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● *Original Contribution*

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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The importance of knowledge on tolerance of normal tissue organs to irradiation by radiation oncologists cannot be overemphasized. Unfortunately, current knowledge is less than adequate. With the increasing use of 3-D treatment planning and dose delivery, this issue, particularly volumetric information, will become even more critical. As a part of the NCI contract N01 CM-47316, a task force, chaired by the primary author, was formed and an extensive literature search was carried out to address this issue. In this manuscript we present the updated information on tolerance of normal tissues of concern in the protocols of this contract, based on available data, with a special emphasis on partial volume effects. Due to a lack of precise and comprehensive data base, opinions and experience of the clinicians from four universities involved in the contract have also been contributory. Obviously, this is not and cannot be a comprehensive work, which is beyond the scope of this contract.

Normal tissue tolerance, Three-dimensional treatment planning, Volume effects, Irradiation.

INTRODUCTION

The aim of the radiation oncologist is uncomplicated loco-regional control of cancer by radiation therapy. To accomplish this goal, precise knowledge of tumoricidal doses and tolerance doses of various normal tissues is most helpful. Unfortunately, after eight decades of radiotherapy practice, current knowledge of both issues is imprecise. The importance of time-dose-volume factors in radiation therapy is well-recognized (36), but has been inadequately studied. In the majority of clinical situations, the radiation oncologist is, admittedly, treating to tolerance doses rather than to specific tumoricidal doses. Thus many radiation oncologists assume that most organs are safely within the tolerance levels of their dose schedules. At the other extreme, many physicians and pathologists believe that irradiation causes all the complications in cancer patients receiving radiation therapy. Mendelsohn (108) has discussed the lack of time-dose data related to patterns of radiation damage in normal tissue and has noted that "some tissues are dealt with effectively, but the bulk of tissues are seldom discussed, poorly documented and have data which are sparse and meaningless." The monumental work of Rubin and Cassarett (153, 154) was a major step in this direction. Unfortunately, with the exception of few sporadic efforts on some specific tissues (99, 100, 192, 193), little comprehensive and systematic work has been done since Rubin and Cassarett's work, despite the vital importance and the urgent need for efforts among radiation oncologists and pathologists to correct this deficiency for the sound practice of radiation oncology. Many of us, in day-to-day routine practice of radiotherapy, refer to the tolerance doses documented by Rubin and Cassarett, published some two decades ago. TD 5/5 (the probability of 5% complication within five years from treatment) and TD 50/5 (the probability of 50% complication within five years), which they introduced (155), are still the most prevalent and dominant concepts in expressing the tolerance of normal tissues to radiation therapy. Only rarely has the issue of gradations of dose across the volume of an organ been addressed (161).

Current practice of radiation therapy, even at major centers which are equipped with relatively sophisticated treatment planning systems, is based on two-dimensional treatment plans using a single cut from a CT scan, either at the level of the gross tumor or at the level of the central axis, with superimposed isodose curves representing the cumulative dose of radiation to the tumor and various

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organs. Utilization of CT scans in this manner during the last decade has resulted in the capability of major improvements to ensure adequate tumor coverage and better sparing of critical normal structures (37, 124, 144, 189). Even with the availability of modern technology and use of sophisticated computers in treatment planning, however, the irradiation tolerance dose of partial volume of normal tissues being irradiated is not known and is, for the most part, a guess on the part of the radiation oncologist based on experience. In the continuing effort to achieve uncomplicated loco-regional tumor control, the predominant pattern of thought has been to minimize the dose of radiation to normal structures while maximizing the dose to the tumor volume.

The availability of fast computers and modern imaging techniques has lead to the development of a new concept of "three dimensional treatment planning and dose delivery" which may eventually assist radiation oncologists in achieving the goal of minimizing doses to normal tissue and maximizing tumor doses (148). During preliminary experimentation with three-dimensional treatment planning, it became apparent that there is a critical need for more accurate information about the tolerance of normal tissue to radiation. This is not only related to the dose-time parameters (181), but specifically to the partial volumes of normal tissue receiving variable dose levels (161). In this communication we will try to address the above subject. Comparative overview of radiation dose tolerance of normal tissue is a major task and beyond the scope of this contract. The diversity of organs, variety of complication endpoints for each organ, endless variations in any combination of radiotherapeutic parameters such as fractionation, volume, overall time, etc., physiological status of these organs prior to commencement of radiation, and the disease and age of the patient are some of the factors that makes this task an enormous undertaking.

METHODS AND MATERIALS

Realizing the importance and the potential impact of three-dimensional treatment planning in the future of radiation oncology, the National Cancer Institute has awarded four contracts to study "three dimensional treatment planning for high energy photons (RFP #NCI-CM-36716-21)." During the working group's first few meetings, after selection of the sites to be studied and the designing of appropriate protocols, the need for more accurate knowledge of the dose-time-volume relationships for normal tissues became very clear. Therefore, a task force was formed which consisted of all the physicians involved in the contract from the four participating institutions. The function of this task force was to search the literature and draw from their own experience to provide the most accurate and updated information about the tolerance of normal tissue to radiation. In order to accomplish this, the task force took the following steps:

1. Through the review of the protocols of the eight sites used in this contract, the task force identified 28 critical sites of normal tissue. These sites were equally apportioned among physicians involved in the contract with specific consideration of their specialized clinical areas of expertise.
2. The task force decided that only conventional fractionation, 180 to 200 cGy per day at 5 days to week schedule, would be considered.
3. To address volume dependence, the most clinically important (i.e., severe) endpoint would be chosen for this research.
4. On the subject of volume, the group decided to arbitrarily divide the total volume of each organ into three categories: one-third, two-thirds, and the whole organ. Appropriate tolerance doses should be assigned to each of these volumes. Admittedly, there will be organs such as the optic nerve, optic chiasm, or lens for which this arbitrary division could not be carried out, and in such cases the whole organ was considered.
5. Only adult tissue tolerance would be considered in this manuscript. Tissue tolerance of pediatric patients, an extremely important subject in itself, should be treated in a separate study.

RESULTS AND DISCUSSION

The results of this investigation were tabulated for the three volume categories described above (one-third, two-thirds, whole organ). For each partial volume, two dose levels (TD 5/5 and TD 50/5) were determined. These results are summarized in Table 1. Some of the tolerance doses are based on hard experimental and clinical investigational data. Other tolerance doses are based on less firm data, but are relatively reliable. Finally, a few tolerance doses are based purely on the experience of the clinicians involved in the task force. A discussion of data for each site follows.

Head and neck

Brain. Late radiation necrosis of the brain typically occurs three months to several years after irradiation. It is manifested by progressive neurological deficits that on clinical and radiological grounds cannot be attributed to recurrent tumors. Histological study of brains irradiated for glioma (17) reveals pallor of white matter consistent with diffuse cerebral edema and demyelination, and more marked changes in the white matter adjacent to the tumor itself. Here in varying degrees, Burger *et al.* (17) found coagulation necrosis, vascular thickening, perivascular fibrosis, calcium deposition, fibrin deposition, fibrin exudation, petechiae, and chronic inflammatory cell infiltrates. These late changes are thought to be due to radiation damage to the fine vasculature of the brain and also to proliferating glial cells, such as oligodendrogliocytes, which produce myelin. Glioblastoma multiforme characteristically con-

Table 1. Normal tissue tolerance to therapeutic irradiation

Organ	TD 5/5 Volume			TD 50/5 Volume			Selected endpoint
	$\frac{1}{3}$	$\frac{2}{3}$	$\frac{3}{3}$	$\frac{1}{3}$	$\frac{2}{3}$	$\frac{3}{3}$	
Kidney I	5000	3000*	2300	—	4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic bladder contracture and volume loss
Bone:							
Femoral Head I and II	—	—	5200	—	—	6500	Necrosis
T-M joint mandible	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Rib cage	5000	—	—	6500	—	—	Pathologic fracture
Skin	$\frac{10\ cm^2}{—}$	$\frac{30\ cm^2}{—}$	$\frac{100\ cm^2}{5000}$	$\frac{10\ cm^2}{—}$	$\frac{30\ cm^2}{—}$	$\frac{100\ cm^2}{6500}$	Telangiectasia
	7000	6000	5500	—	—	7000	Necrosis Ulceration
Brain	6000	5000	4500	7500	6500	6000	Necrosis Infarction
Brain stem	6000	5300	5000	—	—	6500	Necrosis Infarction
Optic nerve I & II	No partial volume		5000	—	—	6500	Blindness
Chiasma	No partial volume		5000	No partial volume		6500	Blindness
Spinal cord	$\frac{5\ cm}{5000}$	$\frac{10\ cm}{5000}$	$\frac{20\ cm}{4700}$	$\frac{5\ cm}{7000}$	$\frac{10\ cm}{7000}$	$\frac{20\ cm}{—}$	Myelitis necrosis
Cauda equina	No volume effect		6000	No volume effect		7500	Clinically apparent nerve damage
Brachial plexus	6200	6100	6000	7700	7600	7500	Clinically apparent nerve damage
Eye lens I and II	No partial volume		1000	—	—	1800	Cataract requiring intervention
Eye retina I and II	No partial volume		4500	—	—	6500	Blindness
Ear mid/external	3000	3000	3000*	4000	4000	4000*	Acute serous otitis
Ear mid/external	5500	5500	5500*	6500	6500	6500*	Chronic serous otitis
Parotid* I and II	—	3200*	3200*	— (TD 100/5 is 5000)	4600*	4600*	Xerostomia
Larynx	7900*	7000*	7000*	9000*	8000*	8000*	Cartilage necrosis
Larynx	—	4500	4500*	—	—	8000*	Laryngeal edema
Lung I	4500	3000	1750	6500	4000	2450	Pneumonitis
Lung II							
Heart	6000	4500	4000	7000	5500	5000	Pericarditis
Esophagus	6000	5800	5500	7200	7000	6800	Clinical stricture/ perforation
Stomach	6000	5500	5000	7000	6700	6500	Ulceration, perforation
Small intestine	5000		4000*	6000		5500	Obstruction perforation/fistula
Colon	5500		4500	6500		5500	Obstruction perforation/ ulceration/fistula
Rectum	Volume 100 cm^3 No volume effect		6000	Volume 100 cm^3 No volume effect		8000	Severe proctitis/ necrosis/fistula, stenosis
Liver	5000	3500	3000	5500	4500	4000	Liver failure

*<50% of volume doesn't make a significant change.

tains areas of necrosis within the tumor and this has to be differentiated from radionecrosis. The specific endpoint chosen for complication of brain is radionecrosis.

Sheline *et al.* (166) reviewed the world literature and found 80 cases of brain necrosis where irradiation was "either the causative agent or a major contributing factor," and a reasonable estimate could be made of the time-dose-fractionation regimen. A majority of these patients had tumors other than gliomas (48 head and neck/skin/pituitary vs. 32 gliomas). They calculated a quantity, the neuret, based on a modification of the Ellis NSD formula (36). Their model gave more weight to N, the fraction size, and less to T, the overall time. There were 20 patients with doses of 5000 cGy or less who developed necrosis, but in nearly all of these the fraction size was large (250 cGy or more). With conventional fractionation of 200 cGy per day, the incidence of necrosis is expected to be low (no more than a few %), but tolerance may be reduced by chemotherapy. In addition, the Sheline report does not provide adequate data on volume effect.

Marks *et al.* (104) attempted to determine the incidence and risk of radiation necrosis by reviewing a series of 152 patients (20 pituitary, 132 primary brain tumors) treated by one radiotherapy center. They reported 7 pathologically confirmed cases of necrosis out of 139 cases (5%) who received 4500 cGy or more in 180–200 cGy fractions. In fact, only one instance was seen at prescribed doses less than 5400 cGy in 30 fractions over 42 days (in this patient there was white matter necrosis in a region receiving as little as 4500 cGy). The minimum field size involved was 6 × 6 cm.

The incidence of radionecrosis tends to be underestimated in series of glioma patients because 1) many patients die early, and 2) the autopsy rate is low. CT scanning has probably improved the detection rate, and an interesting dose/CT study was reported by Mikhael (110). He reported 5 cases where necrosis appeared as areas of low density in white matter with no mass effect on CT; these lesions appeared after 18 months and the lesions were in parts of the brain that had received 4,500 cGy or more. In a further 12 patients who received in excess of 6000 cGy, radionecrosis appeared on the scans either as a localized mass with contrast enhancement (8 cases) or as diffuse lesions with no mass effect (4 cases). It seems that MRI is more sensitive than CT at detecting white matter edema and shows periventricular changes of uncertain significance at doses as low as 2400 cGy (27).

The NTCPs (Normal Tissue Complication Probability) used in this study seem to be consistent with the above studies on necrosis of the brain, although one could argue for an increase in the TD 5/5 for whole brain above 4500 cGy (Table 1). However, it is clear that some patients develop significant necrosis from partial brain doses as low as 5000 cGy. Pezner and Archambeau (134) from a review similar to Sheline's constructed a risk model which suggested a sharp increase in risk for doses of over 6000 cGy, normally fractionated, so that the TD 50/5 figures are also reasonable.

Brain stem. The brain stem has been traditionally regarded as more radiosensitive than the cerebrum. The main rationale for this seems to be an early study by Boden (12) where 6/24 patients treated with orthovoltage to small fields for tumors of the middle ear and nasopharynx developed brain stem necrosis. Sheline *et al.* (166) estimated that the doses of 408–503 cGy delivered over 17 days were equivalent to 5300–6540 cGy in megavoltage terms. The neuret scores were high and would be expected to carry a high risk of necrosis. Brain stem necrosis is not a feature of modern radiotherapy nasopharynx cancer series, and there is no good evidence that the sensitivity of brain stem differs from cerebrum. However, in view of the high concentration of white matter in the brain stem, a reduction of 10% from brain tolerance dose might be advisable. The tolerance may be affected by other influences such as drugs and preexisting vascular pathology (e.g., diabetes), but the available TD 5/5s for partial volumes are probably too conservative. We have suggested that the dose be 6000 cGy for $\frac{1}{3}$ volume (such doses are often given to part of the brain stem at the Harvard cyclotron). Complication endpoint for this site is necrosis.

Chiasm. Hammer (68) reports 4/87 (4.6%) patients with irradiated pituitary tumors who developed chiasmal necrosis. They received 4250 cGy in large fractions (210–280 cGy). Again, fraction size is probably very important and there are no grounds for supposing that chiasmal tolerance is different from the other structures considered above. Reducing the TD 5/5 to 50 Gy and keeping the TD 50/5 at 65 Gy may be appropriate. Similar to optic nerve, endpoint chosen for this site is blindness.

Ear: External/middle. Irradiation to the external and middle ear can result in acute serious otitis externa/media. The development of a painful fullness in the ear due to otitis media is quite common following head and neck irradiation. The TD 50/5 for this acute reaction has been estimated at 4000 cGy while the majority of patients do not develop chronic otitis media (TD 50/5) until doses of 6500–7000 cGy have been exceeded (13, 153, 154). The TD 5/5 is poorly established but an acute TD 5/5 of 3000 cGy and a chronic TD 5/5 of 5500 cGy is estimated. Due to the prevalence of complications, two endpoints were chosen; acute otitis and chronic otitis.

Ear: Inner (sensorineural-vestibular). There are only rare complications due to irradiation of the inner ear since these complications are generally associated with higher doses of radiation than conventionally given. A review of several studies suggests TD 5/5 of 6000 cGy and TD 50/5 of 7000 cGy (30, 51, 92, 119, 153) for sensorineural or vestibular damage.

Eye: Lens. Patients receiving between 500–1000 rads to the lens can be shown to develop lens opacities, but these rarely progress to interfere with vision. The Seattle group [Deeg *et al.* (30)] reviewed the incidence of cataract

post-TBI. For fractionated doses of 12–16 Gy the risk of developing a cataract which required surgery was 20%. Even allowing for the effect of steroids this suggests that the TD 5/5 should be reduced to 1000 cGy. From the same study a TD 50/5 for a single fraction was 10 Gy and the sparing from fractionation was significant. Therefore, the quoted TD 50/5 of 1800 cGy is not unreasonable and might be conservative. The end point chosen for complication of this site is formation of cataract which requires surgical intervention.

Eye: Retina. Parsons *et al.* (131) described radiation retinopathy as clinically similar to diabetic retinopathy with microaneurysms, exudates, hemorrhages, and new vessel formation. Apart from microvascular damage, radiation can also cause retinal artery thrombosis [Shukovsky and Fletcher (168)]. They reported a series of patients irradiated via an anterior field for ethmoid tumors. Of 15 patients evaluable for eye complications, 7 eyes showed progressive visual loss due to retinopathy, 2 due to retinal artery thrombosis. Many of the damaged retinae received very high doses (7000 or more), but the arterial thromboses were associated with doses less than 6000 rads. These authors concluded that doses in excess of 6800 rads in 6 weeks will lead to loss of sight 2–5 years after radiotherapy. From their data this dose produces a high risk of blindness, more akin to a TD 50/5 than TD 5/5.

Parsons *et al.* (131) included only patients in whom at least half the posterior pole of the eye was included in the high dose region. They found a sharp cut-off at 5000 cGy with one instance of retinopathy below this dose and only one eye above 5000 cGy where there was not retinal injury sufficient to produce visual loss (visual acuity $< 20/200$). There were few data between 50 and 55 Gy, but at 60 Gy or above, retinal damage would seem inevitable from their report.

Nakissa *et al.* (127), in a review of 30 patients irradiated for paranasal sinus cancer, reported that all patients receiving more than 45–50 Gy to the retina had detectable damage, but visual loss was found only in patients receiving 6500 cGy or more. Eight patients had functional eyesight after more than 5000 to the retina.

It would seem that the dose response curve is very steep between 50 and 60 Gy, and 45 Gy for a TD 5/5 for visual loss is realistic, as is 65 Gy for the TD 50/5.

Larynx. Laryngeal chondronecrosis occurs rarely (less than 1%) at conventional daily fractions of 200 cGy to total doses of 7000 cGy (70, 131, 172). If larger daily fractions are used the risk increases. We have accepted the TD 5/5 of 7000–7900 cGy and TD 50/5 of 8000–9000 cGy offered by Rubin and Cassarett (153, 154). However, since the larynx is rarely treated to doses of 8000–9000 cGy, complication data for chondronecrosis at conventional doses is difficult to document (70).

Another radiation-related complication of laryngeal treatment, which is far more common than laryngeal chondronecrosis, is laryngeal edema. The TD 5/5 and TD 50/5 of 5000 cGy and 7000 cGy respectively are based on the literature (55, 58, 169). Fu (49) noted a 13.7% incidence of laryngeal edema at doses less than 7000 cGy rising rapidly to 46.2% at doses of 7000 cGy and above. Again, other factors such as initial tumor stage, the patient's social habits of drinking alcohol or smoking, and the treatment volume are also important and were not accounted for in this analysis.

Optic nerve. Shukovsky and Fletcher (168) found three cases of optic neuropathy, but did not differentiate between this risk and retinopathy. Parsons *et al.* (132) distinguished distal ischemic neuropathy from retro-bulbar neuropathy. They found a difference in risk for combined neuropathy depending on fraction size, and quote risks at a dose range of 60–73 Gy of 8% at 165–190 cGy/fraction and 41% at >195 cGy/fraction. Neuropathy was not evident at 55 Gy or less.

Brown *et al.* (15) report 14 cases of radiation optic neuropathy (RON). Some were due to cobalt plaque treatment, but 6 were following external beam therapy. The dose ranged from 3600 to 7200 (no mention of fraction size) with a mean of 55 Gy. Only 1/6 was completely blind. Kline *et al.* (88) reported 4 cases of blindness due to RON with doses of 46–50 Gy (200 cGy fractions). Some of these patients had Cushing's syndrome, and Aristizabal *et al.* (4) suggest that this reduces neural tolerance.

Pezner *et al.* (139) in their review found no difference between optic nerve and other CNS tissues. Given that blindness has occurred with doses of 50 Gy or less, it may be that 55 Gy cannot be justified for the TD 5/5; this should be reduced to 50 Gy, similar to the brain stem. For the TD 50/5, 65 Gy is reasonable.

Parotid. Xerostomia results from irradiation of the salivary glands and is a frequent complication of head and neck irradiation. The majority of salivary output in response to a stimulus is a result of secretion by the parotid gland. Several studies have examined the effect of radiation dose and parotid volume on the development of xerostomia. Unfortunately, precise determinations of tolerance doses cannot be made; however, we have attempted to make estimates on the basis of the literature and clinical experience. The TD 5/5 is not well established. Doses of under 1000 cGy can cause significant decrease in salivary flow, which has been correlated with xerostomia (90, 103, 164). Mira *et al.* (116) reported a recovery in parotid function after doses of greater than 3000 cGy if a treatment break is given. Rubin and Cassarett (153) indicate a TD 5/5 of 5000 cGy for xerostomia due to parotid irradiation which appears too high. Our estimate of the TD 5/5 based on these studies and clinical experience is 3200 cGy.

The TD 50/5 determined from literature review was 4600 cGy. Mossman *et al.* (123) established a TD 50/5 of 40–65 Gy. Other data (103, 116) suggest minimum salivary flow in half the patients at doses of approximately 3000 cGy. Rubin and Cassarett (153) listed a TD 50/5 of 7000 cGy. Thus there is a marked variation in the TD 50/5 inferred from the literature. We have also noted a TD 100/5 of 5000 cGy, which is probably a conservative estimate

since even though nearly all patients have no salivary flow after 5000–6000 cGy (103, 123, 164), some patients may not experience xerostomia.

The volume of parotid tissue irradiated has been studied and the data suggests that more than 50% of the parotids have to be outside of the field to prevent severe xerostomia (116). Marks (103) found xerostomia to be present in about half the patients who received primarily unilateral irradiation only (with less than 1000 cGy to the contralateral parotid). Other factors such as the age of the patient and initial flow rate may be important prognosticators for development of xerostomia and were not taken into account for our estimates.

Thyroid. The clinically relevant endpoint was felt to be clinical hypothyroidism. Although there is an interesting body of information regarding biochemical hypothyroidism, this does not seem to be clinically relevant for management of the patient. Excluding the situation of a patient with a partial thyroidectomy, there is no obvious volume response parameter for less than some arbitrarily large fraction of the whole gland. This was arbitrarily chosen as $\frac{2}{3}$ to all of the thyroid gland as being necessary to be damaged in order to produce clinical hypothyroidism. It should also be noted that surgery or a lymphangiogram prior to radiation appears to reduce the tolerance of the thyroid gland to irradiation, and, therefore, a further stipulation is that these values are only for patients without surgery and not having been prior studied with lymphangiogram. Finally, essentially all of the literature (33, 50, 52, 163, 168, 194), both for external irradiation as well as for radioactive iodine, has wide dose ranges for any individual study. Therefore, determination of data points at any particular dose level can only be considered as estimates.

For the endpoint of clinical hypothyroidism with a volume of the whole thyroid irradiated, the estimated TD 8/5 is 4500 cGy, the estimated TD 13/5 is 6000 cGy, and the TD 35/5 is 7000 cGy. The data in the tables are derived (estimates) of references.

Thorax: Brachial plexus and cauda equina. (Note: Due to similarity of their radiation tolerance, cauda equina was dealt with in this section.)

Data on radiation injury to the cauda equina is limited; available references frequently include patients who may have had injury to the lumbar spinal cord rather than to the cauda. The doses of 6000 and 8000 cGy for TD 5/5 and TD 50/5, respectively, are largely speculative. Available data has been summarized by Kinsella *et al.* (87) who were unable to discern any dose-response relationship. Injury to the cauda is rare, but it has been reported in at least two cases after doses of 67.5 Gy in approximately 3.5 weeks (5). Few if any cases have been observed with doses below 60 Gy, but more would be expected if the cauda dose exceeds 80 Gy. There are no data available to support volume effect estimates. More extensive data for brachial plexus injury (87, 179) would in general support the TD 5/5 and TD 50/5 doses cited for tolerance of the cauda equina.

Gastrointestinal (esophagus). This organ has been dealt with the rest of the GI system (see the Abdomen section).

Heart. Radiation injury to the heart is most often manifested as pericarditis, although other complications such as chronic pericardial effusion or myocardial ischemia may occur. Pericarditis was chosen as an endpoint because of its prevalence and its clinical importance. Significant information and understanding of various aspects of radiation-induced heart disease come from laboratory as well as clinical research of Stewart (173–177) and many others (5, 14, 16, 25, 26, 46, 53, 61, 65, 66, 76, 78, 86, 96, 105, 106, 111, 140, 159, 183). Pathological manifestations are largely from the work of Fajardo *et al.* (42–44). Information on the radiation injuries from whole heart radiation comes mostly from patients with Hodgkin's disease; partial volume radiation-induced heart complications are mostly from patients treated postoperatively for breast cancer (109). TD 5/5 of 4000 cGy whole organ to 6000 cGy for $\frac{1}{3}$ of the organ are solid data and are confirmed by adequate supportive literature. Information on TD 50/5 for partial and whole organ heart complications is mostly speculative and the doses of 7000 cGy (for $\frac{1}{3}$ of the heart volume), 5500 cGy (for $\frac{2}{3}$ of the heart volume), and 5000 cGy for whole organ radiation are from sporadic information in literature, as well as extrapolation from the TD 5/5 data and clinical impressions of the clinicians involved in this contract.

Lung. Pneumonitis and pulmonary fibrosis are the two most important consequences of irradiation of the lungs. Pulmonary fibrosis occurs in almost 100% of patients receiving high doses of radiation (93, 94, 137), but may not be of clinical significance if the volume is small enough. We have chosen the endpoint of radiation-induced pneumonitis for this contract because of its prevalence, its morbid outcome, and its clinical significance (153, 154). The lung is one of the few organs for which an attempt, although nonsystematic, has been made to study the effects of radiation on various volumes of normal tissue (99, 100). A significant number of publications deal with the effect of other agents such as chemotherapy or steroids, etc., in combination with radiation therapy, on pulmonary physiology (pulmonary function) (20, 34, 38, 54, 56, 60, 72, 73, 121, 136, 145, 146, 152, 165, 184, 185). Numerous studies have addressed the effect of time/dose factors on the development of pneumonitis (40, 81, 118, 192). Extensive studies on radiological manifestations of this complication have been published (93). Recently, new attempts have been made to study the early pathology of this complication (158). This material comes from a diverse group of patients afflicted with various diseases of the thoracic region, but mostly from patients with Hodgkin's disease (19, 57, 63, 77, 82, 97, 147), lung carcinoma (9, 71, 151) or a large volume irradiation such as hemibody or total body radiations (41, 48, 83, 188). The doses agreed on by the physicians of this contract and recorded in Table 1 are the results of extensive search of the literature and discussion. In addition, unpublished information from pa-

tients treated with lung cancer within the Radiation Therapy Oncology Group (personal communications), and the clinical experience of the clinicians involved in the contract, has been influential.

Abdomen

Bladder. Extensive experience with bladder tolerance has been accumulated in the treatment of pelvic malignancies, especially more advanced stages of bladder, cervical, and prostatic carcinoma. None of these are ideal for studying bladder tolerance, however. In bladder and in prostatic cancer, treatment is given to an organ whose functional capacity may have already been impaired by the disease itself or by prior attempts at diagnosis or treatment. Functional alterations observed after treatment may be related as much if not more to those factors, rather than to the treatment. In all three diseases the total pelvis, including the entire bladder, usually receives a substantial dose in the range of 45–50 Gy followed by additional irradiation to sites of gross tumor involvement (114). This invariably increases the dose received by at least a portion of the bladder to levels in excess of 68 Gy.

The TD 5/5 data points in the table for whole and $\frac{2}{3}$ volume irradiation, of 65 Gy and 80 Gy, respectively, are entirely consistent with bladder tolerance data cited by Goffinet *et al.* (59) and Miller (115) in patients with bladder cancer; by Ortin and Wolf-Rosenblum (128), Perez *et al.* (133), Strockbine *et al.* (182) and Pourquier *et al.* (143) in cervix cancer patients; and by Pistenma *et al.* (139), Duttenhaver *et al.* (32) and Pilepich *et al.* (138) for prostatic carcinoma. The TD 50/5 data point of 80 Gy is speculative, since the entire bladder rarely receives doses of that magnitude.

Gastrointestinal (esophagus, stomach, small bowel, colon, rectum). The endpoints selected for the complications of these organs by the task force were for serious toxicities only, those requiring intervention. Toxicity scales from cooperative groups such as RTOG have also been consulted and the clinical experience of the physicians involved in this contract was used as well. Acute esophagitis, which is very common, manageable, and self-limited, occurs with relatively modest doses (150). Information for severe toxicities is, therefore, limited (2, 39, 45, 64, 95, 102, 141, 150, 155, 156, 162). These articles were chosen from some 20–30 initially promising sources, which means that there were only two or three key articles for each site. The exclusion of other published articles was due to lack of sufficient dose information and/or inability to ascertain any volume information. The doses chosen for partial organ volume for these sites were modified somewhat by the experience of the task force. The data for most sites of gastrointestinal tract are quite soft (with the exception of the small bowel), especially since few authors have attempted to define a dose-volume relationship. One attempt was made to include a partial organ (intestine) in the potential complication analysis (155, 156), but only one measurement was given, and even that was changed from a volume (cm^3) (155) to a length (cm) (156) by the same investigators. More recently, Gallagher *et al.* (157) have carefully analyzed the volume of small bowel and dose, correlating this with both acute and chronic complications. A 3% incidence of late small bowel obstruction was seen with ≥4500 cGy delivered to an average volume of 664 cm^3 (about $\frac{1}{3}$ of the total small bowel). This is consistent with our TD 5/5 of 5000 cGy. Much of the data, therefore, relied on the clinical judgement of the physicians on the normal tissue task force of this contract.

Kidney. Knowledge regarding human renal tolerance to whole organ irradiation is generally derived from the work of Luxton, Kunkler and co-workers based on their experience with patients who had received whole abdominal irradiation (89, 98). Cohen and Creditor (23) have published iso-effect tables, based on a program which derived best-fitting cell kinetic parameters. They assumed that radiation injury arises from depletion of parenchymal cells in irradiated organs. When data from 12 sources in the literature were incorporated into their model, TD 5/5 ranged from 14 Gy in 2 fractions to Gy in 35 fractions, and was 28 Gy for 25 fractions (23).

TD 5/5 in the Table for whole organ irradiation, 23 Gy, is widely quoted as being a "tolerance dose" when delivered in 5 weeks in several standard references (122, 153, 182, 197). This dose reflects current practice in many radiotherapy departments, and is in general agreement with data from Luxton, Kunkler and co-workers (89, 98), as well as with iso-effect doses generated with the Cohen-Creditor model (23). TD 5/5 for $\frac{1}{3}$ and $\frac{2}{3}$ organ irradiation are in agreement with data from Willett *et al.* (196), Birkhead *et al.* (10) and Kim *et al.* (85) on renal function after partial unilateral kidney irradiation in patients with upper abdominal malignancies, Hodgkin's disease, and non-Hodgkin's lymphoma, respectively.

TD 50/5 for total organ irradiation, 28 Gy, is also based on data from Luxton and Kunkler (89, 98). The 40 Gy level quoted for TD 50/5 for $\frac{2}{3}$ organ irradiation is speculative; no attempt was made to estimate a TD 50/5 for $\frac{1}{3}$ organ irradiation, since this volume of kidney is routinely irradiated in many clinical situations without any major consequences.

Liver. TD 5/5 and TD 50/5 doses of 3000 cGy and 4000 cGy, respectively, for whole organ irradiation are solidly supported by the data of Ingold *et al.* (79) and Kim *et al.* (84). TD 5/5 and TD 50/5 dose points for $\frac{1}{3}$ and $\frac{2}{3}$ organ irradiation are more speculative, but are consistent with reported rates of clinical hepatic injury after partial liver irradiation in patients with non-Hodgkin's lymphoma (67, 142) and Wilm's tumor (180) receiving upper abdominal irradiation. Austin-Seymour *et al.* (7) have analyzed partial volume liver irradiation (charged particles) in 11 patients with carcinoma of the pancreas and bilary system via dose-volume histograms. Hepatitis developed in 1/11 patients. The authors suggested doses of 3000–3500 cGy to the $\frac{1}{3}$ volume of the liver and 1800 cGy to the whole liver (low LET equivalent at the rate of 200 cGy/day). We have

chosen severe hepatitis/liver failure for complication endpoint of this organ.

Bone

Humoral and femoral head. The endpoints, necrosis and femoral neck fracture, were selected as the only clinically relevant means of measuring damage to this area.

Necrosis of the femoral head and/or fracture of the neck of the femur has been discussed in case reports. The incidence varies with the dose and technique; there is no one specific work dealing exclusively with tolerance. Incidence has occurred with doses ranging from 20 Gy to 70 Gy. Rather than cite specific articles which reported on 1–5 cases, the best review is the book (167) *Radiation Injury of Bone* by Shimanovskaya and Shiman. Their summary of the work, as well as our clinical experience, leads to the estimation of 52 Gy as the TD 5/5 and 65 Gy for the TD 50/5. There is no volume data available and all data are very imprecise.

Mandible and temporomandibular joint. The endpoint selected was osteoradionecrosis as this is the most significant morbidity and potential life-threatening complication. Stated in the table is marked limitation of joint function for the temporomandibular joint; however, there is imprecise data for this and it was thought that necrosis was a more viable endpoint for determining a TD 5/5 and TD 50/5.

Osteoradionecrosis of the mandible has been proven to be dependent on the following:

1. tumor location (8, 75, 125)
2. dental status (78, 62, 125, 126)
3. technique (62, 75, 125)
4. total dose (8, 21, 62, 75, 120, 125)

For establishing a TD 5/5 we have assumed: optimal dental care prior to and following treatment; external radiation therapy only; no initial bone involvement with tumor; and dentulous patients.

We concentrated on the recent data because optimal dental care (i.e., fluoride treatments, necessary extractions prior to treatment, etc.) has been more routinely employed. Murray (125) found an incidence of 5.9% for 40–50 Gy and 14% for 50–60 Gy. From 60 Gy to 80 Gy there was a fairly constant incidence of approximately 25%. Studies by Bedwinek (8) and Morrish (120) indicate a higher tolerance. Bedwinek (8) found 0% incidence below 60 Gy, 1.8% from 60–70 Gy, and 9% when greater than 70 Gy was administered. Morrish (120) found 0% below 65 Gy, 27% from 65–75 Gy, and 85% for greater than 75 Gy (all in dentulous patients). Cheng (21) showed 0% incidence if less than 2000 rets (7200 cGy, 200 × 36) was given. Combining this data as well as our own clinical experience we felt that a conservative value for TD 5/5 would be 65 Gy for a small section of the mandible (i.e., $\frac{1}{3}$) and 60 Gy for a larger volume of the mandible. TD 50/5 can be projected as approximately 77 Gy for a small ($\frac{1}{3}$) volume with 72 Gy for the $\frac{2}{3}$ and full volume.

There is no reliable volume data available, however, Grant and Fletcher (62) evaluated field size and found increasing morbidity with increasing field size (using 75 cm^2 as the dividing line).

Rib cage. The endpoint chosen for the rib cage was pathologic fracture. We extended data from the literature on the treatment of intact breast cancer (28, 69, 107, 117, 171). The volume chosen was $\frac{1}{3}$ of the total ipsilateral rib volume: this is purely conjecture based on clinical judgement of the participating physicians. It is of interest that the breast plans which were evaluated for this contract suggest that this may be an overestimate of the volume. Of further note is that no data is available for larger volumes (such as $\frac{2}{3}$ volume) or the entire ipsilateral rib volume.

Our recommendations for TD 2/5 was 4800 cGy, TD 8/5 was 5800 cGy, and TD 20/5 was 6500 cGy. The TD 2/5 seems to be very solid, as multiple centers have reported doses and complications on the order of 4500–5000 cGy for breast tangent fields. The values from the higher dose levels were reported from the Joint Center for Radiotherapy (69). No data for a TD 50/5 are available. Doses in Table 1 are derived from the above data.

Muscle

The endpoint chosen for muscle was clinical myositis. The relevant literature (107, 171) comes from breast tangential irradiation for treatment of the intact breast. The clinicians again estimated the volume and arbitrarily picked $\frac{2}{3}$ of the ipsilateral volume. Of interest is that results from this contract would suggest that this is an overestimation of the volume actually treated to the high dose. No information is available regarding volume effects.

Given the paucity of data, only one recommendation could be made, namely, a TD 1/5 of 5000 cGy. The values in the literature range between 1–5%. However, the figure of 5% from the Martinez paper (107) was considered an overestimation, as these were associated with radioactive implants in close proximity to the muscle. Therefore, the lower figure of 1% was chosen.

Skin

Two different endpoints were chosen for skin: necrosis and telangiectasia. The partial volume irradiation (size dependence) is specified in square centimeters (area), because this is easily measured. The volume of the whole organ does not represent a clinically relevant endpoint for any common radiotherapy treatment. For the endpoint of necrosis, the model by Von Essen (190) was consistent with the experience of the radiotherapists of the Normal Tissue Tolerance Task Force, and others (31, 186, 187, 191). Recommended values were area dependent. For a 100 cm^2 field, the TD 3/5 was 5100 cGy, TD 5/5 was 5500 cGy, and TD 50/5 was 7000 cGy. For a 30 cm^2 field, the TD 3/5 was 5700 cGy. For a 10 cm^2 field, the TD 3/5 was 6900 cGy.

For the endpoint of telangiectasia with an area of

approximately 100 cm^2, the TD 10/5 was 5000 cGy, TD 30/5 was 5900 cGy, and the TD 50/5 was 6500 cGy (187).

Spinal cord

TD 5/5: Dose-volume. Evaluation of the tolerance level of the spinal cord to ionizing radiation has been hampered by variable fraction size and the long latent period of clinical myelitis. The range of the latent period is 5 months to 18 months (74, 160). Since many patients with cord irradiation had thoracic malignancies with a mean survival in that range, it is possible that many died of disease before developing cord damage (74).

The importance of fraction size has been recognized since the first classic publication of cord tolerance by Boden in 1948 (11). Most studies since then confirmed that total dose and the number of fractions, i.e., dose per fraction, not the overall time, was the important variable (6, 129, 135, 193). The earlier studies of Boden (11) and Pallis (129) plotted dose response data on a Strandqvist log-log graph, i.e., dose as a function of treatment duration and total number of days, rather than as the number of fractions.

It wasn't until the work of Atkins (6) in 1966 that dose as a function of fraction number was tabulated and represented in log-log graphs, as proposed by Ellis (35) and Fowler and Stern (47). Atkins' data indicated an increased tolerance with decreasing dose per fraction. Phillips (135) was the first to use an NSD formula and found a slope of 0.5 for dose as a function of fraction number. He proposed a limit of 1500 rets (5000 cGy, 200 cGy × 25) with no cases of radiation myelitis occurring below this dose. The same data base was expanded and analyzed utilizing the NSD concept with some modifications of the formula to arrive at variable tolerance values as follows: Maier (101), 1300 rets (4000 cGy, 200 cGy × 20); Wara (193), 5000 cGy (200 cGy × 25); Abbatucci (1), 1570 rets (5000 cGy, 200 cGy × 25), with all myelitis cases occurring at doses greater than 5500 cGy; and Lambert (91), 5000 cGy.

However, near the end of the 1970's, the Ellis time-dose-fractionation relationship became suspect since it was based on skin data and dealt with acute, not long-term, complications. More recently, several attempts have been made to apply new formulas to the growing data base. Most notably, Cohen (22, 25) used a cell population kinetic model to determine the best fitting iso-effect function. He developed iso-effect lines with multi-target and linear quadratic models. He showed that the data do not follow a Strandqvist straight line but have a steeper change of tolerance with fraction number for large dose-per-fraction regimens. He proposed 4700 cGy as a "tolerance" dose. Wigg (195) also showed the Ellis formula was not appropriate and recommended 4800 cGy as a "threshold" dose.

If one combines all data to date including the more recent analyses, a reasonable value is 5000 cGy as the TD 5/5 with only sporadic, idiosyncratic cases of myelitis occurring below that dose (130).

Volume data has been recognized by Boden (11), 4500 cGy less than 10 cm, 3500 cGy greater than 10 cm; Abbatucci (1), 3–5 vertebral bodies—1570 rets (5000 cGy, 200 cGy × 25) threshold; 6–7 vertebral bodies—1465 rets (4600 cGy, 200 cGy × 23) threshold; Cohen (22) described a length function; Rubin (155), 10 cm length for values given. Most data would indicate 5500 cGy could be allowed for a 5 cm segment, and we recommend this value as the current value of TD 5/5 for 5 cm. For 10 cm, 5000 cGy is reasonable. A value of 4700 cGy was selected for 20 cm since all studies have indicated decreasing tolerance with increasing length. However, actual derived values for an exact 20 cm length are not available.

TD 50/5: Dose-volume. TD 50/5 data for dose values can be derived from the following: Phillips (135) 1750–2000 rets, 50%; Wara (193) 1476 rets, 50%; Rienhold (149) 6500 cGy; Abbatucci (1) 60–65 cGy 36%; Rubin (155) 6500 cGy. We initially selected 7000 cGy for 5 cm and 10 cm, however, 7300 cGy for 5 cm would be a more realistic, conservative value and would reflect the length/volume factor. Again, for 20 cm, this was reduced slightly to 6500 cGy.

The endpoint selected is that which elicits a clinically relevant permanent condition, i.e., transverse myelitis/necrosis. Lhermittes syndrome was not selected as it is: 1) transient and not proven to always lead to myelitis; 2) not clinically significant for a class 1 organ; 3) all data in this report is based on historical accounts of clinically significant radiation-induced myelitis.

SUMMARY

In this communication, we have addressed a limited subset of normal tissue tolerance, namely, complications for organs of concern in the protocols of this contract; of these organs, only the most serious complications are taken as endpoints. Even with this limitation, it became apparent that very few hard data based on solid clinical and laboratory information were available and the information was even more scanty for any volumetric irradiation dose–normal tissue complication. As indicated in the tables and in the text, some of the information provided is based on solid clinical evidence, but by far most of the data are either interpolation or extrapolations from whole organ data or are based purely on the experience of the clinicians involved in this contract. From the work of this contract and similar research with three-dimensional treatment planning, it is hoped that accurate volumetric and dosimetric measurements of normal tissues may ultimately be correlated with normal tissue complications in systematic and more detailed fashion and may make significant contributions to the understanding of the dose-volume relationship for normal tissue tolerance. This data base has already been used for partial volume analytic function (Burman *et al.*) and calculation of normal tissue complication probability (NTCP) (Kutcher *et al.*) in other reports of this contract.

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