

Tumor-Absorbed-Dose Estimates versus Response in Tositumomab Therapy of Previously Untreated Patients with Follicular non-Hodgkin's Lymphoma: Preliminary Report

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I-131-radiolabeled tositumomab (Anti-B1 Antibody), in conjunction with unlabeled tositumomab, was employed in a phase II clinical trial for the therapy of 76 previously-untreated follicular-non-Hodgkin's-lymphoma patients at the University of Michigan Cancer Center. For all patients, conjugate-view images were obtained at six to eight time points on seven consecutive days after a tracer infusion of the antibody. A SPECT image set was obtained on day two or three after the therapy infusion for 57 of the patients. Of these, 55 are suitable for dosimetric evaluation. To date, we have completed analysis and response characterization of 20 patients from the subset of 55. All 20 patients had either a complete response (CR) or a partial response (PR). Conjugate-views provided a time-activity curve for a composite of nearby, individual tumors. These tumors were unresolved in the anterior-posterior projection. Pre-therapy CT provided volume estimates. Therapy radiation dose was computed for the composite tumor by standard MIRD methods. Intra-therapy SPECT allowed the calculation of a separate dose estimate for each individual tumor associated with the composite tumor. Average dose estimates for each patient were also calculated.

*The 30 individual tumors in PR patients had a mean radiation dose of (369 ± 54) cGy, while the 56 individual tumors in CR patients had a mean radiation dose of (720 ± 80) cGy. According to a mixed ANOVA analysis, there was a trend toward a significant difference between the radiation dose absorbed by individual tumors for PR patients and that for CR patients. When the radiation dose depended on only the patient response, the *p* value was 0.04. When the radiation dose depended on the pre-therapy volume of the individual tumor as well as on the patient response, the *p* value was 0.06. Since the patient response was complete in 75% of the patients, the analysis of the total cohort of 55 evaluable patients is needed to have a larger number of PR patients to better test the trend toward a significant difference. A pseudo-prediction analysis for patient-level dose and response was also carried out. The positive predictive value and the negative predictive value were 73% and 80%, respectively when a patient's average radiation dose was used. The predictive values were 73% and 60%, respectively, when the patient's average base-10 logarithm of radiation dose was used. A complete overlap for the dose range of CR patients compared to that for PR patients precluded higher predictive values. In conclusion, there was a trend toward a significant difference in the radiation dose between CR and PR patients, but it was only moderately predictive of response.*

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INTRODUCTION

To date, the University of Michigan has participated in six Phase I, II or III I-131-radiolabeled tositumomab clinical trials for therapy of patients with non-Hodgkin's lymphoma (NHL). Tositumomab is an anti-CD20 monoclonal antibody that was formerly known as Anti-B1 Antibody. Some of the authors for this paper [K.R.Z., S.G.R., M.S.K. and R.L.W.], plus other authors,¹ analyzed data from 80 low-grade and 21 transformed low-grade patients who received a therapeutic dose in any one of the six studies. A multivariate analysis revealed three factors associated with a lower probability of response: high lactate dehydrogenase levels, relapse after prior radiotherapy, and large tumor burden.¹ However, tumor radiation dose estimated from conjugate views was not evaluated as a predictor variable for this group of patients.

The authors of the present paper studied patients from one of the six clinical trials. The particular clinical trial was a phase II trial of patients who had been newly diagnosed with advanced-stage malignant follicular lymphoma. Malignant follicular lymphoma is one subset of low-grade NHL. All patients had been untreated for their disease before tositumomab therapy. A series of post-therapy CT scans was used for response characterization. For the 20 patients we have studied to date, all had either a complete response (CR) or a partial response (PR). We present two analyses below. One is a statistical test of the relationship between the radiation-dose estimates for individual tumors and the degree of response (CR or PR). The other is a measure of the best-case response-predictive value of the tumor radiation dose for a given patient.

MATERIALS AND METHODS

Patients

Seventy-six previously-untreated NHL patients participated in the phase II tositumomab trial at the University of Michigan Cancer Center. A written informed consent was obtained for the therapy protocol, which included conjugate-view imaging. Fifty-seven of these patients also volunteered to undergo intra-therapy SPECT imaging. Since the imaging was not required as part of the therapy

protocol, patients gave a second written informed consent. Of the 57, 55 have data sets complete enough for dosimetric evaluation. Both hybrid-SPECT-conjugate-view tumor-dose estimates and therapy-response characterizations are now available for 20 of these 55. Columns 1 through 3 of Table 1 give the study-identifier number (ID#), the age, and the gender of each of the 20 patients.

It has been determined that the mean radiation dose estimated by hybrid SPECT conjugate views is significantly lower for axillary tumors than for those in the abdomen or pelvis, for unknown reasons.² Because the tumor location would have a confounding effect, we correlated the radiation dose from only abdominal and pelvic tumors against patient response. Therefore, out of all possible patients, we have excluded patients who underwent only axillary SPECT scanning and, for one included patient (ID# = 55), who underwent both axillary and abdominal SPECT imaging, have included dosimetric results from only his abdominal tumors.

Administered Protein Dose

For the 1 week tracer evaluation, patients were given a 450 mg predose of unlabeled tositumomab infused over 1 hour and then an infusion of 35 mg of tositumomab containing an amount of I-131-labeled tositumomab that corresponded to an activity of 185 MBq (5 mCi). This evaluation was then followed by the administration, generally on day 7 post tracer dose, of the patient-specific therapeutic dose. This dose consisted of an infusion of the same amount of predose as used in the evaluation, followed by the administration of 35 mg of tositumomab containing an amount of I-131-labeled tositumomab that typically corresponded to an activity of 3.51 GBq (95 mCi). The specific value of radioactivity was chosen so as to always deliver a whole-body radiation dose of 75cGy. The activity required to deliver this radiation dose was determined by a calculation based on the patient's tracer measurements.³

Image Acquisition

Conjugate-view imaging with the patient supine was carried out six to eight times over seven days after the tracer infusions. A Siemens dual-head whole-body gamma camera was usually employed for the

TABLE 1
Patient ID, Age, Gender, Number of Evaluated Tumors,
Tumor Radiation Dose Values Averaged over that Number, and
Best Patient Response

ID #	Age	Gender	No of individual tumors evaluated per patient	Patient-averaged tumor radiation dose (cGy)	Patient-averaged base-10 log of tumor radiation dose	Best patient response
1	30	m	5	1579	3.08	CR
2	52	m	2	198	2.24	CR
3	38	m	11	219	2.23	PR
5	38	f	1	466	2.67	CR
7	56	m	4	307	2.38	PR
10	28	f	2	573	2.60	CR
13	55	f	2	1379	2.91	CR
14	46	f	2	735	2.87	CR
15	67	m	1	402	2.60	CR
16	32	f	4	817	2.91	CR
27	64	f	5	740	2.85	CR
32	50	m	3	400	2.60	CR
34	41	m	3	526	2.71	PR
37	36	f	5	579	2.72	CR
39	40	m	6	789	2.88	CR
42	52	m	3	903	2.89	PR
43	55	m	9	352	2.52	PR
44	23	f	4	578	2.74	CR
46	55	f	9	545	2.61	CR
55	42	m	5	558	2.68	CR

imaging. The single SPECT acquisition for the chest, abdomen or pelvis on day two or three after the therapy administration employed an imaging time of 20min, and a 360-degree circular orbit with 60 stops. Patients were again imaged supine. Two different-model triple-head Picker cameras were utilized. In phantom tests, the two models yielded similar accuracy.⁴ A CT exam taken shortly before the start of the evaluative imaging was also available and was employed in the evaluation of the other data.

Estimation of Tumor Dose

The complete details of the method used for hybrid SPECT-conjugate-view dose estimation are given in Koral et al, 2000.² An overview outlining the basic approach is shown by a flow chart in Figure 1. Below, we describe that overview.

An explanation of individual tumor and composite tumor is essential for understanding the chart. In brief, an individual tumor was the tumor seen on CT imaging, while a composite tumor was that seen on conjugate-view imaging. In detail, regions of

interest (RoIs) were drawn on the CT images by a trained radiologist (author I.R.F.) to define cancerous regions. One or more of those RoIs were grouped to form a given individual tumor. The criterion for including several RoI into one individual tumor was that the RoI overlapped from CT slice to CT slice, or were contiguous in a given CT slice.

A single RoI surrounding a contiguous high-uptake area on either of the tracer conjugate-view projection images defined the composite tumor. The anterior-to-posterior backprojection of this RoI was compared to the CT RoIs to decide which CT RoIs corresponded with the composite tumor. Advantage was taken of uptake in known regions such as the liver to help in making the correspondence. The anterior-to-posterior backprojection usually included several individual tumors. As an example, cancerous lymph nodes that were within the pelvis on the patient's right side but that were well separated were included as one composite tumor. This composite tumor was called right-pelvic. The cancerous nodes that were anterior and near the skin surface made up the anterior-right-pelvic individual tumor

associated with this composite tumor. The cancerous nodes that were more posterior and deep within the body made up the posterior-right-pelvic individual tumor associated with this composite tumor.

The volume of a given individual tumor was equal to the sum of the areas of the associated ROIs multiplied by 1cm, the thickness of the CT slices. The volume for a given composite tumor was the sum of the volumes for the associated individual tumors.

Turning to the flow chart of Figure 1, the conjugate-view tracer data, shown in the upper left, were analyzed to obtain a tracer-infusion time-activity curve for a given composite tumor. In our example, this was the right-pelvic composite tumor. Each activity on this curve was then multiplied by the ratio of the administered activities to produce a composite-tumor intra-therapy time-activity curve, as indicated. This ratio was therapy administered

activity divided by tracer administered activity. The curve was then utilized in two ways.

Following the left-hand path exiting the box, and using the CT volume for the given composite tumor, one calculated the therapy radiation-dose estimate for the given composite tumor using standard medical internal radiation dose (MIRD) methods⁵. MIRDOSE (version 3.1) software⁶ was employed and the total dose included contributions from activity in the tumor itself (the self dose) and contributions from the gamma irradiation due to I-131 activity in the remainder of the body.

Following the right-hand path exiting the box, and using the CT volume for the composite tumor, right-pelvic in our example, and the CT volume for a given individual tumor, say anterior-right-pelvic, this curve was converted to an initial estimate of the intra-therapy time-activity curve for the anterior-right-pelvic tumor. The conversion was made by

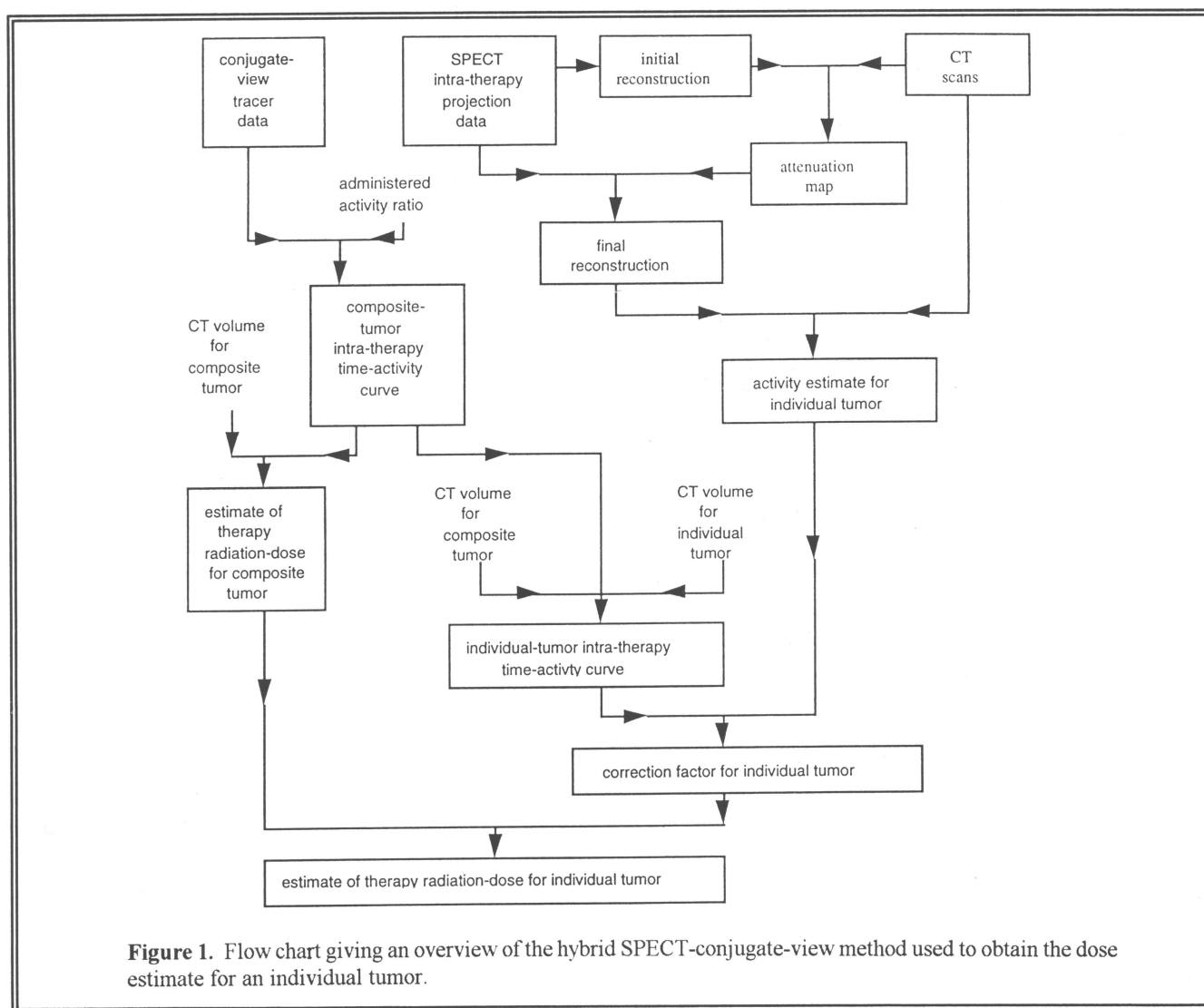


Figure 1. Flow chart giving an overview of the hybrid SPECT-conjugate-view method used to obtain the dose estimate for an individual tumor.

multiplying the activity for each data point by the volume ratio. This ratio was the volume for the individual tumor divided by the volume for the composite tumor.

The SPECT intra-therapy projection data, shown near the middle of the chart at the top, took two paths. An initial reconstruction was obtained without attenuation correction by filtered back projection. The slices from this reconstruction were then compared to the slices from the CT scan and a three-dimensional CT-to-SPECT transformation, T , was obtained. This transformation allowed the CT slices to be superimposed, or fused, with the SPECT slices. After fusion, the CT pixels in Hounsfield units were converted to attenuation coefficients by an energy-extrapolation algorithm. By this conversion, an attenuation map was obtained, as shown on the chart. This map was used in combination with the original SPECT intra-therapy projection data, to yield a final reconstruction. The result of the final reconstruction was fused with the CT scan slices using the inverse of the T transformation. After this inverse fusion, the RoI drawn for individual tumors on the CT slices could be applied to the SPECT slices. By adding reconstructed counts from the appropriate RoI for a given individual tumor, the total reconstructed count was obtained. This reconstructed count was converted to activity by employing our standard calibration procedure.

Next, this activity estimate for the given individual tumor at the post-administration time used for SPECT imaging was compared to the initial estimate of the individual-tumor intra-therapy time-activity curve, which is on the chart at the middle near the bottom. An intra-therapy-SPECT correction factor (also called a normalization factor) was calculated, as shown. This correction factor equaled the SPECT activity for the given individual tumor, divided by the initial estimate of the activity for the given individual tumor. The latter was read off of the individual-tumor intra-therapy time-activity curve at the post-administration time used for SPECT imaging. The estimate of therapy radiation dose for the composite tumor, at the left of the chart, was then multiplied by this correction factor. The multiplication yielded the final radiation dose estimate for the given individual tumor, as shown by the box at the bottom of the chart.

In our example, the above processing yielded

the therapy radiation dose for the anterior-right-pelvic tumor. Intra-therapy SPECT provided a separate, intra-therapy-SPECT correction factor for the posterior-right-pelvic tumor. Using it, the therapy radiation dose for the posterior-right-pelvic tumor was estimated. In addition, a completely different calculation using the left-pelvic composite tumor was carried out for the anterior-left-pelvic tumor and for the posterior-left-pelvic tumor. Thus, dose estimates were obtained for all the individual tumors sampled by SPECT.

Patient Response

For each patient, the response to therapy was assessed by a post-therapy CT scan at 7, 13, and 26 weeks after study entry and every 13 weeks thereafter, until one year was reached or there was disease progression. Study entry was defined as the day of the tracer infusion given for conjugate-view evaluation. The response was assessed for each CT scan. The best response result was used in our analyses. The time of occurrence of this best response was known but was not included in our data workup. Standard National Cancer Institute criteria were utilized to evaluate the response. The pertinent criteria for this report were that a complete response (CR) was complete disappearance of all measurable and evaluable disease for at least four weeks, and that a PR was greater than or equal to a 50% reduction in the sum of the products of the longest perpendicular diameters of measurable lesions for at least four weeks with no new lesions.

Data Analysis

The data were analyzed at the individual-tumor level and at the patient level. At the patient level, radiation dose values were averaged over all evaluated individual tumors for each patient.

At the individual-tumor level, the radiation absorbed dose for an individual tumor was taken to be the dependent variable and the response of the patient was taken to be the independent variable in the statistical analysis. Employing SAS software, a mixed-effects ANOVA⁷ calculation could then account for the correlation between doses for individual tumors within the same patient. A second, similar ANOVA calculation assumed the radiation

dose varied with the pre-therapy volume of the individual tumors as well as with the response. Statistical significance was defined as a *p* value less than 0.05.

At the patient level, a pseudo-prediction analysis was carried out for patient-averaged dose and response. This analysis served two purposes. The first was that the results characterized the effects of dose overlap between PR and CR patients. That is, if there were no overlap, the predictive values would be 100%. Because there was overlap, the values were actually smaller. The second was to provide a set of pseudo-predictive values for previously-untreated patients.

The normal procedure to calculate predictive values would be to first obtain a patient-level dose value that separated PR and CR patients. Then this separation value would be applied to radiation-dose values from an independent cohort of new patients. We expect to use all of our present patients to establish the dose separation value. Also, at the present time, an independent cohort of new patients isn't on the horizon. Therefore, we computed the separation value from our 20 patients and applied it to the same 20 as a best-case estimate of results from an independent subset. It is best-case because it is used on the same patients. New patients would be expected to exhibit different dose values and a slightly different value for best separation. Therefore, using the current separation value on new patients would have a slightly lower predictive accuracy for the new patients than for the present patients.

Two modes were used for the pseudo-prediction analysis at the patient level. Mode 1 employed the radiation dose values. Mode two used the base-ten logarithm of radiation dose values. For both modes, we proceeded in the same way. We first found the average value for all individual tumors in the CR patients and also the average value for all individual tumors in the PR patients. We then calculated the value half way between those two values. This halfway value is the same as the average of the two values. We defined this halfway value as the radiation-dose-separation value on which prediction would be based.

To obtain the predictive values, the patient-level radiation dose values were compared to the separation value. For each patient, the patient-averaged

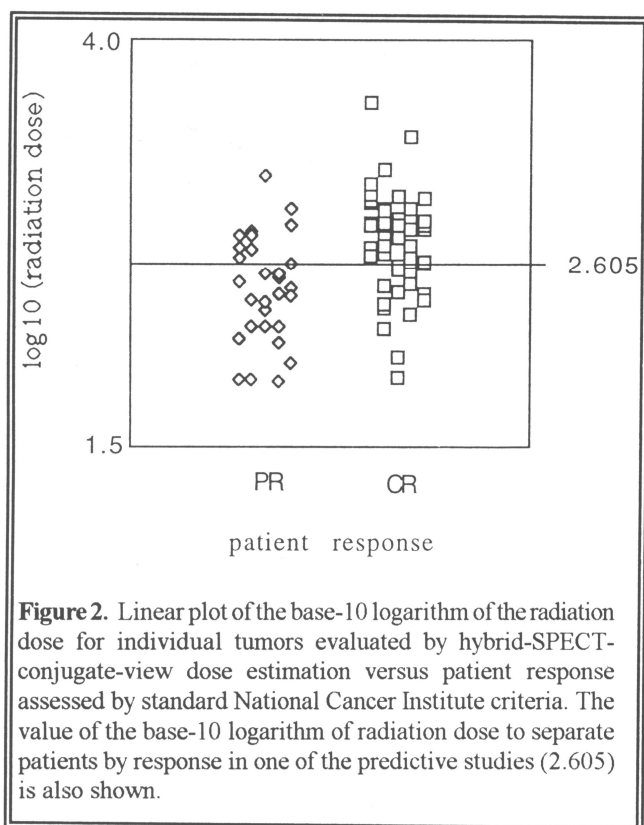
dose value either predicted the true response or not. The percentage of all CR patients who were correctly predicted to have a complete response by their average tumor radiation dose value being greater than the dose-separation value was defined to be the positive predictive value (PPV). The percentage of all PR patients who were correctly predicted to not have a complete response by their average tumor radiation dose value being less than the dose-separation value was defined to be the negative predictive value (NPV).

RESULTS

Results were available for 86 tumors in 20 patients (5 PRs and 15 CRs). The mean, median and range of the tumor volumes were 63.2 cm³, 19.0 cm³ and from 1.61 to 756 cm³, respectively. For each patient, column four and seven of Table 1 gives the number of individual tumors that were evaluated and the patient's best response, respectively. The radiation dose for each individual tumor isn't listed. The 30 tumors in PR patients had a mean radiation dose of (369 ± 54) cGy. The ± value is the standard error (also called the standard deviation of the mean). The corresponding mean value for the base-10 logarithm of radiation dose was 2.45 ± 0.059. The 56 tumors in CR patients had a mean radiation dose of (720 ± 80) cGy. The corresponding mean value for the base-10 logarithm of radiation dose was 2.76 ± 0.040. Because the standard error of the radiation dose was different for the two groups (± 54 compared to ± 80), the base-10 logarithm of the radiation dose was used for the ANOVA calculations.

A plot of the data for the first ANOVA calculation is shown in Figure 2. The first ANOVA result was that there was a statistically significant difference in the base-10 logarithm of the radiation dose of PR patients and that of CR patients (*p* = 0.042). The second ANOVA result was that if the individual tumor volume was included, the *p* value was slightly larger and not significant (*p* = 0.060). We interpret these values as a trend toward significance.

The value of the radiation dose halfway between the average value for PR patients and the average value for CR patients was 545.2 cGy. This value was used as the separation dose for the first of the patient-level tests of prediction. The value of the base-10 logarithm of radiation dose halfway between



the average value for PR patients and the average value for CR patients was 2.605. This value was used as the separation dose for the second of the patient-level tests of prediction.

Columns five and six of Table 1 give the average radiation dose, and the average base-10 logarithm of the radiation dose, for each patient. Note that, in the latter, the logarithm of the dose for each individual tumor was taken first, and then the average of those values for the patient was computed. Because of this ordering of the two operations, the values in column six are not the base-10 logarithm of the values in column five. The range of the patient-averaged radiation dose for PR patients was 219 to 903 cGy. The range of the patient-averaged radiation dose for CR patients was 198 to 1579 cGy. Thus the range for CR patient completely overlapped the range for PR patients. There was almost a complete overlap for the patient-level base-10 logarithm of the radiation dose as well.

The averages for each patient in Table 1, as well as the separation-dose value, were employed in each analysis of predictive value. The separation-dose value of 545.2 cGy was applied to the average radiation dose for each patient. The separation-dose value of 2.605 was applied to the average base-10 logarithm of radiation dose for each patient.

With the radiation dose, the pseudo-prediction results were that the PPV was 73% and the NPV was 80%. With the base-10 logarithm of the radiation dose, the PPV was again 73% while the NPV was 60%.

DISCUSSION

The hybrid-SPECT-conjugate-view method for estimation of tumor radiation dose uses a sequence of tracer conjugate-view measurements and a single intra-therapy SPECT measurement for 1) the convenience of not needing a sequence of intra-therapy SPECT measurements and 2) the potential error reduction from not making SPECT measurements with only a tracer administration of I-131. It is necessary to assume that the composite-tumor intra-therapy time-activity curve has approximately the right shape to serve as a good estimate of the curve for each individual tumor. This should be the case for at least one individual tumor if there is a dominant individual tumor. In general, the assumption requires that the curve shape for each individual tumor is the same. Preliminary patient evidence indicates that the assumption is approximately correct.²

The method estimates the final therapy dose for each individual tumor by multiplying the therapy radiation dose calculated for the corresponding composite tumor by an intra-therapy-SPECT correction factor. This procedure was followed for convenience. A more complicated dose calculation could be carried out for each individual tumor. However, since the main component of the radiation dose comes from the electron irradiation, which simply scales with activity and volume, we expect that the more complicated calculation would yield approximately the same results within 5%. We further expect that other errors, due to measurement, probably exceed a 5% error.

At the individual-tumor level, preliminary results from our study of patients previously not treated for their NHL show a trend toward a significant relationship between the degree of patient response (CR or PR) and the tumor radiation absorbed dose. Since the patient response was complete in 75% of the patients, the analysis of the total cohort of 55 evaluable patients is needed to have a larger number of PR patients to better test the trend toward a significant difference.

The trend observed to date, based on only five PR patients, is intuitively reasonable but must be considered versus the results obtained by others. For I-131 metaiodobenzylguanidine (MIBG) therapy of patients with refractory neuroblastoma, it has been reported that radiation dose did not correlate with reduction in tumor volume.⁸ However, the tumor-therapy system is different than that in the present study. Moreover, the tumor to evaluate was chosen on the basis of measurable size and 131-I-MIBG uptake greater than background. These criteria are reasonable, and the second one is necessary for each tumor in an evaluation procedure that depends on conjugate views without superimposed CT. However, with the procedure, there may be a bias towards larger tumors and those with higher uptake. This bias may be detrimental to a good correspondence of radiation dose with response. Our procedure requires only that a composite tumor have an uptake that is detectable in the conjugate-view scan. By measuring a time-activity-curve shape for this composite tumor, and then assuming that shape for all the associated individual tumors that make up the composite tumor, we are able to assess the absorbed dose for each of the individual tumors detected on CT. Thus, we include tumors that are small and that have small uptake. Therefore, our results are less biased in tumor selection.

For I-131 Lym-1 therapy of lymphoma patients, DeNardo et al⁹ divided the responses into 1) less than PR, 2) PR, and 3) CR. They found no relationship between tumor radiation dose and therapeutic response.⁹ However, in their study, the antibody administered and the patient disease history were different than in the present study. Also, the tumor radiation dose was that during the first administration of multiple doses of a fractionated radioimmunotherapy. Finally, tumors unresolved by conjugate views weren't separated into individual tumors. Any or all of these differences, and/or others, may have been the cause of the different correspondence between tumor radiation dose and patient response to therapy.

In contrast to the results from the studies mentioned above, one recent dose-escalation trial had indications that agree with the trends observed in this paper. The study employed 90-Y-DOTA-biotin with pretargeted NR-LU-10 antibody conjugated to streptavidin. Planar imaging of co-injected 111-In-

DOTA-biotin was the source of the activity estimates. SPECT imaging was not used. Although only a few tumor responses were observed, the authors state that it appeared there was a correspondence between high tumor radiation dose and degree of patient response.¹⁰ Fifty patients with refractory adenocarcinoma were entered into the study. Out of 40 with sufficient data for dose estimation, 14 had tumor-dose estimates. Seven patients out of 50 had responses (3 PR and 4 minimal). Minimal response (MIN) was defined as a 25 to 50% decrease in tumor size. The two patients with the highest tumor radiation dose (5070 and 6040 cGy out of a full range of 551 to 6040 cGy) were among the 14% (7 out of 50) who achieved some response. Of the two patients with the highest tumor radiation dose, the patient with the higher dose had a PR and the patient with the lower dose had a MIN.

In this study, the positive predictive value was 73% and the negative predictive value was 80%, when the patient's average radiation dose was used. They were 73% and 60%, respectively, when the patient's average base-10 logarithm of radiation dose was used. The eventual possibility of early-post-therapy prediction of degree of response from patient-level dose estimation, and even prediction from a tracer administration alone, are of interest if the predictive values maintain these levels, and become less dependent on the mode of analysis, for the complete cohort of patients.

After analyzing the full set of patients, the next step would be prospectively applying the separation value to a new set of previously-untreated tositumomab patients to see if true predictive values approximately match the pseudo-prediction values. If so, future patients could have an early indicator of their likely response. However, the current method requires the determination of a correction factor for each tumor from an intra-therapy SPECT scan. The therapy administration of tositumomab will have already been given. Therefore, the present measurements could not avoid the administration of tositumomab therapy to a patient who was likely to achieve only a PR. Prediction from a tracer administration alone would be needed. Good accuracy from measurements after a tracer administration is inherently more difficult, however, because of the lower counting statistics.

The lack of predictive values that are even larger and that are more independent of method calls for

developing improved methods for ^{131}I quantification and/or CT-SPECT fusion. These improvements would hopefully produce more accurate tumor dose estimation with less overlap so that the predictive values of the radiation dose would be more useful. However, since the histology of these patients was mixed, heterogeneity in radiation dose and response might still occur. Also, since unlabeled anti-CD-20 monoclonal antibodies have considerable anti-tumor effects *in vivo*,^{11,12} the specific delivery of radiation to tumors is probably an important but not the sole factor responsible for tumor treatment response.

CONCLUSIONS

There was a trend toward significance in the difference between the radiation dose absorbed by individual tumors between patients who eventually attained a PR and those who eventually attained a CR ($p = 0.04$ in one analysis and $p = 0.06$ in a second). At the patient level, the radiation dose provided a moderate degree of predictive value. The reason for the lack of better prediction was the overlap in the range of radiation dose for CR patients and PR patients.

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