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Patient Progress Modelling for Small Cell Lung Cancer

Rachel M. Pearce, Stephen Gallivan and R. Raymond P. Jackson

This paper describes the use of a mathematical technique called Patient Progress Modelling to reassess the results of an MRC trial on small cell lung cancer. The trial concerned patients treated initially with chemotherapy and radiotherapy and achieving at least a partial response. It compared the effects of giving maintenance chemotherapy with those of giving no maintenance therapy. The results of the MRC trial established that there was no significant survival difference between the two groups overall. However, it was observed that amongst patients achieving a complete response, those receiving maintenance chemotherapy had a small survival time advantage. The analysis described here suggests the hypothesis that this can be accounted for by differences in the pattern of deaths after relapse. There appeared to be little difference in the disease-free period.
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INTRODUCTION

THIS PAPER describes a study on small cell lung cancer undertaken by the Clinical Operational Research Unit in collaboration with members of the Medical Research Council (MRC) Lung Cancer Working Party. The study used data from the fourth MRC small cell lung cancer study. The MRC trial was prompted by concern about drug toxicity and compared the effects of 12 versus six courses of chemotherapy. No significant overall survival advantage was found in the 12-course group [1], although there did seem to be a small improvement for patients who achieved a complete response. Analysis of the trial, as specified in the trial protocol, was carried out using survival analysis.

Data from the trial have been re-examined using a mathematical model to identify differences which occur in survival patterns. This approach differs from statistical hypothesis testing in that its main aim is to assist the process of framing hypotheses based on available data. The method used, patient progress modelling, has previously been applied to acute myelogenous leukaemia [2, 3], Wilm's tumour [4] and Hodgkin's disease [5], among others.

MATERIALS AND METHODS

The MRC trial [1] involved a total of 497 patients with microscopically proven small cell lung cancer as defined by the WHO classification [6]. All were under the age of 75, with good performance status and renal function and no previous chemotherapy, or recent radiotherapy. All patients were prescribed an initial six courses of chemotherapy with etoposide, cyclophosphamide, methotrexate and vincristine (ECMV) at 3-week intervals; patients with limited disease on admission also received 40 Gy of thoracic radiotherapy between the second and third courses. After five courses of chemotherapy, 295 patients were still responding to treatment [complete response (CR) or partial response (PR) [7]]. Of these, 265 received either a further six courses of maintenance chemotherapy with ECMV (131 patients) after the sixth course, or no maintenance chemotherapy (134 patients). The remaining 30 potentially eligible patients either refused to be randomly allocated treatment, or were excluded from the trial by their clinician.

Data were available in the form of record cards concerning patients' clinical status at the time of each course of chemotherapy or radiotherapy and at each subsequent monthly follow-up assessment. The data included, among other details, the treatment given, an assessment of the response [CR, PR or no response (NR)] and a note of whether a new primary growth was suspected.

For those patients who achieved a complete response, the data were examined to find the first date on which they were judged to be in CR; this was taken to be the date on which CR was achieved. Similarly, the date of relapse was taken to be the first date on which it was suspected that a patient in CR had a recurrent primary growth or distant relapse. The date of start of treatment and the date of death were also available. These data were used for calibrating the mathematical models of the progression of patients through different stages of the disease.

RESULTS

Patient progress modelling is a technique for analysing trial data based on ideas from operational research. It is based on mathematical techniques frequently applied in business and industry. In the past it has been applied to leukaemia [2, 3], Wilm's tumour [4] and Hodgkin's disease [5].

The model used in this study took a form standard for patient progress modelling, with a small number of "states" in which a patient might be at any given time. The variability in the time between entering a state and the transition to another state was modelled using probability distributions reflecting the principal features of the observed data. Based on this information the model describes mathematically the progression of patients between states.

A schematic diagram of the states and transitions used in the patient progress model is shown in Fig. 1. Not all patients who died had a specified date of relapse. In order to accommodate this, a 'dummy' transition from complete response to death was included for such patients. This allows the model to cope with cases where the time spent in relapse is unknown.

The model, calibrated using data from one group of patients,

Correspondence to S. Gallivan.
S. Gallivan, R.M. Pearce and R.R.P. Jackson are at the Clinical Operational Research Unit, Department of Statistical Science, University College London, Gower Street, London WC1E 6BT, U.K.
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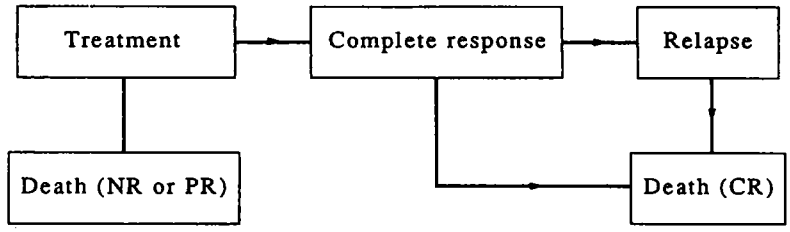

Fig. 1. Schematic diagram of patient progress through the course of their disease.

can be used to make predictions about a second group, assuming they progress in the same way. If the actual progression of the second group does not conform to the model's predictions, it suggests that treatment differences between the two groups are causing different disease progressions. Naturally, care is required not to overinterpret such a model.

The model has two parameter types—the proportion of patients undergoing a particular transition and the parameters describing the distribution of times spent in each state. These parameters were estimated using data for the patients who received maintenance chemotherapy. Any patients allocated to have maintenance chemotherapy, who did not receive it were omitted from this estimation process.

Since the model represents an idealisation of the data, it is unlikely that the model's predictions would agree exactly with the data observed and some differences are to be expected. This is analogous to the scatter of data points around a linear regression line. To assist interpretation, the modelling technique allows the calculation of 95% probability limits for its forecasts, within which 95% of the data points would be expected to lie. It is worth repeating that since the method is not a statistical hypothesis test these limits are only a guide to the goodness of fit of the model.

The model, calibrated to the maintenance patients, was then applied to predict the progression of patients who were allocated to receive no maintenance chemotherapy. The results of this analysis are shown in Fig. 2.

These graphs show that the numbers of patients allocated to no maintenance chemotherapy who died in PR were almost exactly as predicted by the model for the patients who did receive maintenance. Similarly, the numbers in CR stayed well within the 95% bounds of the expected values. However, the numbers in the "relapse" state are below those expected, and the numbers in the "dead having achieved CR" state are consistently higher than would be expected from the model for the maintenance group.

Although this does not rigorously prove that the progression of no maintenance patients is different from that of maintenance patients, it does give grounds for framing a hypothesis. Perhaps the simplest hypothesis consistent with the results shown in Fig. 2 is that non-maintenance patients who have achieved CR die more quickly once they have relapsed.

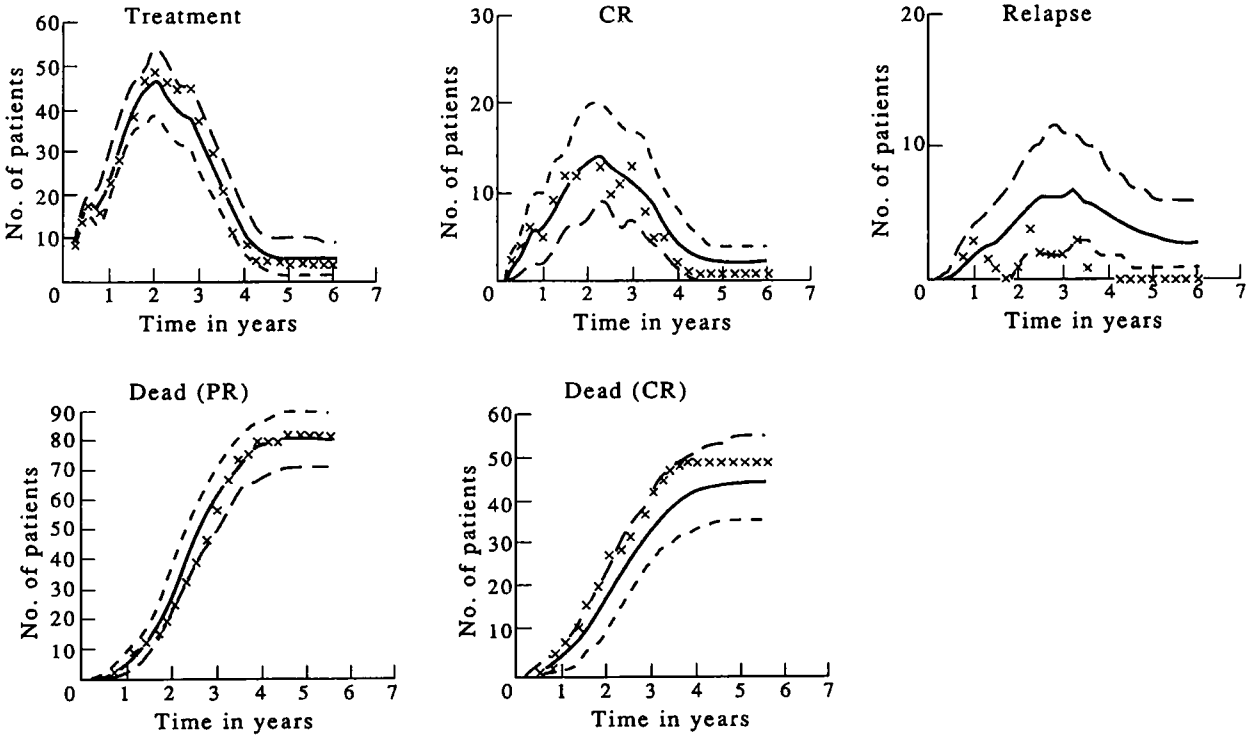

Fig. 2. Application of patient progress model to no maintenance patients. Each graph represents the numbers of patients in a given state throughout the trial. Time 0 is the date of the start of the trial. The actual numbers of no maintenance patients observed in each state are marked by asterisks. The predicted numbers, according to the model calibrated for patients who received maintenance chemotherapy, are shown by a solid line. The dashed lines represent the upper and lower 95% probability limits for these latter estimates.

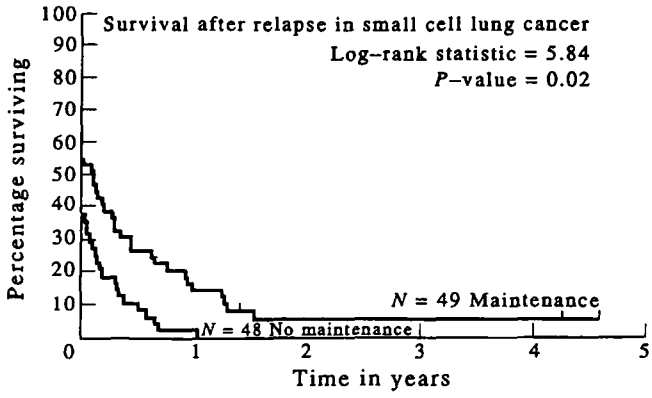

Fig. 3. Comparison of actuarial survival curves for survival after relapse.

To examine this hypothesis further, the model calibrated using data for the maintenance group was modified, the transition rate from relapse to death being changed to the rate observed for the non-maintenance group. Once this was done, the new model predictions approximated what was actually observed for the non-maintenance group. This supports the hypothesis that maintenance therapy reduces the death rate of patients who have achieved CR rather than delaying the onset of relapse.

Other hypotheses were examined using similar modelling techniques but none accounted for the observed differences in patient progress.

DISCUSSION

Patient progress modelling thus suggests the hypothesis that the effect of maintenance chemotherapy was to prolong the survival after relapse for those patients who achieved a response, rather than to extend their initial disease-free period. This hypothesis is supported by examination of actuarial survival curves. Survival after relapse (Fig. 3) was significantly longer for patients given maintenance therapy ($P = 0.02$), but there was no significant difference ($P = 0.77$) in disease-free survival (Fig. 4). Differences between the sample sizes quoted in these figures are due to an exact date of relapse being unavailable for some patients.

Some patients who relapsed and died were still in CR at their last monthly follow-up assessment. For analysis illustrated in Fig. 3, it has been assumed that these patients relapsed on the day that they died. Hence the survival after relapse curves (Fig. 3) drop from 100% at day 0. Another possible assumption is that they relapsed the day after they were last seen. Assuming this leads to slightly different survival curves, but no difference in the conclusions ($P = 0.501$ for disease-free survival and $P = 0.004$ for survival after relapse). Since these two assumptions represent the extremes of what might actually have occurred, the conclusions are robust.

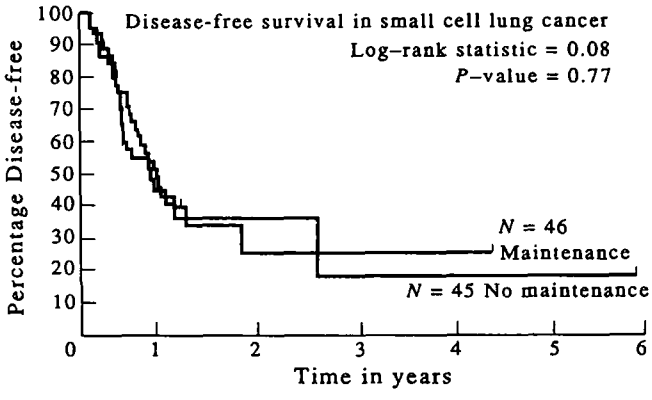

Fig. 4. Comparison of actuarial survival curves for disease-free survival.

This analysis supports the MRC suggestions that maintenance therapy for small cell lung cancer has no survival benefit for patients who have not achieved a CR and the observation of a small benefit in the survival time of those receiving maintenance therapy.

Our mathematical analysis suggests that the source of this increased survival time may be a reduced rate of early deaths after relapse, rather than an extended period of CR. This view has been further supported using survival analysis.

This approach to the analysis of trial data is a useful means of generating hypotheses about the differences if any between the groups.

A simple view of lung cancer chemotherapy is that, once initial therapy ceases, there are residual tumour cells, predominantly resistant to the cytotoxic effects of further treatment, which increase in number until relapse occurs and later, death. Intuitively, any additional treatment that increases survival should do so either by reducing the number of residual tumour cells and/or by reducing their rate of proliferation. In either case, one might also expect the time in remission to be extended. The findings of this study are counter-intuitive since this does not seem to have been the case.

Consider a simple mathematical model: that residual tumour cells proliferate in a homogeneous fashion, with a constant doubling time, and that the events "relapse" and "death" are determined purely by the total number of tumour cells reaching particular critical levels. Even assuming patient-to-patient differences in the numbers of residual drug resistant and drug sensitive tumour cells and their doubling times, the mathematical consequences of such a model are incompatible with the findings of our study. The major assumptions of this model thus deserve scrutiny.

Consider first the assumption that residual tumour cells proliferate in a homogeneous fashion. An alternative hypothesis is that drug resistant tumours cells proliferate less quickly than drug sensitive cells. With such an assumption, it is possible that following initial treatment, the majority of residual tumour cells are drug resistant and that in spite of their slow proliferation, reach numbers that are clinically detectable before the faster dividing drug sensitive cells have a noticeable clinical effect. However, the more rapidly dividing drug sensitive tumour cells would constitute an ever increasing proportion of the tumour cells. With such behaviour, additional chemotherapy might have little effect on the time in remission, but would increase the time in relapse.

Another assumption that can be criticised is that the events "relapse" and "death" are solely related to the *total* number of tumour cells present. This is also too simplistic. A relatively small number of tumour cells may damage a vital organ and cause death; on the other hand a relatively large tumour cell population elsewhere may be more readily detectable while posing little immediate life threat. Thus assuming that relapse and death depend only on the total number of tumour cells is too simplistic. The tumour cells which become so numerous that relapse can be diagnosed may often be in different sites, and perhaps have a different nature, from those which are the

immediate cause of death. Assuming heterogeneity of the cytotoxic effects of chemotherapy could give rise to behaviour compatible with the findings of our study, whereby relapse is a phenomenon associated with relatively large numbers of drug resistant cells while death is sometimes due to relatively small colonies of drug sensitive cells causing the failure of a vital organ.

The two hypotheses, that proliferation rates differ between tumour cells sensitive and resistant to cytotoxic therapy and that chemotherapy has heterogeneous cytotoxic effects in different organs of the body, although biologically plausible, are rather speculative. Data from the present study are insufficient to test either. However, our findings do indicate that an over simplistic view of the effects of chemotherapy can be misleading.

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Lack of Therapeutic Efficacy of Tamoxifen in Advanced Renal Cell Carcinoma

Axel Schomburg, Hartmut Kirchner, Martin Fenner, Thomas Menzel, Hubert Poliwoda and Jens Atzpodien

In the present study, we treated a total of 62 patients with advanced renal cell carcinoma with high-dose tamoxifen (100 mg/m²/day). Patients were treated in the outpatient setting, and were evaluated 8–12 weeks after initiation of therapy or sooner, when clinical disease progression was evident; a total of 15 patients were seen at short regular intervals for evaluation of clinical and laboratory parameters. Of these 62 patients, 59 were evaluable for treatment response, survival and systemic toxicity. One partial remission was achieved (1.7%; 95% confidence interval, 0.04–9.09%), response duration was 3 months. 10 patients presented with stable disease, for a median duration of 4.0 months, and 48 patients exhibited disease progression upon and after therapy. Systemic toxicity was significant; severe fatigue occurred in 5% of patients, and moderate anaemia, dyspnea, alopecia and malaise in almost 20% of patients. Antineoplastic efficacy of tamoxifen at this dosage in this cohort of patients was at best marginal and well in the range associated with the occurrence of spontaneous remissions. Toxicity was substantial, and it was not balanced by therapeutic benefit. This is consistent with the known lack of therapeutic efficacy of endocrine therapy in advanced renal cell carcinoma.
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INTRODUCTION

THE OVERALL prognosis of patients with advanced renal cell carcinoma is poor. While spontaneous regression of a metastatic disease has been reported to occur in 0.5–5% of patients [1], more than 70% of patients succumb to their tumour within 1 year of diagnosis of metastatic renal cancer [2].

Based on experimental tumours in Syrian golden hamster models [3], hormonal manipulations were felt to be justified in advanced renal cancer patients. Patients were treated with a wide variety of hormone agonists and antagonists, such as corticosteroids, progesterones and antioestrogens. As Hrushesky and Murphy noted [4], with the application of stricter response criteria to study populations, response rates of endocrine therapy decreased from 17–33% between 1967 and 1971 to 2% between 1971 and 1976 [5].

Tamoxifen is a non-steroidal antioestrogen which is successfully administered in breast cancer patients [6]. Some breast cancer cells are known to possess oestrogen receptors. However, on renal cell carcinoma cells, previously documented oestrogen

Correspondence to J. Atzpodien.
The authors are at the Abt. Hämatologie und Onkologie (6860), Medizinische Hochschule Hannover, D-3000 Hannover 61, Germany.
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