Prospective Computerized Simulation of Breast Cancer: Comparison of Computer Predictions with Nine Sets of Biological and Clinical Data

Michael W. Retsky, Robert H. Wardwell, Douglas E. Swartzendruber, and David L. Headley


ABSTRACT

A computer program which accepts clinically relevant information can be used to predict breast cancer growth, response to chemotherapy, and disease-free survival. The computer output is patient individualized because the program is highly iterative and simulates up to 2500 patients with exactly the same clinical presentation. Computer predictions have been compared to a broad spectrum of breast cancer data, and a high degree of correlation has been established. There are numerous significant clinical implications which can be derived from the computer model. Among these are the following: (a) Cancer tumors do not grow continuously but may have up to five growth plateaus each lasting from a small fraction of a year up to approximately 8 yr. (b) Adjuvant chemotherapy, such as 6-mo treatment with cyclophosphamide-methotrexate-5-fluorouracil, does not eradicate tumors but just reduces the number of viable cells by a factor of 10 to 100 and sets the eventual growth back by several years. This may partially explain why the age-adjusted death rate from breast cancer has not changed in the past 50 yr. (c) The computer model challenges the underlying principles in support of short-term intensive adjuvant chemotherapy, namely Gompertzian kinetics and genetically acquired tumor resistance to drugs. (d) The computer model questions the evidence opposing long-term maintenance chemotherapy protocols and suggests that maintenance protocols should be reexamined.

INTRODUCTION

Improvements in 5-yr disease-free survival have been demonstrated in recent years, but the number of patients who die of breast cancer has not decreased in spite of enormous investments of time and money. The age-adjusted breast cancer death rate in the United States has not changed from 1930 to 1982, the last year for which such information is available (1). It is time to question the established breast cancer dogma and consider new approaches regarding treatment of breast cancer. This study uses a computer model description of breast cancer treatment with a pragmatic, quantitative viewpoint (2-4). Other mathematical model studies of cancer have been proposed, and many of these are cited in Speer et al. (3), but this new model is distinguished by its careful verification that the model fits published cancer data. Thus, particular attention has been given to correlations between model simulations and equivalent clinical or laboratory data.

The computer model for the growth and treatment of breast cancer has been previously described (2-4). Due to the use of random numerical techniques, the kinetics employed by the computer model is termed stochastic. The program was developed to conform with five sets of clinical data. The data that were used to calibrate the computer model were derived from the following studies: (a) clinically accepted time scales (2, 3); (b) Bloom et al. (5) data on the survival of subjects who refused all treatment after breast cancer was diagnosed; (c) Heuser et al. (6) measurements of primary growth rates in late preclinical breast cancer; (d) Fisher et al. (7) data of disease-free survival grouped by nodes for surgical treatment only; and (e) Bonadonna et al. (8-10) reports of disease-free survival using adjuvant chemotherapy for node-positive patients.

The computer program accepts the following input information: size of primary lesion; number of positive lymph nodes; DNA content of the tumor cells; and proposed treatment which may include surgery and chemotherapy. The output of the program is the probability of the patient truly being Stage IV at presentation, the probability of relapse each year for the succeeding 15 years, and an optimized follow-up protocol based on times of highest probability of relapse.

MATERIALS AND METHODS

The numerical methods that were used to fit the model to the Bloom et al. (5), Heuser et al. (6), Fisher et al. (7), and Bonadonna et al. node-positive CMF chemotherapy (8-10) data have been previously described in detail (2, 3). Folkman et al. (11, 12) angiogenesis studies were considered regarding the observed dormant periods. Hedley et al. (13) data on disease-free survival grouped by DNA content and positive nodal involvement have previously been discussed in relation to the computer model (4). Bonadonna et al. (8, 9) CMF data grouped by nodal involvement are included as an important comparison to the computer model predictions. A recent compilation of the results of all published breast cancer chemotherapy trials by Himel et al. (14) is included as a comparative data set for the computer model.

Estrogen and progesterone receptors have not yet been included in the model. Future versions of the model are expected to incorporate these prognostic parameters as well as other treatment modalities in addition to surgery and chemotherapy.

RESULTS AND DISCUSSION

The model has been tested by comparing the model predictions with nine different data sets. The nine data sets will be presented, and the model predictions will be compared to the clinical or laboratory information. Appropriate clinical implications will also be discussed. The first five data sets were previously discussed (2-4) and will only be summarized here. Table 1 displays the nine data sets. The first five data sets were used to fit the model, and the second four data sets were used to evaluate the model's accuracy. It should be emphasized that there is only one computer program. The program correlates with each of the nine data sets listed below to the extent indicated.

Clinically Accepted Time Scales for Breast Cancer (2, 3, 5). Clinical experience implies that tumors grow from one cell to detection in a minimum of 1 year and eventually become lethal in size. This first data set was the initial reason for questioning Gompertzian kinetics as an accurate description of tumor growth. The computer model (2, 3) suggests that untreated tumors of the breast grow from one cell to detection in 7.8 ± 3.9 (SD) yr and from detection to 1012 (which is normally taken as a lethal tumor burden) in 3.3 ± 2.5 yr. Except for the

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1To whom requests for reprints should be addressed.

2The abbreviation used is: CMF, cyclophosphamide-methotrexate-5-fluorouracil with postscripts 6 and 12 indicating duration (mo) of treatment.

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Table 1 Summary of the nine data sets and equivalent computer model comparisons

<table>
<thead>
<tr>
<th>Data set</th>
<th>Description of data</th>
<th>Model results</th>
<th>Used to develop model?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinically accepted time scale (3), Bloom et al. (5)</td>
<td>Growth &gt;1 yr, and eventually lethal if untreated. Detection to lethal in 3.0 ± 2.8 yr.</td>
<td>To detection in 7.8 ± 3.9 yr. To lethal in 3.3 ± 2.6 yr.</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Bloom et al. (5)</td>
<td>Survival of subjects who refused treatment after diagnosis</td>
<td>Fig. 1</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Heuser et al. (6)</td>
<td>Measurements of growth rates, late preclinical period</td>
<td>Fig. 2</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Fisher et al. (7)</td>
<td>DFS* for surgery only, grouped by nodes</td>
<td>Fig. 3</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Bonadonna et al. (8-10)</td>
<td>DFS, node positive, CMF chemotherapy</td>
<td>Fig. 4</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Bonadonna et al. (8, 9)</td>
<td>DFS, grouped by nodes, CMF chemotherapy</td>
<td>Figs. 5 and 6</td>
<td>No</td>
</tr>
<tr>
<td>7. Folkman et al. (11, 12)</td>
<td>Angiogenesis studies and observed dormancy and growth</td>
<td>Figs. 7 and 8</td>
<td>No</td>
</tr>
<tr>
<td>8. Hedley et al. (13)</td>
<td>DFS, chemotherapy, grouped by nodes and DNA content</td>
<td>Table 2</td>
<td>No</td>
</tr>
<tr>
<td>9. Himel et al. (14)</td>
<td>All published trials. Multiple agent chemotherapy, DFS at 3 and 5 yr.</td>
<td>Data and model agree within 1% at 3 and 5 yr</td>
<td>No</td>
</tr>
</tbody>
</table>

* DFS, disease-free survival.

clinically accepted time scales, there are no data to compare to the model prediction of the elapsed time between one malignant cell and detection. However, there are data for the time between detection and death for untreated patients. Bloom et al. (5) data are 3.0 ± 2.8 yr for 250 subjects. Thus the computer model is in agreement with clinically accepted time scales and the elapsed interval from detection to a lethal tumor burden for untreated patients.

Bloom et al. (5) Data on the Survival of Subjects Who Refused All Treatment after Diagnosis of Breast Cancer. These data show the natural history of the disease from detection to death for 250 subjects in England between 1805 and 1933. This information was used to develop the probability parameters for the model and is therefore in excellent agreement with the model as shown in Fig. 1.

Heuser et al. (6) Data on Measurements of Growth Rates for Breast Tumors in the Late Preclinical Time Period. Heuser and coworkers made yearly mammograms on approximately 10,000 subjects for 3 yr, and whenever cancer was detected, previous mammograms were examined to see if, in retrospect, the tumor could be observed and measured. In that fashion growth rates for 32 tumors were determined. In addition there were at least 17 more tumors that grew too fast to be measured by this technique. This information was used to determine a model parameter that was left unspecified after fitting the model to the Bloom et al. data. The data are shown in Fig. 2a and the model results in Fig. 2b. Considering the missing and biased data, the model apparently agrees with the clinical data. More specifically, the model generates tumors that grow at the same
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rate, measured over a year, as the clinical data indicated. Also, clinically and as the model predicts, some tumors did not grow at all in 1 yr.

Fisher et al. (7) Data of Disease-free Survival for Subjects Treated with Surgical Resection and Grouped by Nodal Involvement. The model accounts for metastatic disease by including a number of sites of tumor growth in addition to the primary and starting at about the same time as the primary. The number of sites of metastatic disease is taken as a linear function of the number of positive lymph nodes. As discussed in Speer et al. (3), there is empirical justification in Fisher et al. data for the linearity assumption. Fisher et al. data and the model calculations are shown in Fig. 3. The agreement is excellent.

Bonadonna et al. (8–10) Studies of Disease-free Survival for Node-positive Subjects Treated with Surgery and Adjuvant Chemotherapy. Bonadonna et al. used CMF12 in this study which has now been followed for 10 yr. The model with simulated chemotherapy was adjusted to fit these data, and the results may be seen in Fig. 4.

It is important to remember that adjusting the model to fit one data set did not alter the fit to any of the other data sets. Thus after adjusting the model to fit Bonadonna et al. node-positive results, the same program would also fit the first four data sets.

Bonadonna et al. (8, 9) Study of Patients Treated with CMF6 and CMF12 and Grouped by Nodes. Bonadonna et al. reported no significant difference in therapeutic advantage between CMF6 and CMF12 (9, 10), so the data are combined. The model, which uses 10 to 50 times as many subjects as Bonadonna et al., predicts a slight advantage of CMF12 over CMF6 (assuming all courses are administered). The model was not adjusted to fit these data, and the results are given in Figs. 5 and 6. The model predicts that chemotherapy does not eradicate metastatic breast cancer tumors but only reduces the number of actively propagating cells by a factor of 10 to 100 and sets back the tumor's eventual growth by 2 or 3 yr.
The model supports the concept that breast cancer is a chronic disease lasting perhaps 15 yr and that 5-yr disease-free survivals must be cautiously interpreted.

Treatment failures which are generally believed to be based on tumor cells becoming resistant to chemotherapy (9, 15) could instead be based on kinetic resistance, whereby the drug is relatively ineffective due to low or no growth at the time of drug administration. The model is able to accurately simulate clinical trials of chemotherapy without resorting to the other known mechanisms of resistance, namely sanctuary and genetic mutation. This does not imply that genetic mutation does not occur but only that it is not necessary to explain the Stage II clinical data.

Long-term maintenance chemotherapy protocols for breast cancer are not considered viable alternatives to short course intensive protocols for two reasons. (a) As previously mentioned, Bonadonna et al. did not detect any therapeutic advantage of CMF12 over CMF6, and (b) currently accepted mathematical models predict treatment failure to be due to genetically acquired drug resistance (9, 15). As already mentioned, both of these reasons are challenged by this study, and maintenance protocols may need reexamination (2, 3, 16).

Folkman et al. (11, 12) Studies of Tumor-induced Angiogenesis. The thesis of Folkman et al. is that tumors are angiogenesis dependent or that every increase in the tumor cell population must be preceded by an increase in new capillaries converging on the tumor. The importance of vascularity to tumors has been known for many years and demonstrated in some remarkable pictures by Algire and Chalkley (17). Folkman et al. studies indicate that tumors induce the host to sprout vasculature that serves to nourish the tumor and allow it to grow. In the absence of this vasculature, nourished by only diffusion mechanisms, tumors will grow to 1 to 3 mm in diameter and stop growing but remain viable for indefinite periods. This has been observed in vivo and in vitro.

Folkman et al. report observations of tumor growth followed by a period of no growth followed in turn by repeated growth. This growth/no growth/growth pattern is predicted by the computer model, and the first growth plateau of the model occurs at approximately 620,000 cells or a sphere of about 1.1 mm in diameter. Fig. 7 shows the Folkman et al. stylized concept of observed growth followed by a dormant period followed in turn by regrowth. This regrowth occurs after the tumor angiogenesis factor is secreted by the tumor which stimulates vascularization. Fig. 8, which shows the growth of three tumors as simulated by the computer model, is presented for comparison with Fig. 7.

It is probable that tumor growth and neovascularization form a symbiotic system. Growth spurts of both the host vasculature and the tumor occur by positive feedback mechanisms initiated by growth of the companion. This biological mechanism would be consistent with stochastic kinetics. Dühning and Vogelsang (18) have developed a computer model on a micro level (i.e., cellular) that incorporates the Folkman et al. concepts. The stochastic model suggests that up to five plateaus occur in the history of a breast tumor, while Folkman et al. have not reported observing more than one plateau per tumor. Stochastic kinetics rather than Gompertzian kinetics would best describe the observations of Folkman et al.

Skipper (19) has speculated that breast cancer recurrences 5, 10, or 15 yr after surgery may be due to viable tumors in G0 or a steady state for years and then for some reason resuming uncontrolled growth. On the basis of the computer model and Folkman et al. studies, the reason for this regrowth may be host neovascularization.

There is additional internal consistency between the clinically accepted time scale, Bloom et al., Heuser et al., and the computer model concept regarding plateaus in growth and subsequent regrowth. Except for the 5% who died from other causes, all of the breast cancer patients reported by Bloom et al. who refused treatment after diagnosis eventually died from breast cancer. This is consistent with the clinically accepted notions. Applying that observation to Heuser et al. data, the tumors which did not grow by measurable amounts in 1 yr would apparently eventually grow to lethal size if untreated. These tumors which did not grow by any measurable amount in approximately 1 yr differed in tumor burden by $10^{23}$ or almost 3 orders of magnitude. Thus, human breast tumors with a range in tumor burden of almost 3 orders of magnitude have been observed to be dormant in size for approximately 1 yr and, from other studies, every tumor has been observed to eventually become lethal if untreated. It is logical to conclude that the observed dormant tumors would eventually regrow in agreement with the model predictions.

Hedley et al. (13) Study of Disease-free Survival Grouped by Nodes and DNA Content of the Tumor for Patients Treated with Adjuvant Chemotherapy. As seen in Table 2, the model predictions correlate closely with Hedley et al. data. The only exception is for the case with diploid DNA and more than 3 nodes, in which case there are very few data cited. It may be seen that, according to the model, unfavorable DNA content is prognostically comparable, in this situation, to 5 positive lymph nodes.
The Hedley et al. data are for an average follow-up of 3.5 yr and a mixture of treatment, primarily CMF12 but no radiation. The computer model used 3.5 yr of follow-up, CMF6 treatment, and 500 subjects in each group. Consistent with Fig. 6, the greater than 3 nodes group was assumed to be representable by 7 positive nodes for purposes of calculation.

<table>
<thead>
<tr>
<th>DNA content</th>
<th>Hedley et al. disease-free survival data (%)</th>
<th>Computer model disease-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–3 nodes</td>
<td>&gt;3 nodes</td>
</tr>
<tr>
<td>Diploid</td>
<td>91 (33)*</td>
<td>55 (20)</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>78 (49)</td>
<td>40 (63)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of subjects.

Himel et al. (14) Study of Published Chemotherapy Trials. Himel et al. reported on a compilation of all published breast cancer adjuvant chemotherapy trials with randomized controls and at least 2-yr follow-up. The difference between controls and multiple agent clinical trials (which applies to the chemotherapy trials reported in this article) is 17 ± 5% at 3 yr based on 1528 patients and 9 ± 8% at 5 yr based on 626 patients. The dispersions used by Himel et al. are 95% confidence intervals, while SD is used consistently in this paper. The 3 and 5-yr results for the computer model simulation of CMF6 from Fig. 4 are 18% and 10%, respectively, which is in very close agreement with Himel et al.

Thus, nine separate clinical and laboratory data sets have been studied and reported that are strongly positively correlated to a unique computer model for breast cancer growth and treatment.

The computer program has been found to accurately predict the result of treatment of breast cancer patients. If the program is instructed to detect but not treat the subjects, they will all attain lethal tumor burdens in accordance with Bloom et al. If growth rates in the late preclinical period are measured, the results will agree with Heuser et al. measurements. The results of surgery alone will agree with Fisher et al. studies. If the program is instructed to simulate CMF chemotherapy, the results will agree with Bonadonna et al., Hedley et al., or Himel et al., depending on whether nodal involvement and DNA content of the tumor are specified. For any situation, growth plateaus may be observed similar to Folkman et al. and Heuser et al. observations. Tumors will grow from one cell to detectable size in at least 1 yr.

Because of the quantity of experimental verifications, serious considerations must be given to this new approach to describing breast cancer growth and treatment. The computer model is significantly different from currently accepted descriptors (15) of breast cancer growth. Model predictions have important implications regarding treatment and follow-up of Stage 0 to III breast cancer patients. The model predictions include the following.

(a) The model supports the concept that breast cancer is a chronic disease lasting up to 15 yr and that 5-yr disease-free survivals must be cautiously interpreted.

(b) Breast tumors do not grow continuously but may have up to five growth plateaus. The plateaus are typically a few years in duration but may extend from fractions of a year to approximately 8 yr.

(c) By the time of detection of primary breast cancer, metastatic foci are often established.

(d) Breast tumors grow from one cell to detection in 7.8 ± 3.9 yr and will grow from detection to lethal size in 3.3 ± 2.5 yr if untreated.

(e) Accurate information concerning the quantitative therapeutic advantages of adjuvant chemotherapy is available from the computer program and can be used when deciding whether to treat individual patients.

(f) Adjuvant chemotherapy, such as CMF6 or CMF12, does not eradicate tumors but rather reduces the number of viable cells by a factor of 10 to 100 and sets the eventual growth back by 2 or 3 yr.

(g) Chemotherapeutic treatment failure is explainable by kinetics alone. Genetically acquired resistance of cells may not be requisite.

(h) DNA content information is comparable in importance to nodal involvement for staging and prognosis.

(i) Conventional chemotherapy does not cure anyone who would not be cured by surgery alone. It simply offsets the time scale for relapse. The eventual failure of adjuvant chemotherapy treatment partially explains why the breast cancer death rate has not changed in the past 50 yr.

(j) Chemotherapy regimens other than conventional ones can be simulated using the computer program. This may result in individually optimized treatment.

(k) Total treatment costs could be accurately predicted for each patient thus enhancing planning.

(l) The model predicts likely periods of time for metastatic relapse. Follow-up examinations could be closely scheduled during these times for early detection of relapse.

(m) Short course intensive chemotherapy, such as CMF6, is widely used for treating breast cancer patients who are staged in groups with historically high risk for relapse. The theory in support of this protocol is based on Gompertzian kinetics and the potential danger of genetically acquired resistance to chemotherapy. In short, aggressive chemotherapy is administered after surgery and over a short time because, from Gompertzian kinetics, the residual tumor will be smallest and therefore growing fastest and therefore most susceptible to cytotoxic drugs. Also the tumor cells will have less time to develop genetically resistant clones if the drugs are administered over a short time period. Both of these underlying principles are called into question by the evidence reported here.

(n) Long-term maintenance chemotherapy which has been discredited on empirical (9, 10) and theoretical (15) grounds should be reexamined in view of the findings reported here.

REFERENCES

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