Normal Tissue Reactions and Complications Following High Energy Neutron Beam Therapy II: Complication rates adjusted for censoring

Abstract

A dose response analysis was performed on patients at risk for significant radiation injuries following neutron radiotherapy. Complication rates were calculated at various dose intervals using a maximum likelihood method that is formally equivalent to the product limit estimator of survival. The variance of each complication rate was used to weight a logistic regression on log dose. The treatment sites that were analyzed were head and neck, pelvis, thorax, and pancreas. Complications of all types were considered collectively at each site and dose increment since there were too few complications to determine dose response functions for individual types of injuries. The single exception to this was a determination of the dose response for radiation osteomyelitis of the mandible. The head and neck was observed to be the site with the highest tolerance to radiation while the thorax was the most sensitive site.

Introduction

In a previous report, the complication rates in various sites treated with neutron irradiation have been estimated. These complication rates were crude, i.e., observed rates in the sense that no adjustment was made for censoring. This report gives censoring-adjusted the dose response functions for complications in the sites previously reported.

Materials and Methods

The patient population used in this study was defined by all patients treated at the Fermilab Neutron Therapy Facility from September 1976 to December 1985. The numbers of patients in each site analyzed were as follows: head and neck - 276, pelvis - 107, thorax - 64, pancreas - 105. More patients were treated than these numbers indicate, but the additional patients fall outside (generally below) the dose ranges used in the analysis.

The doses used are defined as "target absorbed dose." While dose to the organ at risk for injury would be preferable, complications were grouped according to treatment site, and the dose to tissues at risk could not be unambiguously defined. Other treatment details have been previously reported.

The complications consisted of the following. In the head and neck we observed soft tissue necrosis, mandibular necrosis, chondronecrosis, severe fibrosis, with blindness and brain necroses also occurring but not considered because the eye and brain were not at risk in all treatment sites of the head and neck. In addition were found one carotid aneurysm, one subglottic

stenosis, and one case of severe xerostomia. Complications of treatment of the pancreas were gastric hemorrhage and ulceration, fibrosis, small bowel obstruction, and soft tissue necrosis. Complications in the thorax were mainly lung fibrosis with one rib necrosis and one pericarditis. Complications in the pelvis were small bowel obstruction, severe fibrosis, proctitis, and soft tissue necrosis.

The observed complication rate depends strongly on the length of follow-up which is in turn determined by the prognosis of the disease. The following times are the last observed latency in each site: Head and neck - 54 months, thorax - 22 months, pelvis - 40 months, pancreas - 18 months. Complications after 5 years were ignored (two out of 93 total complications).

In the statistical analysis the following notation was used. At a specified dose, D, the probability of complication, P, is given by

$$P = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^k} \tag{1}$$

where D_{50} is the median tolerance dose and the slope at D is $k \cdot P(1-P)/D$. The latent period distribution function is denoted by f(t). This function describes the probability that a patient whose tolerance has been exceeded will express the complication during an interval dt around t. The integral

$$F(t) = \int_0^t f(t')dt'$$

gives the probability that the latent interval is less than t. If we let $\{t_i\}$

denote the set of specific times that complications occur, then f(t) is a discontinuous function with discontinuities at $\{t_i\}$ and

$$F(t) = \sum_{t_i < t} f(t_i)$$

and

$$\sum_{\{t_i\}} f(t_i) = 1.$$

For patients who share the same risk of complication, P, the likelihood function, L, is

$$L = \prod_i P f(t_i) \prod_j [1 - P F(t_j)]$$

where the first product is taken over all patients who express complications with latent intervals given by t_i, and the second product is taken over the patients who are removed from the study for whatever reason at times t_j and are free of complications. P is found by solving

$$\frac{\partial \text{Log}L}{\partial f(t_i)} = 0$$

and the requirement that

$$\sum_{i=1}^{N} f(t_i) = 1$$

where this sum is over the N patients expressing complications. P is given by

$$P = 1 - \prod_{i=1}^{N} \left(1 - \frac{r_i}{n_i}\right) \qquad (2)$$

where r_i is the number of patients expressing injuries at time t_i and n_i is the number of patients who are alive without complications just prior to t_i. This form of P is the same as the product limit formula for survival. Using the asymptotic normal properties of the likelihood expression, the logistic

transform, and Greenwood's formula we obtain the following expression for the upper and lower 95% confidence limits on p

$$\frac{1}{1 + \left(\frac{1-P}{P}\right) \pm 1.96\ S_G/P}$$

where S_G^2 is the variance calculated from Greenwood's formula.

For purposes of curve fitting, the probabilities calculated according to equation (1) were transformed using the logistic transform to

$$Y = \log\left(\frac{1}{P} - 1\right).$$

Y was assumed to depend on log dose as

$$Y = \beta o + \beta_1 \log (\text{dose})$$

with

$$D_{50} = e^{-\beta o/\beta_1}. \qquad (3)$$

and

$$k = -\beta_1$$

In order to satisfy the regression requirements of constant variance, a weighted regression on log dose was performed with the weights being inversely proportional to the variance of the y's, given by

$$\sigma_y^2 = S_G^2/P^2$$

The doses were divided into 2 Gy increments for the calculation of the P's. Doses used in the regression were the central doses in this range except when the average dose in the range was not centrally located. This occurred only for the highest dose values in the head and neck (D = 26.7 Gy), the pancreas (D = 25 Gy), and the lung (D = 22.04 Gy).

Fieller's theorem was used to estimate the 95% confidence on D_{50}. Because of the nonzero covariance of βo and β_1 and the use of log dose, the best estimate of D_{50} will not be centrally located in its 95% confidence range. The 95% confidence interval on the estimated value of the logistic transform Y, were also calculated.

Results

Patients treated for head and neck cancers were evaluated for mandibular necrosis and for other significant complications (exclusive of blindness and brain necrosis). The dose intervals, mandibular necrosis rates, 95% confidence intervals on these rates, and the number of patients in each interval are given in Table I. The confidence range is primarily determined not by the total number of patients entering the study at the dose interval, but rather the smallest value of n_i in equation (2).

Figure 1 shows the dose response curve obtained for these data. The D_{50} estimate is 26.67 Gy with a 95% confidence interval of 25.26 - 30.56 Gy. However as shown in Figure 1, the narrowest confidence region around the regression line occurs not at D_{50} but where the information is greatest, in this case P = 13.1%. This will be true for all regression lines. The 95% confidence limits on $D_{13.1}$ are 22.2 and 23.9 Gy. Thus D_{50} will not generally be as precisely estimated as doses causing lower complication rates. The significance of the regression is given by the probability that $\beta_1 = 0$. In this case we have $p < 0.02$.

Radiation osteomyelitis of the mandible can result from various pathogenic pathways. It is frequently associated with some sort of trauma, such as generally ~~tumor or~~ dental extraction. In this study roughly one half of the patients who developed mandibular necrosis had dental extractions following radiation treatment. The significance of this is impossible to gauge since those patients with dental extractions (or other predisposing factors) but who did not develop osteomyelitis were not identified.

The results of including all significant complications in the head and neck are given in Table 2 and shown in Figure 2. The regression line in Figure 2 is virtually parallel to the line in Figure 1, indicating similar response rates at about a 6% lower dose. The D_{50} is 25.18 Gy with a 95% confidence interval of 23.89 - 31.54 Gy. The probability for the narrowest 95% confidence interval on the dose is at 21.3% and the confidence limits of $D_{21.3}$ are 21.5 - 24.2 Gy. The significance of the regression is given by $p < 0.05$.

Figure 3 show the dose response for complications in treatment of cancer of the pancreas. In contrast to our previous report, cancer of the pancreas was not combined with other diseases because the survival function for this disease is so dissimilar to that of the other cancers in the upper abdomen that it was not advisable to combine complication analysis for all cancers of the upper abdomen. Table III gives the dose intervals and complication rates. The probability with the narrowest confidence limits on dose is 37.8%, and the 95% confidence interval on $D_{37.8}$ is 20.0 - 22.6 Gy. This dose response curve is the shallowest of those studied. Despite this, the significance of the regression is the greatest of all sites studied with $p < 0.01$.

Figure 4 and Table 4 give the dose response curve and data for cancers of the pelvis. Despite being the site with the largest number of different types of complications, the dose response curve for this site is the steepest of all those studied. At P = 43.4% is the narrowest confidence region in Figure 4. The 95% confidence limits on the dose at this point are 19.2 Gy and 22.7 Gy. The significance of the regression is $p < 0.05$.

Only three points were available for complication in the thorax. Even so, the significance of the regression for dose response curve of the thorax is $p < 0.02$. Figure 5 and Table 5 give the dose response curve and data for complications in the thorax. The narrowest range in the 95% confidence region of the regression line occurs at 45.6% where the 95% confidence limits on dose are 19.7 and 21.1 Gy.

A log-log transform on P was also analyzed ($y = \log(-\log P)$). The fit to this transform was inferior to the logistic fit in all sites.

Discussion

Accurate assessment of the probability of radiation injury is confounded by several factors. The dose to the injured tissue is not always unambiguously defined. The censoring of patients as a result of cancer deaths and other causes introduces calculation difficulties. The methods that account for censoring rely upon having the time to onset of injury (latent period). Complications are usually expressed progressively over some time period, and it is not generally possible to state an exact time of onset.

Further difficulties can be introduced if the latency is dose dependent or if the pathogenesis of the injury changes with dose.

For clinical data the simplest analytic procedures can be used if (1) patients are grouped according to the dose to the site at risk, (2) this dose is constant within groups, (3) all patients have the same censoring rate (i.e. have the same life expectancy), and (4) the true complication is sufficiently high that radiation injuries can be analyzed separately. For the data that we have, it was necessary to combine severe complications by site to obtain analyzable dose response data. The exception to this was radiation osteomyelitis of the mandible.

The pathogenesis of radiation osteomyelitis is multifactorial. Although radiation alone can lead directly to this injury, it is more commonly found to occur in patients with predisposing or concomitant factors such as poor oral hygiene, tumor invasion, soft tissue necrosis, or dental extractions. Furthermore it is manifest in a variety of severities from subclinical injury that heals spontaneously to severe necrosis resulting in poor nutrition, septicemia, cachexia, and even death. In patients who have a properly supervised plan of oral hygiene, this complication is rare below 66 Gy (previous) in 2 Gy fractions. In patients whose mandible is included in the high dose region of radiotherapy of head and neck cancers, a 5-10% complication rate is not uncommon. However this complication rate is a crude one (uncorrected for censoring) and is not estimated with the techniques used in this report. Even so, it appears the an RBE ~~in the range of~~ of about 3 (- 3.5) is reasonable. Our results indicate that the lower limit of the 95% confidence interval on the 20% complication dose is 23.2 Gy.

Considering together all severe complications in the head and neck region, the dose response curve is shifted to lower doses. The shift amounts to a 6% reduction in dose. Including all complications, the lower 95% confidence limit on the dose giving a 20% complication rate is 21.3 Gy. Because of the larger residuals in the fit of the data, the 95% confidence region about the regression line is larger for all complications than for osteomyelitis alone.

Analysis of the complication data for cancer of the pancreas gives some interesting problems. The error bars for all complication rates overlap although the highest and lowest complication rates differ significantly ($p < 0.05$). Furthermore the dose response curve for these data is the shallowest of all those obtained. As a result the confidence limits on the dose causing specific complication rates is inflated over what they would be with a steeper curve. However, the significance of the regression for this curve is greater than for any other, thereby reducing these confidence limits. The lower 95% confidence limit on the 20% complication dose for this site is only 16.5 Gy. However it should be noted that in this report, all complication rates quoted are those that should be observed in the absence of censoring from cancer deaths. The observed complication rate at some time after treatment is obtained by multiplying the rate with censoring by the probability of surviving to that time. Clearly for cancer of the pancreas, the observed rate will be much smaller than the true rate.

There is considerable overlap of the confidence limits on the estimates of the complication rates for pelvic treatments. In general, the dose response curve for this site is the least well-determined of all sites studied. The lower limit on the 95% confidence interval for the 20% complication dose is

16.0 Gy. The reasons the pelvis has the broadest confidence region around the regression line is that the residuals for the fit are larger than for any other site.

The lung also show considerable overlap of the confidence interval for the complication rates. Even so, the regression for this site attains a higher significance than for any other. The lower limit on the 95% confidence interval for the 20% complication dose is 16.5 Gy.

For many years, investigators have offered numerous conflicting definitions of tolerance dose in radiation therapy. The reason no unequivocal definition can be established is that radiation tolerance is not an observable. Only when a patient expresses an injury will it become apparent that his tolerance has been exceeded, but it will not be possible to determine to what degree an individual's tolerance was exceeded. Furthermore, being free of injury indicates either that tolerance was not exceeded or that the patient has not yet expressed the injury for which tolerance was exceeded. Presently, the only information that is practicably achievable is the latent period distribution and the distribution of tolerance doses for the analyzed patient population.

What therapists must decide is what maximum fraction of the patient population they are willing to see express a radiation injury in using the treatment regimen that will meet their other treatment objectives. The expected fraction, h, that expresses a radiation injury is by a time t is given by

$$h = P \cdot \int_0^t f(t')S(t')dt'$$

where f(t) is the distribution of latent periods, S(t) is the uncensored survival function of the patient population and P is the probability that a patient's is tolerance will be exceeded by the treatment regimen. Using this expression, an objective of treatment is to achieve a result that includes a fraction of patients with observed complications. If this fraction is zero, then the therapist is implicitly assuming a threshold dose below which no complication occurs.

The above expression for h, gives the expected value for the observed complication rate. If this is the target value that is used in a clinical trial, obtaining smaller or larger values are equally likely. That is, the confidence level for this complication rate is 50%. It is more likely that a confidence level on the upper limit of the observed complication rate would be high, perhaps 95%. To target an observed complication rate, h, with only a 5% probability of exceeding thus rate, the value of P is equation ( ) should be obtained from the upper arm of the hyperbola that defines the 95% confidence limits on P. These hyperbolae are shown in Figures 1-5.

Conclusion

The doses corresponding to 15.8% crude complication rates were used as to define an operational tolerance in our previous publication. For the sites with longer life expectancy ((1) head and neck and pelvis) these doses correspond well with the doses determined in this study. However, in the

sites with poorer life expectancy (thorax and pancreas) the doses were understandably much lower when determined by methods that account for censoring. Clearly crude or observed complication rates in thorax and pelvis correspond to much higher true complication rates in these sites.

Crude dose response curves have been previously published and censoring has been accounted for at single dose points. However, in no other publication have dose response curves been published that account for censoring.

Using the methods described here, complication rates can be predicted, confidence limits on these rates can be predicted, and doses that will result in a given complication rate (with a specified confidence level) can be estimated. Until factors can be identified that increase the relative risk of radiation injury, the above dose response information is the most that is achievable from clinical data.