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ASSESSMENT OF THE RESPONSE OF TUMOURS TO RADIATION: CLINICAL AND EXPERIMENTAL STUDIES

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Summary.—There is an important and active research programme at the laboratory and clinical level to develop indicators of the ultimate local response of tumours to radiation. In order to be of great value clinically indicators should yield a high true positivity and a low false positivity so that revisions of therapeutic strategy will be made only when there is a real need for such a change. The available data in the literature from the clinical studies, when analysed in terms of the true and false positive rates, indicate that the extent of regression at the completion of external beam therapy is not a useful prognostic indicator. This pertains to populations of tumour of a specific histopathological type, tumour size and anatomic site. Studies of laboratory animal tumour models have shown that regression patterns may be useful prognostic indicators for a tumour which is characterized by moderate immunogenicity and where there is close correlation between complete regression and permanent control. In contrast for tumours which are weakly or nonimmunogenic and which regress completely even at low tumour control probabilities, the pattern of regression has not been demonstrated to be of prognostic value.

THE CLINICIAN is in clear need of prognostic indicators of local response of tumour to the planned radiation treatment. This information should be obtainable from the diagnostic evaluation during the course of treatment or be derived from some parameter of response during or at completion of the course of treatment. It is at that time that the radiation therapist must decide whether treatment may be properly stopped, whether additional dose is warranted, or whether surgery should be performed because the likelihood of success by radiation alone is low.

General indicators of response of tumours exist which have clinical utility and these are derived from the histopathology, tumour size, tumour site and certain host characteristics. For example, seminomas regress rapidly and completely at low radiation doses, *viz.* $\simeq 30$ Gy in 4 weeks. However, squamous cell carcinomas, on average, regress more slowly and doses of 65–75 Gy are required to achieve permanent regression in a high proportion of patients. Further, there are data which show that for successful treatment, the total radiation dose must increase with tumour size (Fletcher, 1973). In addition, the pattern of clinical presentation is known to influence the likelihood of permanent regression. For example, squamous carcinomas of the head and neck region which are exophytic and with relatively little infiltration into deep structures regress quickly and the likelihood of local control is high, even though the tumour may be bulky. Contrariwise, squamous cell carcinomas which deeply infiltrate muscle are relatively resistant; large radiation doses are required even for a modest frequency of permanent control. If the carcinoma has directly invaded bone, local control is rarely achieved even when doses are so high as to produce unacceptable levels of damage to normal

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tissue. Host factors also influence tumour response, *e.g.* anaemia (Bush *et al.*, 1978). This knowledge is obviously of great value, but the clinical need for prognostic information is much more particular. In planning the complete management strategy for an individual patient, the clinician wants assistance in predicting the outcome for the patient under consideration, *i.e.* a patient with a tumour of known histological type, site and size. Unfortunately, when he considers a population of tumours which are uniform with respect to clinical characteristics (histopathological type, histopathological grade, anatomical site, tumour size and pattern of presentation, *i.e.* exophytic, invasion of bone, *etc.*) and subjected to a uniform treatment protocol (total dose, number of fractions and spacing of fractions) there is little to serve as a useful guide in distinguishing between the patients whose tumour will respond well from those whose tumour will not.

There are several parameters of tumour response which are under clinical study and have, as yet, to be proven of clinical value. These include: regression pattern during course of fractionated radiation; changes in mitotic index, changes in number and appearance of tumour cells; changes in blood flow, tumour temperature, intercapillary distances; estimation of oxygen tension by polargraphic techniques; immune status of patient, *etc.* Each of these various procedures has had supporters of different degrees of enthusiasm. There has not been published, however, an account of the proven efficacy of any of these procedures for any one tumour type and stage. We hope that further study will be able to demonstrate at least some clinical problems where these or other indicators will be of substantial practical value to the clinician.

Laboratory animal tumour models have also been employed to investigate these same problems. Unfortunately, even here the efforts have not achieved great success. The biologist does, however, have greater flexibility in the range of methods which may be employed to monitor response. Importantly, the biologist can generate complete dose–response curves for any end-point employed. Further, the greater abundance of data from such studies does permit more sophisticated statistical analyses. As stated above, if a prognostic indicator is to be employed at a clinical level, with practical value, information about it must be available during or at the completion of treatment.

The end-point of ultimate interest to the clinician is tumour control, *i.e.* complete and permanent regression. Accordingly, in preclinical studies it probably should be accepted that the reference end-point be the dose–response curve for tumour control, *i.e.* tumour control probability (TCP) *versus* dose. For reasons of experimental convenience, speed and/or economy, there are strong justifications for using end-points other than tumour control frequency. End-points which are appropriate for further and intensive study include: tumour regression pattern, time to complete regression, tumour growth delay, clearance of radioactive labelled cells, tumour blood flow, mean tissue pO_2, parameters of cell proliferation kinetics, assessment of host immune rejection reactions against the tumour, *etc.* The two most popular end-points for assessing response of tumour tissue *in vivo* which do not require disruption of the integrity of the tumour tissue are tumour control and tumour growth delay. Studies of tumour control are usually described in terms of TCD_{50}, the dose which would be expected on the average to achieve control of half the irradiated tumours (Suit *et al.*, 1965). Analysis of tumour growth delay have been described by Thomlinson & Craddock (1967). This end-point is attractive and permits more rapid experimentation than does the TCD_{50}. For tumour growth delay radiation doses are planned, by definition, to permit regrowth, *i.e.* radiations are intended to effect only a delay in growth. Nonetheless, tumour growth delay as an end-point has the important advantage of providing more ready assessment of

response of tumour to lower radiation doses: this is a significant feature for certain types of radiobiological studies.

The principal effort in this presentation will be to consider regression of tumour since this is an end-point which can be scored readily by the clinician, is intuitively reliable and is widely employed. This latter point is especially pertinent now because of the great increase in accuracy of diagnostic radiographic procedures, *i.e.* computerized body or head tomography, xeroradiography and various isotope procedures. With these new techniques the clinician is able now to monitor regression of tumour at almost all sites of the body with an accuracy which was not feasible just a few years ago.

Regression of tumour during radiation therapy as indicator of local response

Historical considerations.—The history of radiation therapy has clearly established that simple reliance upon regression of tumour during treatment as a prognostic indicator can lead to some unfortunate results. For example, up to the mid-1950s, the usual approach to patients with Hodgkin's disease and non-Hodgkin's lymphoma was to employ moderate dose levels because of the clinical fact that regression was prompt and usually complete. Unfortunately, there was a high incidence of local relapse. In 1966 Kaplan published dose–response data which demonstrated that local control could be expected in more than 90% of the patients after doses of $\simeq 40$ Gy. As a result current practice of radiation therapy is that virtually every patient with Hodgkin's disease, who is treated by radiation therapy alone, receives ≥ 40 Gray in 4 weeks, or its equivalent, to affected nodal regions. No regard is given to the early regression. This more aggressive approach has made a significant contribution to the higher survival rates in patients with Hodgkin's disease. On the other hand, several categories of tumours had been considered totally resistant to radiation, partly because they regressed quite slowly, and these were not studied comprehensively by radiation therapists for many years. These tumours include adenocarcinoma, several of the sarcomas of soft tissue, *etc.* Now, clinical data demonstrate that radiation therapy may play a very valuable role in the management of some patients with these tumours (Bagshaw, 1973; Suit & Russell, 1978). The basic point of these comments is to emphasize that the clinician is interested in complete *and permanent* regression, and that the rate at which that regression is achieved is not of much importance unless it has prognostic value.

Experimental studies of pattern of regression following irradiation of murine tumours

The pattern of regression of a tumour following radiation depends upon the interaction of a complex array of parameters of tissue response. These include: (1) number and proportion of tumour cells surviving irradiation; (2) the post-irradiation proliferation kinetics of the radiation-killed and of the surviving cells; (3) kinetics of pyknosis and lysis of the radiation-killed cells or their progeny; (4) capacity of the tumour bed to remove the cellular debris of the lysed tumour cells; (5) character and abundance of the

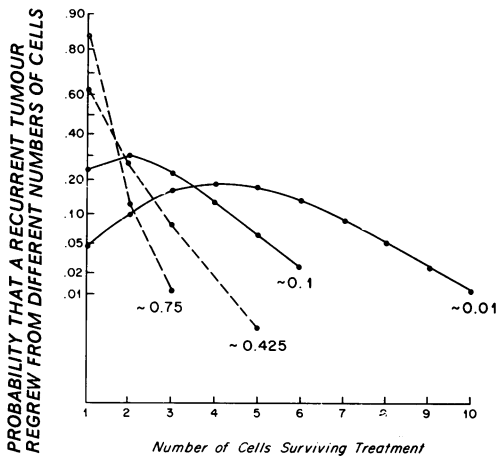

FIG. 1.—The estimated number of cells surviving radiation in those tumours which will recur for treatments yielding tumour control probabilities of 0·01–0·75.

stroma in the tumour and the response of the stroma to irradiation; (6) effectiveness of the host reaction against residual tumour.

Local control requires that all tumour cells be inactivated. For most spontaneous tumours, cell inactivation would be caused only by the radiation dose. The number of tumour cells which would be predicted to survive irradiation in tumours which are unsuccessfully treated are shown in Fig. 1, for treatment yielding tumour control probabilities of 0·01 to 0·75 (Suit *et al.*, 1978). These calculations have been based upon the performance of a model tumour which is characterized by a population of M clonogenic cells and for which tumour eradication requires that all cells be killed by radiation. That is, if one or more cells survived radiation there would ultimately be local failure. From these computations we may infer, for tumour systems in which there is no effective host resistance, that virtually all local failures would represent regrowth from less than 10 cells which survived irradiation. If this model corresponded to clinical reality, it would hardly be surprising if the proliferative activity of 1–10 surviving cells failed to be reflected in the pattern of regression during the initial post-treatment period. Under such circumstances early tumour regression might be expected to be a rather poor predictor of local control.

Barendsen & Broerse (1969) have examined the regression of a rat rhabdomyosarcoma following a single dose of 20 Gy. They measured changes in tumour volume, total number of cells and the number of clonogenic cells. The 20Gy treatment yielded a surviving fraction of $2–3 \times 10^{-3}$. As shown in Fig. 2, the tumour regressed over a period of about 10 days and then began to regrow. The decrease in tumour cell number occurred more promptly and was of greater magnitude. Tumour cell number began to increase about the same time that regrowth was evident. Most importantly, the number of clonogenic cells was observed to be constant for the first several post-treatment days and then increased rapidly during

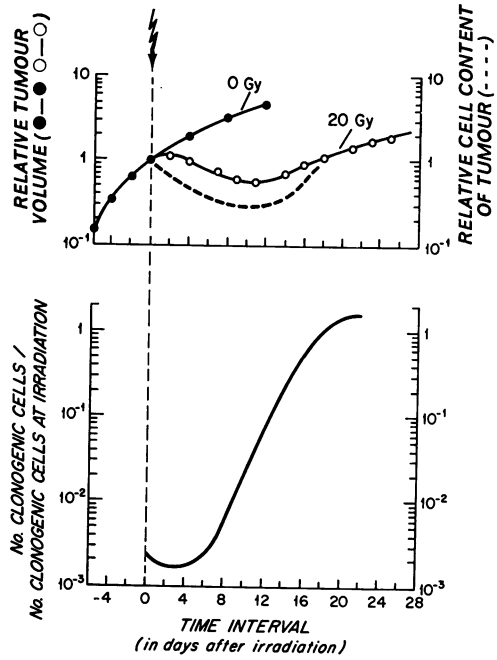

FIG. 2.—Regression of a rat rhabdomyosarcoma after a single radiation dose of 20 Gy. The upper panel shows regression of tumour (○——○) and of the change in relative cell number of the tumour (- - - -). In the lower panel is shown the increase in number of clonogenic cells after treatment. This increase begins while the tumour mass is still regressing.

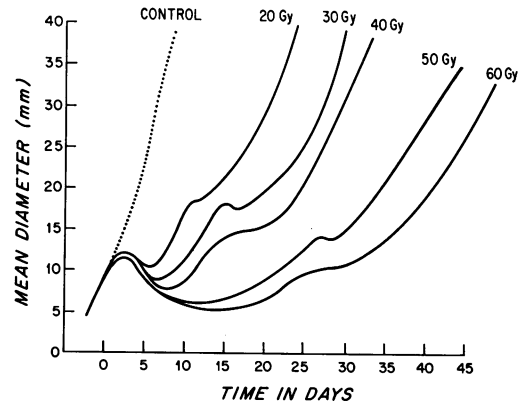

FIG. 3.—Growth, regression and regrowth curves for RIB5 treated by single dose irradiation (after Thomlinson, 1960). The rate of regression of tumour did not show a dependence upon dose.

the later period of tumour regression. From an inspection of their curves, a correlation between initial pattern of regression and tumour control probability would not be expected. That is, regression pattern would not be anticipated to be different for treatments yielding surviving fractions of 10^{-3} or perhaps 10^{-5} or 10^{-6}. This is so unless there is a strong correlation between radiation dose and the suppression of post-irradiation division and/or the rate of clearance of the killed cells from the tumour. Thomlinson (1960) determined the regression and regrowth curves for the RIB5 tumour of the rat following single radiation doses. Fig. 3 is derived from his report; the shape of the early phases of regression curves of the RIB5 tumour was independent of dose. Dose merely determined the time at which regrowth became evident.

In evaluating the utility of residual tumour as a predictor of subsequent recurrence it is necessary to separate two distinct groups of subjects: those who go on to recur and those who do not for a defined period of observation. An ideal predictor would, of course, predict the recurrence in every member of the former group and in no member of the latter group. To use the language of decision theory, the "true positive rate" of the predictor would be 100% and the "false positive rate" 0%.

Using the concepts of true and false positive rates, we have re-examined data published by Denekamp (1977). She studied 5–7mm isotransplants of a murine mammary carcinoma, and found a statistically significant correlation between the extent of residual tumour at the completion of a course of fractionated irradiation and the likelihood of local regrowth. We have reanalysed her data with respect to true positivity (TP) and false (FP) positivity, as shown in Tables I and II, using extent of residual tumour at the completion of the course of treatment as the predictor of local regrowth. Clearly, the extent of residual tumour at completion of radiation therapy did not serve as an ideal or even a very good predictor of outcome, *viz.* FP rates were high.

TABLE I.—*Size of tumour at completion of fractionated irradiations and local control of C3H mouse mammary carcinoma*

	9 fractions in 18 days	
Residual volume	Local control	Local failure
< 10% of initial	45	50
⩾ 10% of initial	14	13
Total	59	63
True positive	13/63 (21%)	
False positive	14/59 (24%)	

	9 fractions in 10 days	
Residual volume	Local control	Local failure
< 10% of initial	37	16
⩾ 10% of initial	7	11
Total	44	27
True positive	11/27 (41%)	
False positive	7/44 (16%)	

From data in paper by Denekamp, 1977.

TABLE II.—*Size of tumour at completion of fractionated irradiations and local control of C3H mouse mammary carcinoma*

Initial tumour size	5–6 mm	6–7 mm	> 7 mm
True positive	8/11 (73%)	12/18 (67%)	4/5 (80%)
False positive	8/20 (40%)	5/12 (42%)	0/2 (0%)

Indicator: Positive means residual tumour volume is > 10% of initial volume; Negative means residual tumour volume is > 10% of initial volume.
From data in paper by Denekamp, 1977.

The issue of the capacity of a test to discriminate between two future outcomes is only distantly related to the issue of statistical significance. To say that residual tumour is "significantly" associated with recurrence is only to say that residual tumour and recurrence are found in conjunction more commonly than would be anticipated on the basis of chance alone. To say that a test is a useful predictor of outcome is to say that a given outcome regularly follows when the test yields a certain value. This latter is a much stronger statement than one of simple statistical significance and addresses the

issues of most immediate concern to the clinician.

We have found that tumour regression is a useful predictor of tumour control probability in only one of several tumours studied. This tumour, fibrosarcoma FSa I, had been induced by methylcholanthrene and was moderately strongly immunogenic (Suit *et al.*, 1977*a*). In this system, local control is achieved at radiation doses which leave many surviving cells; hence, the immune reaction of the host animal appears to be sufficient to inactivate the tumour cells not killed by the radiation dose (Suit & Order, 1974). Fig. 4 shows dose–response curves for complete regression and for local control of 8mm tumours growing as early generation isotransplants in normal hosts. These curves are virtually superimposable. This means that local control is usually achieved for those tumours which regress completely; with very few exceptions local failures are seen only in those tumours which regress partially. Fig. 5 shows growth curves for 8 FSa I tumours subjected to single radiation doses of 25 Gy. By the 11th post-treatment day there was an excellent separation of growth curves for tumours which were successfully and unsuccessfully treated. Specifically, residual tumour at Day 11 was >10% of the initial volume in 4 of 5 tumours which were not locally controlled (solid lines) but in none of 3 tumours which were controlled (dashed lines): TP of 80% and FP of 0%. This same strong relationship between tumour regression and tumour control probability was found for treatment of this tumour at the 8 mm or the 12–14 mm^3 size by single or fractionated dose irradiation.

These powerful prognostic qualities associated with tumour regression have *not* been seen in other tumour systems which we have studied. They have differed from the FSa I in two important respects: (1) they were *very* weakly or non-immunogenic and (2) complete regression was observed in virtually every instance following radiation doses which yielded tumour

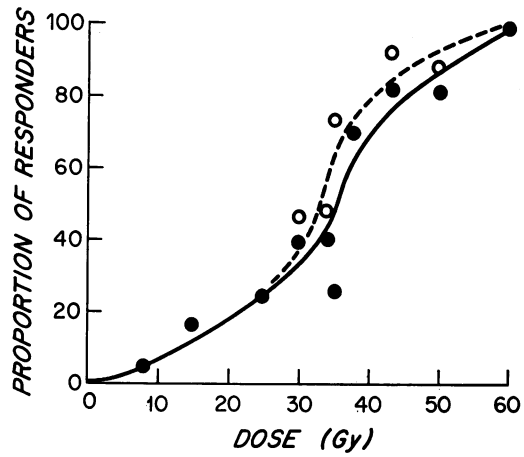

FIG. 4.—Dose–response curves for complete regression (○----○) and local control (>120 days) (●----●) for single dose irradiation of a 250 mm^3 isotransplants of fibrosarcoma (FSa I) of the C3H mouse. ($v=1$.)

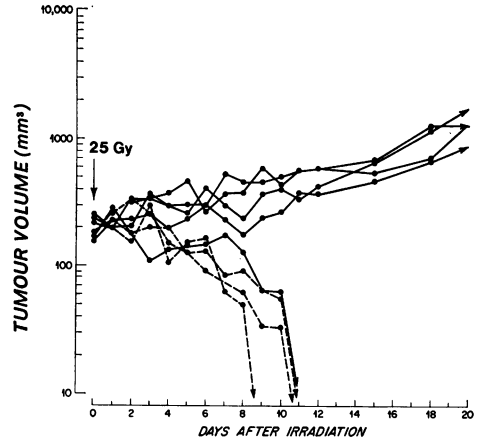

FIG. 5.—Growth curves of 8 individual tumours (FSa I 250 mm^3) after a single radiation dose (25Gy). Local failures (———), local control (– – – –). ($v=1$.)

control probabilities of >10%. We will consider here the C3H mouse mammary carcinoma, MDAH-MCa IV (Suit *et al.*, 1977*b*). Fig. 6 shows dose–response curves for complete regression and local control by irradiation. The tumours were third generation 8 mm isotransplants in the leg treated by 10 equal doses of radiation with one day between fractions. There is a wide separation between the two curves. Com-

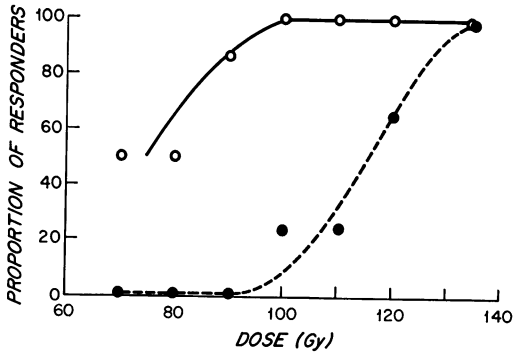

FIG. 6.—Dose response curves for complete regression (○——○) and local control (●- - - -●) for fractionated irradiation (10 equal doses, 1 day between treatments) of 250 mm³ isotransplants of a mammary carcinoma of the C3H mouse (MDAH-MCaIV). ($v=10$, $t_1=1$ day, T=9 days AIR.)

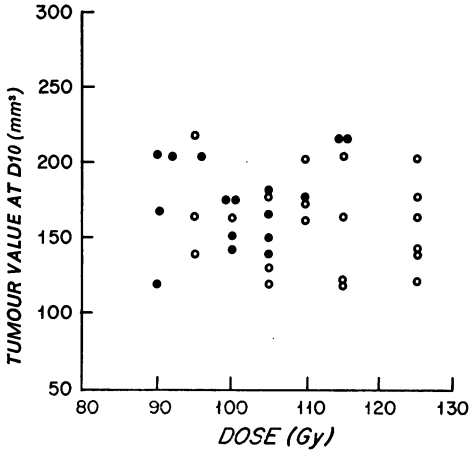

FIG. 7.—Tumour volumes at the 10th treatment of 250 mm³ isotransplants of MDAH-MCa IV. Local control, ○; local failure, ●. ($v=10$, $t_1=1$ day, T=9 days AIR.)

plete regression was observed in all tumours even at doses which yielded low tumour control probability. This means that local recurrences were observed after the tumour had been non-palpable for at least one week. Tumour volumes as measured at the 10th treatment are shown as a scattergram in Fig. 7 for local controls and local failures. At the 10th treatment regression was only partial even at the highest dose level employed. From this Figure it is obvious that there was no dependence of tumour volume at the time of the 10th treatment upon radiation dose. Further, the sizes of tumours at that time period which were treated successfully and unsuccessfully were not separated to a useful extent at any dose level. If the indicator of failure is set as tumour volume of >150 mm³ at the 10th treatment, then the true positive rate would be 11/16 or 69%. There were 20 successes, but 12 of these tumours had volumes >150 mm³, therefore FP=60%. This same tumour was employed in assays where 10 equal doses were administered with 3, 4 or 5 days between fractions. As presented in Table III, many tumours had regressed

TABLE III.—*Regrowth by Dose* 10 *amongst tumours which had regressed completely by Doses* 5–7 *in fractionated irradiation of* 8 *mm MCa IV mouse tumours*

Dose (Gy)	t_1 (days)	CR by Dose 5–6 and regrowth by Dose 10	Local control
110	3	2/4	0/4
155	4	1/3	0/3
200	5	2/5	0/5

Radiation: 10 equal doses with 3, 4 or 5 days between treatments.

completely by Dose 5 or 6 but regrowth was evident by Dose 10, *viz.* local regrowth was observed despite complete regression at the mid-point of a course of fractionated radiation. No tumour in this series was treated successfully by the doses employed.

The stroma of the tumour is clearly an important determinant of regression pattern. This is strikingly illustrated by the regression pattern observed for an osteosarcoma (Choi *et al.*, 1979). This tumour did not regress, regardless of the dose employed or time period of observation, *i.e.* up to 200 days. For successfully treated tumours there was only an absence of any subsequent regrowth, *i.e.* the tumour volume was constant over the entire period of observation following the radiation. Unsuccessfully treated tumours remained at the treatment volume until growth of the tumour was re-initiated.

TABLE IV.—*Residual tumour at completion of fractionated radiation therapy of squamous cell carcinomas of the oropharynx region and local failure*

	1948–1965		1966	1970
Stage	True Positive†	False Positive*	True Positive†	False Positive*
T1	0/6 (0%)	1/35 (2%)	0/1 (0%)	2/19 (11%)
T2	8/29 (28%)	9/53 (17%)	5/11 (45%)	3/37 (8%)
T3	18/41 (44%)	15/37 (41%)	7/16 (44%)	7/26 (27%)
T4	23/33 (70%)	6/7 (86%)	10/10 (100%)	3/5 (60%)

* Non-recurrences incorrectly "predicted" as recurrences by residual tumour.
† Recurrences correctly "predicted" by residual tumour.
Analysis of data in paper by Barkley & Fletcher, 1977.

Clinical estimates of pattern of regression

In the ensuing discussion we shall only consider clinical studies examining the correlation between extent of tumour at the completion of radiation therapy and ultimate local success. This criterion results from a practical consideration: clinicians are not particularly interested in prognostic information if it is not available until some 2 to 3 months following treatment. Useful information needs to be available early on so that the treatment can be modified and hence improve the chance of success in those predicted to be failures.

Three sets of data on response of carcinomas of the head and neck region are available for analysis. Barkley & Fletcher (1977) tabulated the local outcome of 366 patients with squamous cell carcinoma of the oropharynx according to the status of the primary lesion at completion of external beam therapy and with respect to T stage for 2 time periods. They reported a statistically significant correlation between local control and absence of palpable or detectable tumour at the completion of treatment. In Table IV, however, we see that the test (yes or no for residual tumour) was *not* a good predictor, because false positive rates were high (2–86%).

Analyses have been made on similar data published by Fazekas *et al.* (1972) and Sobel *et al.* (1976). Our tabulations of TP and FP rates from their papers using residual tumour at the completion of therapy as the prognostic indicator are given in Tables V and VI. Again, the FP rates are high, *i.e.* the indicator would not be useful clinically to determine treatment policy for individual patients. It is important to note that Sobel *et al.* stated that the residual tumour at several weeks after completion of therapy was a powerful prognostic indicator of local failure.

TABLE V.—*Persistence of tumour at completion of radiation therapy as indicator of local failure of treatment of human squamous cell carcinoma of the oral cavity and oropharynx*

True positive	8/22 (36%)
False positive	10/27 (37%)

After Fazekes *et al.*, 1972.

TABLE VI.—*Persistence of tumour at completion of radiation therapy as indicator of local failure*

Site	True positive	False positive
Oral cavity	21/26 (77%)	13/34 (35%)
Oropharynx	26/34 (70%)	9/34 (30%)
Hypopharynx	8/15 (53%)	1/7 (24%)

After Sobel *et al.*, 1976.

Studies of uterine cancers have led to similar results. Grossman *et al.* (1973) analysed the response of squamous cell carcinoma of the uterine cervix at the time of completion of external beam therapy. They found a significant correlation between extent of regression and likelihood of local failure. Fig. 8 shows an analysis of true *versus* false positive rates for various categories of response which they have listed in their paper. It is evident that true positive rates were

TABLE VII.—*Persistence of tumour at the time of radium insertion as indicator of local failure in treatment of carcinoma of the uterine cervix*

Stage	IIA	IIB	IIIA	IIIB
True positive	7/25 (28%)	36/40 (90%)	30/32 (94%)	28/29 (97%)
False positive	50/88 (57%)	57/70 (81%)	36/41 (88%)	20/21 (95%)

After Marcial & Bosch, 1970.

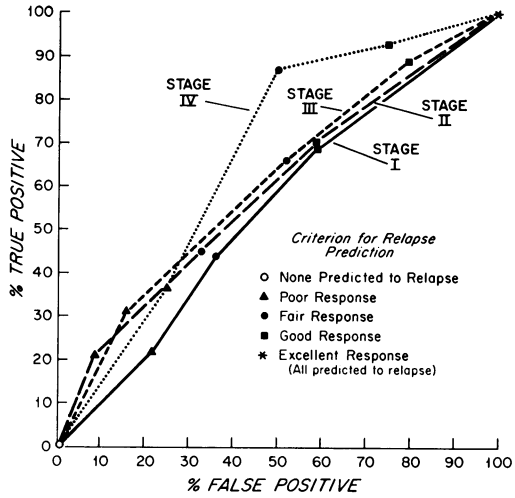

FIG. 8.—Different degrees of tumour response are taken as cutoff points for the prediction of 5 year relapse in cervical carcinoma. The performance of each cutoff is assessed in terms of the fraction of relapses correctly predicted (True Positive Rate) and the fraction of non-relapses incorrectly predicted to relapse (False Positive Rate). A random, that is, useless, predictor should plot to a diagonal line. From Grossman *et al.*, 1973.

closely balanced by false positive rates and the value of the test (regression response) was of little use clinically. In a graph such as Fig. 8, a completely random, *i.e.* useless, predictor would be plotted as a diagonal line. The presence of a statistically significant correlation between prediction and outcome implies only that the deviation from the diagonal is larger than could be anticipated on the basis of chance alone. In Fig. 8, it is apparent that a statistically significant correlation does not imply practical utility. Marcial & Bosch (1970) analysed survival of patients treated by external beam therapy followed by intracavitary radium. They presented data on survival and persistence of tumour at the time of the radium insertion. In Table VII the TP and FP for this indicator of survival for stages IIA–IIIB are shown. Once again, the indicator was not of clinical value.

Analysis of these various data raises the important issue of the relative impact of true and false positive results. The value of a test depends not only upon the relative values of true positivity and false positivity but also upon the consequences of exercising the new therapeutic option. In evaluating a false positive result, consideration has to be given to the morbidity, risk of mortality, loss of function, *etc.* that may occur if a therapeutic option is needlessly exercised. For example, if a positive test merely resulted in some minor alteration in therapy, false positivity might be a minor concern. If, however, a positive test meant that the patient would be subjected to a major surgical procedure, then the loss of anatomy or the consequent morbidity might make a false positive rate of even 5–15% unacceptable. Accordingly, the value of the test is clearly related to the nature of therapeutic options which are to be exercised in the event of a positive test.

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