Risk of metastasis in breast cancer through delay in start of primary therapy

Kathrin Halfter,* Anne Schlesinger-Raab, Gabriele Schubert-Fritschle, and Dieter Hölzel

Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig-Maximilians-University (LMU), Marchioninistraße 15, 81377, Munich, Germany

The Lancet Regional Health - Europe 2023;29: 100645

Published Online 1 May 2023

https://doi.org/10.1016/j.lanepe.2023.100645

COVID-19 has led to treatment shortages and delays. Under these extraordinary circumstances oncologic procedures and treatments had to be postponed. In most cases no patients were acutely harmed. However, a growing tumor carries an inherent risk of metastasis that increases with each delay. In breast cancer (BC) this risk can be calculated. BC mortality is attributed to distant metastasis, therefore the metastatic risk can be estimated by describing the relationship between tumor diameter and mortality using a Gompertz function derived from previously published literature[1,2] and population-based data (Munich Cancer Registry). The starting time can either be a palpatory finding with subsequent diagnostic workup or a screening mammography. For screening the delay is summed starting from the time the patient is informed, through the follow-up appointment, the biopsy procedure, the tumor board recommendation, and until the first day of treatment.

This function is based on the parameters tumor diameter at primary treatment, volume doubling times (VDT), length of time between initial diagnosis and primary therapy in days, and metastatic risk. The resulting function estimates 15-year mortality according to tumor diameter as described in our previous work.[3] We used VDT1 of 103/241 days for HR- (negative)/HR+ (positive) BC obtained via ultrasound by Ryu EB.[1] In addition, we used the 25%/75% percentiles for VDT2 of 41/99 days derived from screening data by Weedon-Fekjaer H.[2] The ratio between HR+/HR- BCs of the VDT1/2 values is 2.33/2.41 and based on our previous work fittingly corresponds to the ratio of median time to metastasis in HR+/HR- BCs.[4] The mean of these two literature-based VDT1 and 2 is modeled and shown as a third group (VDT3) representing a more moderate estimate for VDT. The following function uses VDT3 to estimate 15-year mortality:

$$GF_{15-yr\ Mortality}(a:58.4, b:4.46, c:0.071) = a * exp^{-b * exp^{-c * TD}}$$

For BCs with a diameter of 5/10/20/30 mm mortality increases by 0.6/1.1/1.5/1.3% when the tumor grows by one millimeter. The largest increase in mortality occurs at 20 mm. Assuming a faster VDT2 of 41/99 days a 0.5 mm BC not detected at screening would be 30/2.7 mm after two years. Fig. 1 summarizes all findings for VDT1-3. Adjusting for additional factors such as a biennial screening interval or slow-growing tumors detected during screening in the modeling function merely results in a small shifts of the results shown in Fig. 1. The drawn conclusions remain unchanged.

In Germany, screening during the COVID-19 pandemic was interrupted for five weeks. If all appointments had been delayed by five weeks this would increase 15-year mortality by an estimated 1.1%.[5]

Even if all appointments are scheduled in a timely manner, it can take 35 days to start primary treatment. According to population-based data from Upper Bavaria, it takes a mean of 24.5 days (SD 21.4), and according to NHS screening data, it takes 38 days.[6] This is associated with a worsening prognosis. A similar finding was reported for delayed surgery of more than eight weeks and overall survival.[7] Although a distinct time limit for treatment delay does not seem plausible given the continuously active tumorbiological processes. With each delayed day the risk grows continuously, there is no risk-free interval. However, there are organizational and human limits to the necessary reduction in delay. Organizational processes must be accelerated as much as possible without haste and agitation. At the same time, an appropriate time interval must be allowed for the mental processing of the cancer diagnosis until surgery, especially since there is no emergency situation. Time pressure could be taken away with a neoadjuvant therapy starting as soon as possible.[8]

*Corresponding author.

E-mail addresses: halfter@ibe.med.uni-muenchen.de (K. Halfter), schlesi@ibe.med.uni-muenchen.de (A. Schlesinger-Raab), gabriele.schubert-fritschle@med.uni-muenchen.de (G. Schubert-Fritschle), hoe@ibe.med.uni-muenchen.de (D. Hölzel).

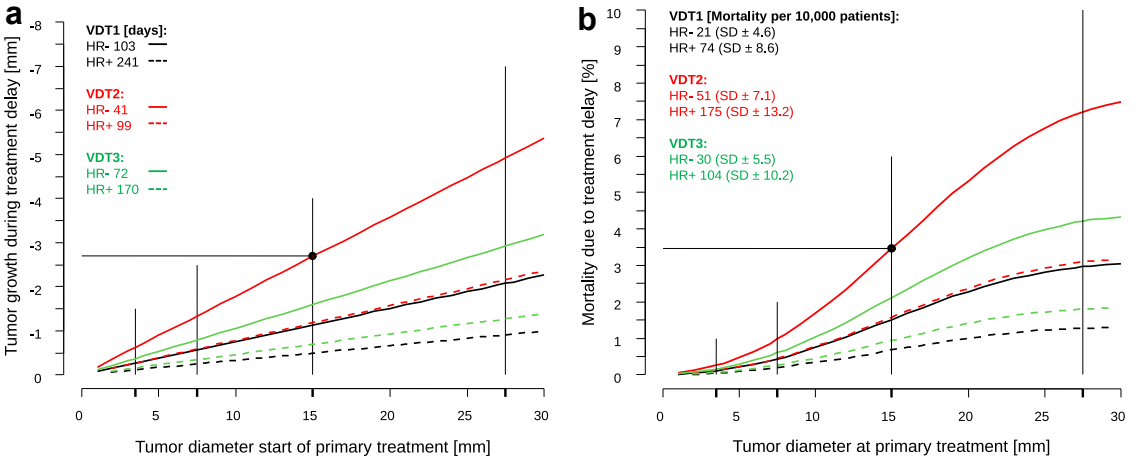

Fig. 1: Tumor growth during primary treatment delay of 35 days and increase in metastasis. Tumor growth during delay is calculated for three different VDT. Solid and dotted lines describe growth (a) and mortality (b) for HR- and HR + BCs, respectively. The highlighted lines on the x-axis represent mean values from pT1a to ≥ pT2-N-M0 BCs obtained from the data of the TRM. a: The dot shows that a 15-mm BC would have had a diameter of 12.3 mm assuming the VDT1 of 41 days if treatment had started 35 days earlier. b: The Gompertz function* results in an increase of 3.5% in metastases initiated during delay growth for the difference in mortality at 15 and 12.3 mm. To estimate the mortality, increase in a population, the mean values for the pT1a/pT1b/pT1c/≥pT2 intervals must be weighted by frequency. For HR + BCs, the weighting is: 0.041/0.164/0.414/0.381). The VDT-dependent mortality refers to 10,000 T-N-M0 BCs. The total mortality increase at 49 days delay for the 3 VDTs is 133 (SD ± 11.5)/315 (SD ± 17.7)/187 (SD ± 13.7) additional deaths. SD: square root of the events as standard deviation for Poisson distributions.

Contributors

KH, Data verification, investigation, validation, software, visualization, writing – original draft

ASR, Data curation, investigation, validation, writing– review & editing

GSF, Data curation, resources, investigation, validation, writing– review & editing

DH, Conceptualization, formal analysis, investigation, software, methodology, writing – original draft

Data sharing statement

The analysis supporting the conclusions of this article are publicly available in the following repositories: Breast cancer statistics from the Munich Cancer Registry (http://www.tumorregister-muenchen.de/facts/specific_analysis.php).

Aggregated patient data on treatment wait times can be supplied from the authors upon reasonable request via email.

Declaration of interests

We declare no competing interests.

Acknowledgements

Funding: No funding source was involved in the work summarized in this article.

References

1 Ryu EB, Chang JM, Seo M, Kim SA, Lim JH, Moon WK. Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound. *Eur Radiol*. 2014;24(9):2227–2235.

2 Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S. Breast cancer tumor growth estimated through mammography screening data. *Breast Cancer Res*. 2008;10(3):R41.

3 Engel J, Weichert W, Jung A, Emeny R, Hölzel D. Lymph node infiltration, parallel metastasis and treatment success in breast cancer. *Breast*. 2019;48:1–6.

4 Engel J, Eckel R, Halfter K, Schubert-Fritschle G, Hölzel D. Breast cancer: emerging principles of metastasis, adjuvant and neo-adjuvant treatment from cancer registry data. *J Cancer Res Clin Oncol*. 2023;149(2):721–735.

5 Hölzel D, Schubert-Fritschle G, Engel J. Estimation of the risk of progression of breast cancer after the COVID-19 lockdown. *Dtsch Arztebl Int*. 2022;119(20):368–369.

6 NHS Digital. Median pathway analysis by patient demographics, stage at diagnosis, route to diagnosis, and geography. Available from: https://www.cancerdata.nhs.uk/median_pathways/tool; 2022.

7 Wiener AA, Hanlon BM, Schumacher JR, Vande Walle KA, Wilke LG, Neuman HB. Reexamining time from breast cancer diagnosis to primary breast surgery. *JAMA Surg*. 2023. https://doi.org/10.1001/jamasurg.2022.8388.

8 Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(11):1477–1486.