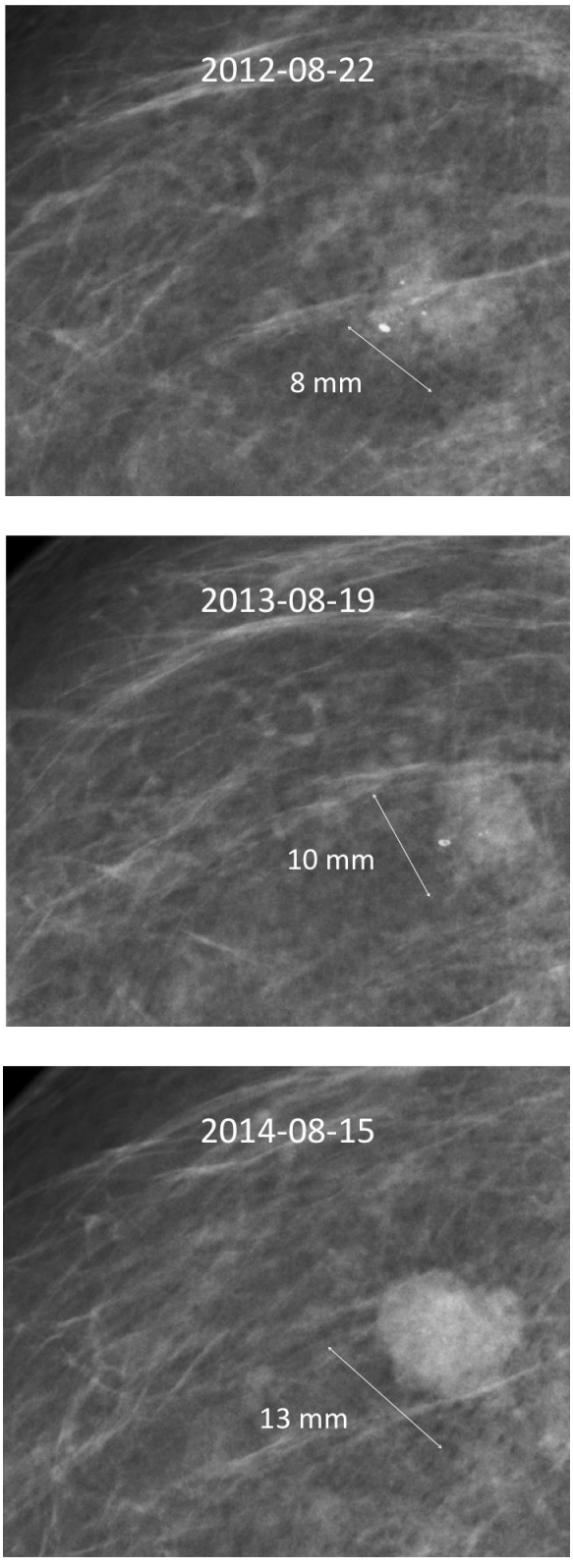

Figure 1. A 66-year-old woman with a measurable tumour on three serial mammograms. Ductal type, grade II, triple negative, Ki-67 score of 30% and estimated t_D of 344 days.

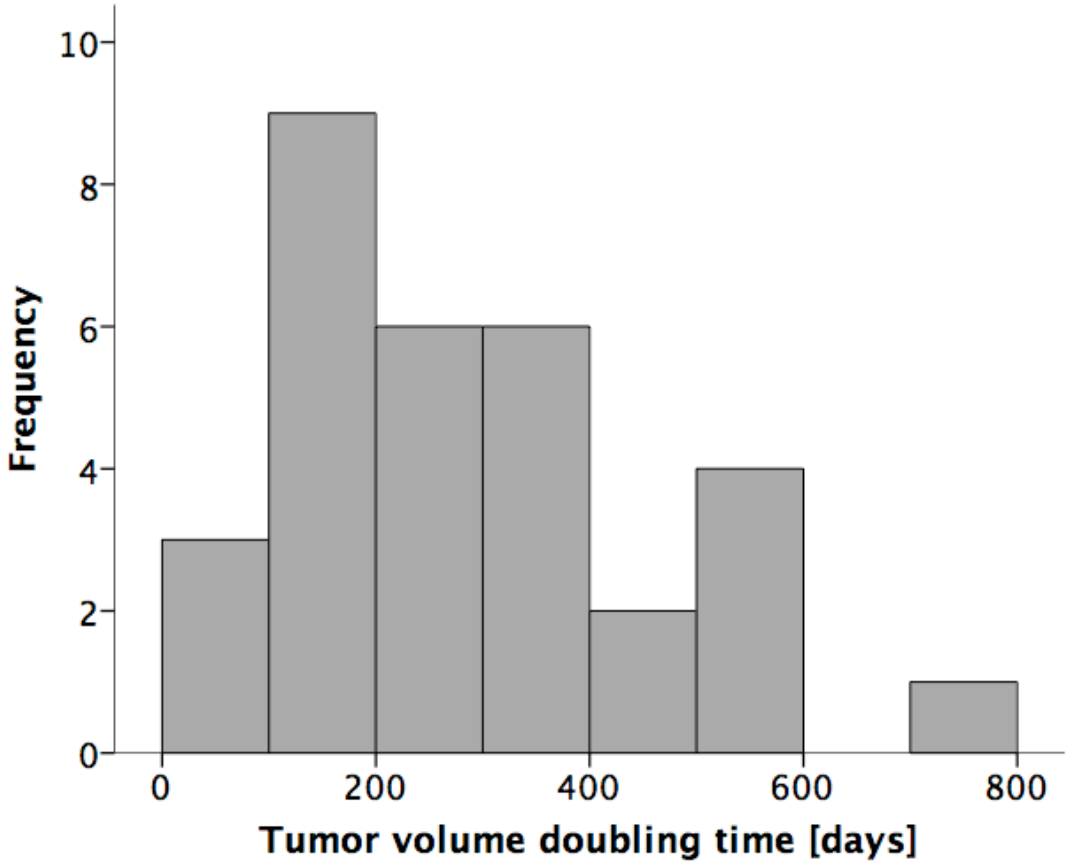

Figure 2. Histogram of the tumour volume doubling time of 31 breast tumours.

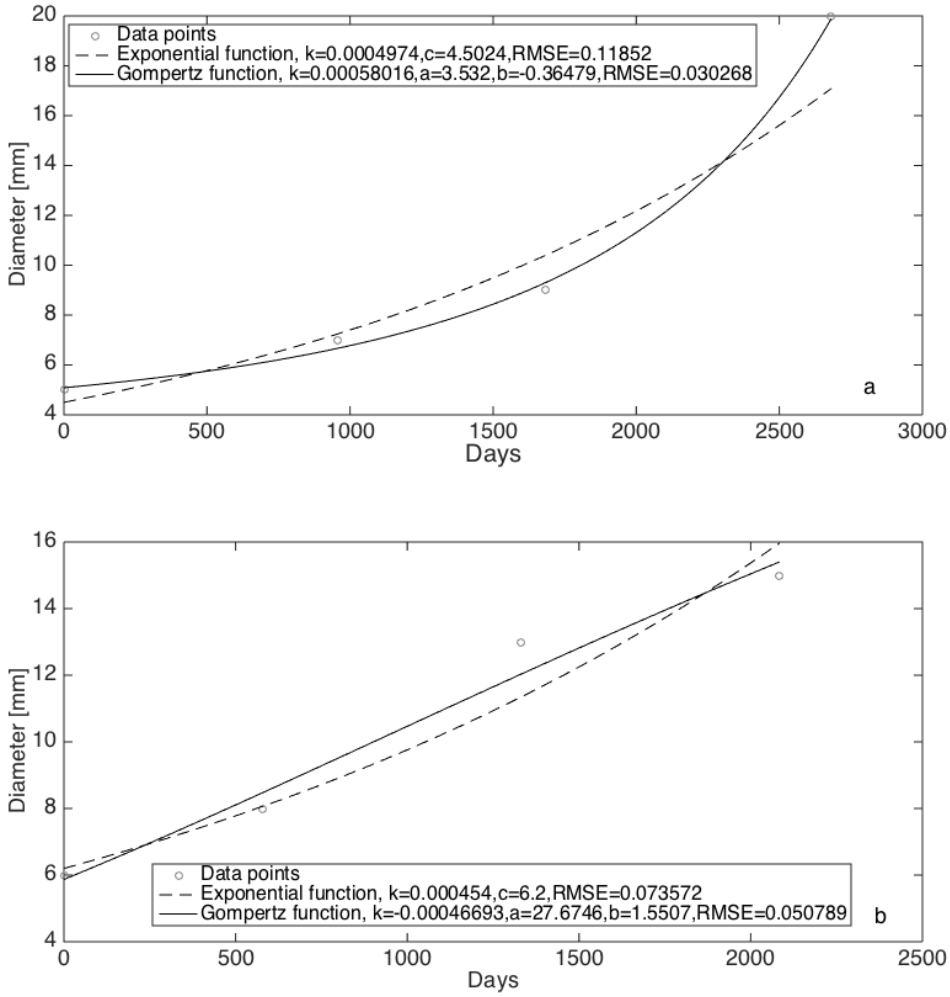

Figure 3. Example of tumour growth curves described by an exponential and a Gompertz function, respectively (a,b). In (b) the Gompertz function is modelled in the late decelerating growth rate phase.

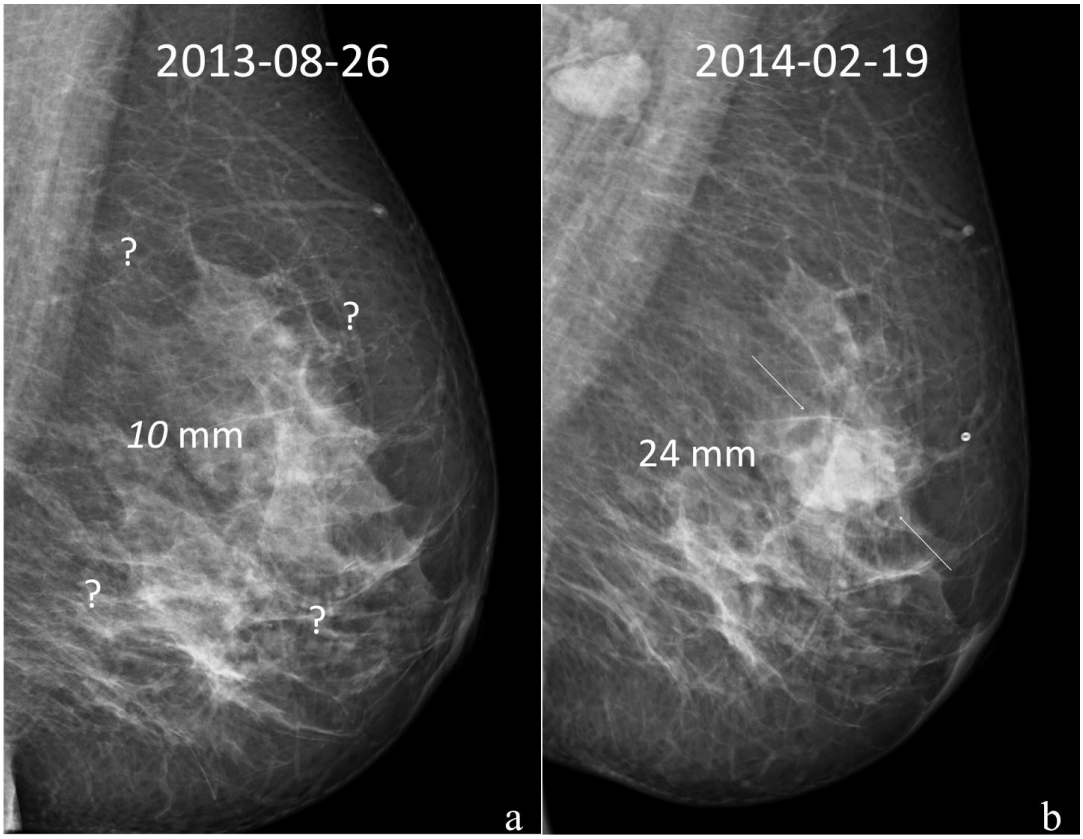

Figure 4. A 50-year-old woman presenting mammographically with a 24 mm interval cancer of ductal type, grade III, oestrogen and progesterone negative, HER2 amplified and Ki-67 score of 70% (b). By assuming a 10 mm size at previous mammogram (a) t_D was estimated to 47 days.