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# Predicting neutropenia dynamics after radiation therapy in multiple myeloma patients receiving first-line bortezomib-based chemotherapy – a pilot study

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**Introduction.** Radiation therapy (RT) is a useful modality for achieving local control and symptom relief in patients with multiple myeloma (MM), but its use can result in adverse effects such as neutropenia, which may be aggravated by prior chemotherapy.

**Material and methods.** In this retrospective study, we analyzed 530 complete blood count results of 32 MM patients who underwent RT for symptomatic bone pain between cycles or after completing first-line bortezomib-based chemotherapy (VCD). To evaluate the dynamics of neutrophil count (ANC) changes, we developed a generalized additive model (GAM) using initial ANC, dosage (BED10), and treatment volume (PTV) as predictors.

**Results.** Our GAM model demonstrated that ANC nadir after RT can be expected approximately 16 days after treatment initiation. The delivery of 8 Gy in 1 fraction resulted in the lowest ANC nadir, while a dose of 30 Gy in 10–15 fractions was deemed the safest. For PTV = 1000 $cm^3$, an initial ANC level of at least $1.42 \times 10^3/\mu l$ was associated with no incidence of severe neutropenia irrespective of the fractionation scheme. Longer courses allowed for treatment delivery without significant neutropenia even with an initial ANC of $1.23 \times 10^3/\mu l$ on the day of RT initiation.

**Conclusions.** Our model could aid in optimizing treatment strategies for MM patients receiving RT and chemotherapy. Further research is needed to validate our findings and evaluate the feasibility of implementing this model in clinical practice.

**Key words:** multiple myeloma, radiotherapy, neutropenia

## Introduction

Multiple myeloma (MM) remains an incurable plasma cell malignancy that tends to affect older adults. Although the mainstay treatment for MM is systemic chemotherapy, even 70–80% of patients with MM have osteolytic lesions at diagnosis [1].

Over the last decade, multiple myeloma patients have experienced several breakthroughs leading to prolonged su-

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rvival. This is mostly attributed to novel effective systemic therapies [2]. Additional radiation therapy (RT) is considered rather supportive, offering very effective symptom relief for tumor deposits (plasmacytomas) in bone or soft tissues [3]. Nevertheless, as plasma cell neoplasms are radiosensitive tumors [4], RT can provide durable local control of symptomatic lesions. In a recent analysis of patients with spinal cord compression caused by myeloma, after RT, 64% of non-ambulatory patients regained their ability to walk again. RT provided excellent 1-year local control of 93% [5].

While high treatment efficacy is desirable, it is important to consider that it may not be achievable without incurring certain adverse effects. High dose irradiation to the larger volume of bone marrow prevents compensatory hyperplasia, which leads to hematological complications like neutropenia [6]. However, in the last decade, we have also experienced the development of modern radiation therapy techniques. These developments result in better conformity of the treatment and fewer adverse effects [7]. Introduction of high-dose treatments like stereotactic body radiation therapy (SBRT) [8] raises the important questions about the updated role of RT in MM management. Although increasingly effective [9], some reports highlight that modern radiation techniques, like VMAT (volumetric modulated arc therapy), can increase the risk of lymphopenia by irradiating large volumes of tissue with low doses of radiation [10]. Cytopenias, including neutropenia, have been associated with worse outcomes in MM [11].

VCD (bortezomib, cyclophosphamide, and dexamethasone) is a chemotherapy regimen commonly used as first line treatment for multiple myeloma. Neutrophils, like other rapidly dividing cells, are sensitive to bortezomib's action on the proteasome, leading to a decrease in their number. After VCD, neutropenia typically occurs around 7–10 days after the start of treatment. The nadir is usually reached 10–14 days after the start of treatment. The duration of neutropenia depends on the individual and the severity of the neutropenia, but it typically resolves within a week or two after the nadir is reached [12]. Although this three-drug combination shows significant efficacy and manageable toxicity as a treatment for MM, its association with significant risk of pneumonia and neutropenia [13] can cause prolongation of RT initiation. Due to the overlap in toxicities, combination treatment is often discouraged.

Postponing the start of radiation treatment due to the risk of exacerbating complications from chemotherapy may, however, be associated with a deterioration in quality of life. Additionally, although interplay between RT and novel drug combinations has not been thoroughly studied, preliminary results suggest that ionizing radiation combined with bortezomib enhances NK cell-mediated anticancer immune responses [14], and bortezomib could promote radiosensitivity [15].

Here, we have developed an advanced preliminary statistical model to predict the expected severity and dynamics of neutropenia after radiation therapy in patients receiving VCD as a first-line treatment. The model utilizes the radiation planning target volume (PTV), biologically effective dose with an alfa/beta value of 10 (BED10), and the initial absolute neutrophil count (ANC) to estimate the rate of ANC decrease and subsequent increase in the days following the start of radiotherapy.

## Material and methods

In this pilot study, we conducted a retrospective analysis of 34 patients with multiple myeloma who received radiation therapy at the Department of Radiotherapy, Copernicus Memorial Hospital in Lodz between 2018 and 2020. We included symptomatic patients (with pain) who received radiation therapy between cycles or after completing first-line bortezomib-based chemotherapy (VCD). As per institutional protocol, radiation and systemic treatments were not overlapped, and all the included patients received their last dose of systemic treatment more than 14 days before starting radiation therapy. All patients received photon-based radiation therapy targeted at the affected bony area. Clinical target volume (CTV) was identified using CT, MRI, or PET-CT scans and was contoured according to guidelines [16]. The planning target volume (PTV) was defined as the geometric extension of the CTV by 7 mm, according to institutional recommendations.

For the selected patients, we identified and collected 534 absolute neutrophil count (ANC) results from complete blood counts with differential (CBC) performed up to 30 days before and up to 90 days after radiotherapy. We excluded patients who had less than five CBC blood tests during this period. The gaps between daily studies were imputed using an exponentially-weighted moving average, with a moving window of 30 days.

We developed a generalized additive model using LOESS (GAM) for log-transformed neutrophil count. Logarithmic transformation ensured a normal distribution. Based on clinical knowledge and expectations, the model included a starting neutrophil count (on the day the radiation therapy started), a biologically effective dose with an alfa/beta value of 10 (BED10), and planning target volume (PTV) as predictors. We used hyperparameter optimization with a 10-fold cross-validation to select optimal degrees of freedom for all terms, and the model with the maximum R-squared was chosen as the final model. We used ANOVA for nonparametric effects to assess the association of predictors with the model output. Neutropenia of grade 2 or higher, according to the CTCAE version 5.0, was defined as an ANC lower than 1500/microliter. All analyses were performed in R (version 4.1.2). Neutropenia was defined according to CTCAE version 5.0. All analyses were performed in R (version 4.1.2).

## Results

The final study material consisted of 530 ANC measurements of 32 patients who experienced various changes in ANC levels after radiotherapy (fig. 1). Two patients had to be excluded

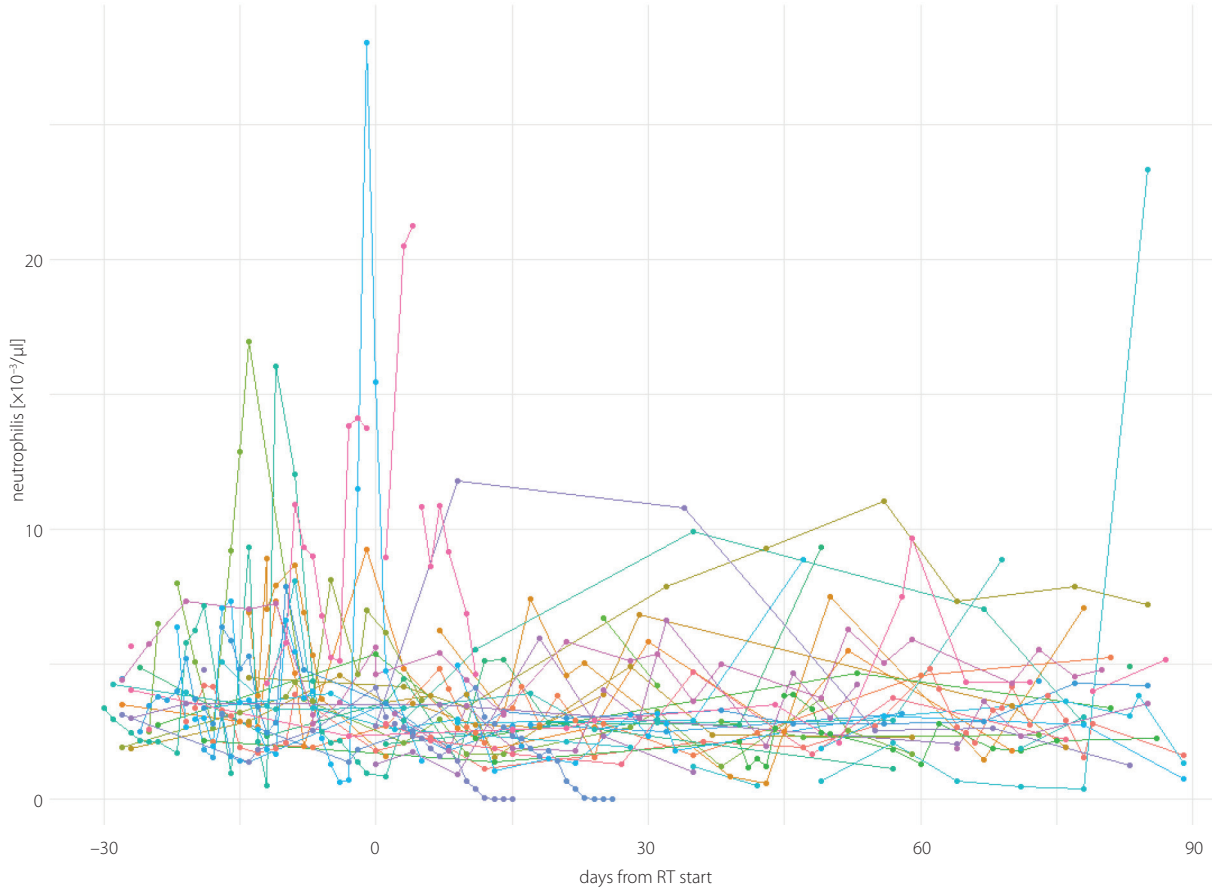


**Figure 1.** Measurements of neutrophils in particular patients up to 30 days before and 90 days after radiation initiation. Zero indicates the start of radiation treatment

due to a lack of sufficient CBC measurements (<5 per patient). Profiles showing the interpolated changes in ANC levels in selected patients are shown in figure 2.

The mean age of the study group at the start of radiation therapy was 64.03 years (range 43 to 84 years, median 61.5 years). The median BED10 of the applied fractionation schemes was 36 Gy (range 14.4 to 55.1 Gy; interquartile range (IQR) = 11), which corresponds to a median EQD2 of 23.5 Gy. The most commonly used fractionation schemes were 30 Gy in 10 fractions (31.2%) and 20 Gy in 5 fractions (25%). The dose was delivered to various volumes (PTV) of bony tissue, with a median volume of 754.5 cm³ (IQR = 726.6 cm³) (fig. 2). The majority of patients were treated with intensity-modulated radiation therapy (IMRT) (68.8%), while the remaining patients were treated with VMAT.

Spline models developed for high and low BED10 and PTV volumes (median split) didn't present significantly different dynamics of normalized ANC change (fig. 2). Developed GAM model showed that decrease in ANC follows initiation of RT and reaches a nadir around 16 days after RT starts (fig. 3). The root mean squared error of the developed model was 589 neutrophils per microliter. ANOVA for nonparametric effects showed that both BED10 and PTV volume, as well as starting ANC, have a significant effect on model outcomes ($p < 0.001$). As seen in figure 3, generally decrease in ANC increased with PTV volume, although the effect was not pronounced in volumes lower than 1000 $cm^3$. Interestingly, delivery of 8 Gy in 1 fraction (BED10 = 14.4 Gy) was associated with the lowest ANC nadir. A dose of 30 Gy in 10 or 15 fractions was associated with the lowest change in ANC levels. The application of 20 Gy in 5 fractions (BED10 = 28 Gy) showed moderately low ANC nadir.

Figure 4 shows the relationships estimated by the GAM model between the starting ANC, nadir, and expected days of grade 3 or higher neutropenia, compared between different fractionation schemes and calculated for a PTV volume of 1000 $cm^3$. Notably, the expected ANC nadir was lowest for 8 Gy in 1 fraction, regardless of the starting ANC level. According to the developed model, a starting level of ANC = $1.42 \times 10^3$/µl was associated with no occurrence of severe neutropenia (grade 3 or 4 according to CTCAE), regardless of the fractionation scheme. The safest fraction was 30 Gy in 15 fractions. As shown by the model, the use of this dosing could provide treatment without severe neutropenia even with ANC = $1.23 \times 10^3$/µl on the day of RT start.

## Discussion

In this pilot study we developed a statistical model explaining neutropenia severity and dynamics after radiation therapy in patients treated with bortezomib-based first-line systemic

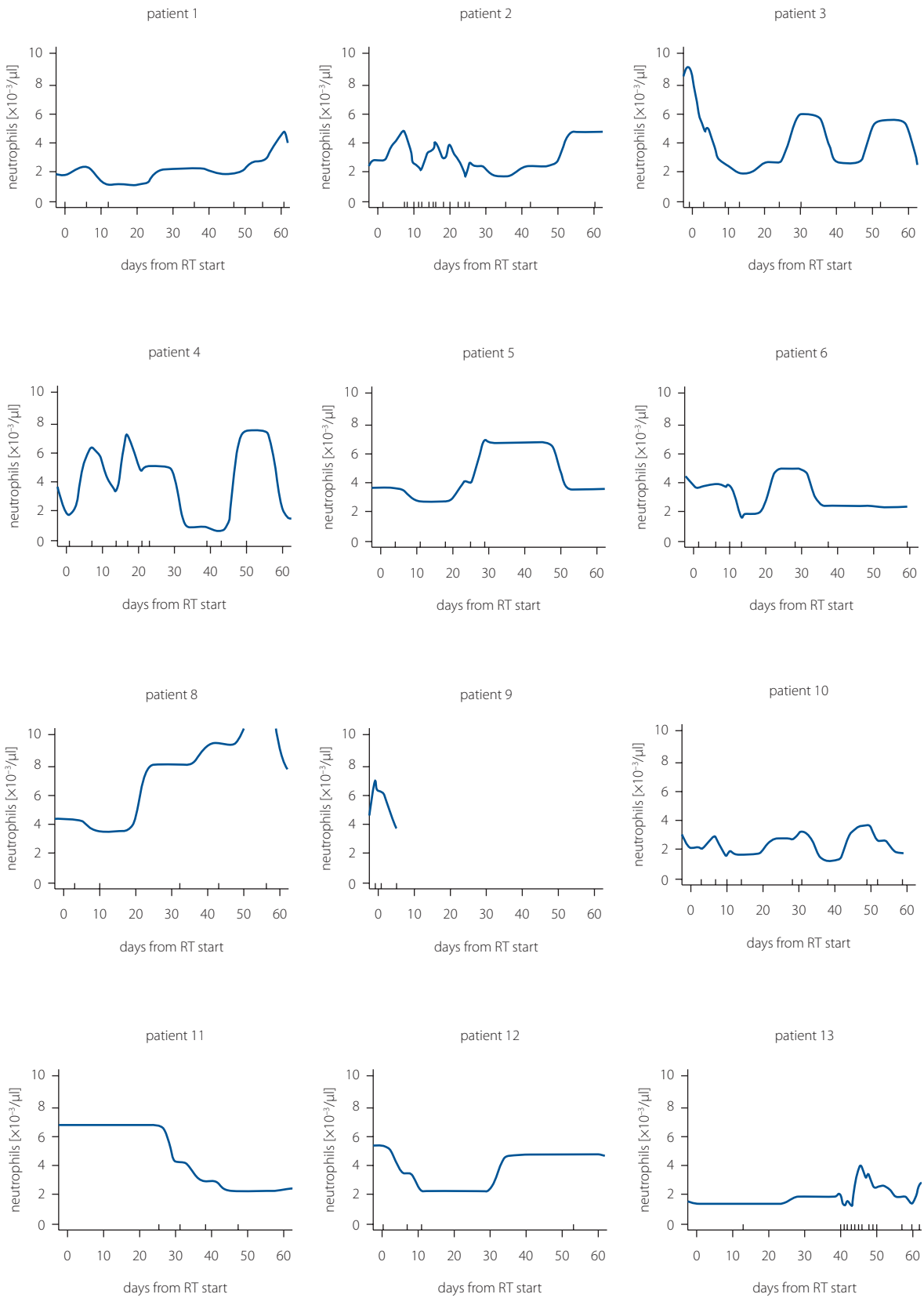


**Figure 2.** Profiles showing the interpolated changes in ANC levels in selected patients

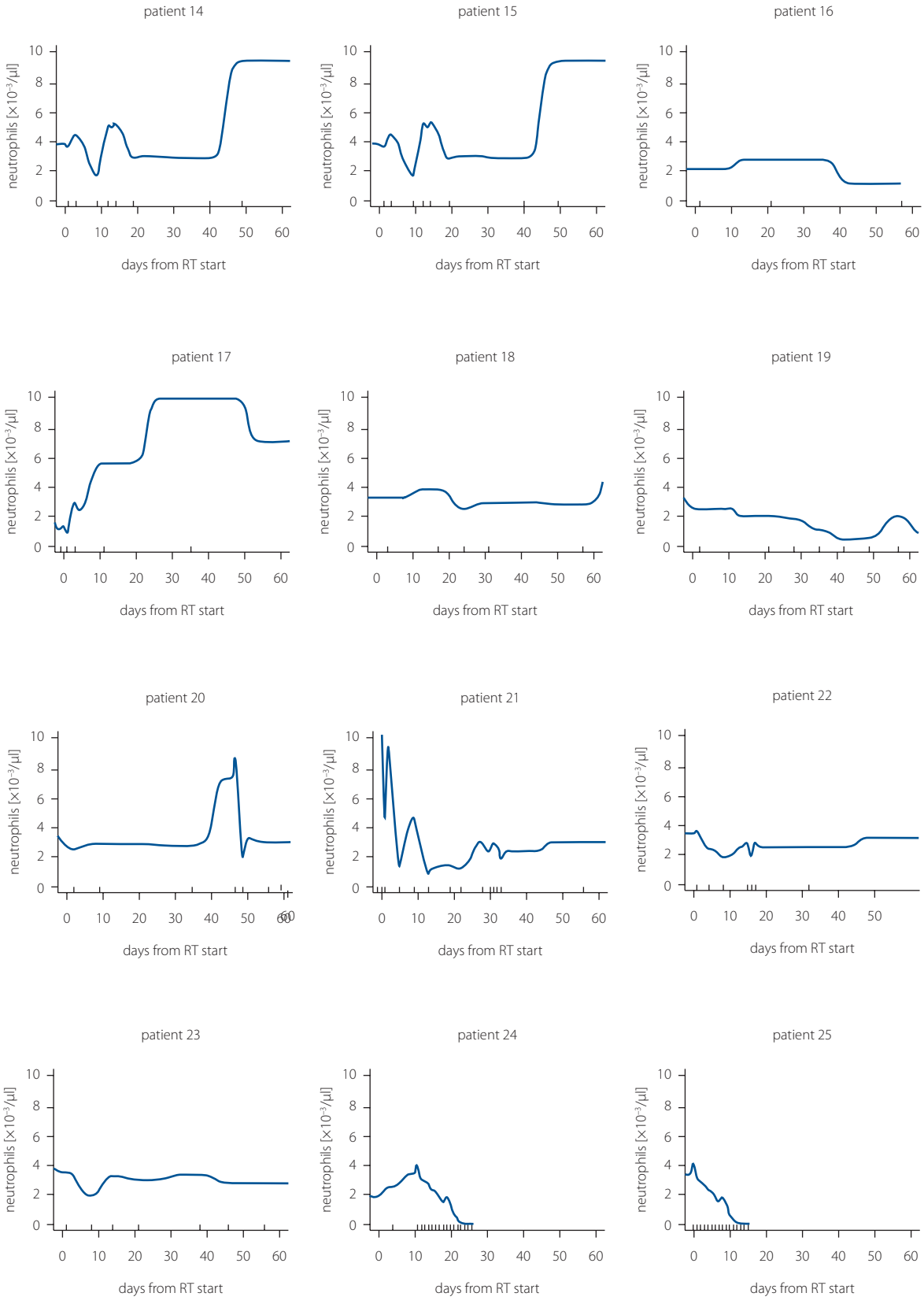


**Figure 2. cont.** Profiles showing the interpolated changes in ANC levels in selected patients

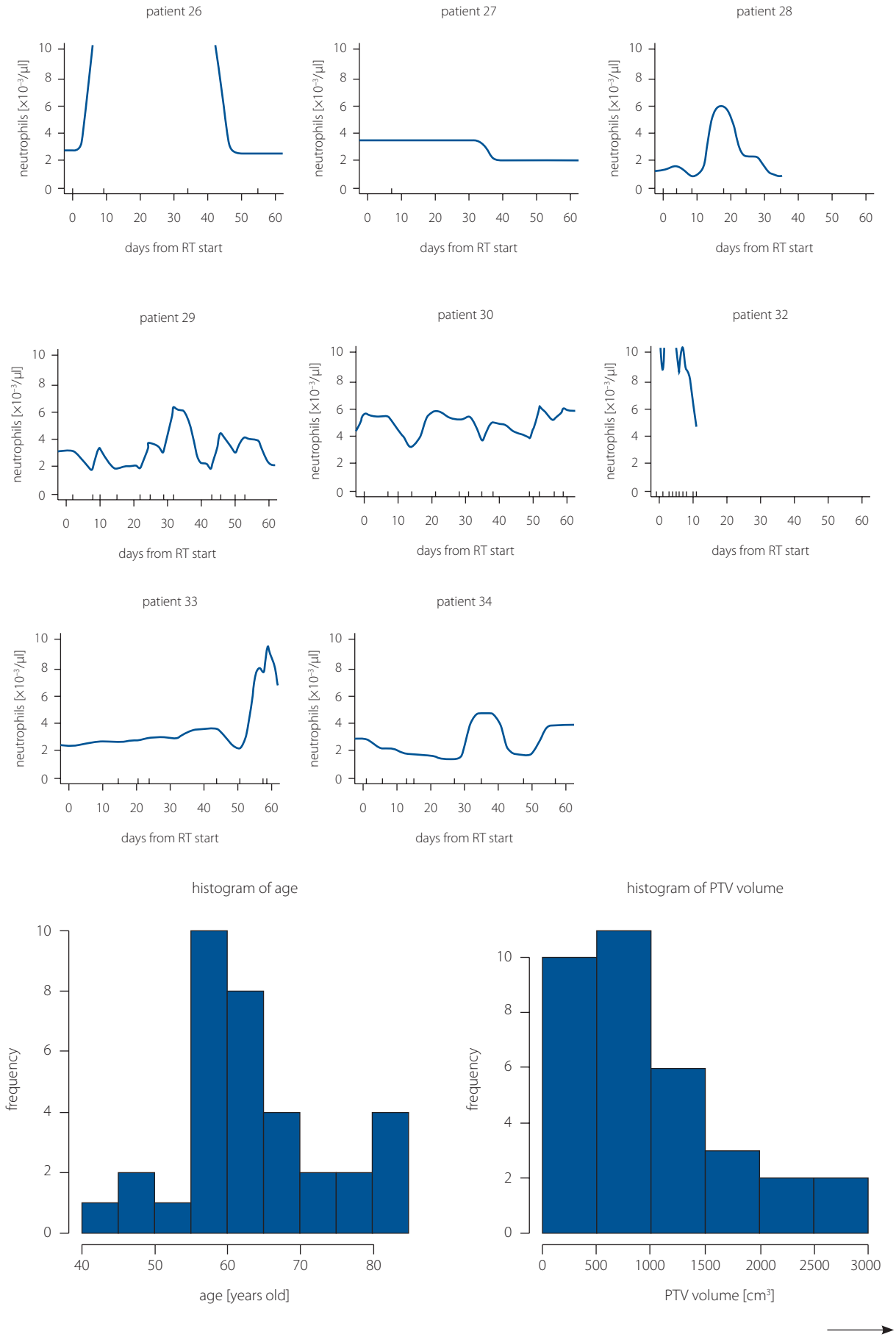


**Figure 2. cont.** Profiles showing the interpolated changes in ANC levels in selected patients

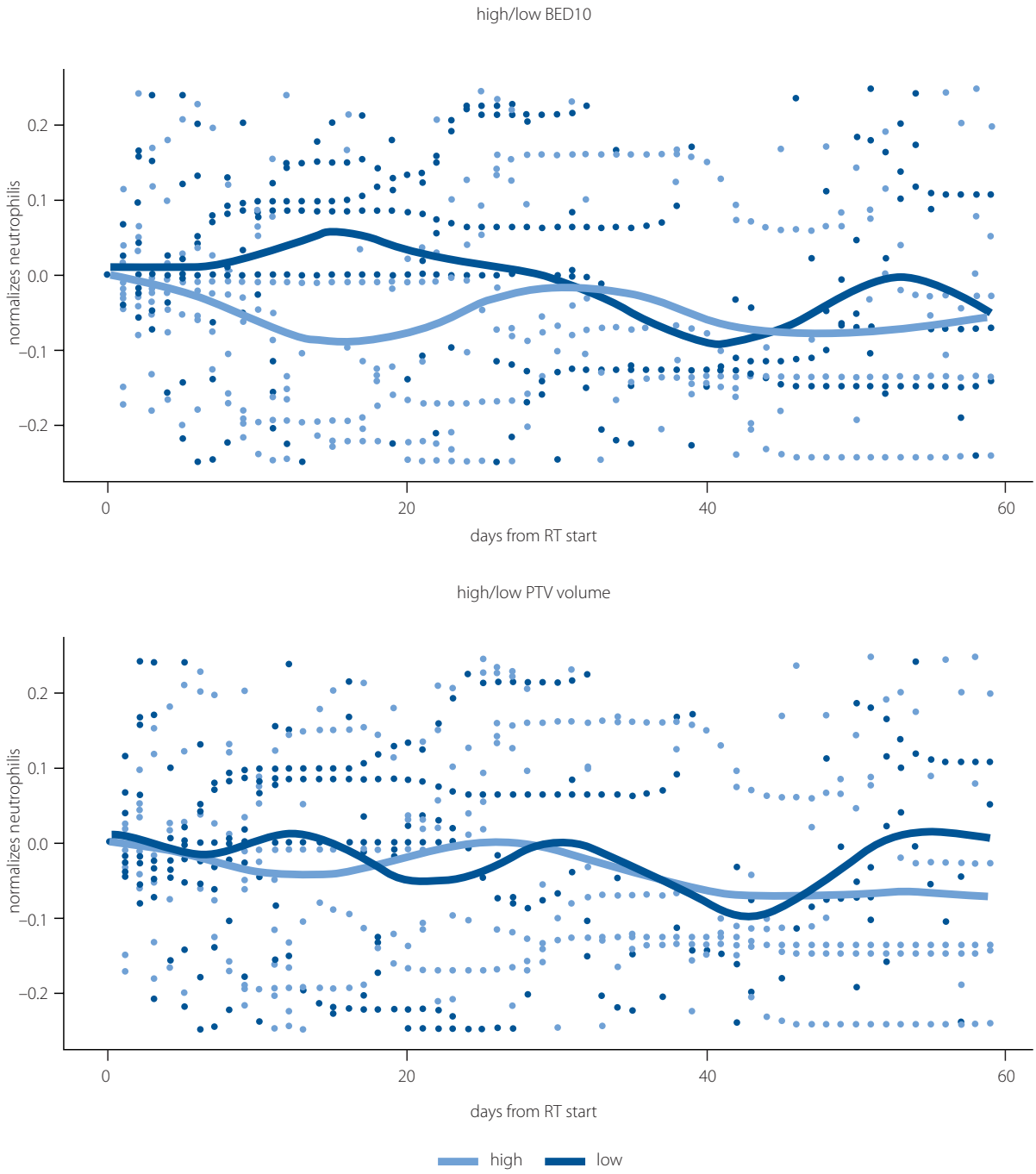


**Figure 2. cont.** Profiles showing the interpolated changes in ANC levels in selected patients

treatment. The model utilized PTV, BED10 and initial ANC to estimate how ANC will change in the days following the start of RT. Although the model metrics could be for sure improved if additional predictors were included, by enforcing low complexity we derived potentially clinically useful observations. All included predictors had significant effect on model outcomes.

The studied group was slightly younger than expected, as the average age at diagnosis with multiple myeloma is 69 years, compared to the observed average age of 64 years in our study [16]. Most often applied fractionation schemes were consistent with guidelines for palliative care of multiple myeloma patients [17]. Each patient 17 CBC results per patient in studied timeframe aligns with the intent of radical systemic treatment.

The developed model provided significant clinically valuable insights. We observed that the ANC nadir after radiotherapy of bony lesions in MM can be expected around 16 days after RT initiation. This is an interesting observation, as most cytotoxic regimens cause neutropenic nadirs between days 10 and 14 [18]. The decrease of ANC seems, however, to be dependent on BED10 (fractionation scheme), PTV volume

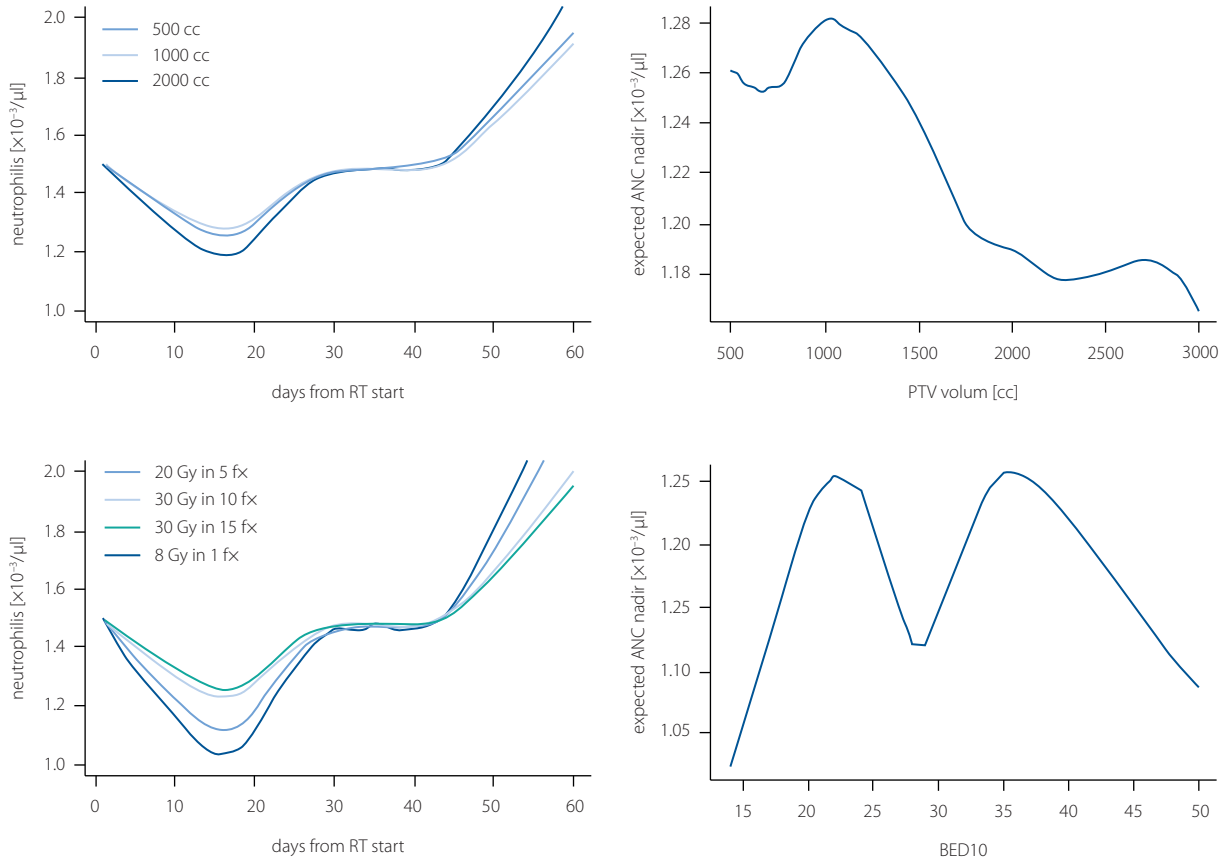


**Figure 3.** Effect of fractionation scheme (BED10) and PTV volume on neutrophil count estimated by GAM model and relationship of ANC nadir and changes in BED10 and PTV volume [cc; $cm^3$]. Median values were considered for non-modified variables. Initial ANC of 1.5 × 103/µl was used for calculations

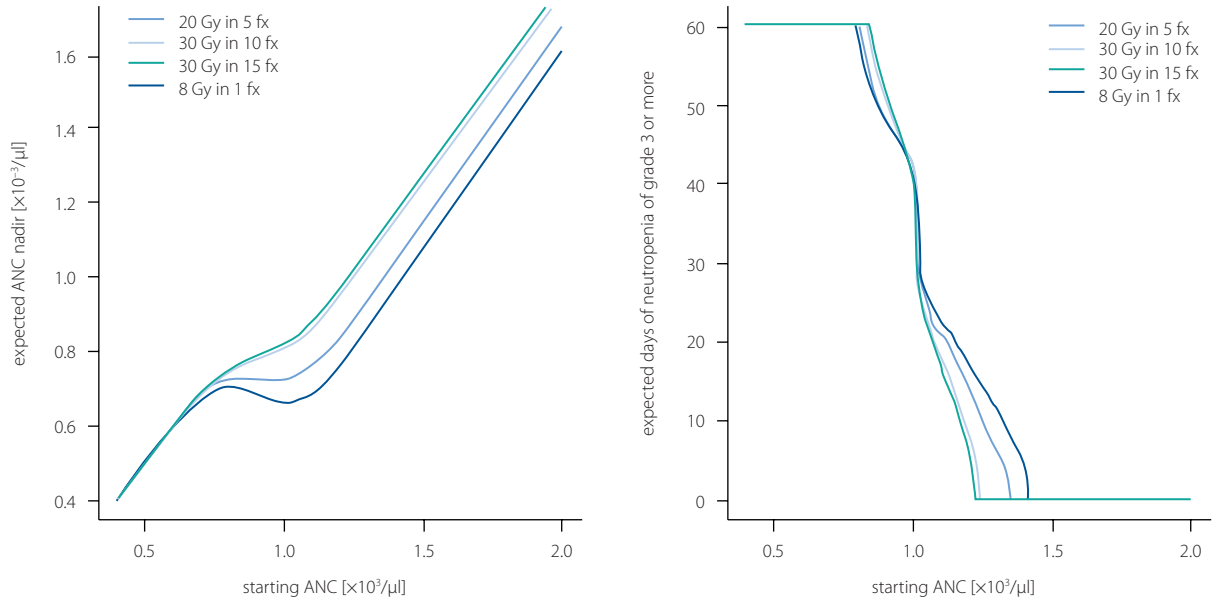


**Figure 4.** Relationship between starting ANC, nadir and expected days of neutropenia of grade 2 or more compared between different fractionation schemes. Calculations were performed for a PTV volume of 1000 $cm^3$

and initial ANC level. As expected, in our data, a greater irradiated volume was associated with a more intense ANC nadir. We noticed, however, that the nadir was lowest for 8 Gy in 1 fraction regardless of starting ANC level. This observation should be treated with caution, considering that radiation oncologists tend to use 8 Gy in 1 fraction as a scheme for fragile patients with poor prognosis [19]. Considering that MM is frequently associated with severe pancytopenia in advanced stages, we

might expect low bone marrow tolerability in these patients. Nevertheless, it is essential to emphasize that patients in our study were treated with bortezomib-based systemic treatment, which requires a good initial performance status.

In our study, the application of a radiation dose of 30 Gy in 15 fractions (2.0 Gy fraction dose) was found to be associated with the smallest decline in absolute neutrophil count (ANC) and was therefore identified as the safest option. Our model indicates that utilization of this treatment schema remains safe even when ANC levels are as low as 1.23 × 103/μl for PTV volumes of 1000 cm³, in contrast to the 1.42 × 103/μl threshold required when 8 Gy in 1 fraction is employed. This observation is interesting in the context of a retrospective review of 172 patients conducted by Rades et al. [20]. In this study, the authors compared shorter courses (8 Gy in 1 fraction, 20 Gy in 5 fractions) with longer courses of RT (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) for spinal cord compression caused by myeloma and concluded that longer courses are associated with improved motor function. Comparable functional outcomes were noted for longer course regimens. Additionally, in a randomized prospective clinical trial by Rudzianskiene et al. [21], a dose of 30 Gy in 10 fractions achieved better quality of life than 8 Gy in 1 fraction. Thus, in the context of our results, 30 Gy in 10 or 15 fractions seems to be not only safer, but also more effective.

Longer survival of multiple myeloma patients promotes the idea of RT dose reduction to reduce long-term toxicity, especially as long-term survivors tend to have multiple courses of RT. A recent retrospective review of 772 patients with the administration of lower dose of 20 Gy in fractions of 2 Gy (BED10 = 24 Gy) per day offers long-lasting pain relief, reduces the occurrence of bone marrow fibrosis, and allows for subsequent effective reirradiation [22]. In this review, a plurality of patients were treated with schemes with BED10 between 20 and 25 Gy (43%). Our model (as illustrated in figure 2) suggests that such regimens are associated with the lowest decrease in absolute neutrophil count (ANC). It is important to note, however, that the authors observed a small but statistically significant increase in reirradiation rates for BED10 ≤ 28 Gy.

This study had several limitations associated with its retrospective design. Firstly, the study did not assess the potential benefit of radiation treatment, such as pain relief or effects on survival. As low doses seem to be effective in MM [22], in the context of important preclinical evidence [14], future work will have to assess if an increased dose is associated with additional benefits beyond quality of life.

In many cases, more intensive treatments are associated with more adverse events but better clinical outcomes [23]. Secondly, the use of G-CSF and steroids prescribed by radiation oncologists and hematologists may have influenced the results. The effects of these drugs can be seen in some patients in this study, as G-CSF shortens the neutropenia period in responsive patients and can greatly impact the model. The cytotoxicity of radiotherapy and chemotherapy leads to a deficiency in all hematopoietic cell lines, but an increase in ANC could also be seen in patients who develop infections [24]. To address these complexities, a 30-day pre-treatment period was included in the analysis so that the dynamics of ANC changes before the start of RT could influence the model parameters. However, future studies should consider these factors in their analysis.

## Conclusions

In the context of systemic therapy for multiple myeloma (MM), the role of radiation therapy (RT) is evolving, and its potential benefits at all stages of treatment are being investigated. However, concerns about the possible addition of toxicities may limit its current application.

In this paper we developed a preliminary model to estimate the dynamics of radiation-induced neutropenia in MM patients who had already undergone bortezomib-based chemotherapy. Our model determined the safety of radiation therapy in this patient population by analyzing the effects of different radiation schemes on absolute neutrophil count (ANC) levels. Our findings indicated that longer radiation schemes, such as 30 Gy in 10–15 fractions, can be safely administered to a volume of PTV = 1000 $cm^3$ – even if the ANC level is as low as 1.23 × 103/μl on the day of RT initiation. These results have the potential to guide clinical decision-making regarding the overlap of radiation and chemotherapy toxicities.

Overall, our study highlights the importance of developing predictive models to optimize treatment strategies in patients with MM undergoing RT and chemotherapy. Further research is needed to validate these findings and determine the feasibility of implementing this model in clinical practice.

**Conflict of interest:** none declared

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