



Original Research Article

Quality-of-life and toxicity in cancer patients treated with multiple courses of radiation therapy

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ABSTRACT

Background: Treatment of metastatic cancer patients with multiple repeat courses of radiotherapy has become more frequent due to their improved overall survival. However, very little is known about their long-term outcome. This analysis reports on the quality-of-life, hematologic toxicity, patient-reported experiences and satisfaction, and psychological distress of cancer patients treated with multiple repeat radiotherapy.

Methods: All patients treated with ≥ 5 courses of radiotherapy between 2011 and 2019 at the Department of Radiation Oncology, University Hospital Zurich (USZ) were screened for this study. A course of radiotherapy was defined as all treatment sessions to one anatomical site under one medical indication. All patients completed two questionnaires: EORTC QLQ-C30 questionnaire for quality-of-life and a questionnaire evaluating psychological distress and patient-reported experiences. Hematologic toxicities were assessed via a recent blood sample.

Results: Of $n = 33$ patients treated with ≥ 5 radiotherapy courses and being alive, 20 (60.6%) participated in this study. The most common primary tumor was non-small cell lung cancer ($n = 14$, 42.4%). The most common sites of irradiation were brain ($n = 78$, 37.1%) and bone metastases ($n = 59$, 28.1%). All participating patients reported that they had experienced a subjective benefit from multiple repeat radiotherapy and denied increased side effects in later radiotherapy courses. Yet, 45% ($n = 9$) of the patients reported an increase of psychological distress with increasing numbers of radiotherapy treatments. While global health status was stable, patients having received multiple repeat radiotherapy reported increased fatigue ($p = <0.006$). Blood analysis showed significantly reduced hemoglobin and lymphocyte levels compared to the healthy population ($p = <0.03$).

Discussion and conclusion: Patient-reported experiences and satisfaction of long-term cancer patients treated with multiple repeat radiotherapy are positive. However, increased levels of fatigue and significantly reduced hemoglobin and lymphocyte levels were observed. These data indicate the need to further investigate the effects of multiple courses of radiotherapy in chronic cancer patients.

1. Introduction

Rapid progress in cancer care and radiation oncology have contributed to longer survival in many cancer patients and thus are contributing to the transformation of cancer into a chronic disease. [1] Every second patient diagnosed with cancer will receive radiotherapy (RT) during their treatment history. [2] Recent studies have shown that improved overall survival of many cancer patients is associated with an increasing number of patients treated with multiple repeat RT (MRRT), in curative or palliative intent. [3] This ongoing transformation of cancer into a chronic disease requires an increased consideration of quality-of-life

(QoL), long-term and cumulative toxicity of multiple anti-center interventions, patient-reported experiences and satisfaction (PRES), and psychological distress to provide optimal cancer care.

Traditional endpoints in clinical cancer research typically include tumor control rate, overall survival, or disease-free survival. However, it is especially important to consider QoL for this patient group. QoL entails global health status, as well as emotional, physical, social and cognitive functioning changes. Various patient- and disease-specific factors and RT modality may affect QoL. [4] Fatigue, a major component of QoL, is one of the most common side effects reported by cancer patients during and after treatment. [5–8] In many cases evaluation of

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QoL in patients having received RT remains challenging, since symptoms of cancer may deteriorate before improvement [9–10] and pre-treatment mental and physical status vary between patient populations. [11–13] Due to heterogeneity of cancer diseases and their clinical manifestations, evaluation of QoL after RT in different cancer patient populations remains problematic to generalize. [14–15]

Chronic hematologic toxicity is another concern in long-term cancer patients treated with multiple courses of systemic therapies and radiotherapy. From a patient perspective, chronic hematologic toxicity may contribute to an exacerbation of infections, fatigue, and increased bleeding time. [16] The site of radiation plays a crucial role in the development of hematological toxicity; pelvic bone marrow contains around 40% of total red bone marrow and thereby its radiation is associated with a higher risk of hematologic toxicity. [16] Despite increasing usage of MRRT, the acute and long-term hematologic toxicities remain largely understudied, thereby creating additional uncertainty regarding the prediction of its tolerability.

This study aims to increase our knowledge in this growing population of chronic cancer patients treated with multiple courses of radiotherapy, with the final goal to optimize the longitudinal treatment of these vulnerable patients throughout their long-term cancer survival. Therefore, we analyzed QoL, hematologic toxicity, PRES, and psychological distress of a highly selected and especially vulnerable group of cancer patients, who received a minimum of five RT courses during their long-term cancer history.

2. Materials and methods

2.1. Patient population

All patients having received a minimum of five RT courses at the Department of Radiation Oncology of the USZ between 2011 and 2019, were included in this study. The inclusion criteria of minimum 5 radiotherapy courses was chosen to investigate the long-term QoL, PRES, hematologic toxicities, and psychologic distress of this under-investigated and especially vulnerable patient cohort, which we described in a previous study. [3] We defined MRRT as a term to describe a minimum of 5 RT courses having been received by the patient. At the time of analysis of this study, 33 patients who had received a minimum of 5 RT courses were alive and were invited to participate in this study. Participating patients were scheduled for a physical follow-up visit. One RT course was defined as a prescribed RT treatment to one anatomical site for one medical indication.

2.2. Electronic patient records

We used our hospital information system (HIS) KISIMTM to extract general patient, disease characteristics, treatment characteristics, and recent blood sample data. Furthermore, we extracted detailed RT specifications, such as treatment site, RT duration, single dose, total dose, RT volume and course count from our treatment planning system ARIA®. This project and its design were approved by the Swiss Cantonal Ethics Committee before study initiation (BASEC# 2021-00104).

2.3. Employed measures for QoL, hematologic toxicity, PRES, and psychological distress

To assess QoL, we used the EORTC QLQ-C30 questionnaire [17], which is the most widely used cancer-specific Health-Related Quality-of-Life instrument containing 30 items and measuring five functioning dimensions (social, emotional, physical, role, and cognitive), three symptom items (pain, nausea/vomiting, fatigue), six single items (appetite loss, diarrhea, constipation, dyspnea, sleep disturbance and financial impact), and a global health and quality-of-life scale. The reference population was the EORTC QLQ-30 cohort. The scoring procedures were conducted as previously described. [18]

We obtained a recent blood sample to analyze hematologic toxicities, electrolyte levels, glucose metabolism, liver-, kidney-, heart- and renal function (detailed overview in [Supplementary File A1](#)). Hematologic and organ toxicities were assessed according to Common Terminology Criteria for Adverse Events Version 5 (CTCAE). [19]

To capture the subjective patient-reported PRES and psychological distress in MRRT patients, we used an in-house developed questionnaire consisting of ten questions, designed by a team of radiation oncologists, a psycho-oncologist, and a palliative care specialist. While several validated assessment tools for psychological distress are available [20], we decided to use our in-house created questionnaire to assess psychological distress and patient-reported experiences combined. Patients were asked to answer ten questions on a four-point Likert scale: 1 = strongly agree, 2 = agree, 3 = disagree, and 4 = strongly disagree. The highest score on all scorable questions was 40, the lowest score was 10. The questionnaire was created in German and, for demonstration in this study, translated to English ([Supplementary File A2](#)).

Patients fulfilling the inclusion criteria were contacted via phone or mail to inquire about their willingness to participate in this study. After completion and signing of written consent, the patients were invited for a clinical visit to obtain a recent blood sample and to complete two questionnaires.

2.4. Data analysis

All clinical and treatment data were recorded in Microsoft® Excel® (Version 16.0). Descriptive statistics were calculated for all variables under study. Statistical differences between different groups of patients were assessed using the Student's t-tests and Mann-Whitney-U test. Statistical significance was set at < 0.05. All statistical analyses were conducted using the Statistical Software Package GraphPad Software® (Version 9.0.0).

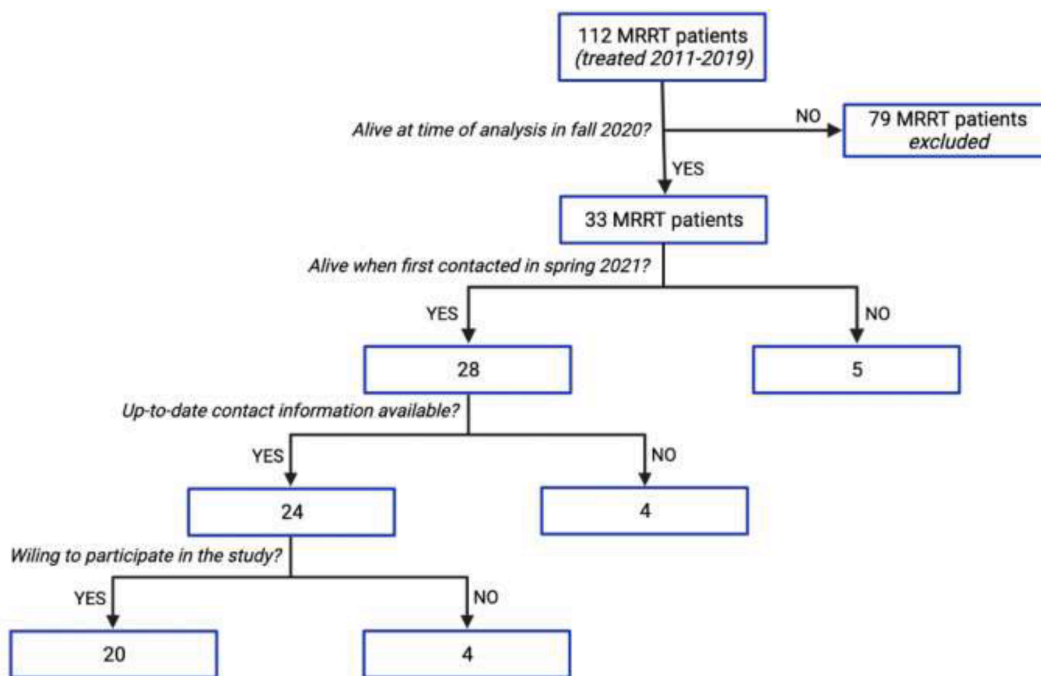
3. Results

3.1. Patient and treatment characteristics

A total of 112 patients were treated with a minimum of five RT courses at the Department of Radiation Oncology at USZ between 2011 and 2019. The total number of RT courses of these patients was 660. By the beginning of this study, 33 MRRT patients were alive and were invited for participation in this study. Of these 33 MRRT patients, five (15.2%) patients had died by the time they were contacted in the spring of 2021. Finally, 20 patients (71.4%) of the initially contacted 28 (84.4%) agreed to participate in this study (see [Fig. 1](#) for a CONSORT diagram). Yet in this study, we included the general patient- and treatment characteristics of all 33 (100%) patients; while QoL, hematologic toxicity, PRES, and psychological distress data is available for 20 (60.6%) patients.

All 33 MRRT patients had at least one histologically confirmed cancer diagnosis. Thirteen patients were female (39.4%) and 20 patients were male (60.6%). The median age at first cancer diagnosis was 55 years (range: 32–75 years). Twenty-eight (84.8%) were alive at the time of data analysis. The most common primary tumor was lung cancer (n = 14, 42.4%) and the most recent median Eastern Cooperative Oncology Group Performance Status (ECOG-PS) before the last RT course was 1 (range, 0–2). Detailed general patient characteristics are presented in [Table 1](#).

In total, the 33 MRRT patients initially included in this study, received 210 RT courses (median: 6, range: 5–9) during their treatment. Fourteen patients were under active systemic therapy: eight patients (40%) were treated with immunotherapy, six patients (30%) with targeted therapy while no patient was treated with conventional chemotherapy at the time of blood analysis. The most common RT treatment sites were brain metastases (n = 78, 37.1%) and bone metastases (n = 59, 28.1%). The median number of fractions was six (range, 1–35) with a



Abbreviations: MRRT = Multiple repeat radiotherapy.

Fig. 1. Consort diagram.

Table 1
General patient characteristics.

Parameter	Data
Total number of MRRT patients	n = 33 patients
Age at diagnosis in years, median (range)	55 (32–75)
Male gender, n (%)	20 (60.6%)
Primary tumor histology, n (%)	
• Lung cancer (SCLC and NSCLC)	14 (42.4%)
• Breast cancer	3 (9.1%)
• Colorectal cancer	3 (9.1%)
• Sarcoma	3 (9.1%)
• Urinary tract cancer	3 (9.1%)
• Other ¹	7 (21.2%)
Alive at time of data analysis, n (%) ²	28 (84.8%)
ECOG-PS before last RT, median (range)	1 (0–2)

Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group Performance Status; SCLC = Small cell lung cancer; NSCLC = Non-small cell lung cancer.

¹ Includes malignant melanoma, head & neck, endocrine, primary brain entities as well as cancer of unknown origin.

² Between time of official study initiation and time of data collection/analysis, 5 patients had died before being included in this study.

median single dose of five (range, 2–20) Gray (Gy), totaling a median dose of 30 (range 6–70) Gy. The median interval between the first and last radiotherapy course was four (range, 1–12) years, specific details regarding treatment characteristics are shown in Table 2.

3.2. Subjective assessment of the quality-of-life

Global health status was not significantly different compared to the general cancer population (mean: 55.8 vs. 61.3, p = ns.). Furthermore, there were no statistically significant differences between MRRT patients and the EORTC QLQ-C30 cancer patient cohort in physical functioning (mean: 72.3 vs 76.7, p = ns.), emotional functioning (mean: 64.2 vs 71.4, p = ns.), and cognitive functioning (mean: 70.8 vs 82.6, p = ns.). Additionally, no significant differences were observed regarding pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, nausea,

Table 2
General treatment characteristics.

Parameter	Data
Total number of RT courses of the 33 MRRT patients	n = 210
Number of RT courses per patient, median (range)	6 (5–9)
Treatment intent, n (%)	
• Curative	46 (21.9%)
• Palliative	164 (78.1%)
Treatment site, n (%)	
• Brain	78 (37.1%)
• Bone	59 (28.1%)
• Lung	37 (17.6%)
• Primary	11 (5.2%)
• Other ¹	26 (11.9%)
Single dose in Gy, median (range)	5 (2–20)
Fractions, median (range)	6 (1–35)
Total dose in Gy, median (range)	30 (6–70)
Total RT volume in cm ³ , median (range) ²	389.6 (19.6–3565.0)
RT volume per course in cm ³ , median (range) ²	20.7 (0.1–1614.3)
Time in years between first and last RT course, median (range)	4 (1–12)
Patients under systemic therapy four weeks before blood analysis ²	14 (70%)
• Immunotherapy	8 (40%)
• Targeted therapy	6 (30%)
• Chemotherapy	0 (0%)

Abbreviations: RT = Radiation therapy.

¹ Includes soft tissue and mediastinal metastasis. ²All 20 participating patients (n = 20).

vomiting, and financial difficulties. The only significant differences observed were increased fatigue (51.1 vs 34.6, p = 0.006), impaired role functioning (56.7 vs 70.5, p = 0.05) and social functioning (57.5 vs 75, p = 0.05). A detailed summary of the EORTC QLQ-30 results is shown in Table 3.

Table 3
QoL results reported by MRRT patients using EORTC QLQ-30 questionnaire.

Parameter		Mean (Study population)	(SD)	Mean (EORTC)	(SD)
Global health status/QoL	QL	55.8	(24.6)	61.3	(24.2)
Physical functioning	PF	72.3	(20.3)	76.7	(23.2)
Role functioning	RF	56.7*	(29.8)	70.5	(32.8)
Emotional functioning	EF	64.2	(28.0)	71.4	(24.2)
Cognitive functioning	CF	70.8	(28.5)	82.6	(21.9)
Social functioning	SF	57.5*	(35.3)	75.0	(29.1)
Fatigue	FA	51.1**	(25.3)	34.6	(27.8)
Nausea and vomiting	NV	10.8	(15.6)	9.1	(19.0)
Pain	PA	21.7	(24.2)	27.0	(29.9)
Dyspnea	DY	36.7	(35.7)	21.0	(28.4)
Insomnia	SL	36.7	(32.3)	28.9	(31.9)
Appetite loss	AP	21.7	(27.1)	21.1	(31.3)
Constipation	CO	21.7	(31.1)	17.5	(28.4)
Diarrhea	DI	8.3	(23.9)	9.0	(20.3)
Financial difficulties	FI	26.7	(25.2)	16.3	(28.1)

All twenty participating patients filled out the EORTC QLQ-30 questionnaire assessing QoL. MRRT patients reported significant deterioration of fatigue, social- and role functioning compared to EORTC QLQ-30 cancer patient cohort, *p = 0.05, **p = 0.006, unpaired Student’s t-test.

3.3. Subjective assessment of PRES and psychological distress

All participating patients (n = 20, 100 %) agreed strongly or agreed to have experienced a subjective benefit from RT in general. Furthermore, 17 (85%) patients reported that their subjective benefit of radiotherapy was maintained or increased during the multiple courses of radiotherapy. A majority of 17 (85%) described no increased side effects with increasing numbers of RTs.

The majority of patients did not report prolonged bleeding times upon superficial tissue injuries (13 patients, 65%) or increased frequency of infections, such as airways- and wound infections (16 patients, 80%). Neuro-cognitive preservation after MRRT showed a mixed picture; 10 patients (50%) agreed strongly or agreed to have experienced a subjective decline of cognitive functions and memory, while 10 patients (50%) did not observe a decline of cognitive functions after MRRT. Eleven patients (55%) reported increased dyspnea, while 9

patients (45%) were free from dyspnea. Thirteen patients (65%) reported decreasing fear of treatment with increasing numbers of RTs, seven patients (35%) reported stable levels of fear of treatment during and after MRRT.

In agreement with the results from the EORTC QLQ-30 questionnaire, ten patients (50%) reported to have experienced more persistent fatigue with increasing numbers of RT courses. Importantly, 9 patients (45%) reported increased psychological distress after and during MRRT, while 11 patients (55%) denied increased psychological distress. For a summary of PRES and psychological distress see Fig. 2.

3.4. Objective assessment of hematologic toxicities and organ-specific blood markers

A blood sample within 30 days of analysis was obtained from all 20 (100%) participating patients. The blood results were compared to normal values of healthy subjects. No differences were detected in blood electrolytes. Renal function was not significantly different in the MRRT population, with preservation of creatinine levels (80.1 µmol/l, normal range: 54 – 129 µmol/l). Liver function parameters showed no significant differences. CRP blood levels and myocardial parameters were not increased in MRRT patients. Blood glucose levels and HBA1c showed likewise no differences, as well as thyroid hormone levels.

MRRT patients showed significantly decreased levels of hemoglobin (mean: 127.7 g/l, range: 73–174 g/l vs. mean: 152 g/l, range: 134–170 g/l, p=<0.03, ≥CTCAE Grade 2 in 20%) and lymphocyte levels (mean: 1.3 G/l, range: 0.55–2.74 G/l vs. mean: 2.75 G/l, range: 1.5–4.0 G/l, p=<0.001, ≥CTCAE Grade 2 in 20%), while leukocyte- and erythrocyte levels showed no significant differences in MRRT patients compared to healthy population. Other hematologic parameters showed no significant difference. An overview of hematologic and organ function toxicities analyzed in a recent blood sample are shown in Table 4, an extensive overview of all measured blood parameters is shown in Table 5.

4. Discussion

This is to our best knowledge the first study to analyze QoL and toxicity in the increasing population of chronic cancer patients treated with multiple courses of radiotherapy. MRRT patients report an overall good tolerance of MRRT. Furthermore, patient-reported experiences and subjective patient-reported benefit from RT, in general, were positive as well. Despite stable QoL and an absence of chronic cumulative side

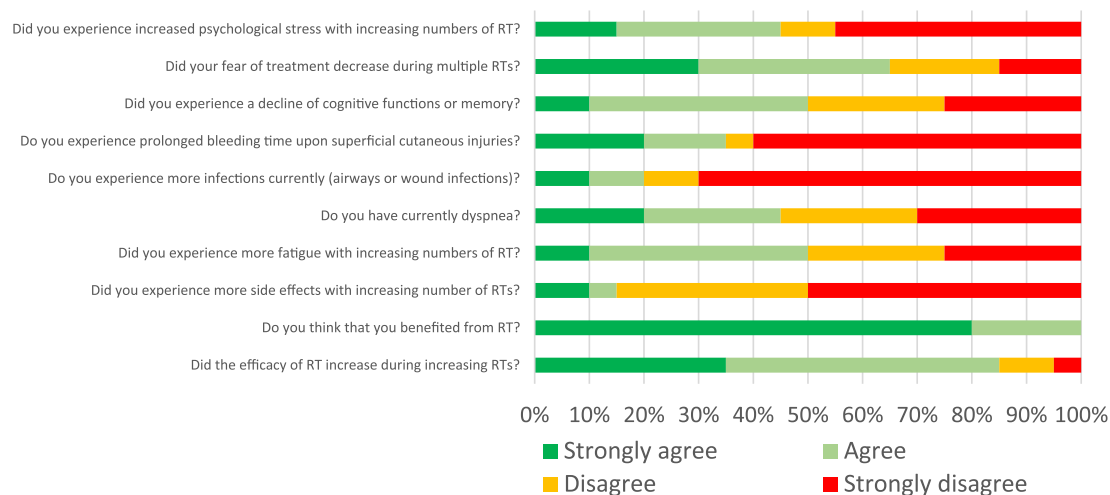


Fig. 2. Patient-reported PRES and psychological distress. A total of 10 questions were answered in the self-made questionnaire assessing PRES and psychological distress by participating patients using a four-point Likert scale (n = 10).

Table 4
Overview of hematologic and organ toxicity according to CTCAE Version 5.

Toxicity	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
Kidney function				
Creatinine increased	1	0	0	0
Liver function				
GGT increased	0	1	1	0
ALP increased	2	0	0	0
Myocardial parameters				
Troponin-T increased	1	0	0	0
NT-proBNP increased	4	0	0	0
Hematology				
Hemoglobin decreased	6	3	1	0
Platelet count decreased	1	0	0	0
Lymphocyte count decreased	9	4	0	0

General overview of toxicities according to CTCAE Version 5, blood parameters with absent toxicities are not shown in this table.

effects after MRRT, MRRT patients reported significantly increased fatigue and social- and role function deterioration. Additionally, hematologic toxicities were observed in form of significantly reduced hemoglobin- and lymphocyte blood levels without increased frequency of infections.

Previous studies have demonstrated that RT has heterogeneous effects on QoL, PRES, psychological distress, and hematologic toxicity. [9–10] *Yucel et al.* [21] analyzed QoL of 167 patients with different cancer diagnoses and stages treated with RT, indicating that RT may have negative acute effects on cancer patients' QoL. Restoration of QoL tended to be rapid one month after RT. Existing studies have also shown that following RT patients report high levels of anxiety, despite good treatment tolerance. [22] Yet, *Cehng et al.* [23] have reported that in elderly patients with solid tumors, adjuvant chemotherapy and RT may not have detrimental effects on QoL. Furthermore, *Mustian et al.* [5] demonstrated that fatigue is one of the most prevalent and severe side effects of cancer treatment reported by cancer patients during and after their treatment. *Spalek et al.* [16] demonstrated that concurrent chemotherapy in addition to RT and increased irradiated areas of bone marrow lead to hematologic toxicities. Information on QoL and hematologic toxicity of patients having undergone multiple RTs remains limited, few studies have studied the effects of multiple RTs – primarily focused on HNC, breast cancer, and glioma. [24–26].

In this study, patients showed no significant reduction of general QoL compared to the EORTC QLQ-C30 general cancer population. Nevertheless, it needs to be considered that this study might lack the necessary power to detect subtle differences due to its small sample size. Furthermore, this cross-sectional study lacks longitudinal data, and cannot answer questions about the causality of the observations. Symptoms often associated with RT, such as pain, dyspnea, insomnia, appetite loss, diarrhea, nausea, and vomiting showed no deterioration after MRRT. Cognitive functioning in EORTC QLQ-C30 remained stable after MRRT. Despite good tolerance of MRRT, patients participating in this study reported significantly increased fatigue, thereby leading to decreased role and social functioning. These results confirm previous studies, which described fatigue as one of the most frequent and QoL-limiting side effects of cancer treatment. Exercise and psychological interventions can be effective to reduce fatigue during and after cancer treatment. [5].

All participating patients in this study reported having experienced a subjective benefit from RT during their cancer treatment history. Moreover, patients in this study described that the efficacy of radiotherapy was maintained or even increased with increasing numbers of

Table 5
Blood results from a recent blood sample.

Electrolytes	Mean (range)	Blood glucose levels	Mean (range)
Na ⁺ 136–145 mmol/l	137.9 (132–144)	Glucose <11.1 mmol/l	6.6 (4.9–14.6)
K ⁺ 3.4–4.5 mmol/l	4.0 (3–4.9)	HbA1C (NGSP) 4.4–5.7 %	5.6 (4.4–7.2)
Calcium (total) 2.2–2.55 mmol/l	2.3 (1.93–2.56)	Thyroid hormone levels THS 0.3–3.18 mU/l	
Magnesium 0.66–0.99 mmol/l	0.8 (0.53–0.96)	2.3 (0.08–6.27)	
Phosphate 0.87–1.45 mmol/l	1.0 (0.47–1.87)	Hematology Hemoglobin 134–170 g/l	
Kidney function		127.7 (73–174)*	
Urea 2.86–8.21 mmol/l	5.5 (3.2–14.3)	Hematocrit 0.4–0.5 l/l	0.4 (0.24–0.49)
Creatinine 62–106 μmol/l	80.1 (54–129)	Erythrocytes 4.2–5.7 G/l	4.2 (2.58–5.45)
GFR (CDK-EPI 2009) 90–120 ml/min	83.4 (47–104)	MCV 80–100 fl	92.6 (82.5–100.6)
Liver function		MCH 26–34 pg	30.9 (26.7–34.2)
AST (GOT) <50 U/l	29.8.0 (13–46)	MCHC 310–360 g/l	333.6 (311–360)
ALT (GPT) <50 U/l	24.5 (8–61)	Thrombocytes 143–400 G/l	220.2 (70–368)
GGT <60 U/l	76.0 (12–741)	Leukocytes 3.0–9.6 G/l	6.0 (2.92–7.97)
ALP 43.5–105 U/l	100.7 (42–224)	Neutrophils 1.4–8.0 G/l (40–74 %)	3.8 (1.98–6.05) 64.5 (51.7–78.2)
Protein 60–80 g/l	68.2 (40–77)	Immature Granulocytes 0.0–0.3 G/l (0–0.5 %)	0.05 (0–0.26) 0.8 (0–4.6)
Albumine 40–49 g/l	41.3 (18–48)	Lymphocytes 1.5–4 G/l (19–48 %)	1.3 (0.55–2.74)** 22.6 (11–38.9)
Inflammation marker		Quick >70 %	105.8 (63–120)
CRP < 5 mg/l	2.8 (0.6–7.6)	INR <1.2	1.0 (0.9–1.2)
Myocardial parameters		aPTT 24–36 s	25.1 (21–34)
CK, total < 190 U/l	118.4 (47–272)	Fibrinogen 1.5–4 g/l	3.9 (2.9–5.9)
Troponin-T < 14 ng/l	12.4 (5–48)		
NT-proBNP <121 ng/l	207.0 (28–1283)		

Blood results showing organ function and hematologic toxicities. *p = 0.03, **p = 0.001, Mann-Whitney-U-Test, n = 20.

Abbreviations: Estimated Glomerular Filtration Rate (eGFR), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRP), brain natriuretic peptide (BNP), creatine kinase (CK), glycated hemoglobin (HbA1c), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and international normalized ratio (INR).

RT. Since these statements may reflect a biased and subjective patient experience, these results can't be equated with objective clinical treatment efficacy but rather patient experience and perception. Furthermore, MRRT patients showed good preservation of health condition, denying increased frequencies of infections, such as airways and superficial skin infections. Yet despite good tolerance of MRRT, roughly 50% of patients treated with MRRT describe persistent psychological distress, fatigue, and decline of cognitive functions in long-term follow-up. As demonstrated by *Mohile et al.* [27], geriatric assessment intervention for older patients with advanced cancer may be effective to reduce serious side effects from cancer treatment.

Blood analysis obtained from participating patients indicate good tolerance of MRRT. However, MRRT patients showed significantly reduced levels of hemoglobin and reduced lymphocytes levels, indicating a long-term hematologic side effect after MRRT and various other systemic therapies. Yet, this study does not indicate a causal effect between the aforementioned hematologic toxicities and RT, since 14 patients (70%) were receiving a systemic therapy 4 weeks prior the blood analysis. Interestingly, several studies reported that high thoracic RT dose increases the risk for radiation-induced lymphopenia (RIL) in lung cancer, HNC and breast cancer patients. [28–30] Furthermore, RIL was a strong prognostic factor for poor survival. [31] Despite reduced lymphocyte levels, MRRT patients did not describe increased frequency of infections, indicating acceptable preservation of the immune system.

The retrospective nature and limited patient number from a single treatment center are some of the main shortcomings of this study. Furthermore, the restriction of our study to patients who have experienced long-term survivorship after receiving a minimum of five RT courses, might bias the study results, since the majority of patients treated with multiple RT receive less than five RTs during their cancer treatment history. Despite a questionnaire response rate of around 60%, the participating patients, which have experienced long-term survival, might have contributed to an upward-bias response. Patients, who were not alive at the time of analysis or declined to participate in this study, might have experienced worse QoL and increased side effects during their treatment history. Their absence in this study contributes to an incomplete picture of QoL, PRES, psychologic distress, and hematologic toxicity in MRRT patients.

Additional systemic therapies and surgeries may also affect QoL and treatment side effects, thereby complicating the search for causal relationships between RT and treatment side effects. Furthermore, cancer progression itself can also compete with radiation in QoL deterioration. In this study, 14 patients (70%) received a systemic therapy four weeks before blood analysis. This factor can in large part contribute to the observed reduction of hemoglobin and lymphocyte levels and increased fatigue. Therefore, one needs to be cautious to draw definitive conclusions and casualties between direct disease progression-associated, RT-associated or systemic therapy-related side effects.

Nevertheless, the main strength of this study is being the first systematic analysis of QoL, PRES, psychologic distress, and hematologic toxicity in MRRT patients. So far, no study in the literature has systematically focused on this understudied and growing patient population. Moreover, the application of a validated and widely used questionnaire for assessment of QoL and recent blood analysis contribute to a holistic picture of QoL and hematologic toxicity in MRRT patients.

Conclusion

Long-term cancer patients receiving multiple courses of RT are a growing patient population. Yet, this highly vulnerable patient population remains largely uninvestigated in the literature. We observed increased levels of fatigue and reduced social functioning in MRRT patients. Patient-reported experiences and satisfaction about their multiple courses of RT were positive, especially concerning efficacy and tolerability of MRRT. Yet, roughly 50% of the patients reported psychological

distress. Furthermore, MRRT patients showed reduced levels of hemoglobin and lymphocytes in hematologic analysis, which could also be caused by systemic therapy. MRRT patients might therefore benefit from additional supportive measures, such as exercise, psychological intervention, regular blood analysis, regular QoL assessment, and geriatric assessment for older patients. Further research is of required to better understand the needs of this growing patient population and to more accurately adapt their inter-disciplinary and multi-modal treatments.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2022.03.006>.

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