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Original Article

Peripheral blood lymphocyte counts during standard conformal radiotherapy and TomoTherapy/IMRT for prostate cancer

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Abstract

Lymphopaenia is the earliest and the most sensitive routinely assessed biological parameter of corporeal radiation exposure in clinical practice; bone marrow, lymph nodes and peripheral blood lymphocyte populations are also at risk. During radical prostate radiotherapy, in 28 patients, the mean peripheral lymphocyte count fell from 1.76×10^9/l (standard deviation (SD) 0.63, 95% confidence interval (conf.) 0.23) to 1.10×10^9/l (SD 0.38, conf. 0.14), ($p<0.05$). The question was asked as to whether intensity-modulated radiation therapy (IMRT) by TomoTherapy would cause more lymphopaenia than three-field conformal radiotherapy, bearing in mind the 'low dose bath' effect of IMRT and the long 'beam-on' times. Thirteen patients receiving three-field conformal radiotherapy experienced a fall in peripheral lymphocyte counts from 2.02 (SD: 0.62. conf. 0.43) to 1.17×10^9/l (SD: 0.47, conf. 0.26) after 34–38 Gy, as compared to a fall from 1.6×10^9/l (SD: 0.6, conf. 0.35) to 1.04×10^9/l (SD: 0.3, conf. 0.15) for 15 TomoTherapy patients—non-significant differences. We conclude that for this (approximately) standard, small-volume pelvic radiotherapy and to the dose under scrutiny, we cannot detect differences between the two radiotherapy techniques in terms of the lymphopaenia accruing. Neutrophil counts were similarly non-significantly different.

Keywords

Conformal radiotherapy; lymphocyte counts; prostate cancer; TomoTherapy

INTRODUCTION

After whole body radiation, the blood count falls in a characteristic manner. Peripheral blood lymphocytes decline within a matter of hours of irradiation, in a dose-dependent fashion. Granulocytes decline after 3–4 days. Platelets fall after >5 days. Although the haemoglobin declines last, the reticulocyte count falls within 24 hours of a whole body radiation dose.[1]

Whole/total body radiation or total nodal radiotherapy has been used for immuno suppression; this subject has been reviewed in ref. 2.

Lymphocytes undergo interphase death after radiation[3] and this explains the early decline in the peripheral blood count after radiation. Extracorporeal radiation of blood produced prompt lymphocytopaenia which was reversible after discontinuation, demonstrating that this event occurs in the circulating blood.[4]

The effects of conventionally fractionated radiotherapy on the peripheral blood count

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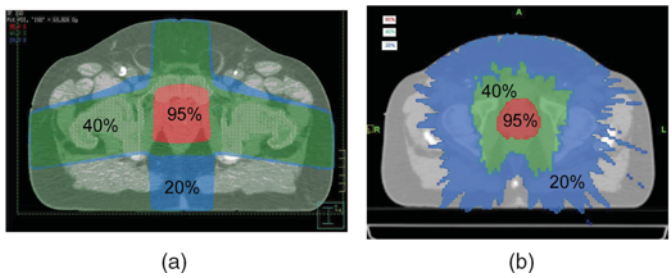

Figure 1. Axial isodose contours 'washed' for the various isodose regions, demonstrating the enhanced region of low-dose encompassment by IMRT technology. (a) Three-field conformal technique; (b) TomoTherapy.

have been the subject of previous work from this centre.[5] Patients receiving wide-field radiotherapy encompassing large quantities of bone marrow were studied: during medulloblastoma neuraxis radiotherapy, the peripheral blood white cell count halved by 7.5 Gy to the cord because the lymphocyte count had more than halved by 5 Gy, the neutrophil count halving after 7.5 Gy and monocytes being the most refractory white cell subset. With regard to specific peripheral lymphocyte levels, the pre-therapy count was $1.6 \pm 0.15 \times 10^9$/l, becoming 0.54 ± 0.07 by 5 Gy, 0.36 ± 0.09 by 12.5 Gy and $0.28 \pm 0.04 \times 10^9$/l by 17.5 Gy (cord). Of course, such data do not probe the question as to whether the lymphocyte decline was due to cell death of circulating lymphocytes rather than nodal/marrow lymphocytes that were about to be released into the circulation—for both are encompassed in the portals. However, it was of interest that a rapid return towards normal lymphocyte numbers was observed as early as 1 week after discontinuation of the neuraxis radiotherapy.[5] The persistence of lymphocyte chromosomal/genetic abnormalities, after radiation exposure, has been the topic of more recent research.[6,7]

With the introduction of intensity-modulated radiation therapy (IMRT), the low-dose radiation 'bath' within the axial planes from the top of the planning target volume (PTV) to the bottom of the PTV is greater than with conventional radiotherapy portals—exposing larger volumes of normal tissues (and circulating blood) within these tissues to low-dose radiation—in contrast to conventional three- to four-field plans from a standard linear accelerator, which exposes confined 'tracks' of tissue through the body to higher (entry and exit) doses (Figure 1).

To compare the effects of radiotherapy by these two modalities, on peripheral blood lymphocyte populations in a cohort of treated patients, it is necessary to select a radiotherapy target volume that is approximately standard for the patients under study. Radical radiotherapy to the prostate would be a good example of such a relatively standard volume, although this is a small volume for high dose radiation compared to some others.

These observations led to the present study which aimed to probe the question as to whether the low dose bath effect associated with IMRT was sufficient to demonstrate a drop in the peripheral blood lymphocyte count compared with both pre-treatment levels and conventional radiotherapy for early prostate cancer.

MATERIALS AND METHODS

Patients with biopsy-proven prostate cancer, organ confined on pelvic magnetic resonance imaging and accepted for radical radiotherapy, were the study population.

Computed tomography planning with the patient in a standard supine position was employed in all cases. The clinical target volume (CTV) and PTV were defined and outlined by the same person with the same strategy of organ coverage for both the linear accelerator and TomoTherapy patients. Pelvic lymph nodes were never included in the CTV in this series of patients.

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A standard linear accelerator (10 MV) delivered conformal radiotherapy via three fixed fields to the prostate: one anterior and two lateral fields.

The mean volume treated (PTV) for the conformal series of patients was 251 cc (standard deviation (SD) 74) whereas the mean volume treated for the TomoTherapy series was 235 cc (SD 76).

TomoTherapy technology (TomoTherapy Inc. Systems, Wisconsin, USA) involves a linear accelerator (6 MV) which travels in spiral around the treatment couch, emitting a narrow 'fan' therapy beam as it does so; this beam may be modified during therapy by multi-leaf collimation. In addition, during treatment, the couch travels through the machine gantry such that new body segments are constantly being brought into the primary beam (or indeed shielded from it by the multi-leaf collimation—hence intensity modulation). However, the technique spreads a low dose 'bath' around the body in the axial planes of therapy and the beam-on time is longer than with conventional therapy (although the codicil that only part of the PTV is being irradiated at any one time, due to the spiralling narrow fan beam, should be noted).[8] The patients described in this article and designated as being treated by TomoTherapy were also treated. The comparison of 'dose wash' isodoses between the two techniques is shown in Figure 1. The low dose 'bath' effects are common to all current IMRT methods.

A blood count including differential white cell count (performed on an autoanalyser; Sysmex, USA) was performed before the start of radiotherapy. Half way through the course of radical radiotherapy, after 34–38 Gy had been delivered at 2 Gy per week-day fractionation (five times per week), the blood count was repeated. These were the routine blood count assessment times in this patient population.

The means and SD were calculated by standard mathematics. The 95% conf. were calculated with reference to the '*t*' distribution for the sample size under study.

RESULTS

Twenty-eight patients with 'organ-confined' prostate cancer, undergoing radical radiotherapy for early prostate cancer, were selected for the study. After 34–38 Gy, the peripheral blood lymphocyte count fell from a mean of 1.76×10^9/l (SD: 0.63; conf. 0.23) to 1.04×10^9/l (SD: 0.29, conf. 0.15), ($p<0.05$). Thirteen patients were treated using conventional three-field, conformal, linear accelerator technology and 15 patients using TomoTherapy. The patients were a consecutive series of patients except for one patient who was excluded from the study because of chronic lymphatic leukaemia. The following observations were made: In the three-field conformal series, the mean volume treated was 251 cc and the mean daily beam-on time was 48 seconds. The blood count before therapy was: mean white blood count: 6.55×10^9/l, mean neutrophil count: 3.93×10^9/l (SD: 1.08, conf. 0.75), and mean lymphocyte count: 2.02×10^9/l (SD: 0.62, conf. 0.43). At the half-way time point (34–38 Gy received), the blood count was: mean white blood count: 5.59×10^9/l (SD 1.13, conf. 0.62), mean neutrophil count: 3.67×10^9/l (SD: 0.93, conf. 0.51), and mean lymphocyte count: 1.17×10^9/l (SD: 0.47, conf. 0.26).

In the TomoTherapy series, the mean volume treated was 235 cc and the mean daily beam-on time was 256 seconds. The blood count before therapy was: mean white blood count: 5.54×10^9/l (SD 1.1, conf. 0.65) mean neutrophil count: 3.23×10^9/l (SD: 0.87, conf. 0.51), and mean lymphocyte count: 1.56×10^9/l (SD: 0.59, conf. 0.35). At the half-way time point (34–38 Gy received) the blood count was: mean white blood count: 5.36×10^9/l (SD 1.71, conf. 0.87), mean neutrophil count: 3.59×10^9/l (SD: 1.6, conf. 0.81), and mean lymphocyte count: 1.04×10^9/l (SD: 0.29, conf. 0.15).

If we eschew the minor differences between the volumes treated, there were no statistically significant differences, comparing three-field conformal radiotherapy versus TomoTherapy/IMRT to standard prostate volumes, taking into account the parameters white blood count,

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neutrophil count and lymphocyte count after 34–38 Gy (conventionally fractionated).

DISCUSSION

The low dose bath effect of IMRT techniques is currently a much discussed topic. There is a concern that the larger volumes of tissues receiving low-dose radiation during IMRT methods may place these tissues at a later risk of radiation sequelae—particularly oncogenesis and, in children, growth disturbances. This is particularly regarded as relevant to the population of radically treated patients who will survive long enough for those risks to manifest. It should be noted here that it is the radical treatment population of patients who are those most likely to gain the benefits of highly conformal radiotherapy/IMRT (with regard to increased chances of cure and the advantage of adjacent normal tissue avoidance) and also the most likely to be vulnerable to these late sequelae.

Prostate cancer radiotherapy was chosen for the study reported here, and particularly for patients being treated with localised small fields to prostate and seminal vesicles only (i.e., not pelvic nodes). On the one hand, this is a good population for study as the patients are treated fairly uniformly with regard to portal sizes and anatomic location/situation; on the other hand, the volumes are usually quite small. The different spread of dosage for low doses between the two techniques is well exemplified in Figure 1.

The lymphocyte count in the peripheral blood is the most sensitive as well as routinely assessed marker for body radiation exposure, as reviewed in the introduction section of this article—it is an *in vivo* bioassay of exposure to ionising radiation.

From the first principle considerations, the peripheral blood lymphocyte count could be affected during prostate radiotherapy because of exposure of the pelvic bone marrow, the pelvic lymph nodes and/or exposure of circulating blood through the vasculature of the pelvis during exposure to the therapy. All the three of these factors could be increased if the dose of radiation is spread wide (and hence our interest here on TomoTherapy/IMRT-treated patients), and the last exposure factor (namely, the exposure of circulating blood lymphocytes) will be further enhanced if there are long 'beam-on' times—although there will be lower dose rates (which will have an effect on total dose received by circulating blood lymphocytes). Of course, individual tracts of pelvic tissues receive higher total doses of radiation in the three-field conformal technique—of potential relevance to the subject under scrutiny.

The fact that TomoTherapy uses a fast spiralling, narrow, fan beam—treating only segments of the axially defined PTV at any one time—probably to a considerable extent offsets the long beam-on-time argument as each individual thin axial body segment will not experience long beam-on times. For this reason, the dramatic 'beam-on' time difference (48 versus 256 seconds) is less significant than it appears at first.

An interesting but probably lesser discussion point is the head leakage rates, which could enhance bath effects; it is of interest that the head leakage rates from the TomoTherapy apparatus are probably only 10% of that from standard linear accelerators, although this may be counteracted when beam-on times are long.

CONCLUSION

It is of interest that we observed for the first time that statistically significant lymphopaenia was detectable after 34–38 Gy of conventionally fractionated radiotherapy to the prostate among the whole study population of 28 patients.

However, when comparing the results of three-field conformal radiotherapy against TomoTherapy IMRT, no significant differences in the degree of lymphopaenia between the two groups of patients could be demonstrated. Whether this would apply to larger target volumes remains the challenge for other studies to explore.

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