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Mathematical modelling of tumour response in primary breast cancer

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Summary  Although breast cancer is perceived to be relatively chemosensitive, cytotoxic drug therapy only leads to cure in the adjuvant setting. In advanced disease, primary resistance and inadequate cell kill may be important in determining the lack of a durable response to cytotoxics, but for an individual patient’s tumour there is no consistent way of determining the importance of these two factors. An adaptation of Skipper’s log cell kill model of tumour response to chemotherapy was applied to serial tumour measurements of 46 locally advanced primary breast carcinomas undergoing neoadjuvant chemotherapy. Assuming a log-normal distribution of errors in the clinically measured volumes, the model produced, for each tumour separately, in vivo estimates of proportional cell kill, initial resistance and tumour doubling times during therapy. After 4 weeks’ treatment, these data could then be used to predict subsequent tumour volumes with good accuracy. In addition, for the 13 tumours that became operable after the neoadjuvant chemotherapy, there was a significant association between the final volume as predicted by the model and the final pathological volume (P<0.05). This approach could be usefully employed to determine those tumours that are primarily resistant to the treatment regimen, permitting changes of therapy to more effective drugs at a time when the tumour is clinically responding but destined to progress.

Keywords: breast cancer; mathematical model; tumour response

It is well recognised, from both clinical and laboratory work, that most cancers exhibit primary or acquired resistance to many cytotoxic drugs, and that overgrowth of these resistant cells leads to ultimate treatment failure (Skipper, 1978). This is one of the main reasons for the failure to cure many malignancies (Harris, 1985). In trying to assess clinically the tumour response to treatment, one has to rely on measurements that are often rather crude. For example, clinical or radiological measurements are only possible if there are at least 10⁶ cells present, and even using the most sensitive tumour markers a total tumour burden of below 10⁵ is usually undetectable. Following chemotherapy, malignancies can be rendered undetectable as defined by clinical or radiological tests – the so-called complete response or CR. But only prolonged follow-up tells if a cure has been achieved.

In the laboratory, one can identify cell lines that respond to treatment and those that do not. However, testing for chemosensitivity of patients’ individual tumours in a manner analogous to anti-microbial sensitivity assays is not generally practicable; indeed in a recent study with single-agent 5-fluorouracil an in vitro sensitivity assay was only possible in 69% of assessable patients (Elledge et al., 1995).

A model of tumour response to therapy, individualised for each tumour, has previously been described for breast cancer (Priere, 1966), but using an S-shaped cumulative dose–response curve, rather than the more generally accepted log-kill response. In this earlier model, the intention was to improve on simple clinical measurements of metastases to permit better assessment of the efficacy of cytotoxic agents. No attempt was made to predict subsequent tumour behaviour or pathological volumes. We hypothesised that incorporating primary resistance as well as cell kill in a model might assist the assessment of the efficacy of the cytotoxics and, furthermore, enhance the prediction of subsequent failure, permitting earlier changes in therapy.

The model

The model assumes exponential cell growth, and derives estimates of the actual proportions of sensitive and resistant cells as a consequence of the change in tumour volume with each treatment cycle. The tumour doubling time d is assumed to be a constant throughout the time of treatment. The theory of the model has been described previously (Birkhead and Gregory, 1984), and validated using small-cell lung cancer monitored with serial computerised tomography (CT) scans (Gregory et al., 1990). It is represented diagrammatically in Figure 1; it assumes that all cells killed by one cycle of therapy can no longer grow and furthermore, that they make no contribution to the tumour volume recorded just before the subsequent cycle.

Skipper et al. (1964) found that in the mouse model of leukaemia a given dose of chemotherapy killed a constant proportion of the cells present, and described this as the log-kill model. We have used this concept to describe the cell kill in our model, representing by k the proportion of the tumour

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Figure 1 Diagram of model showing resistant cells in black growing despite overall tumour shrinkage after two cycles of chemotherapy.
killed by one cycle of chemotherapy. It is also assumed that
at the time of the first treatment there may be cells present
that can never be killed by the treatment applied, and the
proportion of such 'primary resistant' cells is denoted by \( R_0 \).
As with the application in small-cell lung cancer (Gregory et
al., 1990), we have assumed there to be no significant
acquisition of resistance during early therapy. The original
theoretical description (Birkhead and Gregory, 1984) did
include the idea of such secondary resistance, as suggested by
Goldie et al. (1982), but showed that significant differences in
the volume of resistant cells would only be seen for the first
couple of cycles. Thus ignoring the impact of secondary resistance
would not significantly alter the ability of the model to predict
later tumour behaviour.

There are thus three unknown parameters \( (d, R_0 \) and \( k) \) for
each tumour. The tumour volumes from four early
treatment cycles are required to derive these values and then
the model can be extended to predict the tumour volumes for
subsequent treatment cycles.

Patients and methods

Women with primary, non-metastatic inoperable breast
cancer have been managed by the Edinburgh Breast Unit
with cytotoxic protocols (Bowman et al., 1992). Since 1990,
46 such patients with a total of 52 assessable tumours have
been recruited. Women with inflammatory carcinoma were
excluded. There was a clearly palpable primary within
the breast. A total of 18 women with 21 tumours were treated
weekly with bolus doxorubicin 20–30 mg m\(^{-2}\), a 24 h
infusion of 5-fluorouracil 600 mg m\(^{-2}\) on day 1 and oral
cyclophosphamide 150 mg daily for 3 days of each week
(CAF). Subsequently, 27 patients with 31 tumours were
treated with weekly doxorubicin 20–30 mg m\(^{-2}\) and con-
tinuous 5-fluorouracil 200 mg m\(^{-2}\) day\(^{-1}\) (ACF), administered
using a portable electronic pump via a Hickman line, as
originally described by Lokich et al. (1981). In both studies,
treatment was for 12 weeks. As these women all attended
weekly for assessments, blood tests and treatment, sequential
tumour measurements were taken whenever possible by the
same clinician (AB or DC).

At the end of the 12 weeks treatment all patients were
reviewed in a joint Oncological and Surgical Clinic and their
subsequent management decided upon. For 13 of the 46
tumours definitive surgery was undertaken and these cases
afforded a good opportunity to test the predictive power of
the model by comparing the final pathological volume with
that predicted by the model.

For this application in breast cancer, we employed the
model used for small-cell lung cancer (Gregory et al., 1990),
embodied in a suite of programs written in Microsoft Fortran
77, running on an IBM-compatible microcomputer. Further
statistical analysis was performed using Minitab (Minitab
State College, PA, U.S.A.) on the same computer.

In principle, the first four tumour volumes can be used to
drive the three independent parameters \( k, R_0 \) and \( d \) (see
equation 2 in Appendix 1). Occasionally the model cannot be
applied—if, for example, there is a significant increase in
volume after the first cycle with tumour shrinkage after
subsequent cycles, the model cannot fit the observed data
and may not be used to derive the parameters for that tumour.

Even if the three parameters \( k, R_0 \) and \( d \) were known,
the tumour volumes recorded would not be expected to be
identical to those predicted, owing to the potential for errors
in measuring breast tumours. Thus some assumptions about
the error distribution have had to be made. Appendix 2
includes a discussion on the mathematics of these assump-
tions; essentially two versions of the model were run. The
first, as used in small-cell lung cancer (Gregory et al., 1990),
assumed a log-normal distribution of errors, i.e. that the
error increases with increasing tumour size. The second
version assumed that there was a normal distribution of
errors, i.e. that the error distribution is independent of the
volume, but we were unable to fit the model to our data
using this assumption. All data presented have therefore been
generated by the model assuming a log-normal error
distribution.

The clinical tumour measurements were performed using
calipers to provide data for assessment using UICC criteria of
response, and are therefore two orthogonal diameters a and
b. In order to calculate tumour volumes from them, we have
had to approximate to the third dimension as the average of
the other two diameters and have assumed the tumour
volume to be an ellipsoid:

\[
\text{Tumour volume} \approx \frac{\pi}{6} (a x b x (a+b)/2) = \frac{\pi}{12} a^2 b (a+b)
\]

The volume of the tumours that were surgically excised
after the 12 weeks chemotherapy was estimated using the
same formula, unless only one maximum dimension \( a \) was
reported, in which case the formula used was:

\[
\text{Tumour volume} \approx \frac{\pi}{6} a^3
\]

All patients were subjected to a pretreatment biopsy, both
for histological proof of breast cancer and to estimate the
oestrogen receptor concentration. In many cases this was
performed by removing a palpably malignant ipsilateral
axillary node. When this was not possible, a wedge biopsy
of the primary was performed. We have assumed that it is
impossible to determine how this surgical trauma affected
the measured volumes; therefore to minimise this potential source
of error, all biopsied lesions were analysed only from the
start of the fifth week of treatment, thus allowing at least 29
days to elapse from the time of surgery before the tumour
measurements were used. Since the model assumes no
significant acquisition of resistance during therapy, the
parameters can be derived from a minimum of four
sequential measurements at any point during early therapy.

Statistical methods

As we assumed a log-normal error distribution of tumour
volumes, all statistical calculations have been done on the
natural logarithm of the volume. This applies in particular to
the calculation of Pearson's correlation coefficient for
the association between predicted and actual volumes (Figures 4
and 5), and the association between doubling time and initial
volume (Figure 6). The figures for percentage variation
between actual and predicted volumes are also based on
the natural logarithms of those volumes (Figure 3), and Pearson's
correlation coefficient was used.

Results

In 16 patients there were 22 tumours that had not been
biopsied, and the model was applied to the first four tumour
measurements. The cell kinetic parameters are shown in
Table 1. Only six tumours are estimated to have primary
resistant cells, with the highest value being 39%. In 9/22
tumours, the model estimated the tumour doubling time on
therapy to be between 6 and 57 days. However, in the
remaining 13 tumours the model fitted best if there was no
apparent growth during treatment, and the doubling time is
given as \( \infty \) in Table 1—for these tumours the model assumes
an artificially imposed maximum doubling time of 10,000
days.

In 30 patients there were 30 tumours that had been
biopsied before treatment, and these were modelled using
volumes from day 29 onwards. Seven tumours had
insufficient volumes recorded beyond the fourth week
for the model to be applied. In another seven the model
could not be applied: in one case there was no discrete mass at
the start; another had an initial period of enlargement with only
variability between the four parameters during the measure. In for graphically and those measurements tumour unbiopsied lesions the model are those treated in another patients, tumour (10/16) the model estimates that all but one had been treated on the second (AcF) regimen. Although the model could be successfully applied in two of these four tumours (data not shown) using tumour volumes from day 1, this was not possible for all 30 tumours that had been biopsied.

The values for cell kill and resistance for the remaining 16 biopsied tumours (derived from the tumour measurements in the fifth cycle onwards) to which the model was successfully applied, are also seen in Table I and are similar to the unbiopsied lesions with a mean cell kill of 34% and mean resistance of 9%. Again it can be seen that in the majority (10/16) the model estimates that there was no regrowth during the therapy, and the doubling time has been given as ∞.

The model parameters were then used to predict all the tumour measurements recorded, both those used to derive the parameters and those for the subsequent courses. Table II shows the percentage variability between the clinical volumes and those predicted by the model, and this is depicted graphically in Figure 3. The x-axis corresponds to the variability between the four actual volumes to which the model was applied, and the 'best fit' volumes predicted by the model. On the y-axis are the variabilities between the actual and model predicted volumes beyond those first four volumes. There is a good correlation between these two figures, which is statistically significant, suggesting that where there is a good fit over the first four volumes the model will predict the subsequent volumes more accurately.

The final volumes for the 13 patients who had surgery at the end of the 12 weeks' chemotherapy are set out in Table III, and there is a good correlation between the final volume predicted by the model and both the final measured volume and the pathological volume (Figure 4). In three patients there was a complete pathological response, and for these three patients the model estimated zero primary resistance. However, when all 13 patients are assessed this result is not significant at the 5% level, possibly because of the small numbers.

A clear correlation was found between all the actual tumour volumes and those predicted by the model (Figures 5a and b). This was the case both for the tumours that had not been biopsied (Figure 5a, $r^2 = 0.893$, $P < 0.00001$), and those that had been subjected to a biopsy (Figure 5b, $r^2 = 0.964$, $P < 0.00001$). These correlations are of course both a reflection of the 'fit' of the model to the volumes used to determine the model parameters for each tumour, as well as the accuracy with which the model predicts the subsequent tumour volumes. That there is a close fit irrespective of whether or not the tumours had been biopsied confirms that

### Table I Parameters derived from unbiopsied and biopsied tumours

<table>
<thead>
<tr>
<th>Patient</th>
<th>Regimen</th>
<th>Cell kill</th>
<th>Primary resistance</th>
<th>Doubling time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tumour</td>
<td>CAF</td>
<td>0.83</td>
<td>0.032</td>
<td>∞</td>
</tr>
<tr>
<td>2 Right</td>
<td>AcF</td>
<td>0.45</td>
<td>0.390</td>
<td>∞</td>
</tr>
<tr>
<td>3 Right</td>
<td>AcF</td>
<td>0.18</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>4 Tumour</td>
<td>CAF</td>
<td>0.19</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>AcF</td>
<td>0.24</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>6</td>
<td>AcF</td>
<td>0.91</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>7</td>
<td>CAF</td>
<td>0.57</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>8 Tumour</td>
<td>CAF</td>
<td>0.21</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>9 First tumour</td>
<td>CAF</td>
<td>0.33</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>10 Second tumour</td>
<td>CAF</td>
<td>0.34</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>CAF</td>
<td>0.23</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>12</td>
<td>CAF</td>
<td>0.63</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>AcF</td>
<td>0.12</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>14</td>
<td>AcF</td>
<td>0.27</td>
<td>0</td>
<td>∞</td>
</tr>
<tr>
<td>15</td>
<td>AcF</td>
<td>0.54</td>
<td>0.340</td>
<td>∞</td>
</tr>
<tr>
<td>16</td>
<td>AcF</td>
<td>0.35</td>
<td>0.089</td>
<td>∞</td>
</tr>
<tr>
<td>Mean</td>
<td>0.38</td>
<td>0.083</td>
<td>∞</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>57%</td>
<td>6%</td>
<td>6 – 91%</td>
<td>0 – 39%</td>
</tr>
</tbody>
</table>


a very late response; another was always extremely difficult to measure. In four however, there was no obvious reason and their tumour volume curves are shown in Figure 2. It can be seen that most of the response in these four tumours had occurred by day 29, and that the model was therefore attempting to derive the parameters from a plateau in the response curve. There was no other obvious characteristic in these patients, except that all but one had been treated on the second (AcF) regimen. Although the model could be successfully applied in two of these four tumours (data not shown) using tumour volumes from day 1, this was not possible for all 30 tumours that had been biopsied.

The values for cell kill and resistance for the remaining 16 biopsied tumours (derived from the tumour measurements in the fifth cycle onwards) to which the model was successfully applied, are also seen in Table I and are similar to the unbiopsied lesions with a mean cell kill of 34% and mean resistance of 9%. Again it can be seen that in the majority (10/16) the model estimates that there was no regrowth during the therapy, and the doubling time has been given as ∞.

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Figure 2 Tumours unsuccessfully modelled. —□—, patient 1; − ● −, patient 2; − □ −, patient 3; − ○ −, patient 4.

Figure 3 Variability between actual and model predicted volumes. \( r^2=0.35, P<0.05 \).

Table II Comparison of per cent variability for the first four and subsequent volumes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Regimen</th>
<th>Per cent variability between model and actual volumes</th>
<th>Subsequent volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAF</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>AcF</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>CAF</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>AcF</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>AcF</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>CAF</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>CAF</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>CAF</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>AcF</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>CAF</td>
<td>30</td>
<td>191 (16% without one small volume)</td>
</tr>
<tr>
<td>11</td>
<td>CAF</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>AcF</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>AcF</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>AcF</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>AcF</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>CAF</td>
<td>2</td>
<td>909 (9% without one small volume)</td>
</tr>
<tr>
<td>17</td>
<td>CAF</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>CAF</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>CAF</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>CAF</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>21</td>
<td>CAF</td>
<td>9</td>
<td>196 (small volumes)</td>
</tr>
<tr>
<td>22</td>
<td>CAF</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>AcF</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>AcF</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>25</td>
<td>AcF</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>26</td>
<td>AcF</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>AcF</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>AcF</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>29</td>
<td>AcF</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>30</td>
<td>AcF</td>
<td>13</td>
<td>60</td>
</tr>
<tr>
<td>31</td>
<td>AcF</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>32</td>
<td>CAF</td>
<td>2</td>
<td>43</td>
</tr>
</tbody>
</table>

the application of the model to volumes only after the fourth week of chemotherapy does not appear to impair its ability to predict subsequent volumes, with the caveat that there were four biopsied tumours to which the model could not be applied after week 4, as almost all of the response had already occurred by that time.

Figure 6 shows a plot of the doubling time \( d \) against the actual initial volume. It can be seen there is a trend for \( d \) to rise with the larger tumours, and if we ignore the tumours with no effective growth during the treatment (and thus for whom \( d \) is essentially \( \infty \)) this is significant \( (P<0.05) \).
Table III  Cell kinetic parameters and pathological volumes for those tumours having surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cell kill</th>
<th>Primary resistance</th>
<th>Doubling time</th>
<th>Clinical</th>
<th>Volumes</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.23</td>
<td>0</td>
<td>∞</td>
<td>0</td>
<td>2.7</td>
<td>DCIS only</td>
</tr>
<tr>
<td>11</td>
<td>0.63</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>9.7</td>
<td>0.10</td>
</tr>
<tr>
<td>12</td>
<td>0.12</td>
<td>0</td>
<td>∞</td>
<td>0</td>
<td>7.0</td>
<td>0.88</td>
</tr>
<tr>
<td>13</td>
<td>0.27</td>
<td>0</td>
<td>∞</td>
<td>0</td>
<td>9.4</td>
<td>1.1</td>
</tr>
<tr>
<td>14</td>
<td>0.54</td>
<td>0.340</td>
<td>∞</td>
<td>39</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>15</td>
<td>0.35</td>
<td>0.089</td>
<td>∞</td>
<td>2.5</td>
<td>3.8</td>
<td>0.70</td>
</tr>
<tr>
<td>16</td>
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<td>0.083</td>
<td>∞</td>
<td>37</td>
<td>24</td>
<td>5.6</td>
</tr>
<tr>
<td>27</td>
<td>0.21</td>
<td>0</td>
<td>76</td>
<td>55</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>28</td>
<td>0.16</td>
<td>0</td>
<td>∞</td>
<td>35</td>
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DCIS, ductal carcinoma in situ.

Discussion

It is difficult to measure cell cycle parameters in breast tumours, because one cannot establish cell lines from all breast cancers and, even if established, such cell lines cannot easily provide data on true doubling times because they cannot allow for the effect of stroma and vasculature on growth or for cell loss rates or for sampling selection. Furthermore, there is no standard method at present of using an in vitro estimate of resistance to chemotherapy to plan treatment, or even predict subsequent tumour behaviour, although attempts have been made (see Von Hoff, 1990). A recent development, using a [3H]uridine uptake assay to assess resistance to single-agent 5-fluorouracil, has overcome some of these problems (Elledge et al., 1995). However, no assay was available in 11/36 clinically assessable metastatic tumours, and the prediction was only for response or 'no response'. In the management of locally advanced breast cancer, the degree of response is important, as one of the aims of neoadjuvant treatment is to improve the operability of the tumour.

![Figure 4](image1.png)

**Figure 4** Pathological volume vs actual and predicted final volume (not including cases with only DCIS or in pathological complete response). ■, actual volume; +, predicted volume; —, ideal line.

![Figure 5](image2.png)

**Figure 5** Actual and predicted volumes for (a) unbiopsied tumours ($r^2=0.893$, $P<0.00001$) and (b) biopsied tumours ($r^2=0.964$, $P<0.00001$).

There is little doubt that changes in cell proliferation, and in the expression of c-erbB-2 and p53 (Gardin et al., 1994), can occur as a consequence of neoadjuvant chemotherapy, but there are no firm data on how these changes could be
were positive so imply that a to estimate help predict before suggest data after. It or in the first entered survival. Koh et al., 1992 found that clinical measurements overestimate the size of small breast tumours and underestimate large ones, although they concluded overall that ultrasound was no better, tending to underestimate tumour size. Forouhi et al., 1994, on the other hand found a much better correlation between pathological size and that measured by ultrasound, although there was also a significant correlation between pathological and clinically measured tumours. Pain et al., 1992 suggest that clinical measurements are impressive, although they were not able to compare the actual measurements with a ‘gold standard’ pathological size, as in the above two studies. As the tumours in our study all regressed on chemotherapy, these studies all suggest that there are likely to be significant errors in the clinical measurements that will not lessen as the tumours shrink. Indeed, Figures 5a and b, together with Table II, suggests that the error in the clinical volume may be larger for smaller tumours. It is unclear how this could be best accommodated mathematically, as such smaller volumes only appear during subsequent treatment cycles. However, it does not pose a significant problem for the model derivation of the cell-kinetic parameters as, with the exceptions of the nodes measured in patients 4 and 8, all other volumes used to derive the parameters were based on tumour dimensions of greater than 1.5 cm.

There were a small number of tumours to which the model could not be applied. In most cases this was because of unreliable or inadequate clinical volume measurements, but in four cases that had all been biopsied it transpired that the model was applied to a plateau of tumour response (see Figure 2). Earlier application of the model in two of these four cases was successful, but as it was only with the knowledge of the subsequent volumes that the presence of a response plateau was apparent, such an approach could not be entertained when using this model to prospectively predict tumour behaviour. Indeed, if the model was applied from the first treatment cycle for all tumours, thus ignoring the impact of surgical trauma on tumour measurements, it does not provide overall as close a fit to the measured volumes. Clearly, it would be helpful to either avoid biopsy of the tumour to be measured, or to have a method of differentiating the tumour from any haematoma.

Figure 6 shows that there is a trend for the tumour doubling time to rise with initial tumour volume, which is in keeping with a different model of tumour growth, such as Gompertzian (Gompertz, 1825; Laird, 1964). It would be interesting to apply such a model to tumours of different volumes, but it would require estimation of one additional parameter, $\beta$ (which represents the rate at which the growth falls away from exponential). Given the potential for errors in the measurements as discussed above, it might be better to get more accurate volume measurements first, for example using ultrasound. In contrast however, Brown et al., 1984 showed that in a large series of primary breast cancers there was no
The model presented is relatively simple, in both its assumptions and applicability. No explicit allowance has been made for the fact that only a part of the tumour may be proliferating, or for the possibility of recruitment of further cells into proliferation following treatment, or for cell loss caused other than by therapy. Thus, the parameter values cannot be taken as an accurate prediction of those that would be obtained by a biological estimation, were it possible (which it is not). What the model does permit is an empirical approach to volume extrapolation for tumours undergoing treatment, and this series of tumours has shown that prediction of subsequent behaviour is accurate. This model can also be applied to measurements of primary breast cancers given conventional 3 weekly preoperative chemotherapy. Current approaches to response to treatment depend heavily on the UICC definitions of CR, PR etc (Hayward et al., 1977) and provide no method of prediction of subsequent volumes, and do not predict which continuing treatment will render the tumour operable. In contrast, this model can help in that decision, as if further treatment is predicted to result in little further regression, then a change of therapy could be employed. Until recently there was no effective non-anthracycline-based systemic option, but with the high response rates reported in anthracycline-resistant disease for paclitaxel (O'Shaughnessy and Cowan, 1995), there is now a viable alternative to radiotherapy for unresponsive and persistently incompletely locally advanced breast cancer. This approach needs further testing, and more accurate tumour volumes as measured by ultrasound or even magnetic resonance might improve the accuracy of the model predictions.

References


Appendix

The model predicts that the sequential tumour volumes before treatment \((X_0, X_1, X_2, \ldots, X_n)\) will be described by the equation:

\[
X_i = \frac{1 - a - (1 - a^i)k_0}{1 - a}X_0e^{at} \quad (1)
\]

where \(a = (1 - k)\) and \(k_0 = k(1 - R_0)\). \(R_0\) is the proportion of the tumour initially resistant, \(\alpha\) is the growth rate, \(t_i\) is the time between the first treatment and treatment cycle \(i + 1\) and \(i\) is the treatment cycle number itself. Then, from equation (1)

\[
\log X_i = \log \left[ \frac{1 - a - (1 - a^i)k_0}{1 - a} \right] + \log X_0 + \alpha t
\]

Let the actual tumour volumes be \(V_0, V_1, \ldots, V_n\). We have assumed that these are log-normally distributed about the true volumes with some constant standard deviation \(\sigma\) (this is equivalent to the assumption that the same percentage error can be expected at each tumour volume).

Then the likelihood \(L\) of the (log of) these volumes under the model is:

\[
L(\log V_0, \log V_1, \ldots, \log V_n) = N(\log V_0, \log X_0, \sigma) \times 
N(\log V_1, \log X_1, \sigma) \times 
\ldots \times 
N(\log V_n, \log X_n, \sigma)
\]

\[
= \prod_{i=0}^n N(\log V_i, \log X_i, \sigma)
\]

where \(N(x, \mu, \sigma)\) is the value of a normal distribution with mean \(\mu\) and variance \(\sigma^2\) at \(x\). Hence

\[
\log L = \sum_{i=0}^n \log N(\log V_i, \log X_i, \sigma)
\]

Now

\[
N(x, \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp \left[ -\frac{(x - \mu)^2}{2\sigma^2} \right]
\]

Thus

\[
\log L = \sum_{i=0}^n \log \left[ \frac{1}{\sigma\sqrt{2\pi}} \exp \left[ -\frac{(\log X_i - \log V_i)^2}{2\sigma^2} \right] \right] \quad (2)
\]

The maximum likelihood estimates (MLEs) for \(X_0, k, R_0, \alpha\) and \(\sigma\) (i.e. the values of these parameters that produce the closest fit between the model’s predictions and the data) can then be determined by maximising \(L\) from equation (2). This can be achieved by differentiating \(\log L\) with respect to each of the parameters \(X_0, k, R_0, \alpha\) and \(\sigma\) and maximising \(\log L\) based on the values of these derivatives using a semi-Newtonian algorithm.