Cox’s proportional hazard model is now widely used to evaluate prognostic factors of diseases. But it has been often pointed out that the Cox’s method is sometimes not sufficient because it assumes temporally constant effects of prognostic factors on the disease process. In this paper we developed a new evaluation method of prognostic factors, based on the more detailed modeling of the course of the disease. This method describes the disease process by longitudinal Markov model (temporal succession of simple Markov model) and the prognostic factors are evaluated by the multiple logistic regression analysis.

Stage II breast cancer is chosen as the subject in this study. Data are retrospective ones, collected in National Cancer Center Central Hospital.

As first step, a longitudinal Markov model was constructed to describe the longitudinal disease state transition of a breast cancer. Then based on the detailed investigation of the longitudinal change of transition probability between each disease state, we discriminated the breast cancer patients by two groups, good and poor prognosis one, by using a nonparametric test. We extracted a patient group who showed a recurrence for the first two and a half years as the poor prognosis group (p < 0.05), which corresponds to clinical accepted view.

As second step, a multiple logistic regression analysis was applied to evaluate prognostic factors that contribute the discrimination between good and poor prognostic group, and the results were obtained that three factors (n-classification of pathological diagnosis, ductal spread, and existence of estrogen receptor) were considered as the major prognostic factors for the early death in Stage II breast cancer.

These results well correspond to the clinically accepted view concerning the prognostic factors of breast cancer, so that this method would be an efficient quantification method to transform clinical impressions to objective evidences in prognosis of diseases.

(Keywords: prognostic factor, Markov chain model, multiple logistic regression analysis, breast cancer)

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Introduction

A long-term survival is usually expected for the early breast cancer. But some early breast cancer patients have a poor prognosis. Thus, it is worth investigating to evaluate the influential patient attributions (prognostic factors) that cause the poor prognosis in the early breast cancer patients.

The proportional hazard model (Cox’s life...
regression analysis) is generally used to evaluate
the prognosis factors of the disease. But it has
been often pointed out that the Cox’s method is
sometimes not sufficient. This is because, in the
Cox’s method, temporal pattern of the survival
curve of the disease is described by the baseline
function and the effect of prognostic factors is
taken into account in the multiplication (proportional coefficients) of this baseline function.
Hence, Cox’s method is not appropriate in the
case where the patient group of different progno-
sitic factors shows the temporally different pattern
of the disease course.

On the other hand, Markov chain model is also
used to evaluate a prognosis. Markov chain
model is a typical stochastic process model. Basic
Markov chain model is very simple, which as-
sumes several states (e.g. healthy, disease, death)
and the transition probabilities between states.
Markov chain model has been improved to solve
various real problems. In general Markov chain
model, the state transition probabilities are sup-
posed to be constant. In the prognostic analysis,
the state transition probabilities are varying de-
pends on the patient attributes and it would be an
important index to discriminate the poor progno-
sis group. Furthermore, the transition probability
changes, depending on the time interval while
patients have stayed in the previous states. In
this study, to overcome these difficulties, a new
type of Markov chain model that we call longitudi-
nal (non-homogeneous) Markov chain model
is developed to extract prognosis factors from the
disease course.

Thus our method comprised of (1) modeling of
the disease course by longitudinal Markov chain
model, (2) discriminating the poor prognosis
group based on the change of the transition prob-
ability of Markov chain model.

The prime purpose in this study is to evaluate
the prognostic factors of the early breast cancer

| Table 1 Classification of Stage II Breast Cancer in Japan |
|----------------------------------|--|--|--|--|
| Size (cm) Fixation Edema or Axillary Clavicular |
| to thorax infiltration lymph lymph node node |
| Unrecognized (-) (-) (+) (-) |
| -2.0 (-) (-) (+) (-) |
| 2.1–5.0 (-) (-) (-) (-) |
| 2.1–5.0 (-) (-) (+) (-) |
| 2.1–5.0 (-) (-) (+) (-) |

Fig. 1 Age

Fig. 2 Size of tumor
with a poor prognosis. The second purpose is to make a new prognostic factor analysis based on a non-homogeneous Markov chain model to overcome an insufficiencies of a proportional hazard model.

Subject

Stage II breast cancer was selected as the subject of the disease for our prognostic analysis. This is because the patients of this stage have a moderate portion of the poor prognosis group. Stage II has about a half of breast cancer patients. Table 1 shows the classification of Stage II Breast Cancer in Japan.9)

Patient data are retrospective, consisted by 758 cases treated in National Cancer Center Central Hospital between 1984 and 1990. And for all cases, the follow-up has been done for five years or more. The average age is 51.91 (S.D. = 11.21), and 5 years survival rate is 86.2%. Figure 1 shows the histogram of the age.

Figure 2 shows the histogram of the tumor size. The average size is 2.99 cm (S.D. = 0.81), and the distribution is normal.

Table 2 shows the occurrence area of a tumor. The area of the most frequent occurrence was the outside upper area, and inside and outside upper areas had about 70 percent occurrence of Stage II breast cancer.

Methods

(1) Construction of Markov chain model

To evaluate the prognosis factors, we tried to separate between a poor prognosis group and a good prognosis group statistically. Longitudinal Markov chain model was used to separate the poor prognosis group.

The Markov chain model is a basic stochastic process model that is widely used for modeling the probabilistic dynamics in the various fields. In the medical field, the Markov chain model was first applied for describing the course of the disease in 1980’s.10) In 1990’s, the Markov chain model was also introduced in the clinical analysis.11–13) In the Markov chain model, it is widely assumed that the state transition probabilities are constant, but it is not appropriate in dealing with disease process. In this study, we developed a new usage of Markov chain model in which the state transition probabilities change in the course of disease. We realize this by temporal succession of a simple Markov models that describe the dynamics within a temporal unit. We call this kind of Markov chain model longitudinal Markov chain

<table>
<thead>
<tr>
<th>Table 2 Tumor occurrence area</th>
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</thead>
<tbody>
<tr>
<td>Numbers</td>
</tr>
<tr>
<td>Outside lower</td>
</tr>
<tr>
<td>Outside upper</td>
</tr>
<tr>
<td>Inside lower</td>
</tr>
<tr>
<td>Inside upper</td>
</tr>
<tr>
<td>Center (Under areola)</td>
</tr>
</tbody>
</table>

Fig. 3 Markov chain model
model.

The concrete form of this Markov model applied to Stage II breast cancer patient is shown in Figure 3. The start point is the day of the surgery. And the temporal unit was defined as 6 months, considering the occurrence rates of the events (recurrence, death) and inexactness of the date that the recurrence had been confirmed.

The number of the patients who transit along each branch was counted to calculate the state transition probabilities.

(2) Discrimination of the poor prognosis group

The transition probability from state $A$ to state $B$ can be derived as

$$R_{AB}(t) = \frac{N_{AB}(t)}{N_A(t-1)}$$

$N_A(t-1)$ is the number of the patients in state $A$, and $N_{AB}(t)$ is number of the transited patients from state $A$ to state $B$ between the time $(t-1)$ to the time $(t)$. In a simple Markov chain model, it is supposed that the state transition probability is constant in each time period. And the state transition probability does not depend on the past history of the patients. This basic concept is called Markov property, and this basic model is called homogeneous Markov chain model. But, this basic property is not appropriate to describe the detailed phenomena of the prognosis. In our analysis, average transition probability between each state is decomposed into several sub-probabilities (rates) according to difference of the previous histories. That is, we take into account “the multiple property (multiplicity) of the state transition.”

This multiple property of the state transitions was examined to understand which group has a true poor prognosis. In concrete, the state transition from recurrence to death has two groups if we consider previously stayed state. One is sequentially worsening group from no-event through recurrence to death (we call this “linear transition”) and the other is that recurrence occurred several time units before and at time $t$ the transition to death is occurred as shown in Figure 4. The linear transition group is considered as patients who died for a short term after the recurrence.

The model that the Markov property is not assume is called non-homogeneous Markov chain model. So we call our method longitudinal non-homogeneous Markov analysis.

To discriminate the poor prognosis group, the average state transition probabilities from recurrence to death were not considered but instead we focused on this “linear transition” group.

The number of the linear transition to death (transits from state $A$ to state $B$, then transit from state $B$ to state $C$ in the next period) is displayed as $N_{ABC}(t)$. Figure 5 shows the path of the linear transition to death.

The transition rate from $A$ to $B$ to $C$ is defined as

$$R_{ABC}(t) = \frac{N_{ABC}(t)}{N_B(t-1)}$$
To determine the poor prognosis group, we examine the time point at which this linear transition rate remarkably decreases. We applied Mann-Whiney’s U test to detect critical time point, beyond which the linear transition rates show significant difference.

Thus we collected the patient group who showed linear transition before the critical time points and considered them the group who showed early breast cancer death.

(3) Evaluation of prognosis factors
The next step is to extract the prognostic factors that characterize this poor prognosis group. Multiple logistic regression analysis was used to evaluate the prognosis factors. This poor prognosis group is set as the case group, and control group is set as the group without events for five years.

Results
(1) State transition rates
Table 3 shows the death rates for each period. The first row is the average death rates without the consideration of the multiplicity property, and the next one is the death rates of linear transition from recurrence to death directly after the transition from no event to recurrence. The numbers of the linear transition to death had decreased with the time passage. $N_B(4.5)$ and $N_{ABC}(5)$ were both just one patient.

(2) Poor prognosis group
First, the patients who had got a recurrence for four years were discriminated as the poor prognosis group by Mann-Whitney’s test ($p < 0.05$) if we treat $R_{BC}(t)$. But under consideration of the multiplicity property, the patients who had got a recurrence for the first two and a half years (thirty months) were discriminated as the poor prognosis group ($p < 0.05$). The first group is not a true poor prognosis group, because many patients were alive for a long term. The next group is a true poor prognosis group. Almost of them is died for a short term after a recurrence.

(3) Logistic regression analysis
The patients who got recurrences until thirty months was chosen as a poor prognosis group, and the patients who got no event for five years was chosen as a good prognosis group in a multiple logistic regression analysis. The poor prognosis group had 49 cases, and the good prognosis group had 314 cases in this study. The mean of ages had no significant variance between the poor prognosis group and the good prognosis group. Figure 6 shows the age of the good prognosis group and the poor prognosis group.
poor prognosis group. It has no significant variance. Thirty variables were used as the independent variables in the logistic regression analysis (forward stepwise selection). The independent variables include the patient attributes, anamnesis, diagnosis, radiation and mammography opinions, treatments, and the pathological diagnosis. And three variables were selected as the prognostic factors. They were all pathological factors as the following, “n classification” of the pathological diagnosis, “ductal spread,” and “estrogen receptor.” Table 4 shows the $R$ statistic of these factors. $R$ statistic means the partial correlation between the dependent variable and each independent variable.

The fitness of logistic model was evaluated by comparing the predictions to the observed outcomes, and 85.95% cases were correctly classified by these three variables.

Especially, $n$ classification ($n0$, $n1\alpha$, $n1\beta$, $n2$) has a strong partial correlation with the early death in Stage II breast cancer. Figure 7 shows the survival curves separated by $n$ classification. Table 5 shows the log-rank statistics and their significance to test the difference of survival curve between each $n$ classification group. It has significant differences of survival curve except for between $n1\beta$ and $n2$ groups but the early death is not observed by this survival analysis.

**Table 4** Partial correlation ($R$ statistic)

<table>
<thead>
<tr>
<th></th>
<th>Wals statistic</th>
<th>$R$ statistic</th>
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</thead>
<tbody>
<tr>
<td>n classification</td>
<td>22.896</td>
<td>0.243</td>
</tr>
<tr>
<td>Ductal spread</td>
<td>7.653</td>
<td>0.076</td>
</tr>
<tr>
<td>ER</td>
<td>7.595</td>
<td>0.075</td>
</tr>
</tbody>
</table>

**Table 5** Log-rank statistic and significance

<table>
<thead>
<tr>
<th></th>
<th>$n0$</th>
<th>$n1\alpha$</th>
<th>$n1\beta$</th>
<th>$n2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n0$</td>
<td></td>
<td></td>
<td>8.69</td>
<td>(0.003)</td>
</tr>
<tr>
<td>$n1\alpha$</td>
<td>57.93</td>
<td>16.06</td>
<td>(0.000)</td>
<td>(0.000)</td>
</tr>
<tr>
<td>$n1\beta$</td>
<td></td>
<td></td>
<td></td>
<td>(0.000)</td>
</tr>
<tr>
<td>$n2$</td>
<td>64.01</td>
<td>21.45</td>
<td>1.23</td>
<td>(0.267)</td>
</tr>
</tbody>
</table>

**Fig. 7** Survival curves separated by $n$ classification

Discussion

As first step, we counted the number of the state transition for each branch described as Figure 3. And we could discriminate the poor prognosis group as the patients who had got a recurrence for four years.

But the true state transitions are complex like as Figure 4. After separation of state transitions as Figure 5, the discrimination time point changed. So the normal non-homogeneous Markov chain model is not sufficient to describe the state transitions in detail. It is important to consider the multiple property of the state transitions.

The result that the patients who had got a recurrence for the first two and a half years were discriminated as the poor prognosis group correspond with the clinical experience.

The result of the logistic regression analysis has an important meaning, because just three pathological tests were selected as the prognostic factors. All treatments and all diagnostic items (without the pathological tests) were independent to the early death of Stage II breast cancer. The Stage II breast cancer patients who died for a short term might be died by the cause of their pathological
status. Especially, n classification of pathological tests was the most influential prognostic factor.

Because R statistic (partial correlation) was very large (see Table 4) and the model fits just using n classification as the independent variable was 86.5%. Ductal spread and estrogen receptor had also a significant relation, but the relation between n classification and the early death was too strong. The future of the patients with a bad pathological status might be predicted.

On the other hand, the survival analysis including proportional hazard model could not observe the poor prognosis group. Because the number of the poor prognosis patients is small, the poor prognosis group has been buried in the population if we assume average survival curve. The result of this study could not be obtained by a proportional hazard model.

**Conclusion**

Our new model using the longitudinal non-homogeneous Markov chain model could discriminate the poor prognosis patients. This is quite different from the usage of the simple Markov chain model that has been used to evaluate the prognosis, and the concept of the state transition probability is quite different too. The concept that the state transition rate is not constant and depends on the past history is very crucial in this study, would be used in other prognosis analysis using Markov chain models. Otherwise, the discrimination of the poor prognosis group might have been impossible in another study.

The result of the discrimination of the poor prognosis group, that is, the patients who had a recurrence for thirty months after an operation are corresponding to the clinical experience. And if the past histories were not considered, these results might not have been derived. At first, the poor prognosis group was discriminated as the patients who had a recurrence for four years, but that result did not represent the truth. So this study shows that it is crucial to consider the past history of the state transition rate.

The result of logistic regression analysis shows the patients who have a poor prognosis are not died by the cause of the treatments or other factitious acts. The poor prognosis had a strong relation with the lymph node translations. These prognostic factors are the results of pathologic inspections. If the aspect is changed, the prognosis of the early breast cancer patients who have a poor prognosis may be determined by their pathological status.

Our result is not obtained by a proportional hazard model. It is necessary to investigate the state transitions in detail to evaluate the prognostic factors. And our analysis has enabled it. We propose this analysis as the advanced prognostic factor analysis.

The defect of this analysis is that many patients and high quality databases are necessary to investigate the multiple property of the state transitions.

On the other hand, non-homogeneous Markov chain model considered the multiple property should be used to evaluate the prognosis. Because the state transition probabilities may not be constant, it is crucial to investigate the temporal changes of the transition probabilities and the multiple property of the state transitions.

**References**

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