Lack of Relevant Haemogram Changes During Percutaneous Radiotherapy of Localised Prostate Cancer

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Abstract. *Background/Aim: In percutaneous radiotherapy dose-distribution and volumetric-load of normal tissue varies in different radiation-techniques. Haematotoxicity may lead to deficiencies of the immune and blood system or to secondary malignancies. Therefore, regular blood-counts are carried out during fractionated radiotherapy. The aim was to investigate patient haemogram courses during radiotherapy of localised prostate-cancer treated with different radiation-techniques (n=3). Patients and Methods: In this prospective study, blood count changes were examined during fractionated radiotherapy (3D-conformal-RT/step-and-shoot-IMRT/helical-IMRT) on the prostate-region in localised prostate-cancer cases (n=50). Results: The whole patient group displayed a small but significant reduction in leukocytes. This reduction was higher in the two IMRT groups compared to the 3D-group but without any case of leukopenia. Haemoglobin- or thrombocyte-levels did not significantly change. Conclusion: Regardless of the delivery mode used, localised fractionated irradiation of prostate region did not cause any clinically relevant haemogram changes in this study. These findings question the necessity of regular blood counts during fractionated radiotherapy of the prostate region for patients without any risk factors.*

The use of radiation therapy for cancer treatment has two primary goals: a) to effectively combat the tumour tissue and b) to protect the patient's unaffected, normal tissue as much

as possible (1-3). The normal tissue or organs that do not require treatment may be close to the target volume of the affected, treated tissue. In general, the closer the two tissue types are, the higher the risk of radiation exposure, and the higher the risk of acute or late organ damage. The quality of radiation and delivery mode varies in curative percutaneous radiation therapy. Gamma rays, electrons, hadrons, and photons (in the form of high-energy X-rays generated by a linear accelerator) are used. A range of delivery modalities are used for percutaneous photon radiation. The traditional mode is three-dimensional (3D) conformal radiation therapy, while the intensity-modulated radiation therapy (IMRT) offers options, such as the step-and-shoot IMRT and helical IMRT (also known as tomotherapy) schemes. These different percutaneous modes are responsible for the different transversal and longitudinal distributions of the integral dose in normal body tissues, which are not the targets of the primary radiation. The integrated transversal dose comprises primary radiation segments, secondary, and tertiary radiation, and small amounts of leakage radiation from the primary/multileaf collimator and the linear accelerator itself. The longitudinal integral dose consists primarily of secondary, tertiary, and leakage radiations from the appliance (4-7). In comparison to the 3D conformal mode, the intensity-modulated radiation therapy mode causes lower medium-dose and high-dose exposure, and increased low-dose exposure in the surrounding normal tissue (8, 9).

In general, the higher the integral dose is in relation to the total body volume, the higher the dose exposure is in the haematopoietic bone marrow that is particularly sensitive to radiation. The key factors here are the volume of the tumour to be irradiated and the delivery mode used for the radiation. In particular, fractionated radiation over a long period can potentially cause acute changes to the blood count, associated weakness of the immune system, and increased risk of infection. One possible late side-effect is the increased risk of leukaemia (10). Even a low-dose exposure in normal tissue causes a risk of a secondary malignant tumour (11).

The concentration of haematopoietic bone marrow in the pelvic region means that it is particularly important to consider these associations when dealing with radiation therapy in this area. For example, in the pelvic region, dose-volume effects increase the haematotoxicity and the risk of viral and bacterial infections (12, 13).

The information outlined above explains why it is a standard clinical procedure to carry out blood counts every 1-2 weeks throughout any course of fractionated radiation therapy which lasts several weeks. In this context, Cozzarini *et al.* carried out a retrospective analysis which showed statistically significant rates of leukocytopenia and thrombocytopenia in patients who underwent fractionated radiation of the prostate region (70.4 Gy) and of the whole pelvic lymphatic drainage system (50.2 Gy). No statistically significant differences were observed between the different IMRT delivery modes used (static field IMRT, modulated arc therapy, helical IMRT) (14).

Pinkawa *et al.* compared the irradiation of the whole pelvis in prostate cancer to the irradiation of the prostate region only. In their research, the irradiation of the pelvis led to a statistically significant increase in the rates of leukopenia and anaemia (grade 2) (15). A study by Sanguineti *et al.* compared leukocyte counts by following hypofractionated *versus* conventional fractionated radiation treatments for localised prostate cancer. Treatments were delivered with the use of the 3D conformal mode. The conventional fractionated group displayed a statistically significant leukocyte count drop (16).

For this prospective study, we examined changes to the blood count (haemoglobin, leukocytes, and thrombocytes) in patients who underwent a course of conventional fractionated radiation therapy on the prostate region for localised prostate cancer. Treatment was delivered by one of the following modes: 3D, IMRT, or TOMO. Radiation therapy of the prostate is a frequent indication. Given this indication, the impact on the blood count of different radiation delivery modes that imposes different distributions of the integral dose are of clinical interest.

Patients and Methods

Patients. Patients were all males and investigated within a single-centre prospective study. The median age was 70 years (range=52-82 years). In all the studied cases, irradiation of the prostate region was indicated because of a localised prostate carcinoma. This was either a primary radiation therapy of the prostate gland or additive/adjuvant radiation therapy after primary prostatectomy. The exclusion criteria were: the indication for additional radiation of lymphatic regions of the pelvis and prior radiation indicated in the patient's medical history. Fifty patients were recruited in total: 15 for 3D, 15 for IMRT, and 20 for TOMO. All participating patients provided written informed consent. The study was conducted according to the World Medical Association Declaration of Helsinki

Table I. *Technical data of the used irradiation techniques: 3D, IMRT and TOMO.*

	3D	IMRT	TOMO
Single doses	2 Gy	2Gy/2.17 Gy	2 Gy/2.17 Gy
Cumulative doses	66-70 Gy	70 Gy/76 Gy	70 Gy/76 Gy
Boost	Sequential	Integrated	Integrated
Beams	4	7 or 9	Helical
Energy	6 MV photons	6 MV photons	6 MV photons
IGRT	kilo-voltage	kilo-voltage	mega-voltage

and the ICMJE Recommendations for the Protection of Research Participants and was approved by the ethics committee at the Heidelberg University in Germany.

Radiation therapy. Patient treatment was not influenced by the study, and they were arbitrarily assigned to the delivery-mode groups as part of the hospital routine, thus emulating a pseudo randomisation assignment scheme. The clinical target volume (CTV) and the planning target volume (PTV) were determined in accordance with the Institute's guidelines. Planning CT scans were performed with a slice thickness of 3 mm with a full bladder and an empty rectum. PTV comprised of the prostate gland and seminal vesicle or the prostatic fossa, the bottom part of the bladder, and the anterior rectal wall with a dorsal margin of 0.5 cm and a margin of 0.8 cm in other directions. The dose on the anterior rectal wall (1/3 of the total circumference) did not exceed a median value of 70 Gy. Inverse treatment planning for the IMRT group was performed using the KonRad software developed at the German Cancer Research Centre (DKFZ). The planning process for the IMRT treatment has already been described in detail by Schlegel *et al.* (17). Inverse planning for regular TOMO delivery was performed with the use of the planning software TomoTherapy®. For the 3D group, treatment was planned with the use of the software Pinnacle. The planning data provided information on the absolute PTV in each patient. Radiotherapy was performed using the department's linear accelerators: a) Oncor (Siemens, Germany) for 3D and IMRT and b) TomoTherapy® Hi-Art (Accuray, USA) for helical IMRT (TOMO). Radiotherapy courses were performed in 33-35 fractions over 7 weeks. The technical parameters and the prescribed doses, which were used for the different radiation delivery modes, are listed in Table I. Transversal dose distributions, which depended on the used radiation technique, are shown in Figure 1. At the end of radiotherapy, no side-effects were observed that exceeded grade 3 (Radiation Therapy Oncology Group). As required by the national guidelines, clinical follow-up after radiation therapy was carried out by each patient's attending urologist.

Blood samples. Blood (7.5 ml) was obtained from peripheral veins from all patients every week during radiotherapy. The first sample was obtained immediately before the first fraction of radiotherapy (initial value). All additional samples were collected in the middle of the treatment period in weeks 2-7. Only patients who attended all blood test appointments throughout the seven-week period were included in the analysis. This means that 41 out of the 50 recruited patients were included in our analysis, 13 were in the 3D group, 10 were in the IMRT group, and 18 in the TOMO group.
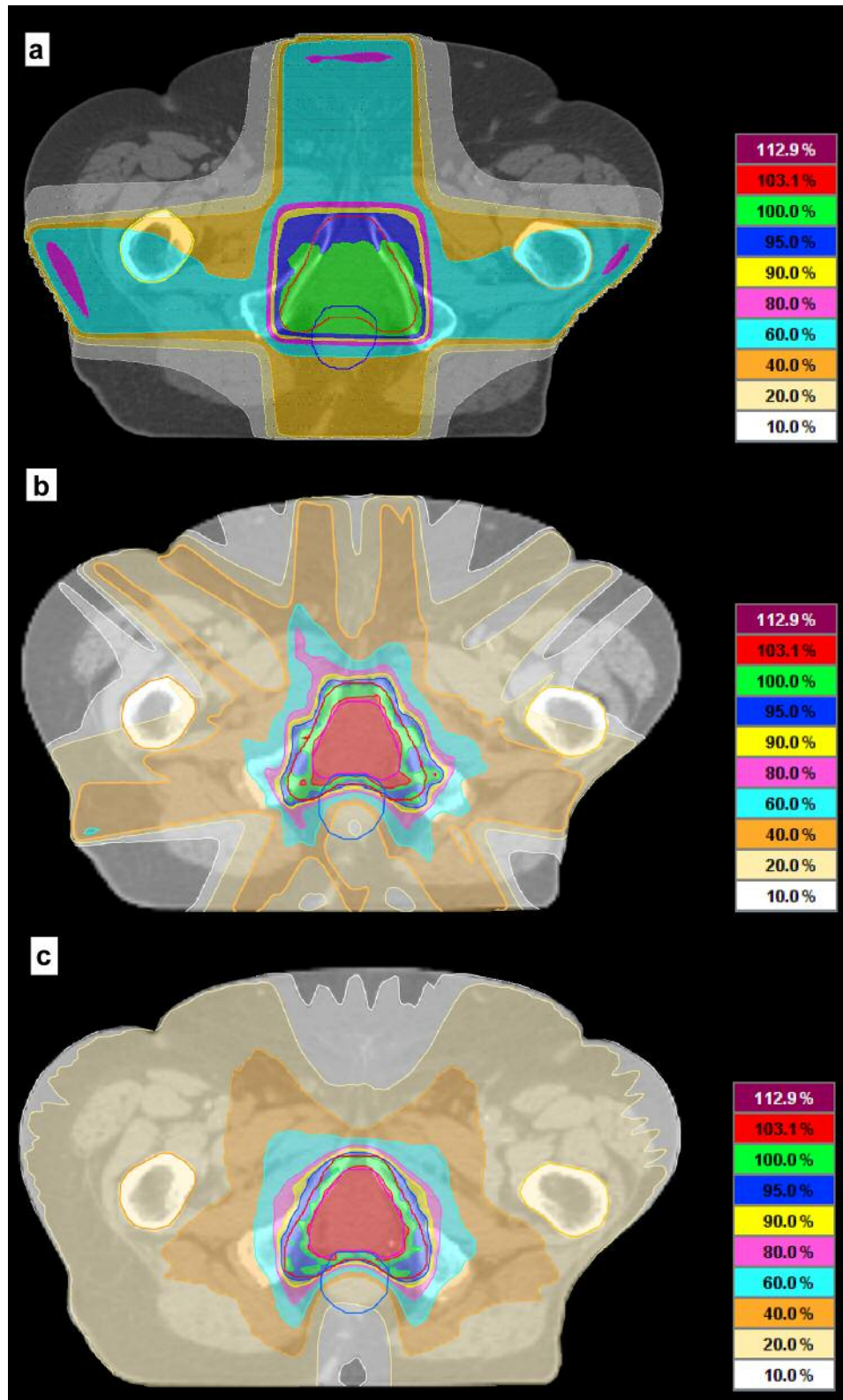
Figure 1. *Typical transversal CT scan of the prostate region with transversal dose distribution of the applied radiotherapy depending on the used irradiation technique: (a) 3D, (b) IMRT, (c) TOMO. Planning target volume (PTV) is defined by the red line. Isodoses relative to the described cumulative dose (100%) were shown; see also Table I.*
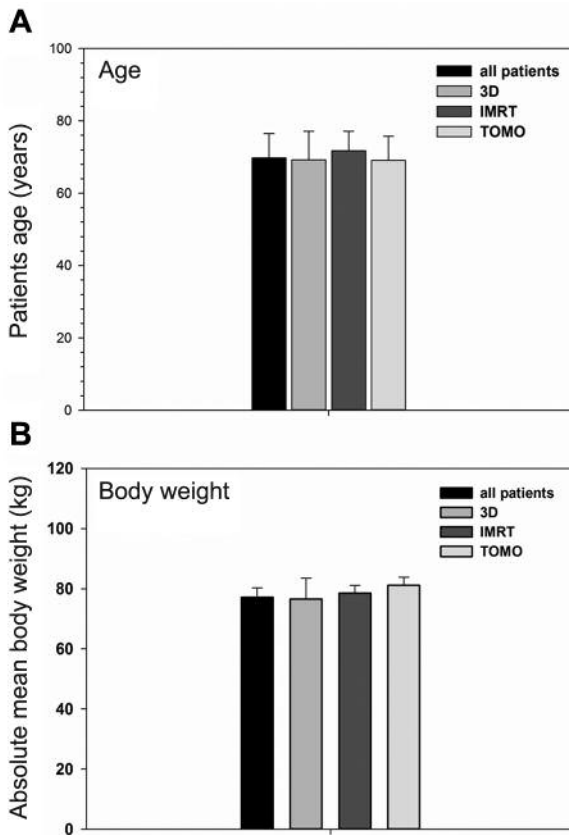
Figure 2. *Patient age (a) and body weight (b).*

Blood sample analyses were carried out using standardised methods in the University hospital to minimise variability and ensure comparability among samples. All samples were coded to prevent bias during manual scoring. The following data were determined: absolute numbers of leukocytes and thrombocytes per ml blood, and the concentration of haemoglobin in the blood (mg/dl). Laboratory-specific norm values for haemoglobin concentration ranged from 13 mg/dl to 17 mg/dl. For leukocyte counts per ml, the range was 4×10^6 to 10×10^6. The thrombocyte count per ml ranged from 150×10^6 to 400×10^6.

Body weight. The body weight of all patients was determined on the day of first treatment before the onset of radiotherapy. To calculate the total body volume, the following formula was used as published for male individuals: body volume (l)=body weight (kg)×1.075 (l/kg) (18).

Statistical analysis. The statistics were processed in Sigma Plot 10.0® . Student's *t*-tests were used, and *p*-values <0.05 were defined as statistically significant.

Results

The different treatment groups had almost identical median ages: 70.0 years for 3D, 70.5 years for IMRT, and 69.5 years for TOMO. Measurements of the median total body weight
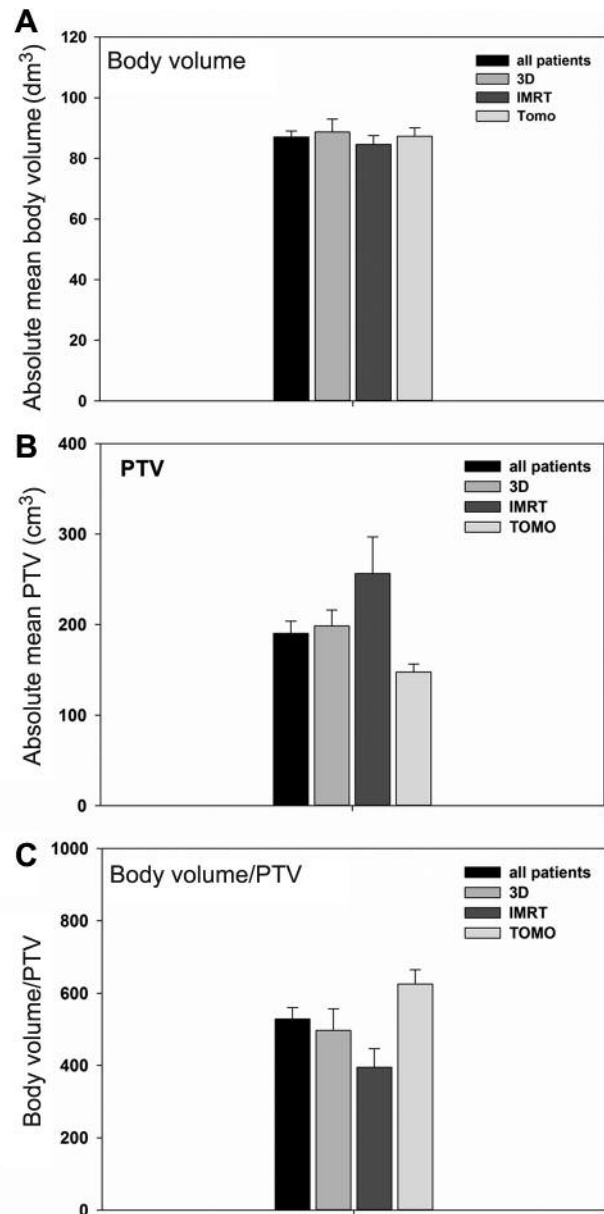

Figure 3. *Patient body volume (a), planning target volume (PTV) (b)and body volume/PTV (c).*

also showed similar results for all three groups: 79.5 kg for 3D, 79.0 kg for IMRT and 80.5 kg for TOMO. The median total body weight for all patients was 80.0 kg (see also Figure 2).

Correspondingly, there was no relevant difference in the median total body volume (TBV) between the groups: 3D at 86.00 dm³ , IMRT at 85.46 dm³ , and TOMO at 89.76 dm³ . The median TBV of all patients was 86.00 dm³ . Mean values are shown in Figure 3. The PTV depends on the individual's anatomy and prostate size. We calculated the following median values for the different groups: 185.50 cm³ for 3D,
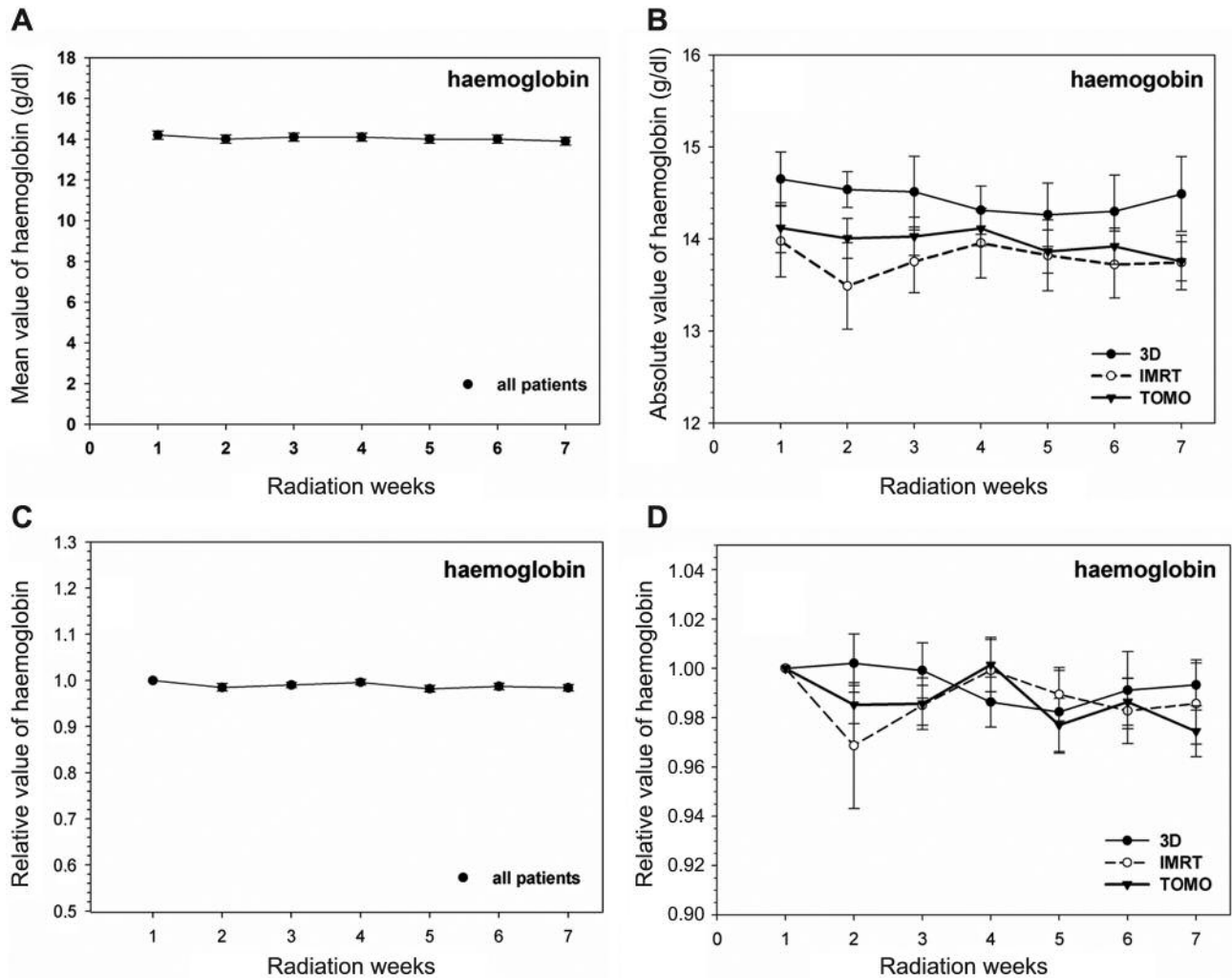
Figure 4. *(a) Median absolute concentration of hemoglobin in the blood (g/dl) across all study patients, shown over the course of 7 weeks of conventional fractionated radiation therapy. (b) Absolute results split by delivery mode used for radiation. (c) Relative measurements averaged for all patients. (d) Relative measurements split by delivery mode used for radiation. Standard errors are shown.*

228.15 cm^3 for IMRT, and 135.89 cm^3 for TOMO. The median PTV calculated for all patients was 171.29 cm^3. Mean values are shown in Figure 3. The value of TBV/PTV was calculated for each patient and led to a median quotient value of 522 for all patients. Accordingly, the three studied groups yielded median quotients of a) 407 (3D), b) 402 (IMRT), and c) 645 (TOMO). The mean values are shown in Figure 3.

Blood measurements. Over the 7 weeks of radiation therapy to the prostate/prostatic fossa, the haemoglobin concentration (g/dl) and leukocyte and thrombocyte counts per ml were analyzed.

The estimated median absolute blood concentration of haemoglobin for all patients did not change in a statistically significant manner over the course of radiotherapy, nor were any statistically significant changes observed in any of the three subgroups (3D, IMRT, and TOMO). The same is true for the relative changes to the mean haemoglobin concentration (Figure 4).

A small, but statistically significant, decrease was observed in absolute mean leukocyte counts per ml blood when all the patients were considered after the first week of radiation: 7.5×10^6 (standard error $+/-0.2 \times 10^6$) *vs.* 6.6×10^6 ($+/-0.2 \times 10^6$), $p=0.05$. This difference was maintained constant from the onset and during the rest of the treatment period. In the 7th week of treatment, the mean count was 6.3×10^6 ($+/-0.2 \times 10^6$). Regarding the three subgroups, it is evident that this effect was mainly caused by the two IMRT groups (IMRT and TOMO). In the TOMO group leukocytes decreased from 7.03×10^6 ($+/-0.3 \times 10^6$) in the 1st week to
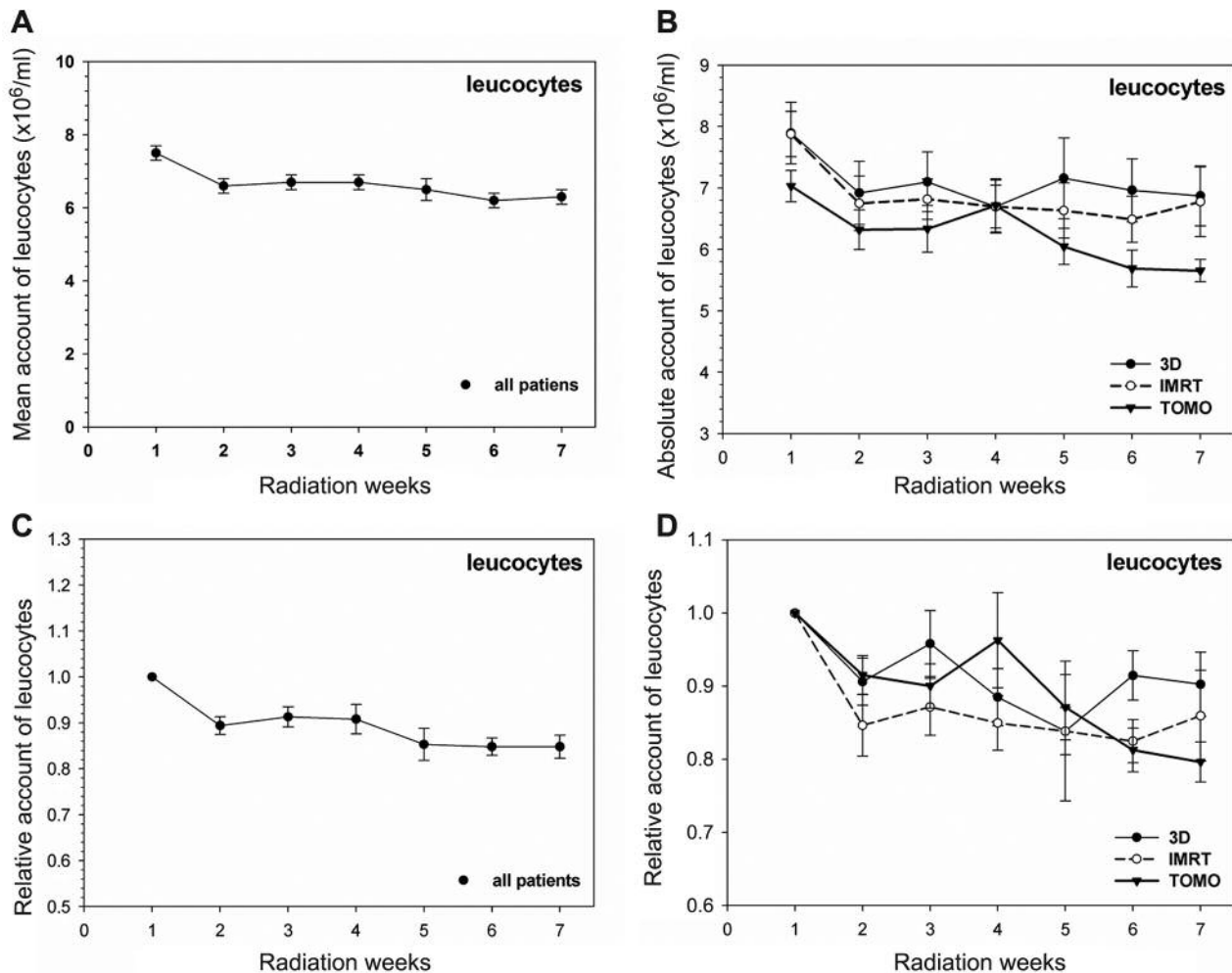
Figure 5. *(a) Median absolute leukocyte count per ml blood across all study patients, shown over the course of 7 weeks of conventional fractionated radiation therapy. (b) Absolute results split by delivery mode used for radiation. (c) Relative measurements averaged for all patients. (d) Relative measurements split by delivery mode used for radiation. Standard errors are shown.*

5.65×10^6 $(+/-0.2 \times 10^6)$ in the 7th week of radiation, $(p=0.05)$. Furthermore, in the 7th week of radiation, the TOMO group displayed a statistically significant lower mean leukocyte count compared to the 3D group $(p=0.05)$.

This slight decrease never led to leukopenia, (*i.e.* in counts $<4 \times 10^6$/ml) (Figure 4). A similar pattern was observed in the case of the mean relative leukocyte count (Figure 5).

Neither the absolute nor the relative mean thrombocyte counts were statistically significant over the course of radiation therapy in the case of the group as a whole or the subgroups (Figure 6).

Discussion

The ages of the subgroups of participants (3D, IMRT, TOMO) were almost identical and the total body volumes were comparable. The TBV/PTV values were larger in the TOMO group than in the 3D or IMRT groups (645 *vs*. 407 and 402). The trend in blood counts across the entire patient group yielded no statistically significant drops in the haemoglobin concentration or thrombocyte count over the course of radiation therapy to the prostate region. There were also no statistically significant changes within the three subgroups. A small, but statistically significant, decrease in leukocyte count was observed for the entire group. This was particularly noticeable in the TOMO group although the median PTV was somewhat smaller for this group. This meant that the TBV/PTV value was larger than for the other groups. At no point during the course of radiation, however, was this decrease clinically relevant, nor did it result in any cases of leukocytopenia (grades 1-4). This prospective study, therefore, showed that (primary or additive) conventional
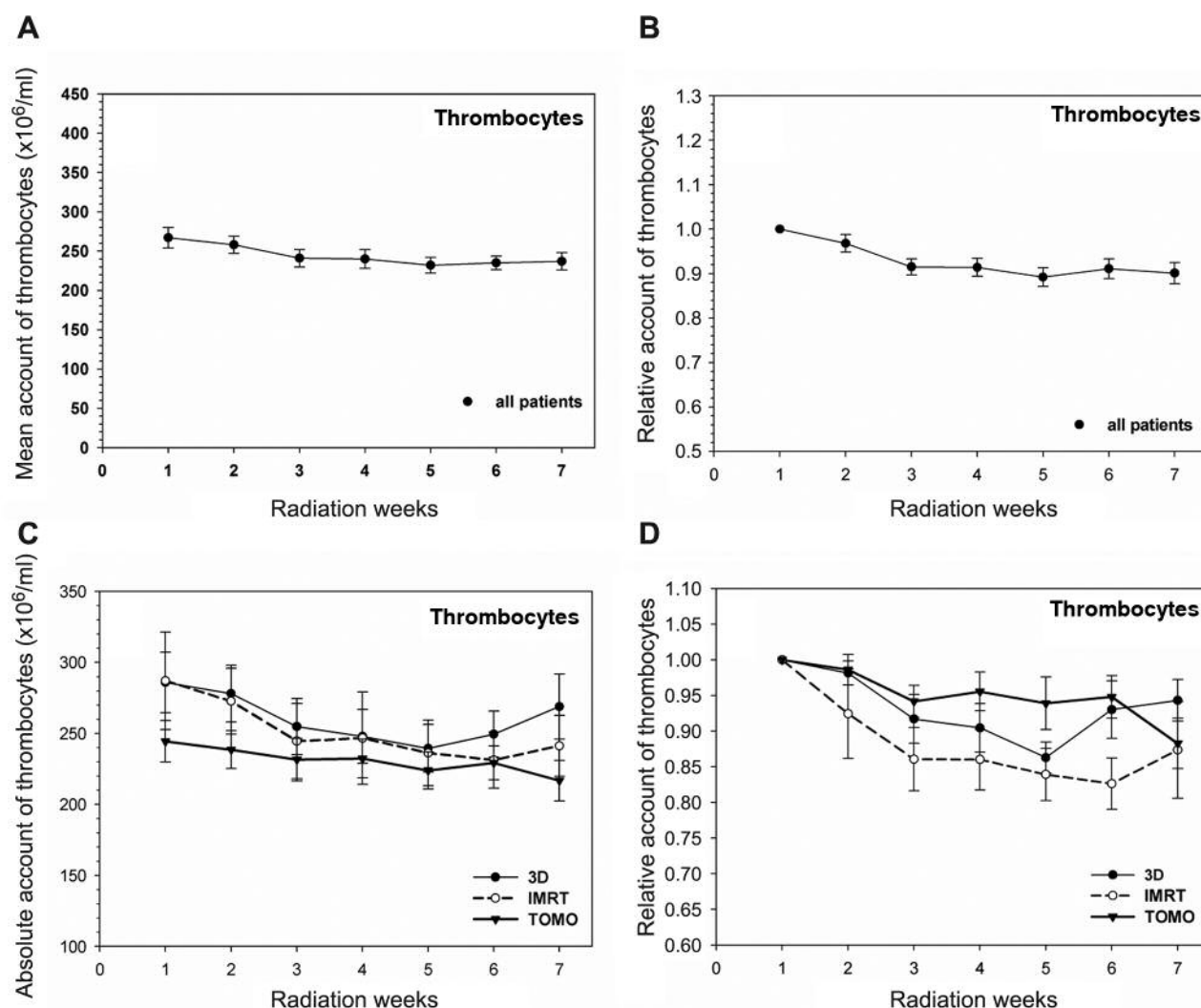
Figure 6. *(a) Median absolute thrombocyte count per ml blood across all study patients, shown over the course of 7 weeks of conventional fractionated radiation therapy. (b) Relative measurements averaged for all patients. (c) Absolute results split by delivery mode used for radiation. (d) Relative measurements split by delivery mode used for radiation. Standard errors are shown.*

fractionated radiotherapy for localised prostate cancer delivered by 3D, or by one of two different IMRT techniques (IMRT or TOMO), did not lead to any clinically relevant changes to the partial blood count over the course of treatments. This finding is important because IMRT is associated with a higher transversal integral dose in the normal tissue compared to 3D conformal RT in the irradiation of the pelvis (19). Tomotherapy causes increased low-dose exposure and a relatively moderate medium-dose exposure of the surrounding normal tissue (12).

A study by Brixey *et al*. in 2002 examined the impacts of radiation therapy and radiochemotherapy for gynaecological tumours on blood counts. The study used IMRT and 3D conformal radiation therapy on the entire pelvic lymphatic drainage system. It was shown that 10% of patients who received only radiation therapy displayed grade 3 leukopenia (or a higher grade). No statistically significant difference was observed between the two delivery modes. As expected, parallel chemotherapy led to a statistically significant increase in the number of cases of leukopenia (13).

It has also been demonstrated that in post-surgical radiation therapy for cervix carcinoma, the reduction of size of the irradiated area from 16×18 cm (whole pelvis) to 14×10 cm (pelvis minor) led to statistically significant decreases in the rate of leukocytopenia (grades 1-3, from 80.5% to 52.2%) (20).

In 2016, Sini *et al*. published a study that showed that the IMRT of the prostate, including the pelvic lymphatic drainage

system, was commonly associated with a statistically significant reduction in the number of white blood cells of the order of ~30%. A retrospective article by Pinkawa *et al.* (15) compared prostate cancer treatments using radiation therapy to the pelvis *vs.* the prostatic fossa. The delivery mode used was conventional fractionated five-field IMRT. Irradiation of the pelvis led to a significantly higher rate of grade 2 leukopenia (15% *vs.* 2%). In our prospective study of conventional fractionated radiation therapy of the prostate region delivered by any of the three studied methods (3D, IMRT, or TOMO), indicated that treatments did not lead to any cases of clinically relevant leukocytopenia (grades 1-4), thrombocytopenia, or anaemia.

In the case at which only the prostate/prostate-region was treated, the study by Sanguineti *et al.* (16) compared leukocyte counts by following hypofractionated *versus* conventional fractionated radiation treatments for localised prostate cancer. Treatment was delivered using the 3D conformal mode. The conventional-fractionated group displayed a statistically significant drop in their leukocyte count (20% *vs.* 15%). The prospective study presented herein led to a maximum drop of 15% in week 5 of radiation therapy in the 3D group. In our study the maximum overall drop in leukocyte count was observed in the TOMO group in week 7 of the treatment. Absolute counts remained at approximately 4×10^6/ml at all times. These values did not qualify as true leukocytopenia cases.

Based on the results of this study, we may infer that regular blood counts are not necessary during courses of radiation therapy of only the prostate/prostatic fossa when the PTV was <230 cm^3, regardless of which delivery mode was used (3D, IMRT, or TOMO). Regular blood counts should continue to be carried out when risk factors are present, such as immunodeficiency or clinical symptoms.

Discussion may also be warranted as to whether regular blood counts are required for target volumes <230 cm^3 localised in any part of the patients' body in case of absent risk factors. The area for irradiation in this study is located within the pelvic area, *i.e.* the most significant area in the body for haematopoiesis. Therefore, the risk of blood count changes should not be greater in other regions when the tumour volume is the same. For example, this may be the case when singular bone metastases are irradiated. As well relevant changes to the blood count is not supposable when hypo-fractionated radiation regimes are used for radiotherapy of the prostate gland with daily single dose upper than 2.5 Gy, because treatment time-period is shortened. However, additional clinical research is required to confirm or disapprove these assertions.

For many patients, venipuncture is an unpleasant and sometimes painful procedure. Possible side-effects include bruising, infections (abscess, phlebitis, erysipelas), and damages to cutaneous nerves. Therefore, venipuncture should only be carried out when is medically necessary, *i.e.*

when it provides information that reliably leads to a medical or therapeutic consequence. Based on the results of this study, blood tests are unnecessary in this case.

From a financial perspective, the health service costs can be reduced if weekly blood withdrawals and lab analyses are stopped in the cases of localised prostate cancer patients (PTV<230 cm^3) who are undergoing radiation therapy and who do not display any risk factors. To calculate the potential savings, we must consider the cost of materials (needles, blood collection tubes, swabs and plasters), lab analyses, and the man hours for the medical staff drawing the blood. On this basis, the cost of an individual blood test is approximately 15 EUR, *i.e.* 100 EUR per patient for the total course of seven tests.

Each year, around 60,000 new cases of prostate cancer are diagnosed in Germany (21). According to data recorded by the German Cancer Society (DKG), approximately 20% of these patients undergo radiation therapy of the prostate region at some point in their cancer history (22). This results in approximately 10,000 courses of treatments per year in Germany. Weekly blood counts over 7 weeks, each incurring costs of 15 EUR, adds annual costs to the German health system of up to ~1,000,000 EUR annually.

Based on these figures, one may extrapolate an approximate cost for the 1.1 million new diagnoses made annually around the world (23). An additional option for consideration would be to carry out just one blood count at the onset of the conventional fractionated radiation therapy of the prostate region and continue with additional blood counts during the course of radiation treatment only if a) the initial test yield abnormal results, or b) the patient presents risk factors, or c) the patient shows clinical infection symptoms.

Irradiation of the prostate region for localised prostate cancer is very commonly indicated in Germany, Europe, and around the world. This prospective study may thus contribute to the optimisation of treatment delivery.

Conclusion

Regardless of the delivery mode used, localised fractionated irradiation of the prostate region did not cause any clinically relevant changes to the blood count in this study. Accordingly, these findings question the necessity of regular blood counts during courses of radiation therapy of the prostate region for patients who do not display any risk factors.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

F.Z., K.H. and H.H. initiated and supervised the project. B.S. and F.Z. collected data and carried out the data analysis. F.Z., B.S.,

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