Criteria for evaluating patients undergoing chemotherapy for malignant brain tumors

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The authors describe their criteria for evaluating brain-tumor patients, and present a numerical rating scale devised to designate response to testing. They discuss the reliability of test combinations that permit accurate prediction of response or deterioration during therapy in their experience with 100 patients treated on the Chemotherapy Service at the Brain Tumor Research Center, University of California, San Francisco School of Medicine. Specifically, the paper summarizes the predictive value of the neurological examination, radionuclide scintiscan, computerized tomographic brain scan (CT scan), and electroencephalogram (EEG), in the determination of response (tumor regression) or deterioration (tumor growth) during brain-tumor chemotherapy and chemotherapy-radiotherapy.

By retrospective analysis, the neurological examination, radionuclide scintiscan, and CT scan were of equal value individually as tests to predict response to therapy. However, the prognostic values of the neurological examination or the radionuclide scintiscan proved moderately superior to the CT scan in predicting deterioration during therapy. Under circumstances whereby a neurological examination, radionuclide scintiscan, and CT scan were all performed during the same testing session, and steroid dosage was carefully monitored, two of the three tests accurately predicted deterioration in 65% of patients, and response to therapy in 82% of patients. Two of the three tests correctly established deterioration in the remaining 35% of patients, and response in the remaining 18% of patients, when the two positively correlated tests had occurred within a mean period of 7 weeks.

Key Words: brain tumor, computerized tomography, CNS chemotherapy, electroencephalography, radionuclide brain scan

The two end-points used to evaluate and compare treatment regimens for patients with brain tumors have been survival, and tumor regrowth or progression. Survival is an obvious and definite end-point, while status of tumor is a more subjective one. However, a reliable means of determining whether a patient’s condition is deteriorating, that is, if the tumor is regrowing or continuing to grow, is crucial if alternative therapies are to be instituted before irreversible brain damage and tumor growth occur. In previous reports we have described the general guidelines used by our staff to evaluate patients in terms of deterioration and response to therapy. In this paper we dis-
cuss the system we have developed to evaluate response to chemotherapy and the reliability of this system.

The analysis is a retrospective study of those tests (electroencephalography (EEG), neurological examination, radionuclide (RN) scan, and computerized tomography (CT) scan) that accurately predicted the effect of therapy. For example, if a patient showed a response to therapy based on neurological examination and RN scan, then we reviewed the results of all four tests listed above performed before the date of confirmation of response. During this review we determined which test(s) was (were) the first to indicate that the patient was responding to therapy. This (these) test(s) then became the most reliable predictor(s) of response for that patient. The same method was followed for determining the most reliable predictor(s) of deterioration for patients who were therapeutic failures.

Materials and Methods

One hundred patients undergoing therapy (chemotherapy alone or in combination with radiotherapy) for malignant brain tumors were evaluated with neurological examination, RN scan, CT scan, and EEG at intervals of 4 to 8 weeks after the initiation of therapy. Therapy included one of the nitrosoureas (1,3 bis (2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-choroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), or methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (MeCCNU)), alone or in combination with procarbazine, vincristine, hydroxyurea, or 5-fluorouracil. The therapies were part of ongoing protocols of the University of California, San Francisco, Brain Tumor Research Center, the Brain Tumor Study Group, or the Western Cancer Study Group.

To avoid any confusion between deterioration due to tumor regrowth and post-irradiation encephalopathy, examinations conducted during the initial 3 months following the completion of radiotherapy were not included in the analysis to be reported here.

Neurological Examination

The neurological examination was performed by one of us (D.C.) or a neurosurgical resident and reconfirmed by another observer (C. W. or V. L.). Emphasis was placed on any changes in the neurological examination that had occurred in the interval since the last examination. Consideration was given to other disease processes, such as urinary tract infection, that might cause clinical deterioration but would not necessarily indicate actual tumor progression. In this evaluation the relative steroid dose was also taken into account to differentiate steroid-mediated clinical improvement from improvement due to cytotoxic therapy.1 The following scale was used to designate relative changes in clinical neurological status:

-3 = markedly better
-2 = definitely better
-1 = possibly better
0 = unchanged
+1 = possibly worse
+2 = definitely worse
+3 = markedly worse.

Radionuclide Brain Scan

Patients were injected intravenously with 15 to 20 mCi of 99mTc diethylenetriaminepentaacetic acid sodium salt (DTPA). A radionuclide angiogram was obtained only on the first postoperative study. Conventional imaging was performed 1 to 1½ hours after injection using a Searle Pho Gamma IV Camera* with a low-energy all-purpose (LEAP) collimator. Anterior, posterior, right and left lateral, and vertex images were obtained in all patients; 400,000 count images were obtained except when the imaging time for the view exceeded 5 minutes, in which case 300,000 count views were obtained. Additional delayed views were occasionally obtained when clinically indicated but were not used in the scoring of changes in lesions.

Lesion change was defined as a change in size or number of lesions only, and not as a function of lesion intensity, that is, the amount of radionuclide uptake. All scans were initially scored by a resident but all scores were reviewed by a member of the nuclear medicine staff familiar with the experimental protocol. A designation of +1 or -1 was reserved for equivocal change in lesion size. Any lesion with definite size change, no matter how small, was recorded as +2 or

*Pho Gamma IV Camera manufactured by Searle Laboratories, Des Plaines, Illinois.
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-2. Scores of +3 or -3 were reserved for cases with marked change in lesion size between examinations. Appearance of a new lesion was considered definite evidence of deterioration and was given a rating of -2 or lower. Similarly, a score of +2 was assigned if a secondary lesion disappeared. Care was taken to distinguish postoperative change or radionuclide uptake associated with burr holes from changes due to actual lesions. Changes in calvarial activity due to operative or shunt procedures were disregarded in the ratings of lesion change.

**Computerized Tomographic Brain Scans**

Initial evaluation consisted of a complete CT scan before and after the intravenous administration of 300 cc of 30% meglumine iothalamate (Conray 30) (double scan). We used an EMI scanner† 4½-minute scan, with a 160 x 160 matrix in 60% of patients, and an 80 x 80 matrix in 40% of patients. The infusion technique consisted of an initial administration of 150 cc of 30 meglumine iothalamate immediately before scanning, with the remaining 150 cc administered during the 20-minute period required to complete the series of four scans. For reasons of economy, follow-up scans were performed after contrast administration only, unless there was a marked change in the patient's clinical condition, at which time both pre- and postcontrast scans were again performed. Double scans were routinely obtained at 4- to 5-month intervals to establish a new baseline. The following CT scan parameters were evaluated:

1. Tumor size
2. Central lucency
3. Degree of contrast enhancement
4. Surrounding edema
5. Ventricular size.

Tumor size and central lucency were measured directly from the polaroid images. Contrast enhancement, surrounding edema, and ventricular size were evaluated on consecutive studies and “grades” were assigned on a scale of -3 to +3 by two independent observers.

**Electroencephalographic Recordings**

Electroencephalographic recordings were made on a 16-channel Grass polygraph‡ using the International montage. Deterioration and response relative to the immediately preceding visit and examination were evaluated using a sliding scale of -3 to +3. The major criteria of change were the amplitude and abundance of slow-wave activity. The same observer (J.P.S.) made all observations independent of any clinical information other than the fact that the patient was receiving chemotherapy with or without radiotherapy for a brain tumor.

**Criteria for Response**

In these, as in previous studies,5,6 response was defined as an unequivocal improvement in the clinical neurological status and isotope scintiscan while the patient was on non-escalating doses of dexamethasone. Steroid doses were either decreased from the previous visit or unchanged. If the steroid dose had been increased at the time of the previous examination, response could not be designated until the second examination following the dose change.

**Criteria for Deterioration**

These criteria were really the converse of the above. Deterioration in spite of therapy was designated when the patient showed worsening in the neurological examination (not attributable to systemic complications) and deterioration in the RN scintiscan. When steroid doses had to be increased to stabilize or slow the rate of neurological deterioration, they were either increased after the RN or CT scans had been obtained or, if steroid dose escalation occurred before the RN and CT scans, the subsequent RN and CT scans had to show deterioration in order for the designation to apply.

**Results**

Figures 1 and 2 show the relationship of symptoms and previous therapy to chemotherapy (in this case BCNU-procarbazine), dexamethasone therapy, and the

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†EMI scanner manufactured by EMI Tronics, Inc., 3605 Woodhead Drive, Northbrook, Illinois.

‡Polygraph manufactured by Grass Instruments Company, Quincy, Massachusetts.
FIG. 1. Relationship of cytotoxic therapy (bars) to numerical responses (−4 to +4) of clinical neurological examination, isotope scan, electroencephalogram (EEG), and computerized tomography (CT) scan in a patient with a malignant astrocytoma.

Various response parameters. If one recalls that a response of zero indicates no change since the previous evaluation period, it can be appreciated that the patient in Fig. 1 showed initial deterioration in the isotope scintiscan and EEG before improvement occurred. This patient would not have been designated a responder until Week 24, based on simultaneous response grades of +2 for the clinical examination and scintiscan. The transient deterioration in the scintiscan and EEG would not have been included in the table of

FIG. 2. Relationship of cytotoxic therapy (bars), and dexamethasone therapy (broken line, lower) to numerical response (−4 to +4) of clinical neurological examination, isotope scan, and electroencephalogram (EEG, upper) in a patient with glioblastoma multiforme.
deteriorating patients since eventual response was the trend over the 30-week period depicted in Fig. 1.

Figure 2 shows the course of a patient who had an initial improvement (+3) in clinical status at 4 weeks, scintiscan improvement by 10 weeks, but subsequent deterioration even when the dexamethasone dose was increased (Week 16). Thus this patient was not designated a responder, even though the scintiscan markedly improved, because both tests were never equal to or greater than +2 at the same time. Such a patient would be a "probable responder" at 4 weeks, but did not show a clear-cut deterioration by our original response criteria until 32 weeks.

To determine the relative merits of the various diagnostic tests, we posed the following question. If one or more of the examinations (neurological examination, RN scan, CT scan, or EEG) changes significantly in either direction (+2 or -2), what is the probability that this initial change accurately predicts the patient's subsequent course? From the histograms presented in Fig. 3 it can be seen that a change in the neurological examination predicted tumor regression or response to therapy with an 80% probability, and tumor regrowth or deterioration with a 58% probability. A change in the RN scan predicted regression with a 74% probability and regrowth with a 61% probability. The CT scan predicted regression with a 72% probability and regrowth with a 42% probability, slightly less than for the neurological examination or RN scan. The EEG was much less predictive in that regression was predicted with only a 28% probability; regrowth was more accurately predicted, however, with a 52% probability.

**Discussion**

Table 1 summarizes the probability of accurate prediction of response or deterioration if multiple tests are administered simultaneously, and compares the effect of considering one or more of these simultaneous tests in deciding whether regression (response) or regrowth (deterioration) will occur. In order to become a statistic in the response or deterioration column at least one of the tests in the group must be +2 or greater, or -2 or less, while the remaining tests are similarly correlated or show no definite change (that is, they must be -1, 0, or +1). For the sake of discussion, it was assumed that only the combination of tests cited in Table 1 were actually administered.

The conclusions drawn from Table 1 were that the EEG actually detracted from the predictability of the neurological examination by false negative scores. Specifically, instead of improving on the 80% probability of accurately predicting tumor regression with the neurological examination alone, the EEG
TABLE 1

Probability of accurate prediction of response or deterioration based on one or more initially positive tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Responders*</th>
<th>Deteriorators*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>clinical examinations, scintiscan</td>
<td>33/34</td>
<td>60/66</td>
</tr>
<tr>
<td>clinical examination, CT scan</td>
<td>18/18</td>
<td>23/37</td>
</tr>
<tr>
<td>clinical examination, EEG</td>
<td>17/25</td>
<td>33/48</td>
</tr>
<tr>
<td>scintiscan, CT scan, EEG</td>
<td>8/10</td>
<td>27/29</td>
</tr>
</tbody>
</table>

*Only those patients with a definite response of +2 or greater (responders) or those with −2 or less (deteriorators) are included in this Table.

with 3% false negative (−2) scores brought the probability down to 68%. It can also be appreciated that the CT scan allowed the designation of only 4% more patients in the regrowth or deterioration category than deserved for the neurological examination alone.

Although not advocated, it was observed that deterioration could be predicted 93% of the time by the combination of RN scan, CT scan, and EEG without reliance on a neurological examination.

If the EEG observations are neglected for the determination of response and deterioration, and it is assumed that all patients received a neurological examination, RN scan, CT scan, and careful dexamethasone dose adjustments, then a number of valuable calculations of predictability and reliability of tumor growth trends can be made. The data in Table 2 show that if one considers only cases where any two of the above three tests were positively correlated at the same time, accuracy is improved to the extent that results from all patients correctly predicted the disease trend. Unfortunately, two positively correlated tests at the same time were seen 65% of the time in the deteriorators and 82% in the responders. The occurrence of three positively correlated tests at the same time was observed in only 30% to 35% of patients.

A compromise position would be to accept two positive tests, each occurring separately during sequential evaluation periods. For both the response and deterioration groups the second test observations occurred in a mean of 7 weeks from the first observation. This period coincided roughly with the interval between courses of therapy. For practical purposes, if the second test observation is not

TABLE 2

Probability of accurate prediction of responders and deteriorators based on any two of three simultaneous or sequential clinical examination, scintiscan, and CT scan scores of −2 or +2

<table>
<thead>
<tr>
<th>Predictive Criteria</th>
<th>Responders (34)</th>
<th>Deteriorators (66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>two or more tests positively correlated at same examining period</td>
<td>82%*</td>
<td>65%†</td>
</tr>
<tr>
<td>second test confirmation obtained at a sequential examination period for trend prediction mean time by which second test confirmed</td>
<td>18%‡</td>
<td>35%§</td>
</tr>
<tr>
<td>three or more tests positively correlated at same examining period</td>
<td>7 wks</td>
<td>7 wks</td>
</tr>
<tr>
<td></td>
<td>35%∥</td>
<td>30%†</td>
</tr>
</tbody>
</table>

*False negative responses: 10.7% −2 EEG's, 7.1% −1 CT scans, and 3.6% −1 EEG's.
†False positive responses: none.
‡False negative responses: 16.7% −2 scintiscans and CT scans, and 16.7% −1 EEG's and neurological examinations.
§False positive responses: 4.3% +2 neurological examinations, and 4.3% +1 CT scan and neurological examinations.
∥False negative responses: none.
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seen at the immediately following evaluation period it is unlikely to occur.

Of note is the low level of false positive responses in the group of deteriorating patients; of the 66 patients in this group only one patient had a +2 neurological examination response and one patient had a +1 CT scan and neurological examination response. The group of 34 responding patients fared slightly worse in false negative responses; three had a +2 EEG response, three a +1 CT scan, two a −1 EEG, one a −2 scintiscan and CT scan, and one a −1 neurological examination. If the EEG results are discounted, there was only one patient with a clearly false negative scintiscan and CT scan (same patient) and four others with equivocal false negative tests. Thus, in the cases where patients are clearly deteriorating (that is, with a score of −2 or lower), a trend which is clearly more important than response, our testing system requiring two simultaneous or sequential ratings of −2 or less in two of the four test areas is quite accurate and predictive.

In conclusion, the use of an evaluation schema of a neurological examination, CT and RN scintiscans, and careful consideration and maintenance of minimal dexamethasone doses is sufficient to predict deterioration (that is, tumor regrowth) and response to chemotherapy with or without radiotherapy of patients harboring malignant brain tumors. Two positively correlated tests occurring at the same time or within one course of therapy are adequate for these predictions. At the time this paper was prepared, the efficacy of the CT scan in the appraisal of tumor regrowth was not as great as that of the RN scan.

Many variables may have affected the discrepancy in accuracy of the CT scan versus RN scans in evaluating tumors under therapy. The 80 × 80 matrix was used for 40% of the scans, and spatial resolution was significantly less than with the 160 × 160 matrix; also sensitivity to motion was marked. Motion artifact is now a less pronounced problem, but is still present in the current CT scanning equipment. The advent of fast-scan technology with scans taking 5 to 60 seconds should considerably reduce motion artifact. Presently, a combination of neurological examination, RN scintiscan, and careful steroid dose optimization are the minimum tests necessary for accurate prediction of brain-tumor regrowth in patients undergoing chemotherapy and/or radiotherapy.

References


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