The Natural History of Undiagnosed Breast Cancer in the Modern Era

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Introduction

• The growth of breast cancer has traditionally been estimated using mathematical models of tumor “doubling time”.

• We sought to measure the real-time progression of undiagnosed, untreated breast cancer missed on serial mammograms in a large metropolitan area.

Methods

Study design: Retrospective cohort study

Patients:
• Women with biopsy-proven breast cancer presented to the Maimonides Breast Center between February 2011 and June 2017.
• Patients whose breast cancers were found to have been missed on previous serial mammograms at outside breast screening centers were eligible for the study, but only patients with invasive estrogen receptor positive, Her2 negative tumors were included in this analysis.

Data collection and Calculations:
• Two attending radiologists reviewed the mammograms to record tumor dimensions at different time points.
• Tumor volumes were calculated for at least two points in time.
• When only two dimensions were available, the oblate spheroid formula was used. When three dimensions were available, the ellipsoid formula was used (see Figure 1).
• Rates of change in volume (tumor growth velocities) were calculated in mm$^3$/day.
• Non-parametric statistics were employed to correlate mean tumor volume growth velocity to patient age, stage at presentation, grade, pathologic tumor size, Oncotype Dx, and spheroid-ellipsoid discrepancy (SED).

Figure 1. Figure 1. Definitions and Formulas

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Formulas</th>
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</thead>
<tbody>
<tr>
<td>STV: spherical total volume</td>
<td>Oblate Spheroid: $4/3 \cdot \pi \cdot (a/2 \cdot b/2 \cdot c/2)$</td>
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<tr>
<td>ETV: ellipsoid total volume</td>
<td>Ellipsoid: $4/3 \cdot \pi \cdot (a/2 \cdot b/2 \cdot c/2)$</td>
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<td>SED: spheroid-ellipsoid discrepancy</td>
<td>SED=($STV-ETV)/STV$</td>
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Results

72 Cancers in 64 Patients

46 Invasive Cancers

36 ER+/Her2- Tumors

Table 1 Patient Characteristics

| Age, median (range) | 70 (44-83) |
| BRCA mutation heterozygotes* | 1 % |
| Presented with pain (%) | 8 % |
| Presented with palpable mass (%) | 11 % |
| Found to have ≥ pN1 on diagnosis (%) | 17 % |
| Oncotype Dx, Recurrence Score (n=14) | 14 (1-55) |

Figure 2. Tumor Growth Velocities of ER-positive, Her2-negative Tumors Over Time

• Median follow-up was about 23 months
• 94% of tumors increased in volume
• Growth rates varied, but 63.9% of tumors at least doubled in volume over a median follow-up of 689 days (287-2267)
• Median growth velocity was 0.8mm$^3$/day (-0.4-24.3)
• Grade (H=6.2, p=0.04), size (rho=0.54 p=0.001), and pT stage (H=11.9, p=0.04) were positively correlated to growth velocity
• Age, pT, Oncotype Dx, follow-up time, SED were not related to growth velocity

Table 2. Tumor Growth Characteristics

| Proportion of tumors that increased in size | 94.4% |
| Tumor volume change over study period | 591.7 (-304-11,592) mm$^3$ |
| Final volume:initial volume ratio | 2.3 (0.9-53.8) |
| Mean time between measurements | 576.3 (190-1749) |
| Follow-up time per tumor | 689 (287-2267) |
| Volume increase per day | 0.8 (-0.4-24.3) mm$^3$/day |

Conclusions

• This is the only available quantitative assessment of the rate of growth of untreated ER+/Her2- cancer over time.
• The growth velocities of this homogeneous group of invasive cancers varied widely, could not be predicted.
• From a medicolegal context, it is impossible to predict at what time point a cancer became clinically or radiologically apparent.
• Biologic factors such as tumor microenvironment may play a more significant role in tumor growth rates than traditional clinicopathologic characteristics.

References