Evaluation of dose homogenization and radiation carcinogenesis risk in total body irradiation for bone marrow transplantation

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The purpose of this study is to report on the dose homogeneity in total body irradiated patients undergoing Bone Marrow Transplantation (BMT), and carcinogenic risk in surviving patients. Between 1987 and 2001, 105 patients received hyperfractionated (6 fractions in 3 days) 12 Gy Total Body Irradiation (TBI) in our institution with lateral opposed fields. All the patients had measurements with thermoluminiscence dosimetry (TLD_{100}) placed on seven bilateral body sites *in vivo,* controlled by the randophantom measurements to verify reasonable dose homogeneity achievement. The comorbid effects in the whole TBI conditioning group with at least three months post BMT follow-up were noted and surviving patients who had a minimum 5-year and maximum 14-year follow-up (median 7.8 years) have been evaluated for carcinogenic radiation risk on the basis of tissue weighting factors as defined by ICRP 60. Reasonable dose homogeneity by lateral opposed beam TBI has been obtained in all 105 patients in whom lateral TLD_{100} measurement means were within $\pm 5\%$ of the planned doses. Calculated carcinogenesis risk factor was 11.34% for males and 12.40% for females, and no second-cancer has been detected whilst radiation-induced 5 cataracts and 10 interstitial pneumonia comorbidities were noted. Dose homogenization can be well achieved for hyperfractionated lateral-beam TBI with acceptable comorbidities and estimated second-cancer risk is significant but relatively low compared to the risk from the clinical indications for TBI.

Key words: Total body irradiation, bone marrow transplantation, carcinogenesis risk.

Total body irradiation (TBI) is a systemic type of irradiation clinically used in the conditioning regimen of allogeneic or autologous bone marrow transplantation (BMT) for leukemias, lymphomas, and malignant and non-malignant immune system disorders. In allogeneic BMT, conditioning regimen serves the need for immunosuppression necessary for donor cell engraftment and rejection prevention, and tumor eradication as a cytotoxic agent in radiosensitive malignancies, but in autologous BMT, immunosuppression is not required and tumor cell kill is the purpose of the conditioning regimen.

The reported dose of TBI necessary for successful engraftment ranges from a single dose 750 cGy to 1320 cGy when given hypefractionally in BMT conditioning [9].

In the hyperfractionated TBI applications, leukemia, lymphoma and immune competent cells fail to repair the sublethal damage and therefore are not protected by fractionation of radiation, but pulmonary and hepatic cells make use of protective effect of fractionation [10]. The delivery of a uniform radiation dose over the entire target volume is vitally important in all radiotherapy applications. However, when total body fields are considered, difficulty results from the complexity of the dose distribution for this type of treatment. Wide variations in the dose from point to point are common; the maximum dose typically exceeding the minimum dose by 15% can cause inhomogeneities [3, 9].

As the TBI-conditioned BMT treatment becomes more successful, the number of long-term survivors is relatively increasing.

Secondary cancer development is a potential complication of cytotoxic cancer therapy either by chemotherapeutic agents and/or irradiation. The main source of epidemiological evaluation for human radiocarcinogenesis is Hiroshima and Nagasaki atomic bomb survivors [8], who had been subject to inhomogeneous, undefined portaled irradiation and different types of radiation.

Extrapolation of inbred rodent and rhesus monkey radiocarcinogenesis studies following TBI has been done [1].

This study is designed by using the TLD_{100} measurements on 105 TBI-applied BMT patients and on randophantoms for dose homogenization verification. It also reports on comorbidities experienced by the patients and analysis of the International Commission on Radiological Protection 60 (ICRP-60) based secondary carcinogenic risk evaluation of the minimum 5-year followed up surviving patients [5] and on clinical outcome.

Patients and methods

Between 1987 and 2001, 105 patients whose diagnosis and transplantation type are described in Table 1, received 12 Gy hyperfractionated TBI in 6 fractions, 2 Gy/fr in 3 days with 6-hour gap between 2 fractions each day, at a low dose rate of 1.59–7.95 cGy/min with Co-60 1.25 MeV teletherapy machine at SAD=370–413.5 cm and diagonal field sizes 174.5–195 cm.

The choice of TBI technique significantly affects the success of BMT and particularly the rate of complications. The target volume of TBI is the entire body, fitting the whole body into the limited-size radiation field. The inevitable need to provide homogeneous dose distributions to all sites despite the irregularity in body contour and tissue heterogeneity and limiting the dose to several critical organs imposes major difficulties in treatment planning and radiation delivery.

In our fractionated TBI program, the daily positioning of the patients is reproducible providing consistency of dose distribution within each fraction. In our technique shown in Figure 1, the thin body sites such as head, neck and legs were in the region of decreasing exposure intensity.

Despite individualized phantom calculations and measurements of the neck sites, using of bolus was necessary for homogenization.

In the TBI program, the patients lie supine with legs bent on a mobile couch, which has motorized vertical movement. The head and neck are supported, and partially immobilized by a comfortable moulded head-base placed between the rigidly mounted compensators. Partial lung shielding is established by the patient's arms. The position of the patient in the beam is shown in Figure 1. The length of the body is fitted to the 1.62 m (85% isodose).

Dosimetry. The beam profile is scanned both vertically and horizontally at points in the diagonal axes in the radiation field at source axis distance (SAD) of 370–413.5 cm with a thimble ion chamber with an appropriate build-up cap for Co-60 beam quality being used for the exposure measurement. At each measurement position, the produced ionizations is integrated for 5 minutes by an electrometer (Farmer 2570/1B) (Fig. 2). At 81 cm from the

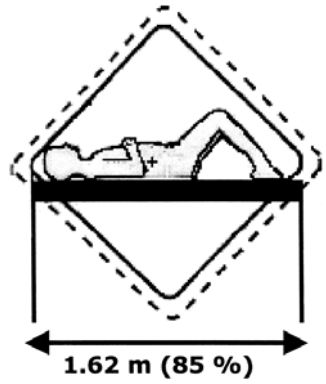

Figure 1. TBI patient treatment position.

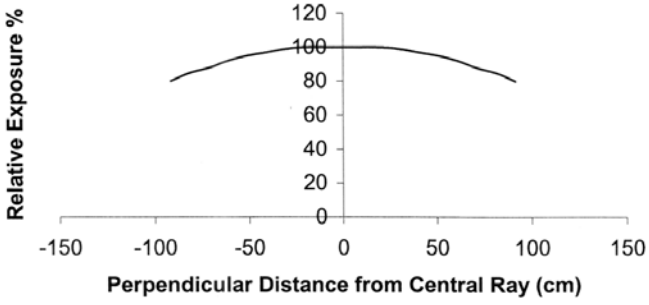

Figure 2. Horizontal exposure profile at midplane SAD=413.5.

midpoint in the horizontal direction, the exposure intensity is reduced to 85% of the maximum value. However, in the vertical direction 85% of the maximum value is at 80 cm from the midpoint.

The air dose in the center of irradiation field was measured with a thimble ion chamber with a mounted build-up cap.

Our dosimetry assumptions and calculations follow those outlined by JOHNS and CUNNINGHAM [3, 6]. Treatment times are based on delivering 200 cGy/fr midplane in the umbilicus. The midplane umbilicus dose rate was given by the equation:

$\dot{D}_t(f',A'') = \dot{D}_a(f',A').TAR(t,A'')$

where;

$\dot{D}_a(f',A')$: is the dose rate in air to a small equilibrium mass of tissue.

f': is the source-axis-distance

A': is the field area at f'

t: is some depth in the patient at which the dose is desired.

A": is the equivalent square area of the patient.

TAR: is the tissue-air ratio.

$\dot{D}_t$: is the dose rate in tissue of depth t.

TAR values for Co-60 are published for a depth of 30 cm and 75x75 cm field size [7].

For randophantom measurements TLD_{100} was placed in the holes of all slices. After irradiation, all TLD_{100}s were

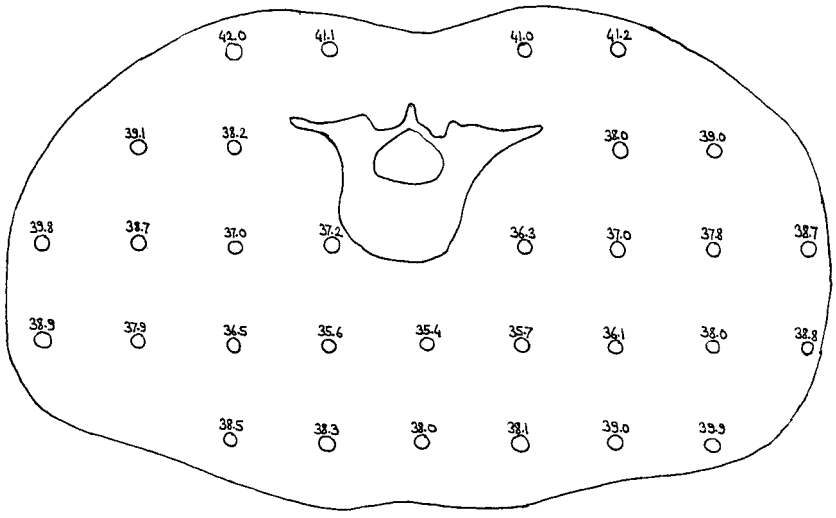

Figure 3. TLD_{100} placed abdominal randophantom (slice 26) with 5-minute test dose values.

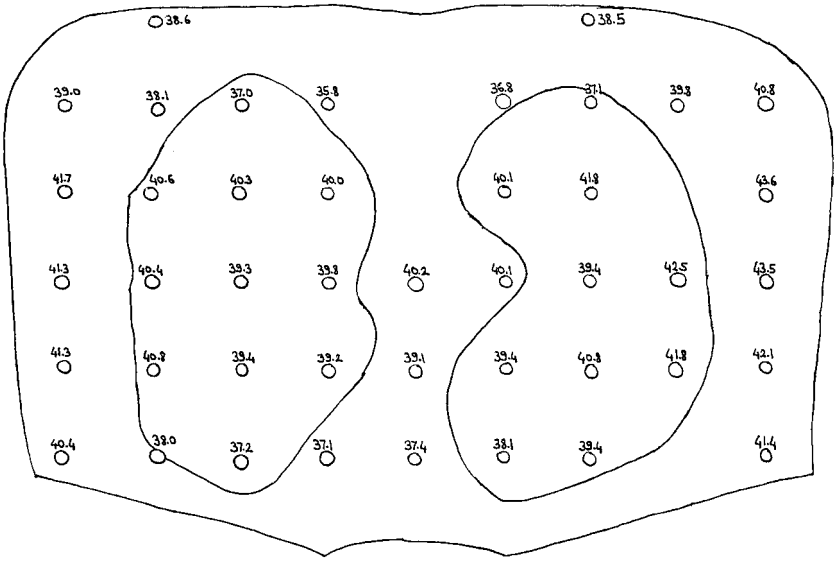

Figure 4. TLD_{100} placed thorax randophantom (slice 17) with 5-minute test dose values.

read with Victoreen 2800 TLD reader while TLD_{100}s were placed on the seven bilateral body sites as a representative sampling of the whole body (head, neck, axillary midplane, umbilicus, pelvis, thigh and leg) to crosscheck the appropriateness of calculated and given irradiation doses.

For the patient measurements, TLD_{100}s were placed by being taped under the bolus to the patients on bilateral seven body sites to confirm the planned doses *in vivo*.

To assess the risk of carcinogenesis after irradiation, we estimated the effective dose for every patient on randophantom on the basis of tissue-weighting factors as defined by the ICRP 60 [5] The calculations were made with TLD_{100} on a male and a female randophantom. Lung dose correction factor has been adjusted for low-density lung tissue versus individual patient thickness. All the TLD_{100} measurements were made three times.

For secondary cancer evaluation 11 evaluable surviving patients who had minimum 5-year and maximum 14-year follow-up with a median follow-up period being 7.18 years were assessed.

Results

Calculated dose and measured dose consistency has been done with TLD_{100} measurements both on randophantom and individual patients as described in Patients and methods. TLD_{100} umbilicus-normalized measured and calculated randophantom midpoint dose values are shown in Table 2.

Sample dose distributions on the section through the abdomen at umbilicus and section through the thorax with our lateral irradiation technique are shown in Figures 3 and 4.

The results of *in vivo* measurements done on bilateral seven body sites are shown in Table 3.

All 105 patients received TBI followed by BMT from 1987 to 2001. Forty six out of 105 patients were treated before 1996 and 11 of these patients (4 female, 7 male) who were still alive in 2001 were evaluated for carcinogenesis with minimum 5-year follow-up.

To assess the risk of radiation carcinogenesis after TBI, we have estimated the effective dose for a female and a male randophantom on the basis of tissue weighting factors as defined by the ICRP 60. Our calculation with TLD_{100} is shown in Table 4.

ICRP recommends that, in those exceptional cases in which a single one of the remainder tissues or organs receives an equivalent dose in any of twelve organs for which a weighting factor is special, a weighting factor should be applied to that tissue or organ [7]. Therefore, we used 0.025 as the weighting factor for the brain. Red bone marrow tissue has been excluded from effective dose calculations, since most of the TBI patients had diseased bone marrow being targeted for eradication necessitating bone marrow rescue resulting in replaced donor bone marrow.

The total effective dose for our dosimetric calculations with TLD is 1.1438 Sv for males and 1.2444 Sv for females.

Table 1. Diagnosis and transplantation types of the patients

Diagnosis	Number of patients (%)	Allogeneic BMT	Autologous BMT
AML	34 (32.38%)	+	–
CML	22 (20.95%)	+	–
ALL	12 (11.42%)	+	–
MM	5 (4.76%)	+	–
MDS	6 (5.71%)	+	–
Myelofibrosis	1 (0.95%)	+	–
NHL	5 (4.76%)	+	–
Lymphoblastic lymphoma	11 (10.47%)	–	+
Burkitt lymphoma	9 (8.57%)	–	+
TOTAL	105(100%)	85(80.95%)	20(19.04%)

AML – acute myeloid leukemia; CML – chronic myeloid leukemia; ALL – acute lymphoblastic leukemia; MM – multiple myeloma; MDS – myelodysplastic syndrom; NHL – non-hodgkin lymphoma; BMT – bone marrow transplantation.

Table 2. TLD_{100} umbilicus-normalized measured and calculated randophantom midpoint dose values

Slice number	Measured dose	Calculated dose	% Error
2 (head)	1.08	1.10	–1.8
3 (head)	1.06	1.10	–3.6
4 (head)	1.05	1.10	–4.5
9 (neck)	1.03	1.05	–1.9
13 (thorax)	0.96	0.95	+1.1
14 (thorax)	0.98	0.97	+1.0
16 (thorax)	1.05	1.07	–1.9
17 (thorax)	1.09	1.11	–1.8
18 (thorax)	1.12	1.10	+1.8
19 (thorax)	1.09	1.11	–1.8
20 (thorax)	1.14	1.10	+3.6
21 (thorax)	1.03	1.05	–1.9
26 (umbilicus)	1.05	1.00	+5.0
27 (abdomen)	0.94	0.96	–2.1
29 (pelvis)	0.93	0.98	–5.1
30 (pelvis)	0.93	0.96	–3.2
31 (pelvis)	0.88	0.92	–4.3

Table 3. Typical *in vivo* measured and calculated dose values

Site	Measured dose (cGy)	Calculated dose (cGy)	% Error
Head(orbita)	214	210	+1.9
Neck	208	196	+6.1
Lung(carina)	170	174	–2.3
Umbilicus	205	200	+2.5
Pelvis	182	192	–5.2
Thigh	200	220	–5.0
Leg	222	230	–3.5

Table 4. Our calculations with TLD on the male and female randophantoms

Organ	Average dose (Gy)		Tissue weighting factor	Effective dose (Sv)	
	Male	Female		Male	Female
Thyroid	2.02	2.00	0.050	0.1010	0.1000
Esophagus	1.80	1.84	0.050	0.0900	0.0920
Lung	1.60	1.70	0.120	0.1920	0.2040
Bone surface	1.94	1.96	0.010	0.0194	0.0196
Skin	2.00	2.02	0.010	0.0200	0.0202
Breast	–	1.94	0.050	–	0.0970
Liver	2.00	1.96	0.050	0.1000	0.0980
Colon	1.86	1.90	0.120	0.2232	0.2280
Stomach	1.98	1.94	0.120	0.2376	0.2328
Bladder	1.94	1.90	0.050	0.0970	0.0950
Remainder (brain)	2.16	2.12	0.025	0.0540	0.0530
T O T A L				1.1342	1.2396

The risk factor for fatal cancers in the high-dose region, as derived from human epidemiological data, is presently assumed to be 10% per Sv [5].

Consequently, a risk factor of 11.34% for males (113 per 1000 persons or about 1 out of 9 person) and 12.40% for females (124 per 1000 persons or about 1 out of 8 person) radiogenic cancers exists in our total body irradiated patients. The comorbid complications we have noted in the whole TBI conditioned group with at least 3-month post-BMT survival are: 5 cataracts in the eyes of three patients, 10 interstitial pneumonias, 2 venooclusive disease of the liver. No clinically-detected secondary cancers were observed.

Discussion

Dose homogenization is vitally important in TBI conditioning regimen for BMT to effectively ablate diseased and normal bone marrow and solid malignant soft tissue deposits with adequate immunosuppression to avoid graft rejection and to open hematopoietic microenvironment for the graft.

We have obtained reasonable dose homogeneity by lateral opposed beam hyperfractionated TBI in all 105 patients with TLD_{100} measurements done on randophantom and *in vivo*.

It is estimated that about 5% of all second cancers can be convincingly linked to prior radiation therapy for the first malignant disease [4].

Neoplastic transformation and carcinogenesis processes are "in competition" with the cell killing effects of ionizing radiation [4].

The therapeutic TBI we use, is mostly for leukemia and lymphoma conditioning, so survival duration after BMT is limiting our observation period for second human cancers.

Solid tumors have a minimum latent period of 10 years but some authors report shorter latent periods of 5 years [2].

For TBI-induced second cancers, interaction of radiotherapy with environmental carcinogens such as smoking and genetic susceptibility may be important.

Carcinogenic risk of TBI in the Rhesus monkeys is similar to that of the Hiroshima and Nagasaki atomic bomb survivors. The increase of the risk by a relative risk factor of 8%, observed in the monkeys suggests that patients are likely to develop malignancies more frequently and much earlier in life after TBI than non-exposed individuals [1]. The carcinogenic risk factor we have estimated for humans undergoing therapeutic TBI is 11.34 for males and 12.40 for females, and it is similar to that of monkeys and although significant, it is relatively low compared to the risk from the clinical indications for TBI. Although comorbid complications we have noted are resultant complications of conditioning TBI and BMT, characteristic radiation comorbidities were minimally noted due to fractionated, dominantly low-dose rate conditioning TBI. However, long-term follow-up for human carcinogenesis is needed.

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References

[1] Broerse JJ, Bartstra RW, van Bekkum DW, van der Hage MH, Zurcher C, van Zwieten MJ, Hollander CF. The carcinonogenic risk of high dose total body irradiation in non-human primates. Radiat Oncol 2000; 54: 247–253.

[2] Dowd SB, Tilson ER. Practical Radiation Protection and Applied Radiobiology. 2nd ed. Philedelphia: WB Saunders Company 1999: 150.

[3] Glasgow P, Glenn M, William B. Cobalt-60 total body irradiation dosimetry at 220 cm source-axis distance. Int J Radiat Oncol Biol Phys 1980; 6: 773–777.

[4] Hall E. Radiobiology for the Radiologists. 4th ed. Philadelphia: JB Lippincott, 1994: 385–409.

[5] ICRP Publication 60 1990 Recommendations for the International Commission on Radiological Protection. Oxford: Pergamon Press, 1991.

[6] Johns HE, Cunningham JR. The Physics of Radiology. 3rd ed. Springfield, 1971: 750.

[7] McKenzie AL. Co-60 gamma-ray beams. In: Central axis depth dose data for use in radiotherapy. BJR Supplement 1996; 25: 46–61.

[8] Mettler F, Upton A. Medical Effects of Ionizing Radiation. 2nd ed. Philadelphia: WB Saunders Company, 1995.

[9] Shank B. Techniques of magna-field irradiation. Int J Radiat Oncol Biol Phys 1983; 9: 1925–1931.

[10] Wara W, Philips T, Margolis L. Radiation pneumonitis: A new approach to the derivation of time-dose factors. Cancer 1973; 32: 547–552.