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SIGNIFICANT FACTORS IN RED CELL MASS CHANGES AFTER FRACTIONATED LOCAL RADIOTHERAPY

by

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Recently (LEVITT et coll. 1965) reported the results of serial studies of plasma volume and red cell mass measured simultaneously with ^{51}Cr and ^{125}I, employing the method of WOOD & LEVITT (1965). Thirty patients, 16 males and 14 females, undergoing local fractionated irradiation for malignant disease were examined in this manner. Sixteen received irradiation to the thorax, nine to the pelvis and six to the head and neck. In seven of the thirty patients we found a decrease in red cell mass during radiation therapy with a subsequent rise one month after completion of the treatment. There was a concomitant increase in plasma volume during the treatment and a subsequent drop after treatment was completed. This phenomenon seemed to occur most frequently in patients treated for carcinoma of the lung (three of nine) and those treated with large fields (three of eight) or in patients receiving irradiation to the thorax (five of six).

Such studies have now been carried out in a further thirty patients. The findings in the first group and the later one have been combined and the values obtained have been studied to determine the statistical significance of the observed changes and to determine the significant factors.

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Material and Method. Sixty cases, 36 males and 24 females, were treated by either a 2 MV Van de Graaf or a Theratron 80 cobalt 60 unit. The sites of the neoplastic disease treated were as follows:

Carcinoma of the lung	22
Carcinoma of the breast	13
Carcinoma of the cervix	6
Carcinoma of the oral cavity and oropharynx	11
Carcinoma of the bladder	3
Carcinoma of the brain	3
Carcinoma of the ovary	1
Carcinoma of the gastrointestinal tract	1

The age ranged from 25 to 85 years with an average of 55.

The parameters studied were venous hematocrit, computed hematocrit, RBC mass, plasma volume, total blood volume and estimated blood volume. The plasma volume and red cell mass were determined simultaneously using ^{51}Cr and ^{125}I as previously described (Wood & Levitt 1965). The estimated blood volumes were calculated by the method of Nadler et coll. (1962).

These investigations were made before, at the mid-point, at the end, and one month after completion of radiation therapy, and an attempt was made to have all these studies completed in all the cases. This was accomplished in the majority of cases but not in all due to technical difficulties.

For statistical purposes, the means of the above parameters were further categorized on the basis of site treated, field size, and tumor dose. The sites of treatment were separated into 'head and neck', 'chest', and 'pelvis'. The field sizes were divided into categories of less than 150 cm^2, 150 to 300 cm^2, and more than 300 cm^2. The total tumor doses were divided into categories of less than 5 000 rad, 5 000 to 6 000 rad and over 6 000 rad.

The significance of field size, site treated and tumor dose upon the means of the parameters studied was evaluated by computation of the standard error (S. E.) for the mean value of visit 1, and the 95 % confidence limit (0.95 CL) for this same mean value. The means for visits 2, 3 and 4 were then examined to see if they were included in the 0.95 CL. If not, the difference was considered statistically significant at $p < 0.05$.

Results

Site treated. The RBC mass was found to decrease significantly at the end of treatment in patients having the chest treated. There was a subsequent rise one month post therapy although the mean remained significantly lower than the initial level (Table 1).

Table 1

Red cell mass values on different occasions in relation to the site of irradiation therapy

Site treated	Visit	1	2	3	4
Pelvis	N.	11	9	11	9
	Mean	1322	1346	1215	1338
	S. E.	86.5			
	0.95 CL	1129—1515			
Chest and mediastinum	N.	35	31	35	25
	Mean	1620	1609	1380*	1421
	S. E.	60.4			
	0.95 CL	1497—1743			
Head and neck	N.	13	12	12	10
	Mean	1664	1840	1733	1761
	S. E.	113.1			
	0.95 CL	1417—1911			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$; all other comparisons are not significant.

Plasma volume, venous hematocrit and estimated blood volume did not show a significant variation with the site of irradiation. The total blood volumes and computed (isotope) hematocrit showed a significant variation at the end of therapy in patients who had mediastinum and breast irradiated. This is explained by the change in red cell mass.

Tumor dose. There was a significant decrease in red cell mass at the end of treatment and subsequent rise one month post treatment in patients treated to tumor doses of less than 5 000 rad and 5 000 to 5 999 rad but not in the group receiving 6 000 rad or more. There was no significant variation in plasma volume, venous hematocrit or estimated blood volume related to tumor dose (Table 2).

Field size. There was a significant drop in red cell mass at the completion of therapy in patients receiving irradiation to field sizes of 150 to 300 cm^2. There was no significant change in patients whose fields were less than 150 cm^2 or over 300 cm^2 (Table 3).

Further analysis. In view of the findings of the significant drop in red cell mass in patients receiving irradiation to the breast and chest fields, it was felt that the significant factor in red cell mass change was that of irradiation of the

Table 2

Red cell mass values on different occasions in patients receiving different irradiation doses

Range rad	Visit	1	2	3	4
3 000—4 999	N.	13	11	12	16
	Mean	1562	1534	1263*	1405
	S. E.	110			
	0,95 CL	1322—1802			
5 000—5 999	N.	18	16	16	13
	Mean	1465	1488	1271*	1410
	S. E.	78.5			
	0.95 CL	1299—1631			
6 000 or more	N.	29	22	27	20
	Mean	1660	1780	1574	1616
	S. E.	72.5			
	0.95 CL	1511—1809			

* Denotes that this mean is significantly different from visit 1 at $p<0.05$; all other comparisons are not significant.

Table 3

Red cell mass values on different occasions in relation to field sizes irradiated

	Visit	1	2	3	4
150 cm^2, or less	N.	17	15	16	15
	Mean	1650	1772	1636	1673
	S. E.	93			
	0.95 CL	1453—1847			
151—299 cm^2	N.	28	23	28	20
	Mean	1578	1627	1351*	1391*
	S.E.	72			
	0.95 CL	1430—1726			
300 cm^2, or over	N.	15	15	15	12
	Mean	1452	1394	1295	1461
	S. E.	78			
	0.95 CL	1295—1619			

* Denotes that this mean is significantly different from visit 1 at $p<0.05$; all other comparisons are not significant.

Table 4

Red cell mass values on different occasions in relation to field sizes in patients receiving mediastinal therapy only

	Visit	1	2	3	4
Less than 150 cm^2	N.	11	10	11	8
	Mean	1439	1345	1290	1374
	S. E.	96			
	0.95 CL	1225—1653			
150—300 cm^2	N.	20	17	15	20
	Mean	1751	1786	1425*	1464*
	S. E.	78.5			
	0.95 CL	1587—1915			

* Denotes that this mean is significantly different from visit 1 at $p<0.05$; all other comparisons are not significant.

chest wall, the mediastinum, or both. To test this hypothesis and further evaluate the effect of field size and dose on the chest wall, statistical studies were carried out on all patients receiving chest wall irradiation in which the consideration of only the dose to the thorax and only the size of the thoracic field irradiated were evaluated.

Size of thoracic field. Field sizes of less than 150 cm^2 and 151 cm^2 to 300 cm^2 were evaluated. Because of the small number of cases, fields larger than 300 cm^2 could not be adequately evaluated. There was a significant drop in red cell mass at the end of therapy in patients with field sizes between 150 to 300 cm^2 (Table 4).

Thoracic tumor dose. There was a significant decrease in red cell mass at the completion of therapy or one month later in all groups divided on a basis of dose to the thorax (Table 5). There was no significant change in plasma volume or total blood volume in these patients.

Discussion

Our previous study (Levitt et coll. 1965) demonstrated that there appeared to be a decrease in red cell mass following local irradiation in certain patients who were treated for carcinoma of the lung and had large multiple areas treated or who had thoracic irradiation.

The present study has demonstrated that the changes in red cell mass are of

Table 5

Red cell mass values on different occasions in relation to the doses given in patients receiving mediastinal therapy only

Range rad	Visit	1	2	3	4
3 000—4 999	N.	10	6	8	6
	Mean	1640	1765	1226*	1326
	S. E.	140			
	0.95 CL	1324—1956			
5 000—5 999	N.	14	13	14	10
	Mean	1474	1469	1252*	1371
	S. E.	84			
	0.95 CL	1293—1655			
Over 6 000	N.	11	9	10	7
	Mean	1862	1770	1661	1580*
	S. E.	90			
	0.95 CL	1616—2063			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$; all other comparisons are not significant.

a significant nature and are related to thoracic irradiation and fields of at least 150 cm^2 to 300 cm^2 in size. The change in red cell mass appears to be related to the total field size of the thorax irradiated but does not appear to be related to the dose.

Previous work suggested that local fractionated irradiation does not significantly affect peripheral red cell counts (Goswitz et coll. 1963, Hutaff & Belding 1955, Jacobson & Marke 1947, Kornblum et coll. 1938, Mossberg 1943, Stewart & Dische 1956, Sykes et coll. 1960). This change in the red cell mass has probably not been shown in these previous studies because of the methods of measurement used, i.e. hematocrit, hemoglobin, and red cell count do not accurately reflect the true red cell mass. Berlin, and others (Berlin et coll. 1952, 1955, Densted 1943, Fundenberg et coll. 1961, Gregerson & Rawson 1959) have demonstrated the inaccuracies in evaluating the red cell mass by the use of any method other than the measurement of the actual red cell mass. The necessity of evaluating the red cell mass and plasma volume by separate techniques has again been demonstrated in this study, as has the possibility of error involved in calculating the red cell mass or plasma volume by estimation rather than by direct measurement.

The most likely mechanism for decrease in red cell mass is the depression of the blood producing bone marrow of the sternum, vertebra and ribs, since the ribs, bone marrow and vertebrae make up a great percentage of the blood-producing marrow in patients in the cancer age range (WINTROBE 1961). GOSWITZ's report (GOSWITZ et coll. 1963) on serial bone marrow studies in patients receiving portal irradiation tends to confirm this hypothesis. (Two of these patients received thoracic irradiation.) A definite decrease in red cells precursors and the more immature granulocyte was noted at approximately midpoint of therapy. This finding of localized bone marrow depression (without a decrease in red cell count) following localized irradiation has been confirmed by other investigators (HUTAFF & BELDING; KORNBLUM et coll.; STEWART & DISCHE; SYKES et coll.).

Our findings that patients receiving thoracic irradiation had significant red cell mass changes, regardless of dose, probably can be accounted for by the fact that all doses were 3 000 rad or more. SYKES et coll. have demonstrated that the sternal marrow is depressed, and usually does not regenerate, in patients receiving 3 000 rad or more. Although we made no bone marrow studies in these patients, it is reasonable to assume a similar event in our patients. In this regard, it is interesting to note that when all patients receiving a dose of 6 000 rad are considered there are no significant red cell mass changes, whereas when patients receiving mediastinal irradiation to 6 000 rad are considered separately there is a significant change. This is most likely explained by the fact that most of the patients receiving irradiation to this dose were treated to the head and neck or pelvis.

Another possible cause in the decrease in red cell mass may be the effect of irradiation on the capillaries of the lung. It has been shown that increased capillary permeability follows total body irradiation, due to capillary wall damage (FUNDENBERG et coll. 1961, KAHN & FURTH 1952, ROSS et coll. 1952, SZABO et coll. 1958, WISH et coll. 1952). It is conceivable that this increased capillary permeability would account for some part of the change in red cell mass, in view of the large numbers of capillary spaces in the lung.

This change in the red cell mass does not appear to be due to an abscopal effect since it was not found to be significant with pelvic or head and neck irradiations. Further, the change in red cell mass does not appear to be related to the course of the disease in that there is an increase in red cell mass after completion of therapy.

Conclusion

A significant decrease in red cell mass at the completion of fractionated local irradiation to the thorax was observed. This change does not seem to be related to dose, since it was significant in all patients receiving thoracic irradiation at the three dose levels evaluated. The change may be related to the total area of the thorax irradiated since it was not significant in fields smaller than 150 cm^2. Assuming that the data represent normal distribution and the observations were independent, these findings would represent significant changes, with a probability level of less than 0.5 that they are associated by chance.

SUMMARY

In sixty patients treated with fractionated local irradiation to the head and neck, thorax, and pelvis, serial studies with determination of the venous hematocrit, computed hematocrit, red cell mass, plasma volume, total blood volume and estimated blood volume were performed. A significant decrease in red cell mass during treatment, apparently due to irradiation, was only noted in patients receiving thoracic irradiation. This was related to field size, but not to dose. The possible reasons for this phenomenon are discussed.

ZUSAMMENFASSUNG

In 60 Patienten, die mit fraktionierter lokaler Bestrahlung von Kopf, Hals, Thorax und Becken behandelt wurden, wurde eine Reihe von Studien vorgenommen, in denen der venöse Hämatokrit und der berechnete Hämatokrit, die Menge der Erythrocyten, das Plasmavolumen und das totale sowie berechnete Blutvolumen festgestellt wurden. Eine signifikante Abnahme der Erythrocytenmenge wurde nur in denjenigen Patienten observiert, die Strahlenbehandlung des Thorax erhielten. Die Abnahme war mit der Feldgrösse aber nicht mit der Dosis verbunden. Die Ursache des Auftretens dieses Phänomen wird diskutiert.

RÉSUMÉ

Les auteurs ont fait des examens en série de l'hématocrite veineux, de l'hématocrite calculée, de la masse des érythrocytes, du volume plasmatique et du volume sanguin total chez 60 malades traités par irradiation locale fractionnée de la tête et du cou, du thorax et du bassin. Ils n'ont constaté une diminution significative de la masse érythrocytaire au cours du traitement, apparemment sous l'effet de l'irradiation, que chez les malades soumis à une irradiation thoracique. Cette diminution est en rapport avec la dimension du champ mais non avec la dose. Les auteurs discutent les raisons possibles de ces phénomènes.

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