行政院國家科學委員會專題研究計畫成果報告

乳癌患者治療癒後局部復發對存活率之影響

Effects of Survival Rates Following Local Recurrences in Breast Cancer

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I. Abstract (中英文摘要)

臨床醫師常問是否乳癌患者治療癒後局部復發對存活有影響。有關局部治療控制癌細胞對患者存活的影響，已引起醫學界對早期乳癌最佳療法的爭議。因此本研究應用統計上的計數程序法，提出一套完整的疾病存活多狀態分析，針對 767 位平均被追蹤 19 年的乳癌患者手術後之復發死亡情形爲樣本。結果顯示局部復發影響轉移復發(P<0.0001)和死亡(P=0.014)，並且癒後時間越長與手術時腫瘤越大發生這些競爭事故的機率也越大。此結果有助於臨床醫師在乳癌患者手術後復發時輔予適當治療以改進患者生命品質並延長其生命。

關鍵詞：生命品質、多狀態疾病死亡競爭模式、存活、計數程序

In breast cancer, the question of whether local recurrences affect survival has been asked. The importance of local control in affecting survival has generated controversy regarding the optimal treatment of early breast cancer. Thus, this research applied multi-state failure models using counting processes to a sample of 767 breast cancer patients whose median follow-up was 19 years. Results showed that local recurrences affected distant recurrences (P<0.0001) and death (P=0.014). The longer a patient stayed in a state and the larger tumor size at surgery is, the more chance she will recur or die.

Keywords: Quality of life, Multi-state failure models, Survival, Counting processes

II. Introduction and Purpose(緣由與目的)

In breast cancer, the question has been asked if local recurrences affect survival and what is the effect of time length on the risk of death or other events (e.g., distant recurrences). From literature review of several breast cancer clinical trials, although some researchers concluded that the local radiation therapy reduces breast cancer deaths significantly [1][2], some did not have the same significant finding [3]. Does this imply that local recurrences are not important? How are various competing risks interpreted? This information may be important to clinicians attempting to improve patients' quality of life and extend their survival.

In the preceding examples, one question emerges: is there a way to evaluate the impact of recurrences (local recurrences in breast cancer) on a final outcome such as survival? This assumes that initial and subsequent failures will be observed and recorded (censoring is also allowed). To our knowledge, most of current statistical methods do not provide enough information to answer these problems. Chen* (1995) developed one of such statistical methods, and this project will be worked to apply and extend this method [4].

Some examples of currently conventional methods are briefly introduced in the following. The Kaplan-Meier (KM) estimator (estimated probability of surviving) [5] as-

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sumes only a single failure type and independent censoring. Its related comparisons of outcome among subgroups are conventional tests such as the log-rank tests and the Cox proportional hazards model with time-dependent covariates [5]. Cause-specific cumulative incidence functions [5] focus only on time to the "first" failure in the presence of competing risks. The method of counting processes [6] has only recently been applied to medical research. The method of counting processes is flexible and easy to apply for many complicated medical questions. However, most of the applications have only focused on time to the first failure in the presence of competing risks [7]. Other clinical examples using multi-state models to AIDS or liver data do not apply counting process methods [8][9]. Therefore, the use of a single multi-state survival approach for these clinical data may be particularly informative and useful by counting process methods.

The purpose of this project is as follows. (i) Multi-state illness-death competing risk models with censored data using counting process methods are further extended to compare clinical breast cancer data. (ii) Specific time factors considered for breast cancer data are the length of time from study entry or an intermediate state to the start of any subsequent state, and the length of time in the current state. Other risk factors are the baseline measurement of a factor measured at study entry (e.g., tumor size) and its effect with the passage of time, and the number of states previously entered. (iii) The relative best model of a breast cancer study is searched. (iv) These methods can provide tools for answering questions such as the impact of an intermediate state (e.g., a specific type of recurrence) on an ultimate state (e.g., death, or a serious disease condition).

III. Research Methods (研究方法)

Genuine multiple failure time data exist when each study subject is followed beyond the time of her first failure for subsequent failures. For example, Figure 1 shows a possible disease history of a patient with breast cancer. Each patient begins with no evidence of disease (NED: state 0) immediately after surgery. She may then develop a local recurrence (L: state 1), a distant recurrence (Dt: state 2), a combination of both (state 3), or die (state 4) in various orders of occurrence as indicated in the figure.

When various causes of failure are competing, that is, any one could be observed first and may preclude the occurrence of others, or alter the probability of the occurrence of the other, the problem is called a "competing risks" problem. A patient may also be censored without developing any event or censored alive with recurrence at her date of last follow-up. This type of administrative censoring commonly occurs in clinical studies because of the variable entry times of patients and a fixed time from study initiation to analysis. She may also have withdrawn from the study for a reason unrelated to her disease condition. These types of censoring are assumed to be right-censored and independent of the failure process throughout this project.

Models in this project for comparisons included a simple time-homogeneous Markov model [6], time-heterogeneous models, time-heterogeneous and other covariates added models. Counting processes were applied and maximum likelihood estimates of hazard rates were computed. The detailed theories and related proof of research methods for this project can be seen in Chen (1995) [4].

IV. Results and Discussion (結果與討論)

In this project, we used a sample of 767 women patients who had negative lymph node and no metastases at mastectomy. Subsets of this breast cancer data were analyzed previously using conventional methods, and detailed data collection and designs can be found in Rosen et al. (1992) [10].

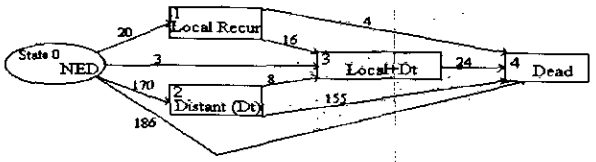

Figure 1: No. of patients who experienced each event

The median follow-up time was 19 years and the number of patients who experienced each event is also shown in Figure 1. For example, 767 patients began in state 0 (alive and NED), 20 of them later developed local recurrence (state 1) as their first event, 4 of these 20 died (state 4) after their first event and 16 of them developed distant recurrences (state 2) as their second event.

The results showed that a relative optimal model is a log-linear time-heterogeneous with one other covariate (tumor size at surgery) added hazard model. Furthermore, it is demonstrated that local recurrences affected distant recurrences ($P<0.0001$) and death ($P=0.014$). The longer a patient stayed in a state and the larger tumor size at surgery is, the more chance she will recur or die.

The results of this study may give medical researchers suggestions regarding improvement and extension of patients' life in breast cancer. In addition, these approaches can be easily applied to many other diseases and cancers.

V. Evaluation of Results (計畫成果自評)

Less statistical research on multi-state models going beyond the time to the first failure has been done in the previous medical setting. However, in the current era of cheap and fast computing, then with available data sets, it is feasible to develop formal statistical methods to address these clinical questions. In this project, we have successfully shown examples of such approaches in one empirical breast cancer data set, even with small sample size in some states.

Further studies will be in the problems of sample size and power calculation. A larger data set in a specific disease collected from Taiwan will be highly desired for research although it will require long-term follow-up. These proposed methods can provide tools for answering questions such as the impact of an intermediate state (e.g., a specific type of recurrence) on an ultimate state (e.g., death, or a serious disease condition) to many other diseases and cancers.

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VI. References (參考文獻)

[1] Levitt, S. H. (1994), "The Importance of Locoregional Control in the Treatment of Breast Cancer and its Impact on Survival," *Cancer*, 74, 1840-1846.

[2] Cuzick, J., Stewart, H., Rutqvist, L., Houghton, J., Ewards, R., Redmond, C., Peto, R., Baum, M., Fisher, B., Host, H., and et al. (1994), "Cause-Specific Mortality in Long-Term Survivors of Breast Cancer Who Participated in Trials of Radiotherapy," *Journal of Clinical Oncology*, 12, 447-453.

[3] Liljegren, G., Holmberg, L., Adami, H.-O., Westman, G., Graffman, S., Bergh, J., and Uppsala-Örebro Breast Cancer Study Group (1994), "Sector Resection With or Without Postoperative Radiotherapy for Stage I Breast Cancer: Five-Year Results of a Randomized Trial," *Journal of the National Cancer Institute*, 86, 717-722.

[4] Chen, S-C. (1995), "Multi-State Failure Models with Competing Risks and Censored Data for Medical Research," *Ph.D. Dissertation*, University of Southern California, August.

[5] Kalbfleisch, J. D., and Prentice, R. L. (1980), *The Statistical Analysis of Failure Time Data*, New York: John Wiley.

[6] Andersen, P. K., Borgan, Ø., Gill, R. D., and Keiding, N. (1993), *Statistical Models Based on Counting Processes*, New York: Springer-Verlag.

[7] Pepe, M. S., and Mori, M. (1993), "Kaplan-Meier, Marginal or Conditional Probability Curves in Summarizing Competing Risks Failure Time Data, *Statistics in Medicine*, 12, 737-751.

[8] Gentleman, R. C., Lawless, J. F., Lindsey, J. C., and Yan, P. (1994), "Multi-State Markov Models for Analyzing Incomplete Disease History Data with Illustrations for HIV Disease," *Statistics in Medicine*, 13, 805-821.

[9] Hansen, B. E., Thorogood, J., Hermans, J., Ploeg, R. J., Van Bcokel, J. H., and Van Houwelingen, J. C. (1994), "Multistate Modelling for Liver Transplantation Data," *Statistics in Medicine*, 13, 2517-2529.

[10] Rosen, P. P., Groshen, S., and Kinne, D. W. (1992), "Survival and Prognostic Factors in Node-Negative Breast Cancer: Results of Long-Term Follow-Up Studies," *Monographs / National Cancer Institute*, 11, 159-162.