

Dissertation

**The impact of radiotherapy on cellular senescence
and chronic inflammation**

submitted by
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under the Supervision of
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Statutory Declaration

"I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used.

Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".

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Disclosures

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Doctoral student Lek. Katarzyna Paal was enrolled in the Doctoral School of General and Clinical Pathophysiology, later Doctoral School of Neuroscience.

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1 Abbreviations

ADL	Activities of Daily Living
ADT	Androgen deprivation therapy
ALL	Acute lymphoblastic leukaemia
ANOVA	Analysis of variance
AS	Active surveillance
BMD	Bone mineral density
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
EORTC	European Organisation for Research and Treatment of Cancer
GA	Geriatric Assessment
GDS	Geriatric Depression Scale
Gy	Gray
IADL	Instrumental Activities of Daily Living
kb	Kilobase
kDa	Kilodalton
IL	Interleukin
LTL	Leucocyte telomere length
MMSE	Mini-Mental State Examination
MNA	Mini Nutritional Assessment
mtDNA	Mitochondrial DNA
NLR	Neutrophil to lymphocyte ratio

PCa	Prostate Cancer
PCR	Polymerase chain reaction
PLR	Platelet to lymphocyte ratio
PSA	Prostate specific antigen
RLE	Relative life expectancy
RNA	Ribonucleic acid
RPE	Radical prostatectomy
RT	Radiation therapy
RTL	Relative telomere length
RTL-qPCR	Quantitative PCR based relative telomere length
RTOG	Radiation Therapy Oncology Group
SIOG	International Society of Geriatric Oncology
SOS	Social status and support Survey
TERC	Telomerase RNA Component
TERT	Telomerase reverse transcriptase
TGF	Transforming growth factor
TNF	Tumour necrosis factor
TUG	Timed Up&Go
VMAT	Volumetric Modulated Arc Therapy

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4 Abstract in German

Hintergrund: Alterung ist ein Prozess, der zu einem allmählichen Funktionsverlust auf Zell-, Gewebe- und Organebene führt. Altersbedingte Prozesse können durch vielfältige extrinsische und intrinsische Faktoren beschleunigt werden. Krebsgerichtete Therapien, einschließlich Strahlentherapie, können zur Aktivierung chronischer Entzündungsprozesse führen, was zu einer Verringerung der physiologischen Reserve und damit zu einem vorzeitigen Auftreten altersbedingter Symptome führt. Die Beurteilung der Manifestationen des Alterungsprozesses kann durch die Messung von Biomarkern des Alterns im Blut, die Beurteilung des Gesundheitszustands mit den Instrumenten des umfassenden geriatrischen Assessment sowie durch die Untersuchung zellulärer Seneszenz mit Hilfe der Messung von Telomerlängen erfolgen. Da es sich bei einem erheblichen Anteil der Krebspatienten um ältere Menschen handelt, erlangt die Untersuchung des Einflusses der Krebstherapie auf das Altern und die Beschleunigung von altersassoziierten Veränderungen in der Wissenschaft immer mehr Aufmerksamkeit.

Methoden: In unsere prospektive Beobachtungsstudie wurden 314 Patienten, die an der Universitätsklinik für Strahlentherapie-Radioonkologie an der Medizinischen Universität Graz mit kurativer definitiver Strahlentherapie (RT) bei Prostatakrebs behandelt wurden, eingeschlossen und einer umfassenden Gesundheitszustandserfassung mit den Instrumenten der geriatrischen Assessments (GA) sowie der Bestimmung der Entzündungsparametern im Blut und der Bestimmung der Telomerlänge vor Behandlungsbeginn und in zwei Nachuntersuchungen 3 und 15 Monate nach Abschluss der Bestrahlung unterzogen. Am Ende der Bestrahlungsserie erfolgte eine zusätzliche Blutentnahme zur Bestimmung der altersassoziierten Biomarker. Die Veränderungen klinischer, biochemischer und molekularer Komponenten des Alterns wurden mit nichtparametrischen Tests ausgewertet. Darüber hinaus wurden Korrelationen zwischen den prätherapeutischen GA - Ergebnissen und Biomarkern untersucht.

Ergebnisse: Während des Beobachtungszeitraums konnte eine signifikante Verschlechterung der sozialen Situation ($p < 0.001$), des Stimmungszustandes ($p < 0.001$), des Ernährungszustandes ($p < 0.001$) und der Fähigkeiten in den instrumentellen Aktivitäten des täglichen Lebens ($p = 0.005$) beobachtet werden. Die Fähigkeit, die grundlegenden Aktivitäten des täglichen Lebens auszuführen, und der Komorbiditätsstatus änderten sich vom Ausgangswert bis zur zweiten Nachuntersuchung nicht signifikant ($p > 0,05$). Überraschenderweise konnte zwischen der Ausgangssituation und einer der Kontrollen eine Verbesserung der kognitiven Funktion ($p = 0.004$) und der Mobilität der Patienten beobachtet werden ($p = 0.032$). Die Ergebnisse biochemischer Alterungsmarker zeigten einen signifikanten Anstieg von Fibrinogen ($p < 0.001$), Neutrophilen-Lymphozyten-Ratio ($p < 0.001$) und Thrombozyten-Lymphozyten-Ratio ($p < 0.001$) zwischen dem Ausgangswert und mindestens einer der durchgeführten Kontrollen. Die Ergebnisse der Albumin- und Cholesterinwerte deuten auf eine Verringerung der Stoffwechselreserve während des RT-Verlaufs ($p < 0.001$) mit einer signifikanten Erholungsfähigkeit nach abgeschlossener Strahlentherapie ($p < 0.001$) hin.

Die Analyse der Telomerlängen ergab eine signifikante Verminderung der relativen Telomerenlänge 15 Monate nach Abschluss der Strahlentherapie im Vergleich zur Ausgangssituation ($p=0.048$) und Ende der Strahlentherapiesserie ($p=0.040$).

Darüber hinaus konnten signifikante Zusammenhänge zwischen den klinischen, biochemischen und molekularen Parametern des Alterns festgestellt werden.

Schlussfolgerungen: Die in unserer Studienkohorte beobachteten Veränderungen deuten auf einen negativen Einfluss der kurativen Strahlentherapie auf die Mehrzahl der von uns gemessenen Gesundheitskomponenten hin. Die anhaltende Erhöhung der Entzündungsparameter und die erniedrigten Albumin- und Cholesterinspiegel in der längeren Beobachtung lassen darauf schließen, dass bereits eine Kleinfeld-RT einen chronischen Entzündungsprozess aktivieren kann. Die gemessene relative Telomerlänge impliziert, dass Strahlentherapie Alterungsvorgänge auf zellulärer Ebene beeinflusst.

Darüber hinaus könnten Korrelationen, welche zwischen den klinischen und biochemischen altersbezogenen Parametern identifiziert wurden, in der klinischen Praxis zur Erkennung biologisch älterer Patienten und zur Entscheidungsfindung in der Krebstherapie genutzt werden.

5 Abstract in English

Background: Ageing is a process leading to a gradual loss of function on cell, tissue and organ level. Age-related processes can be accelerated by a wide range of extrinsic and intrinsic stimuli. Cancer-directed therapies, including radiation therapy, can lead to the activation of chronic inflammatory processes, leading to the shrinkage of physiologic reserve, and therefore to the premature onset of age-related signs and symptoms. The assessment of the manifestations of ageing process can be conducted by the measurement of biomarkers of ageing in the blood, evaluations of the health status with the tools of comprehensive geriatric assessment as well as with the estimation of cellular senescence by the means of measurement of the telomere erosion on the chromosomes. Since the considerable percentage of cancer patients are elderly individuals, the investigation of the influence of cancer therapy on the ageing process gains more and more attention in science.

Methods: A total of 314 patients treated with definitive radiation therapy (RT) for prostate cancer at the Department of Therapeutic Radiology and Oncology, Medical University of Graz were enrolled into our observational prospective study and underwent a comprehensive health status evaluation with the tools of geriatric assessment (GA) as well as the assessment of inflammatory parameters and measurement of leucocyte telomere length prior to the start of treatment and at two follow-ups 3 and 15 months after the completion of radiation. Blood sampling and measurement of biomarkers of ageing was also conducted at the end of RT course. The alterations of clinical, biochemical and molecular domains of ageing were evaluated with non-parametric tests. Additionally, correlations between pretherapeutic GA results and ageing-related biomarkers were analysed.

Results: During the observation time, a significant decline was observed in patients' social situation ($p < 0.001$), mood state ($p < 0.001$), nutritional status ($p < 0.001$), and in instrumental activities of daily living ($p = 0.005$). The ability to perform the basic activities of daily living and comorbidity burden did not change from the baseline to the second follow-up ($p > 0.05$). Furthermore, we could observe an improvement in cognitive function ($p = 0.004$) and patients' mobility ($p = 0.032$) between the pretherapeutic status and one of the reassessments. The results of biochemical markers of ageing showed a significant increase of fibrinogen ($p < 0.001$), neutrophil to lymphocyte ratio ($p < 0.001$), and platelet to lymphocyte ratio ($p < 0.001$) between the baseline and at least one of the follow-up examinations. The results of the albumin and cholesterol levels in blood indicate a lowering of the metabolic reserve during the RT course ($p < 0.001$) with a significant ability to recover after completed radiation therapy ($p < 0.001$). Telomere length analysis showed a significant reduction in the relative telomere length 15 months after completion of radiotherapy compared to baseline ($p = 0.048$) and the end of the radiotherapy series ($p = 0.040$)

Furthermore, several correlations between the clinical GA results and biochemical and molecular parameters of ageing could be detected.

Conclusions: The alterations observed in our study cohort suggest a negative influence of curative radiation therapy on the majority of health components measured in our assessments. The prolonged elevation of the inflammatory parameters and the decrease of albumin and cholesterol levels during the longer observation period suggest that even small field RT can activate the chronic inflammatory process. The changes in relative telomere length imply that

radiotherapy influences aging processes at the cellular level. In addition, the correlations detected between clinical and biochemical age-related parameters could be utilized in clinical practice for the identification of biologically older patients and for decision-making in cancer therapy.

6 Introduction

6.1 Ageing - definition

The term “ageing” describes a gradual and inevitable decline of the functions of tissues and organs. According to the World Health Organization “ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease and ultimately death.”

In the literature, the age of 65 years is commonly used as a cut-off to designate an “elderly patient”. Since ageing is a multidimensional process complex, there is a need of classification of its major components which are described in detail in this chapter.

6.2 Clinical changes

6.2.1 Physical changes – sarcopenia, osteoporosis and decline in mobility.

Alterations in visual appearance represent the most conspicuous aspect of development, maturation, and ageing. Over the lifespan, the visible changes encompass the color and structure of the hair, skin elasticity, hydration status, and structure as well as general body shape alterations that strongly correlate with the mass and structure of the connective tissue in the body, which includes the muscle, bone, and fat mass.

Both bone and muscle mass increases continuously in childhood, accelerates rapidly in the adolescence, reaches a peak between 20 and 30 year of life and remains stable over the (1,2). The growth of bone and muscle mass is strongly dependent on nutrition and is also influenced by anabolic hormones and physical activity (3). From the age of 20-25 years, body fat starts to increase gradually until approximately 65 years which is a result of a decrease in basal (resting) metabolic rate (4).

A reduction in muscle mass of approximately 20-40% typically occurs by the age of 70, leading to the condition known as sarcopenia (4). The loss of muscle tissue can be caused by multiple factors, including malnutrition, physical inactivity, hormonal changes, inflammation, increased catabolism, and anabolic resistance.

Bone mineral density (BMD), used as a proxy for the assessment of fracture risk, declines with age starting at about the age of 50 years. The increase in the bone turnover rate, driven by the increased bone resorption has been proposed to lead to the bone loss observed in the elderly (5).

Osteopenia and its advanced stadium called osteoporosis, are in turn a result of continuous loss of the bone mass, reached in the early adulthood. The decrease in bone tissue is triggered by malnutrition, inflammation, intake of certain medication such as NSAIDs antirheumatics,

psychotropic drugs, antacids, statins, vitamin K, antagonists, sex steroids, bisphosphonates, and anti-cancer treatment(6) as well as physiological hormonal alterations occurring in advanced age(7).

As the loss of bone and muscle tissue shares a common spectrum of underlying causes, both conditions frequently co-occur and are described as osteosarcopenia (2). However, it is important to distinguish between sarcopenia and dynapenia, which is the decline in muscle strength and does not necessarily occur in direct proportion to muscle mass loss (4).

Besides mass and structure, the function of the musculoskeletal system also changes over the lifespan. Joint overload and stiffness, shortening, and rigidity of tendons are indicators of the degenerative ageing process in the elderly (8). Decreased mobility in older individuals includes reduced muscle strength, a decrease in walking speed and stride length, as well as impaired balance and gait leading to an increased risk of falling. In previous studies, improved mobility in people 50-69 years was associated with a higher quality of life (9), in contrast, reduced mobility correlated with increased all-cause mortality in elderly persons (10).

6.2.2 Neurological changes, neurocognition and mood changes

Various structural and functional alterations in the central and peripheral nervous system have been described as a part of physiological ageing. The decrease in grey matter already begins in early adulthood ((11)). The most prominent loss of grey matter can be observed in the prefrontal cortex, smaller changes have been shown in the area of the hippocampus (12).

Interestingly, the age-related decrease of grey matter volume is not only caused by the loss of neuron cells, but also by a decrease in size of neurons and number of synapses (13,14). Morphologic changes encompass a lower complexity of dendrite arborization, and decreased dendrite length and neuritic spines that can contribute to the decrease in the number of synapses (15). In a model by Terry and Katzman, by the age of 130 years a cognitively normal adult would have a synaptic density equivalent to an individual diagnosed with Alzheimer Disease (13).

Furthermore, accumulation of beta-amyloid in grey matter can be found in 20-30% of healthy adults (16,17). Some authors suggest that cognitive normal patients with an accumulation of beta-amyloid in the brain are at higher risk of developing Alzheimer's disease (16,18).

In contrast to grey matter, the extent of white matter loss is significantly greater (19). A prior study demonstrated a reduction in white matter volume of 16-20% in the precentral gyrus, gyrus rectus, and corpus callosum among autopsy specimens from individuals aged over 70 years whereas the loss of grey matter in these areas was shown to be less than 6%. (12). Furthermore, Rogalski et al described changes in parahippocampal white matter indicating restricted interaction with hippocampal structures, which may provide an explanation for memory decline in elderly individuals (20).

Due to the progressive alterations in the nervous system, a neurocognitive decline is commonly observed in elderly people. In observational studies, dementia is estimated to have a prevalence of 6.4%, with Alzheimer's Disease being the primary cause, accounting for 54% of cases (21). There is a growing body of evidence suggesting that traumatic brain injury, mid-life obesity, mid-life hypertension, smoking, diabetes, depression, and sleep disturbances

represent risk factors for dementia and cognitive decline in age (22,23). In addition, worsening of the general physical condition, that may lead to the reduction of social contacts also negatively influences cognition. In a 10-years longitudinal study, a higher degree of loneliness correlated with poorer cognitive function and was associated with a more pronounced decline in memory and verbal fluency over the duration of observance (24). In contrast, modifiable factors such as the number of years of formal education, physical activity, Mediterranean diet, cognitive training, moderate amount of alcohol, and social engagement could have a protective influence against dementia (23).

Psychiatric problems are also not uncommon in the elderly. About one fifth of elderly patients suffer from a psychiatric disorder with the leading diagnoses of depression with an estimated prevalence of 5-10% and anxiety disorder with a prevalence of 6-12% in individuals over 65 years (25). Additionally, a row of studies performed on non-psychiatric in-patients revealed that undiagnosed psychiatric comorbidities were present in 17-62% of hospitalized individuals (26).

Depression in elderly can lead to a considerable decrease of functionality, deterioration of physical condition and worse recovery from disabilities caused by somatic diseases (27).

6.2.3 Ability to perform daily activities.

Independence in performing the basic and more advanced activities of daily living (ADLs) is one of the most important issues in elderly (28). Basic physical activities encompass eating, personal hygiene, dressing, toileting, the ability to move from one position to another and to walk independently (29). Reduced physical, psychical, and cognitive status can pose an obstacle in covering those fundamental needs. More advanced, instrumental activities of daily living (IADLs) include tasks requiring organisational skills. This group of tasks consists of the organisation of transportation, management of finances, preparation of meals, household maintenance as well as the ability to go shopping, to use phone, and to take medications correctly (29).

A lot of age-related changes such as musculoskeletal and neurological decline, cardiovascular diseases, cognitive impairment, social isolation, and side effects of medications can lead to a decreased ability to perform basic ADL (30,31). Worsening of ADLs can also be a result of acute illness and hospitalisation (32). Furthermore, frailty, depression, and reduced participation in social groups has previously been correlated with reduced independence in the instrumental ADLs (33).

Mamikonian-Zarpas and Laganá demonstrated that lower scores in the items of ADL and IADL tools correlated with a higher risk of falls in frail, but also in not frail and not dizzy patients (34). Beltz et al. showed that basic ADLs measured with the Katz-Index as well as IADLs significantly associated with the self-assessed quality of life in patients over 70 years (35).

6.2.4 Socioeconomic situation of elderly

Throughout lifetime, the individual's socioeconomic situation, i.e. work experience, occupation, access to resources, social position, and household income undergoes substantial changes. One of the most important issues in the elderly is age-related poverty (36). Retirement, the

loss of a partner, declining health, and rising healthcare expenses all contribute to a decrease in financial security. Growing old introduces a substantial, added risk of experiencing poverty or remaining in a state of poverty (37). In the US, 12.9% of people aged 80 and older, 9.5% among individuals aged 75-79, 9.7% among those aged 70-74, and 9.6% among aged 65-69 live in poverty(36). In the elderly population, the poverty rate is also higher among people living alone compared to married individuals or people living with a spouse(36). Financial planning over the adult life, employment and education, governmental support, and social support from family and friends are postulated as factors with a major influence on elderly poverty (38,39).

The socioeconomic situation significantly impacts quality of life and strongly correlates with an individual's health. Furthermore, a higher socioeconomic status measured as education, income, or as occupational prestige correlated with decreased mortality in individuals > 65 years (40).

In addition, age-related loneliness is a noteworthy issue, with 9% of the European population reporting feelings of loneliness (41). Subjective loneliness is significantly influenced by factors such as chronic illness, mental health conditions, reduced IADLs (Instrumental Activities of Daily Living), living environment, and social connections (42). Social isolation has a negative impact on physical health, nutrition, sleep, physical activity, and cognition(43) and also correlates with the occurrence of depression, decreased quality of life, and increased all-cause mortality (43–45).

Social and economical factors also influence psychological resources such as optimistic self-beliefs, self-efficacy, and perceived autonomy, which have a positive impact on the health condition of geriatric patients (46,47).

6.3 Comprehensive geriatric assessment

Since chronological age offers limited knowledge about the patient's health status, assessing the various aspects of health appears essential in guiding diagnostic and treatment decisions.

The comprehensive geriatric assessment is group of diagnostic tools which enable a profound examination of the functional capacity of elderly patients. The GA assesses multiple domains of illness and health, including functional status, comorbidity, nutritional status, cognition, social support, polypharmacy, and psychological state (e.g., depression, anxiety, and distress) (48).

Geriatric assessment (GA) tools can help to identify previously unrecognized conditions that can affect relative life expectancy (RLE) and treatment tolerance and efficacy (49,50). Alterations in health status, as assessed through geriatric evaluation tools, as well as interventions guided by geriatric assessment demonstrated a correlation with therapy adherence, outcome, and quality of life in geriatric patients undergoing cancer therapy (49–51).

Results of the GA have also been found to be predictive of chemotherapy toxicity and survival in geriatric oncology samples (50,52,53).

Thus, the International Society of Geriatric Oncology (SIOG) has recommended that the decision-making process for treating older cancer patients should be based on a systematic evaluation of health status using a geriatric assessment (54).

The main health domains assessed through geriatric evaluation tools are categorized into the following areas:

- Physical status, frailty, and mobility: assessment of malnutrition, self-reported exhaustion, low energy expenditure, slow gait speed, weak grip strength.
- Neurocognitive status and mood: assessment of cognitive decline and alterations in the mood status with focus on detection of depression.
- Socioeconomical situation: evaluation of household, financial resources, as well as the support and obligations from and toward next family and friends. It also focuses on the activity and self-care demonstrated by the ability to continue or undertake hobbies and take part in the social events.
- Functional health: assessment of the (in)dependency in performing the basic and instrumental activities of daily living.
- Co-morbidity status: description of comorbidity burden, either in a quantitative or quantitative-weighted manner.
- Polypharmacy: assessment of the status of currently taken medications.

6.4 Cellular and molecular changes in the ageing process

Ageing cells undergo a multitude of morphological and functional changes influenced by both internal and external factors. The observable morphological shifts in ageing cells encompass changes in both cell size and shape, and reflect a decline in the functionality of cellular subunits (55,56).

As a result of the ageing process, increased granularity, large but dysfunctional mitochondria, the appearance of chromatin fragments in the cytoplasm as well as senescence-associated heterochromatin and DNA damage foci can be observed (57–59). Moreover, the cellular membrane undergoes deformation as a consequence of cytoskeleton degradation, resulting in the dysregulation of cell signalling pathways(57,60,61).

Impairments in mitochondrial morphology and function have also been associated with ageing process (62). Mechanisms responsible for mitochondrial dysfunction include mtDNA mutations, mitochondrial turnover, and signaling through mTOR (62). Beyond disturbed chemical energy production, mitochondrial deterioration can result in the leak of ROS and mitochondria-specific enzymes into the cytosol, which may generate further damage and lead the cell to apoptosis (63).

The nucleus is the central component of the eucaryotic cell. The eukaryotic nuclear pore complex (NPC) plays a crucial role in facilitating signal exchange between the nucleus and cytoplasm (64). Degradation of nucleoporins results in reduced integrity of the nuclear membrane, which impairs the transport of proteins and genetic messages that has been linked with cellular senescence and decreased responsiveness to cellular stress (65).

Furthermore, altered organisation of the lamins in the nuclear envelope has a strong impact on genome organisation (66). Lamin damage can result in higher sensitivity to reactive oxygen species leading to increased oxidative damage(67). Changes in nuclear lamins have been noted in aged and compromised stem cells, in addition, laminopathies are observed in individuals with Hutchinson–Gilford progeria who exhibit phenotypic hallmarks of ageing at a young age (68).

Autophagy is a cellular process responsible for the degradation of non-functional cellular components, and the inhibition of autophagy leads to the manifestation of ageing-related hallmarks in cells (69). The autophagic clearance of damaged proteins, protein aggregates, organelles, and lipids may be essential for providing the raw materials necessary to maintain cellular physiological function (69). Disturbances in autophagy have been noted in patients with Parkinson’s disease, where the autophagy is downregulated, while in patients with Chaperone -Mediated Autophagy this process, autophagy is dysregulated (70,71). Conversely, in patients with Alzheimer’s disease, this process is upregulated (72). The diverse implications of variously altered autophagy underscore the complexity of its role in age-related conditions.

6.4.1 Cellular senescence

The ability to undergo division represents a fundamental indicator of a healthy, functional cell, however, this process is limited over time. In a study on fibroblasts, Hayflic et al. observed that after 40-60 cycles of mitosis, the cell population ceased further growth(73). This finding has altered our understanding of the capacity of cells and tissue for recovery and renewal.

Apoptosis and senescence are two types of cellular response to damages, whereas apoptosis is a programmed suicide of a cell in response to exogenous stimuli or intrinsic signals to maintain homeostasis of the organism. In contrast, senescence represents a stress-induced, durable cell-cycle arrest of previously replication-competent cells. Cellular senescence occurs throughout life and can be triggered by a variety of cell-intrinsic and extrinsic stimuli. It plays beneficial roles in a variety of physiological and pathological processes. However, the accumulation of senescent cells with age also carries adverse consequences and contributes to ageing related- conditions and morbidity.

Although there are no senescence-specific biomarkers, mean telomere length is one of the few indicators proposed to reliably identify senescent cells.

6.4.2 Mean telomere length

Telomeres are protein-bound DNA repeat structures (5'-CCCCAA-3' and 3'-TTGGGG-5' hexanucleotide sequences) at the end of chromosomes which are protecting chromosomes from damage i.e. degradation, rearrangements, end-to end fusions, and chromosome loss during each cell division and, thus, play a critical role in maintaining chromosomal stability (74,75). During somatic-cell replication, telomere length progressively shortens because of the inability of DNA polymerase to fully replicate the 3' end of the DNA strand(76). Once a critically short telomere length is reached, the cell is triggered to enter replicative senescence, which subsequently leads to cell death (77).

Mean telomere length exhibits considerable inter-individual variability and has high heritability with estimates varying between 44% and 80% (78). In cross-sectional population studies, mean telomere length is inversely associated with age declining by between 20–40 base pairs per year (79). Because telomere length decreases with increasing age, average telomere length has been proposed to serve as “biological” clock (80). Besides ageing, many different endogenous and environmental factors, such as oxidative stress, an unhealthy lifestyle and genotoxic stress, can modify telomere length (81).

There is growing evidence that indicates a significant correlation between telomere length and cellular senescence (81). Short telomeres have also been associated with stem cell exhaustion that represents a major mechanism of ageing (82).

In previous studies, telomere length has directly been associated with lifespan. Short telomeres have been correlated with decreased length of life, on contrary, organisms with long telomeres showed longevity(83). In a meta-analysis by Boonekamp et al., a correlation between short telomeres and mortality risk has been demonstrated (84).

Shorter age-adjusted and sex-adjusted mean telomere length has also been found to be associated with risk of several age-related diseases, including coronary artery disease, diabetes mellitus, hypertension, Alzheimer’s disease status, and cancer, (85,86). Telomere length has also been linked with functional status, cognitive function or mortality (87,88), in addition, a correlation between telomere length and radiosensitivity has been detected (89).

Most of the previously performed studies have measured mean telomere length in blood leukocytes. Within an individual, mean leucocyte telomere length (LTL) and telomere length in other tissues are highly correlated, making the use of telomere length obtained from peripheral blood leukocytes a potential biomarker of ageing (90,91).

Among young adult survivors of childhood ALL, shorter LTL has been detected when compared with age-matched controls, the strongest difference has been detected among those who had undergone cranial radiotherapy (92). Similar results have been obtained in long-term survivors of neuroblastoma suggesting premature senescence in leukocytes of the survivors (93).

6.4.3 Modulation of telomere length

In germ cells and other stem cells that require renewal, telomere length is maintained by the enzyme telomerase, a ribonucleoprotein that contains the RNA template TERC and a reverse transcriptase TERT (94). Telomerase represents a key mediator of senescence. Alterations in telomerase activity affecting telomere length have been shown to enhance or reverse senescence and ageing-associated phenotypes (95). For example, telomerase-deficient humans demonstrate an excess incidence of some age-related phenotypes such as pulmonary fibrosis, emphysema, greying, bone marrow hypoplasia, and cirrhosis suggesting that the premature activation of senescence in such individuals causes various aspects of ageing (96).

6.4.4 Chronic inflammation

With increasing age, there is a growing occurrence of senescent cells. Although these cells no longer perform the typical functions of their original tissue and system, they can release various

inflammatory cytokines causing an imbalanced secretion of proinflammatory mediators, cytokines, and chemokines, leading to a chronic inflammatory process. This capability is proposed as the primary contributor to inflammaging in the context of both ageing and age-related conditions like atherosclerosis, cancer, and diabetes. The diminished functioning of cytokines also leads to the occurrence of senescence in immune system cells, a phenomenon referred to as immunosenescence.

A role for inflammation in the process of ageing and age-related disease has clearly been established in epidemiological studies of non-oncological older adults.

Several reports have described an increase in pro-inflammatory cytokines (mainly interleukin (IL)- 1, IL- 6, transforming growth factor (TGF)- β , and tumour necrosis factor (TNF)- α), chemokines, and C-reactive protein (CRP), with increasing age even in healthy elderly persons without apparent presence of acute inflammation (97–100). Pro-thrombotic factors have also been noted to be increased with chronic inflammation, likely because of a co-stimulatory effect between the two processes (101). Additionally, low serum cholesterol and albumin have been suggested to indicate subclinical levels of chronic inflammation and/or dysregulation of the inflammatory processes that can contribute to an “ageing” phenotype (102).

Recent studies have demonstrated that a composite panel of inflammatory markers—designed to measure overall “Inflammatory” burden—may provide a valuable information about an elderly patient’s overall health status. In an analysis of women age 65 years and older on the Women’s Health and Aging Study, higher baseline IL-6 levels were associated with significantly higher levels of functional decline compared with women with lower IL-6 levels (103) (104). Another study including 110 patients older than age 75 years evaluated a combination of inflammatory markers including CRP and low albumin and their relationship to several different clinical measures of frailty and showed that the degree of clinical frailty independently correlated with increased inflammatory marker levels and lower albumin levels (102).

Elevated inflammatory markers have also been associated with mortality risk in the elderly (105,106). In a cohort of high-functioning elderly patients, elevated levels of CRP (≥ 3.19 pg/mL) were found to be an independent risk factor associated with a nearly 2-fold increased risk of death (104). In another study, patients with hypoalbuminemia (< 35 g/L) were found to be at higher risk of all-cause mortality. Even in the group of patients with normal albumin levels (35-50 g/L), investigators found a graded increase in all-cause mortality from patients with highest normal to those with lowest normal values (107).

Chronic inflammatory markers may have the ability to predict both decline in function and mortality (108–111) and have been suggested to have a strong predictive ability among patients without baseline functional impairments and may also identify patients with functional impairments that may not otherwise have been identified without extensive geriatric assessment testing.

In general, pro-inflammatory mediators increase with age, even among healthy individuals and are proposed to accelerate the ageing process and exacerbate multiple age-related diseases.

6.5 The impact of cancer treatment on the ageing process

Chemotherapy and radiation therapy are highly effective cancer treatment options. Both modalities rely on direct and indirect interactions with cellular DNA that may induce degradation of DNA strands, disrupt DNA synthesis and repair processes and lead to a significant reduction in cell division potential. As a result, the diminished ability for cell division contributes to a decline in the number of stem and progenitor cells, promoting cellular senescence and triggering chronic inflammation.

6.5.1 Cancer treatment and the acceleration of ageing

Large epidemiologic studies have reported the premature onset of age-related conditions in childhood cancer survivors, decades earlier than in their peers independent of organ-specific, treatment-related toxicities. Adults treated for childhood cancer are at an increased risk of chronic health conditions, frequent hospitalization and early mortality (112–114). Elevated rates of other outcomes typically associated with ageing, such as minimal cognitive dysfunction, reduced muscle strength, and poor exercise tolerance, are also reported to appear decades earlier than expected (112,115–118). Frailty is evident in about 8% of childhood cancer survivors a decade after treatment (112). Among individuals aged 70 and older, the prevalence of frailty rises to 60%, contrasting with a 10% frailty rate in the general population aged over 65 (119). In addition, Armenian et al. found that individuals aged 20 years who have been treated for cancer in childhood are at the same risk of developing chronic diseases as their siblings at the age of 50 years (120). Furthermore, 95% of childhood cancer survivors have at least one health problem at the age of 45 years (121,122).

Observational studies have also shown that survivors of adult-onset cancers have a higher burden of mobility limitations, comorbid conditions, and pain, as well as a greater risk of functional and cognitive impairments compared to healthy, age-matched controls (123–128). For instance, Alfano and colleagues found evidence for an accelerated ageing phenotype in breast cancer survivors characterized by the accumulation of excess comorbidities within a follow-up time of 18 months (129).

Although a phenotype of accelerated ageing after exposure to chemotherapeutic agents and ionizing radiation has been described, the mechanisms that drive accelerated ageing in cancer survivors are not understood.

Evidence from preclinical models shows that radiation and cytotoxic anticancer therapies cause physiological changes consistent with several molecular and cellular hallmarks of ageing (130). Asymptomatic cancer survivors have been found to demonstrate a biologic profile of chronic inflammation and telomere attrition, consistent with an early onset of cellular processes that drive accelerated ageing (131,132).

6.5.2 Prostate cancer radiotherapy

Prostate cancer (PCa) is the second most frequent cancer diagnosis in men and the fifth leading cause of death worldwide. In Austria, PCa is the most diagnosed cancer type in men (133,134). In 2018, 6018 patients were newly diagnosed with PCa and 1215 patients died from PCa(135). PCa is predominantly a disease of senior adults with a median age at diagnosis of 66 years (136). With the ageing of the population and the increasing life expectancy, especially in developed countries, the burden due to prostate cancer is expected to increase substantially in the future.

Radiation therapy represents a well-established, highly efficient, non-operative treatment modality for patients with prostate cancer who are unsuitable for radical prostatectomy because of very advanced age, comorbidities, or reduced performance status. Thus, the number of patients, especially patients aged ≥ 70 years, referred for radiotherapy has increased significantly during the last years.

The choice of the treatment for PCa depends on the initial PSA level, tumour grading and staging different as well as the age and health status of the patient. However, management of PCa is often challenging because disease progression can occur slowly in many patients, even without treatment (137). However, amongst all types of localized disease, a high-risk group of PCa exists, defined by stage T2c or PSA level >20 ng/mL or Gleason score ≥ 8 , which has the most potential to develop biochemical progression, local recurrence, or even metastatic disease.

Life-expectancy is a major determinant of the potential for benefit from curative therapy. In PCa, predicted life expectancy has been directly incorporated into treatment guidelines (138,139). However, life expectancy varies substantially between individuals within a given age group. For example, 75-year-old men are expected to live for a further 8.3 years (median), but $\approx 25\%$ (the upper quartile) will live for at least 14.2 years, whereas another 25% (the lower quartile) will live for 4.9 years (140). Life-expectancy estimates represent a useful tool for public healthcare but are not valid for a given individual.

Because chronologic age alone is a poor descriptor of the heterogeneity in the ageing process, the geriatric assessment has been proposed as a tool for separating patients likely to benefit from standard cancer treatment and those who are at high risk of complications and/or are too vulnerable to receive aggressive therapy. Commonly used geriatric assessment (GA) tools can help to identify previously unrecognized conditions that can affect relative life expectancy (RLE) and PCa treatment tolerance and efficacy (49,141,142). Previous studies have shown that older patients with PCa undergoing various treatments have significant impairments on GA tests of function, cognition, and physical performance (143,144).

Thus, systematic evaluations of functional status, cognitive status, comorbidities, self-assessed health status, mobility, nutritional status, psychological status, and social circumstances may support therapeutic decisions in PCa (145). However, little is known about the impact of PCa therapies including radiotherapy on functional outcome and on the development or acceleration of age-related chronic conditions. Furthermore, the knowledge about the processes that underlie ageing-related consequences of cancer treatment is very limited.

7 Project hypothesis and objectives

7.1 Hypothesis

We hypothesized that prostate cancer radiotherapy accelerates ageing-related processes and contributes to the development or progression of age-related conditions as well as cellular senescence and systemic inflammation.

7.2 Objectives

The purpose of the present study was to analyse the influence of radiation therapy on the clinical, molecular and biochemical changes related to the ageing process.

Objective 1

The primary objective of the study is to determine if prostate cancer radiotherapy influences the development or acceleration of ageing-related clinical conditions measured by the tools of comprehensive geriatric assessment as well as to investigate the consequences of radiation treatment on cellular senescence and systemic inflammation.

Objective 2

To determine the relationship between ageing related biomarkers (i.e. telomere length and inflammatory markers) and age- related clinical conditions.

8 Materials and Methods

8.1 Study participants

The present prospective cohort study was performed including 314 prostate cancer patients. Patient recruitment was performed from 10/2019 to 12/2021 at the Department of Therapeutic Radiology and Oncology / Medical University of Graz / Austria.

Eligible patients were invited to take part by the local investigators prior to the start of radiotherapy and had to fulfil the following inclusion criteria:

- Diagnosis of localized prostate cancer
- Age \geq 65 years
- Candidate for definitive radiation treatment
- Written informed consent.
- Ability to give informed consent.

Written informed consent was obtained from all study participants prior to study inclusion. A total of 7 patients have withdrawn informed consent, 1 patient was excluded from the study because of very poor performance status.

At study inclusion, all study participants completed a routine clinical questionnaire including family history, medication, previous surgery, co-morbidities, and smoking habits. Furthermore, the following data about tumour and treatment characteristics such as prostate specific antigen (PSA) level at the time of diagnosis, pre-irradiation PSA level, tumour node metastasis (TNM) stage, Gleason score, and information on androgen deprivation treatment were obtained from all participants.

8.2 Information on radiation treatment

Image-guided radiotherapy with high energy photons was generally performed using volumetric intensity modulated arc therapy (VMAT) techniques to encompass the prostate and seminal vesicles. The total dose, prescribed to the International Commission on Radiation Units and Measurement point, ranged from 74-78 Gy delivered in 2 Gy per fraction dependent on risk situation. Hypofractionated radiotherapy with a total dose of 60 Gy (3 Gy per single fraction) was delivered in 13 patients. Treatment was performed daily, 5 days/week. Acute genitourinary and gastrointestinal toxicity was regularly assessed during the radiation therapy course and graded according to standard EORTC / RTOG criteria.

8.3 Follow-up investigations

Follow-up investigations were performed 3 and 15 months after completion of radiotherapy. A total of 268 patients underwent the first follow-up investigation, the second follow-up investigation was performed in 250 patients.

In Figure 8.1, the structure of the cohort during the study is demonstrated.

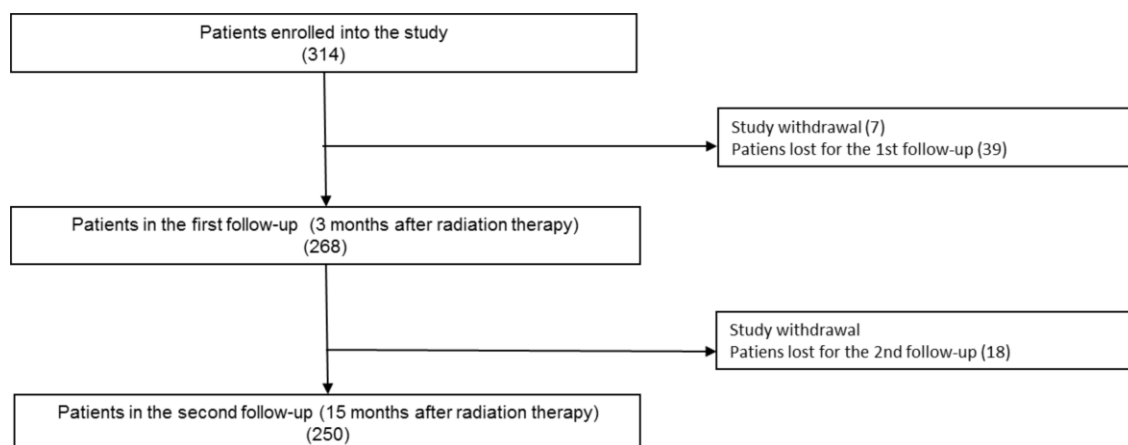


Figure 8.1 Study cohort

8.4 Study- related procedures

8.4.1 Clinical evaluations

Within 2 weeks before start of radiotherapy, 3 months and 15 months after completion of radiotherapy, patients underwent a comprehensive geriatric assessment for a systematic evaluation of functional and cognitive status, comorbidities, health status, mobility, nutritional status, psychological status, and social circumstances. The time to perform the GA in an individual was approximately 30 minutes.

The GA tools selected for the evaluation are summarized in Table 8.1.

Domain	Measure	Description
Functional status	Activities of Daily Living (ADL) (146)	GA tool designed to assess 10 activities related to the basic functions which includes bathing and showering, toileting and bladder/bowel management, dressing, eating (self-feeding), functional mobility and personal hygiene.
	Instrumental Activities of Daily Living (IADL) (147)	Assessment of 8 complex activities that allow an individual to live independently in a community. The assessed skills are using a telephone, taking medications, using the private

Domain	Measure	Description
		or public transport, maintaining a household, preparing meals, washing, and ability to handling finances.
	Timed Get-UP and Go-Test (TUG)(148)	A test measuring the patients' mobility and probability of falls in elderly. The test is performed with a use of chair, on which a patient is sitting. The patients is instructed to get up, walk a distance of 3 meters, turn back and return to the chair. The time of the whole procedure is measured. The patients with a need of using external device or tool are allowed to do so.
Nutritional status	Mini Nutritional Assessment (MNA) (149)	An 18-item screening tool used to identify older adults (> 65 years) at risk of malnutrition, encompassing the quality and quantity of the meals as well as the physical and psychical disorders, which could considerably influence the nutritional status.
Social status and support	Social status and support Survey (SOS)(150)	Measures the perceived availability of social support and level of social activity
Cognition	Mini-Mental State Examination (MMSE) (151)	A 30-point questionnaire that used for a screening of dementia and to measure the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over the time.
Mood	Mini-Geriatric Depression Scale (mini-GDS) (152)	A questionnaire designed for the assessment of depressive symptomatology in elderly people. The 15-question version excludes any questions relating to the physical symptoms of depression common in old age.
Co-morbidities	Charlson Comorbidity Index (CCI) (153)	A score of 19 selected, weighted conditions which was designed to predict the 1-year mortality of hospitalized patients. The assessment includes cardiovascular, pulmonal conditions, the disorders of soft tissue, diabetes and the malignancy. For the use of this study the diagnosis of prostate cancer was not included into the score.

Domain	Measure	Description
Polypharmacy	Number of medications	Assesses the number of currently prescribed medications

Table 8.1 Health domains measured with geriatric assessment tools. Paal, K., Stranz, B., Thurner, EM. et al. Comprehensive geriatric assessment predicts radiation-induced acute toxicity in prostate cancer patients. *Strahlenther Onkol* (2023). <https://doi.org/10.1007/s00066-023-02132-3>, Reproduced with permission from Springer Nature

8.4.2 Analysis of cellular senescence and chronic inflammation

At each study visit, blood samples for laboratory measurements were obtained. Laboratory parameters were assessed at baseline (within 2 weeks prior to initiation of radiation therapy), at the end of radiotherapy as well as 3 and 15 months after completion of radiotherapy.

In addition to routine procedures, blood tubes were collected and stored at the Biobank of the Medical University of Graz for further analyses (www.meduni-graz.at/biobank; certified according to EN/ISO 9001:2008).

Cellular senescence was assessed by the analysis of leucocyte telomere length. Chronic inflammation was evaluated using inflammatory markers previously associated with age-related conditions or mortality. The inflammatory parameters that have been assessed in the peripheral blood are displayed in Table 8.2.

Inflammatory marker	Reported association	Reference
Platelet / lymphocyte ratio	<ul style="list-style-type: none">• Mortality	(154,155)
Neutrophil / lymphocyte ratio	<ul style="list-style-type: none">• Mortality	(156)
C-reactive protein	<ul style="list-style-type: none">• Clinical frailty• Decline in function• Mortality	(102,157–160)
Fibrinogen	<ul style="list-style-type: none">• Age-related diseases• Mortality	(157)
Hypoalbuminaemia	<ul style="list-style-type: none">• Clinical frailty	(102,107)
Low total cholesterol	<ul style="list-style-type: none">• Clinical frailty	(102)

Table 8.2 Summary of inflammatory parameters

8.5 Laboratory analyses

8.5.1 Isolation of genomic DNA

DNA has been isolated using the Nucleospin Blood Genomic DNA Kit from Macherey&Nagel. The kit combines the advantages of silica binding with a microspin format, and eliminates the need for expensive resins, alcohol precipitation, and hazardous organic compounds such as phenol and chloroform. Isolation was done according to the protocol provided by the manufacturer.

The starting material was lysed in a chaotropic salt-containing solution to insure the thorough denaturation of macromolecules. The addition of ethanol causes the DNA to bind when the lysate is spun through a silica membrane in a microcentrifuge tube. A Prewash Solution is provided to help remove contaminants that are associated with aged (older than 24 hours) whole blood samples. After washing to remove contaminants, the DNA is eluted in 200 µl of a Tris-EDTA solution. The isolated expected yields of genomic DNA will typically be about 4-10 µg. DNA purified with this kit has an A260/A280 ratio between 1.6 and 1.9 and is ready for downstream applications such as PCR and sequencing reactions. Storage of isolated DNA will be at -20°C.

8.5.2 Analysis of telomere length

RTL-qPCR: This assay was developed by Cawthon (161) and quantifies the ratio of average telomere length to a single-gene copy (RPLP0, previously denoted as "36B4"), which allows the determination of a mean relative telomere length (RTL). All qPCR analyses were performed in triplicates in 96-well plates on a CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, Vienna Austria). Each run included a standard curve based on dilutions of available HeLa-DNA (New England Biolabs, Frankfurt, Germany) to determine the quantity of targeted templates in each sample relative to the HeLa-DNA. RTL was calculated as the ratio of telomere quantity to single copy gene quantity.

8.6 Statistical analysis

8.6.1 Endpoints

The primary endpoint of the study was the development / progression of age-related conditions.

8.6.2 Sample size and power analysis

Minimum sample size was calculated using the Statulator online statistical calculator [Dhand, N. K., & Khatkar, M. S. (2014). Statulator: An online statistical calculator. Sample Size Calculator for Comparing Two Paired Means. Accessed 19 November 2019 at <http://statulator.com/SampleSize/ss2PM.html>].

Effect size was calculated by dividing the mean of paired differences by the standard deviation of paired differences, and therefore was a scale indicating the number of standard deviations by which the means differ. Effect sizes of 0.8, 0.5 and 0.2 were considered as large, medium and small effect sizes.

Assumptions and statistical parameters:

Significance level (α): 0.05

Statistical power: 0.80

Effect size: 0.2

Minimum sample size: 199

To allow for an adequate reserve, a sample size of 250 patients was chosen for the present study.

8.6.3 Statistical tests

Comparison of groups was done using appropriate statistical tests (student's t-test, rank sum test, chi2 test, ANOVA). Alterations in the clinical conditions measured by the tools of CGA as well as changes in laboratory parameters were analyzed with the use two-way variance analysis for related samples and non-parametric tests for related samples. The criterion for statistical significance was $p < 0.05$. All analyses were carried out using SPSS (SPSS inc. 1989) and Stata (statcorp 1995).

8.7 Ethical considerations

The study complied with the Declaration of Helsinki and was performed according to the national law. The protocol has been approved by the local Ethical Committee (approval number: EK 31-437 ex 18/19). Data were stored electronically with strict data protection according to the Austrian Gene Technology Act, the Data Protection Regulation, and to the guidelines of the Ethical Committee of the Medical University Graz. Written informed consent was obtained from all participants.

9 Results

9.1 Baseline patient and treatment characteristics

The median age of diagnosis was 74 years, with a mean age of 73.5 ± 5.59 years. Among the participants, 28 patients (8.9%) had low-risk prostate cancer, 139 patients (44.3%) had intermediate risk, and 147 patients (46.8%) had high-risk prostate cancer. Neoadjuvant androgen deprivation therapy (ADT) was given to 294 patients (93.6%). A summary of patient and treatment characteristics can be found in Table 9.1.

Patients' characteristics	
Age	
<70	68(21.7%)
70-80	217(69.1%)
>80	29(9.2%)
Antikoagulation	
Yes	135 (43.0%)
No	178(56.7%)
Missing data	1(0.3%)
Arterial hypertension	
Yes	177 (56.4%)
No	136 (43.3%)
Missing data	1(0.3%)
Diabetes mellitus	
Yes	56 (17.8%)
No	257 (81.8%)
Missing data	1 (0.3%)
Smoking status	

Current	13 (4.1%)
Former or never	300 (95.5%)
Missing data	1 (0.3%)
Risk group	
High risk	147 (46.8%)
Intermediate risk	139 (44.3%)
Low risk	28 (8.9%)
Missing data	1 (0.3%)
Tumour stage	
T1-T2	255 (81.2%)
T3-T4	55 (17.5%)
Missing data	4 (1.4%)
Lymph node involvement	7 (2.2%)
Yes	306 (97.5%)
No	1 (0.3%)
Missing data	
Gleason Score	
≤ 6	49 (15.6%)
7	149 (47.5%)
8-10	116 (36.9%)
Initial PSA level	
<10	205(65.3%)
10-20	73(23.2%)
>20	32(10.2%)
Median (mean ± SD)	8.2 (13.5 ± 24.3)
Missing data	4(1.3%)

Neoadjuvant androgen deprivation	
	294 (93.6%)
Yes	18 (5.7%)
No	2 (0.6%)
Missing data	
PSA before the RT (ng/ml)	
	11 (3.5%)
<0,01	200 (63.7%)
0,01-1,00	101 (32.2%)
>1,00	0.45 (1.38 ± 2.96)
Median (mean ± SD)	2 (0.6%)
Missing data	
Radiation therapy	
Conventional fractionation	301 (95.9%)
Hypofractionation	13 (4.1%)
Total dose	
≤ 76 Gy	121 (38.5%)
>76 Gy	193 (61.5%)
Median (mean ± SD)	78 Gy (76.3 ± 4.1)

Table 9.1 Baseline patient and treatment characteristics. Paal, K., Stranz, B., Thurner, EM. et al. Comprehensive geriatric assessment predicts radiation-induced acute toxicity in prostate cancer patients. *Strahlenther Onkol* (2023). <https://doi.org/10.1007/s00066-023-02132-3>, Reproduced with permission from Springer Nature.

9.2 Results of comprehensive geriatric assessments

9.2.1 Polypharmacy

Polypharmacy was assessed in 314 patients before the initiation of radiation therapy course. The number of daily medications ranged from 0 to 19, with a mean intake of 3.73 ± 3.25 drugs (see Figure 9.1). Less than 10% of patients did not consume any medications on a daily basis, while the majority took 1-2 medicines per day. Extensive polypharmacy defined as the daily intake of at least 5 different substances was reported in 6.7 percent of patients.

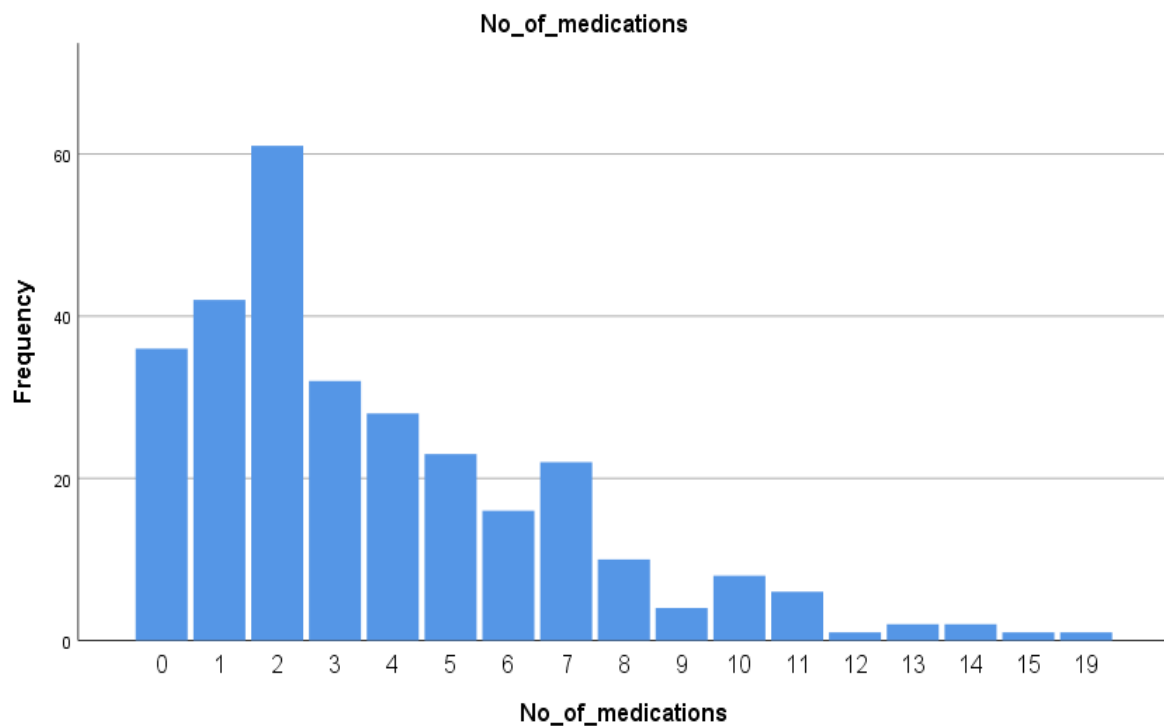


Figure 9.1 Distribution of medication intake survey in the study cohort

9.2.2 Mini-Mental State Examination

Mini-Mental State Examination (MMSE) was performed in 283 patients before start of RT, in 253 patients 3 months after completion of RT and in 231 patients 15 months after RT, respectively. The mean values of the Mini-Mental State Examination (MMSE) score were 28.4 ± 1.68 at baseline, 28.74 ± 1.29 at the first follow-up, and 28.74 ± 1.54 and at the second follow up, respectively. The results of the MMSE are shown in Figure 9.2.

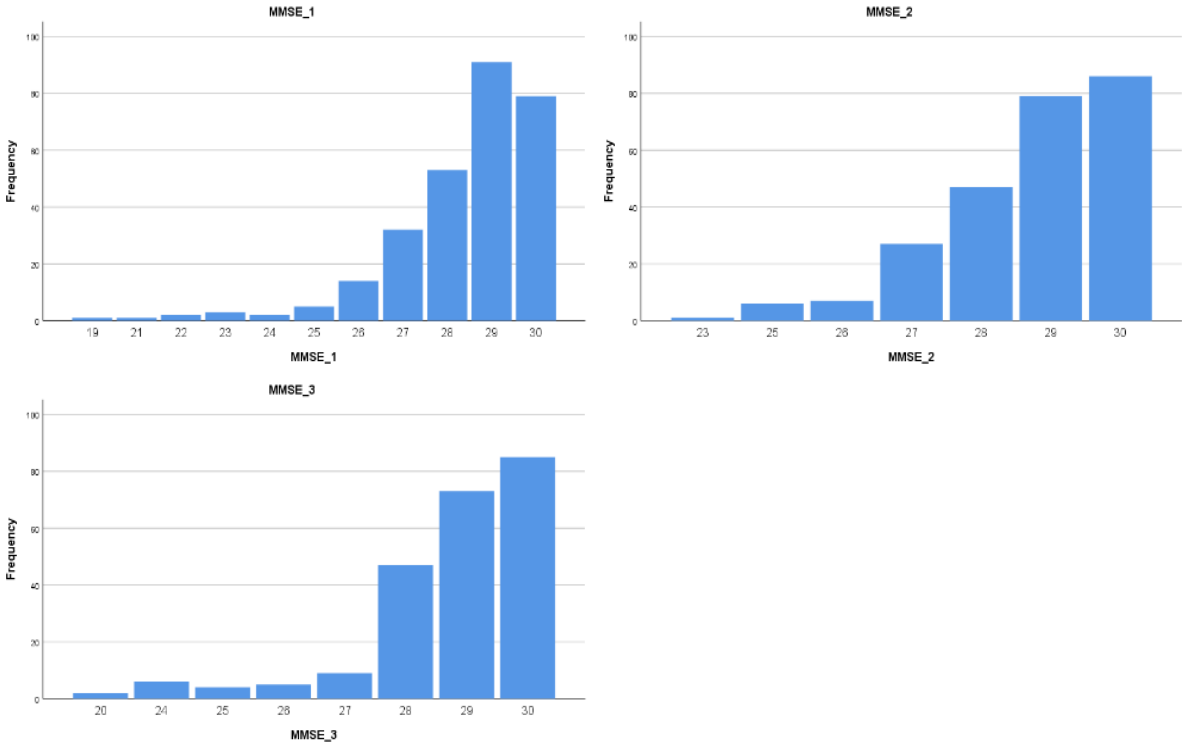


Figure 9.2 Results of the distribution of the Mini-Mental State Examination at the baseline (MMSE_1), at the first (MMSE_2), and at the second follow-up (MMSE_3)

9.2.3 Social status and support Survey

Social situation describing a current patients' situation regarding close interpersonal relationships, social activity, housing and financial situation was assessed with social status and support Survey (SOS). The assessments were performed in 281 patients at baseline (prior to RT), in 270 patients at the first follow-up (3 months after RT), and in 240 patients at the second follow-up (15 months after RT), respectively (Figure 9.3). The mean values of the SOS were 23.1 ± 1.65 , 22.47 ± 1.86 , and 22.26 ± 2.01 respectively. 2 (0.6%) patients had a score under 17 points. However, no intervention of social workers was actively undertaken by the study team due to observational character of the study.

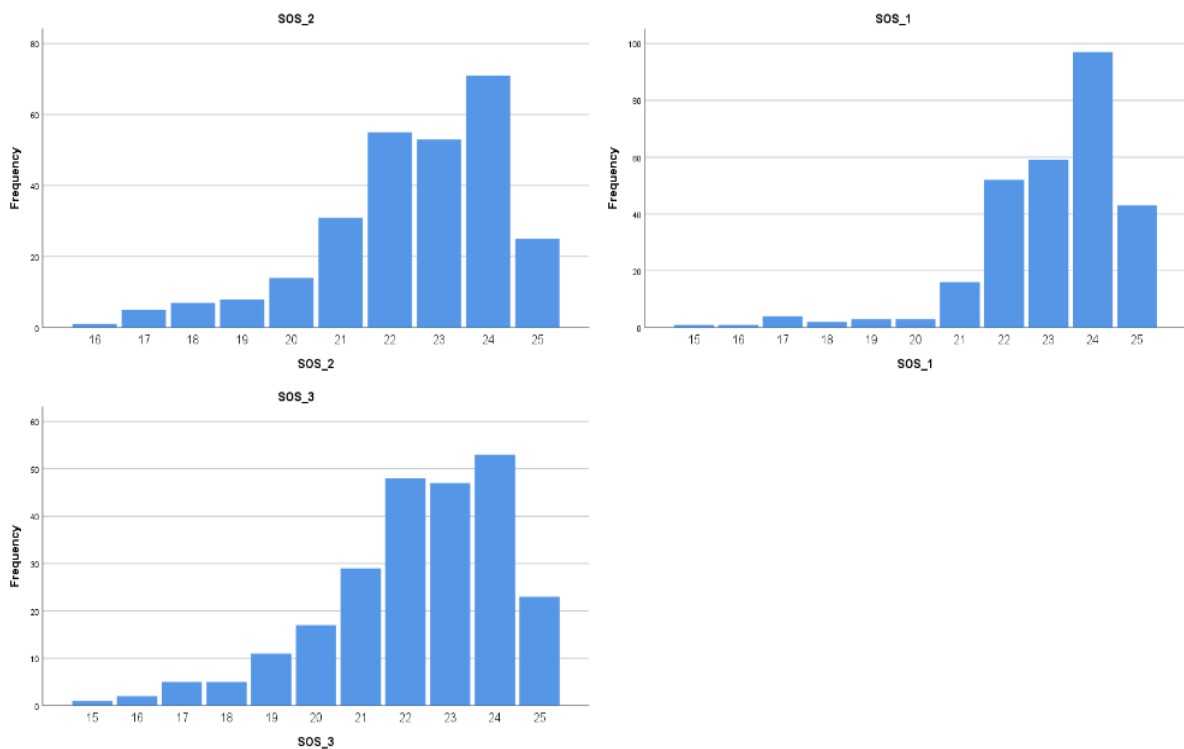


Figure 9.3 Results of the distribution of the SOS at the baseline (SOS_1), at the first (SOS_2), and at the second follow-up (SOS_3)

9.2.4 Activities of Daily Living

The assessment of basic activities of daily living (ADL) and instrumental activities of daily living (IADL) was performed in 282 patients at baseline, in 272 Patients at first follow-up, and in 241 patients at the second follow-up, respectively.

The patients displayed an excellent ability to perform the basic ADL at the baseline assessment (mean 99.4) as well as at both reassessments at first and second follow up (mean 99.44 and 99.62).

The mean values of the IADL at the three assessments were 7.75, 7.69 and 7.63 respectively, suggesting a high ability to perform the instrumental activities of daily living.

The results of the ADL and IADL are shown in Figure 9.4 and Figure 9.5.

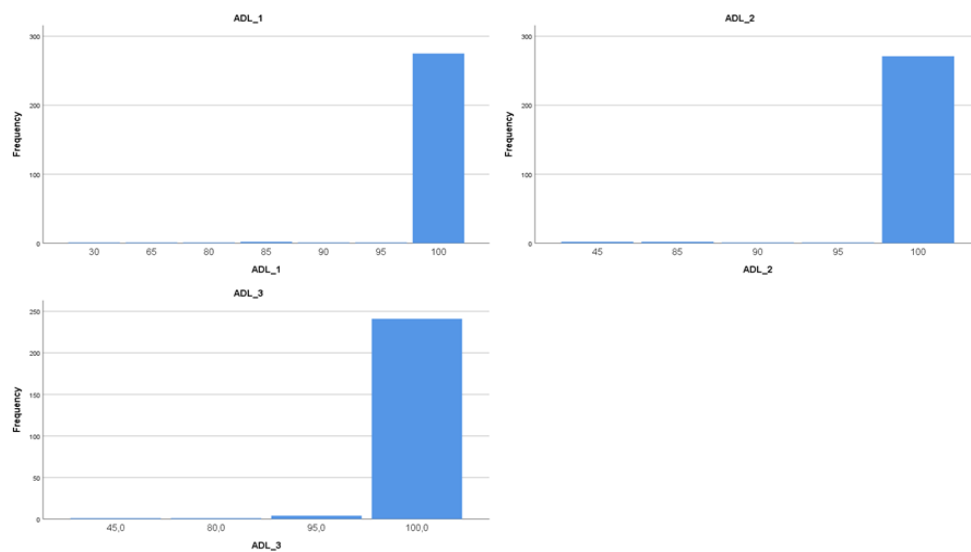


Figure 9.4 Results of the distribution of the ADL at the baseline (ADL_1), at the first (ADL_2), and at the second follow-up (ADL_3).

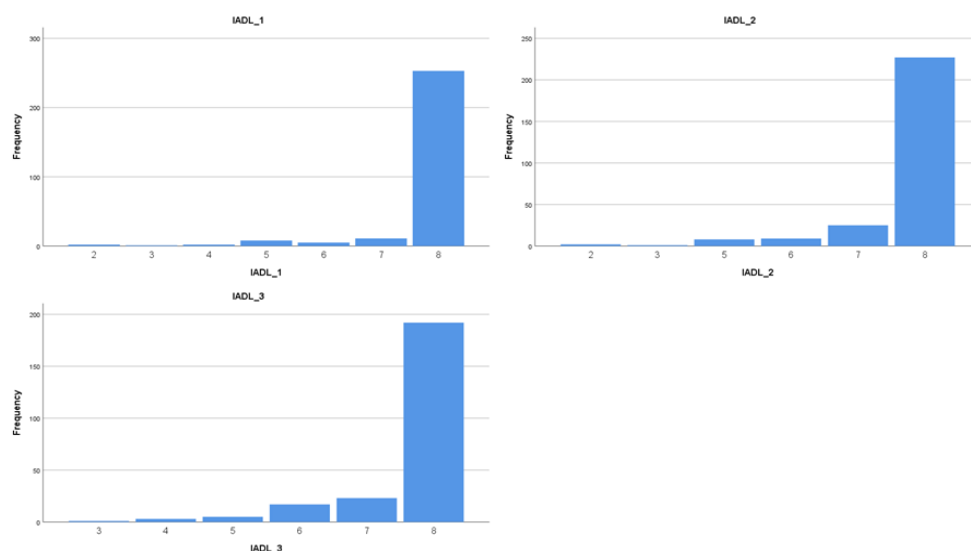


Figure 9.5 Results of the distribution of the IADL at the baseline (IADL_1), at the first (IADL_2), and at the second follow-up (IADL_3).

9.2.5 Geriatric Depression Scale

The assessment of depression using the geriatric depression scale (GDS) was performed in 265, 272, and 240 patients at baseline, 3 months and 15 months after RT, respectively (Figure 9.6). The mean values on the GDS at the three timepoints were 1.51 ± 2.08 , 1.76 ± 2.26 and 2.01 ± 2.25 , respectively. 23(7.3%) patients reached scores above 5 points, which is considered as a cut-off for further diagnostic procedures.

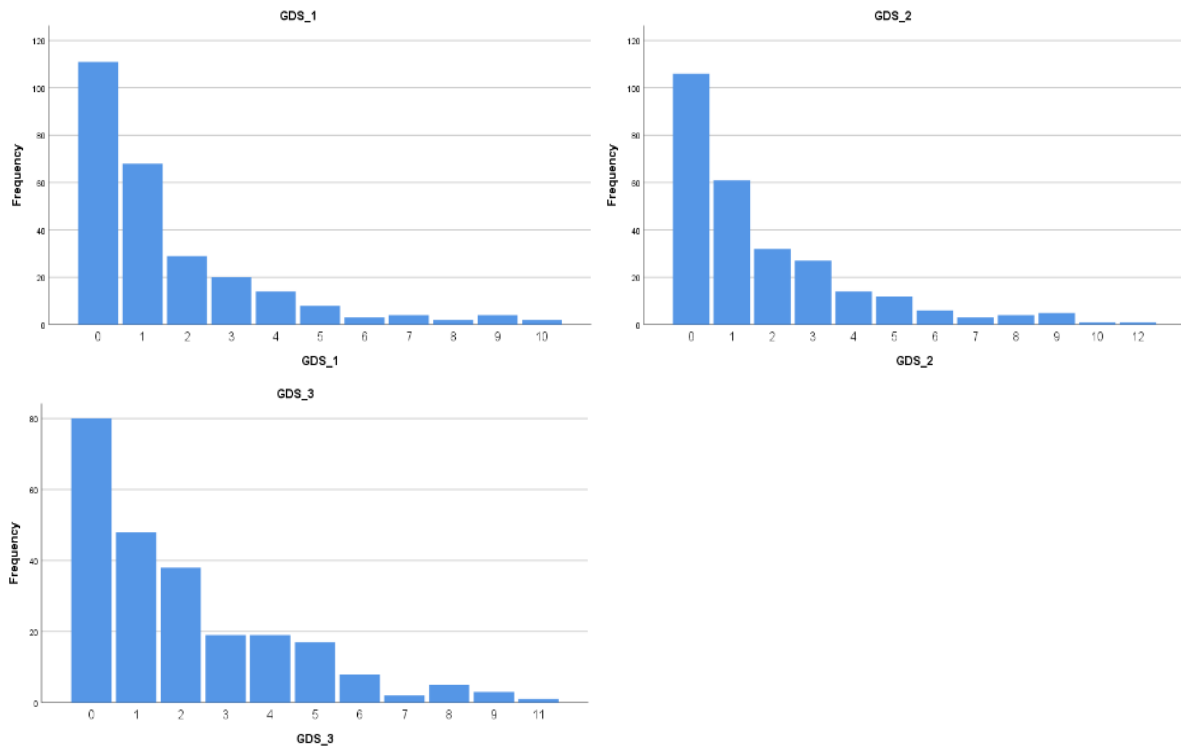


Figure 9.6 Results of the distribution of the GDS at the baseline (GDS_1), at the first (GDS_2) and at the second follow-up (GDS_3).

9.2.6 Time Up and Go Test

Mobility was measured with the use of the Time Up and Go test (TUG) that was applied in 275 patients at baseline, in 248 at the first follow-up, and in 230 patients at the second follow-up. The mean time needed for getting up, going 3 meters, turning round, coming back and sitting back on the study chair were 10.6 ± 2.68 , 10.4 ± 2.65 and 10.41 ± 2.44 seconds at baseline, at first follow-up and at second follow-up, respectively. The results of the TUG are displayed in Figure 9.7.

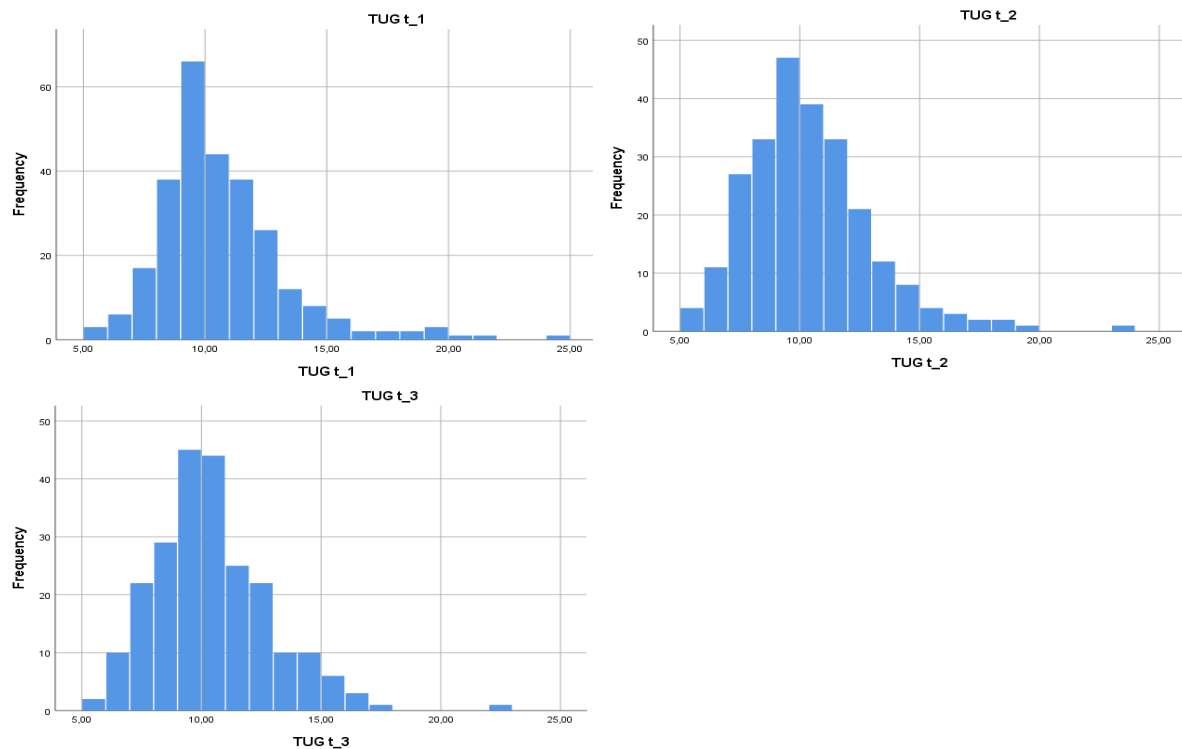


Figure 9.7 Results of the distribution of the TUG at the baseline (TUG_1), at the first (TUG_2), and at the second follow-up (TUG_3).

9.2.7 Mini Nutritional Assessment

The nutritional status was assessed in 275, 272 and 240 patients at baseline, at the first, and second follow-up investigation, respectively. The mean values of the mini nutritional assessment (MNA) were 27.64, 27.14 and 27.16 at baseline, at the first and the second follow-up, respectively. The results of the MNA are provided in Figure 9.8.

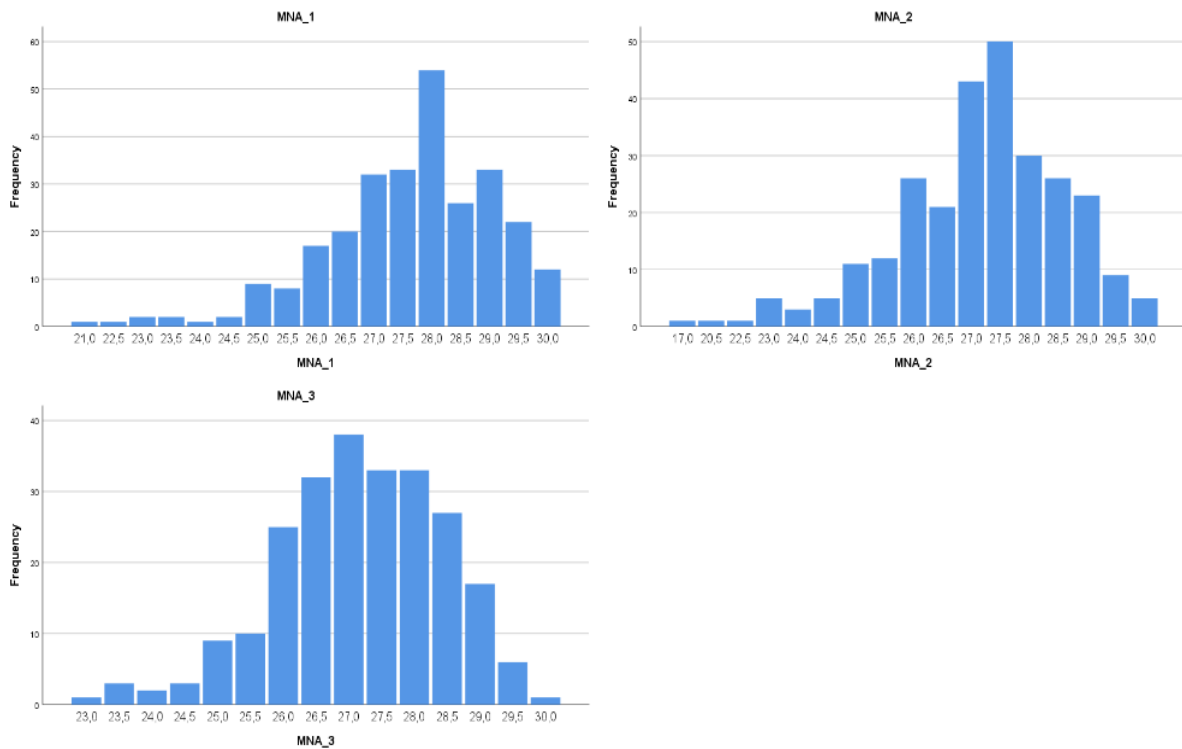


Figure 9.8 Results of the distribution of the MNA at the baseline (MNA_1), at the first (MNA_2), and at the second follow-up (MNA_3).

9.2.8 Charlson Comorbidity Index

The assessment of comorbidities using the Charlson Comorbidity Index (CCI) was performed in 284 patients at baseline, in 277 patients at the first follow-up, and in 244 patients at the second follow-up investigation, respectively. The mean values of the CCI were 0.62, 0.63 and 0.64 at the three time points. Results of the CCI are displayed in Figure 9.9.

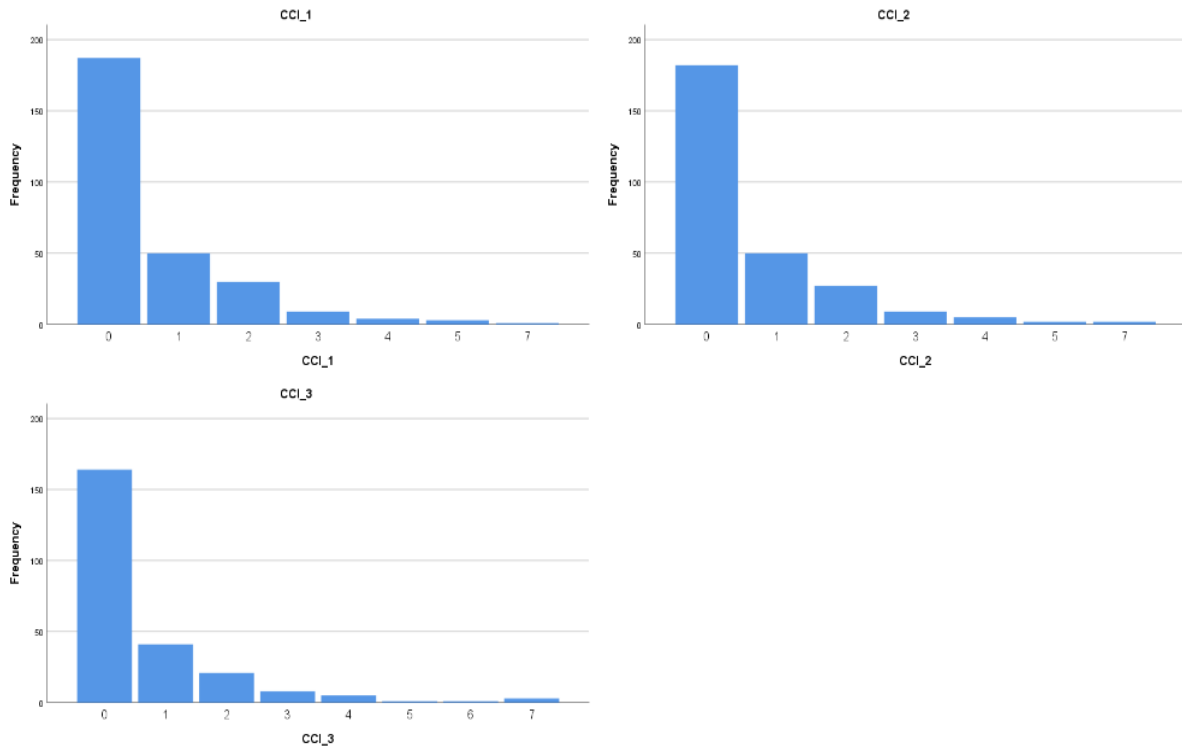


Figure 9.9 Results of the distribution of the CCI at the baseline (CCI_1), at the first (CCI_2) and at the second follow-up (CCI_3).

9.3 Results of chronic inflammatory parameters

9.3.1 Neutrophil to lymphocyte ratio

The neutrophil to lymphocyte ratio (NLR) calculated as the quotient of absolute neutrophil count to absolute lymphocyte count was evaluated in 308 patients at baseline, in 293 patients at the end of radiotherapy, in 290 patients at the first, and in 246 patients at the second follow-up, respectively. The mean values of the NLR were 3.06 ± 1.41 , 4.18 ± 2.22 , 3.57 ± 1.83 , and 3.19 ± 1.46 , respectively. The distribution of the NLR results is displayed in Figure 9.10.

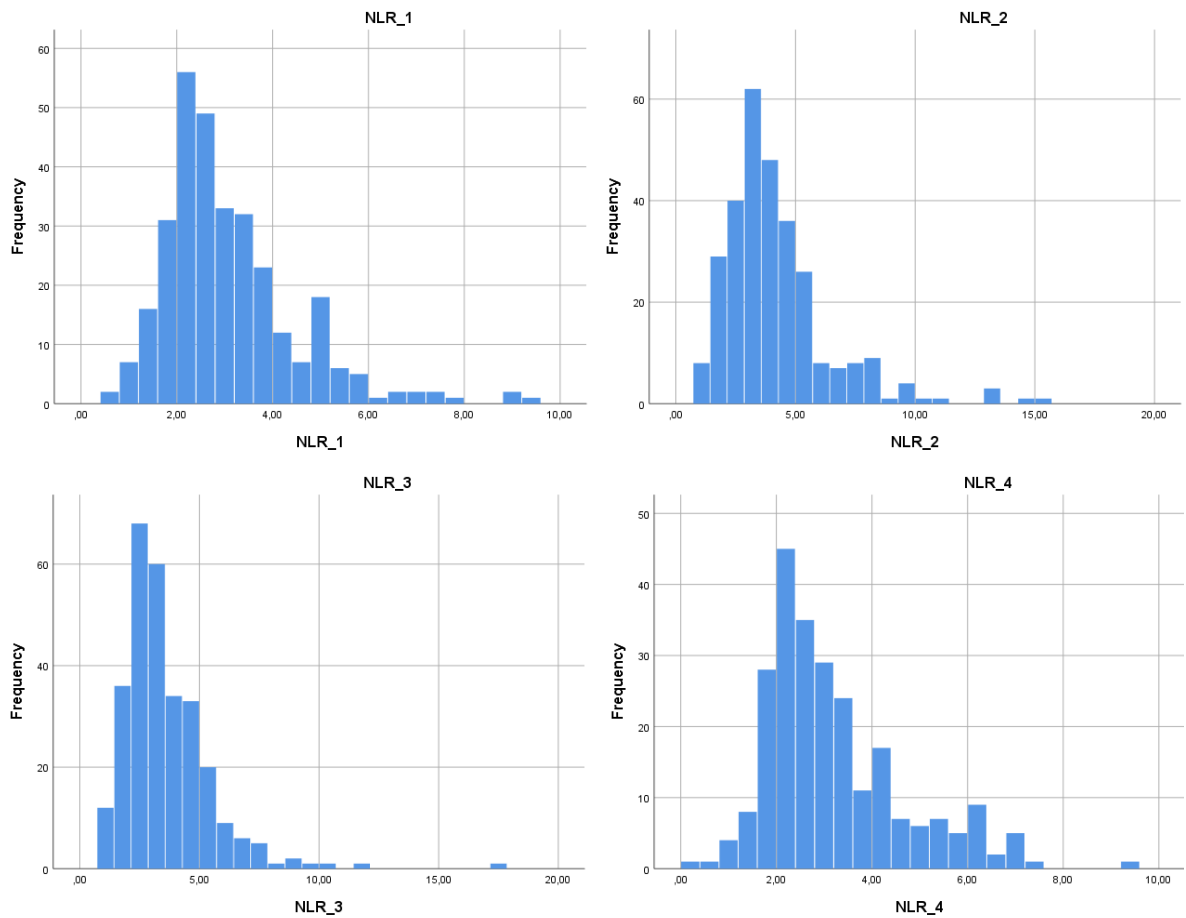


Figure 9.10 Results of the distribution of the NLR at the baseline (NLR_1), at the end of RT course (NLR_2), at the first (NLR_3), and at the second follow-up (NLR_4).

9.3.2 Platelet to lymphocyte ratio

The platelet to lymphocyte ratio (PLR) was calculated as the quotient of absolute platelet count to absolute lymphocyte count and analyzed in 308 patients at baseline, in 293 patients at the end of radiotherapy, in 291 patients at the first, and in 246 patients at the second follow-up, respectively. The mean values of the PLR were 149.15 ± 63.37 , 219.77 ± 101.59 , 194.04 ± 86.07 , and 171.63 ± 70.69 , respectively. The distribution of the PLR results is displayed in Figure 9.11.

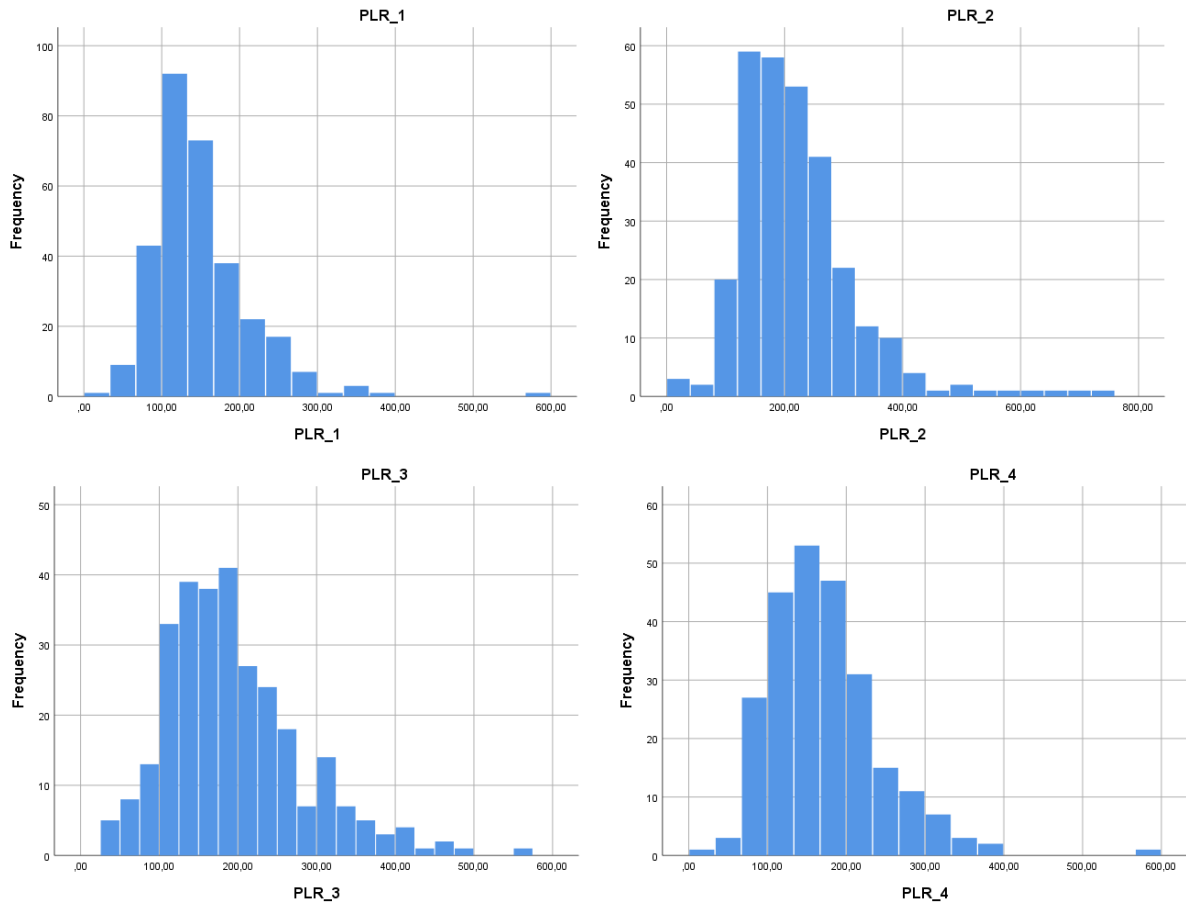


Figure 9.11 Results of the distribution of the PLR at the baseline (PLR_1), at the end of RT course (PLR_2), at the first (PLR_3), and at the second follow-up (PLR_4).

9.3.3 C-reactive protein

The c-reactive protein (CRP) was analyzed in 308 patients at baseline, in 293 patients at the end of radiotherapy, in 287 patients at the first, and in 247 patients at the second follow-up, respectively. The mean values of the CRP were 3.34 ± 9.83 mg/l, 2.96 ± 4.76 mg/l, 2.76 ± 4.09 mg/l, and 2.73 ± 4.23 mg/l, respectively. The distribution of the CRP results is displayed in Figure 9.12.

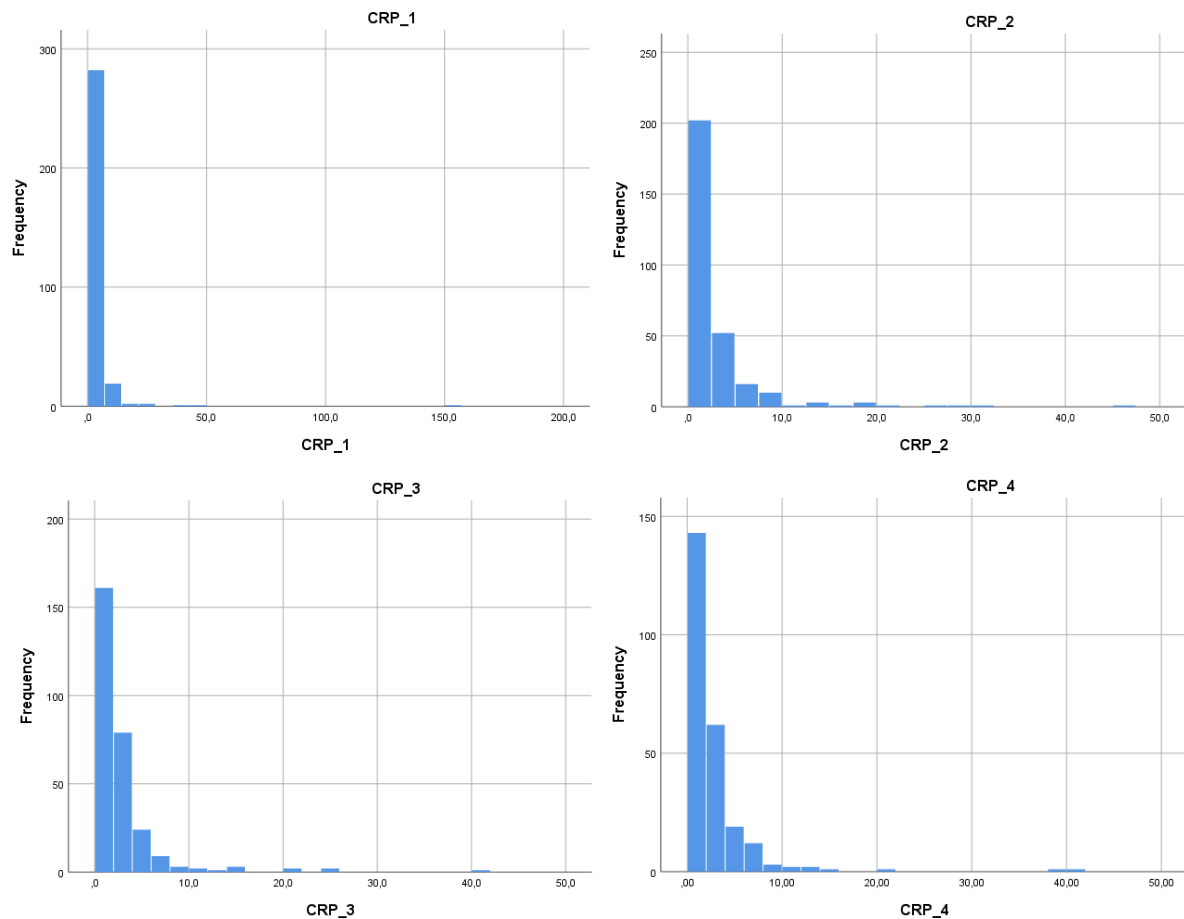


Figure 9.12 Results of the distribution of the CRP at the baseline (CRP_1), at the end of RT course (CRP_2), at the first (CRP_3), and at the second follow-up (CRP_4).

9.3.4 Albumin

Albumin was analyzed in 308 patients at baseline, in 247 patients at the end of radiotherapy, in 278 patients at the first, and in 244 patients at the second follow-up, respectively. The mean albumin values were 4.45 ± 0.24 g/dl, 4.32 ± 0.23 g/dl, 4.37 ± 0.25 g/dl, and 4.41 ± 0.28 g/dl, respectively. The distribution of the albumin results is displayed in Figure 9.13.

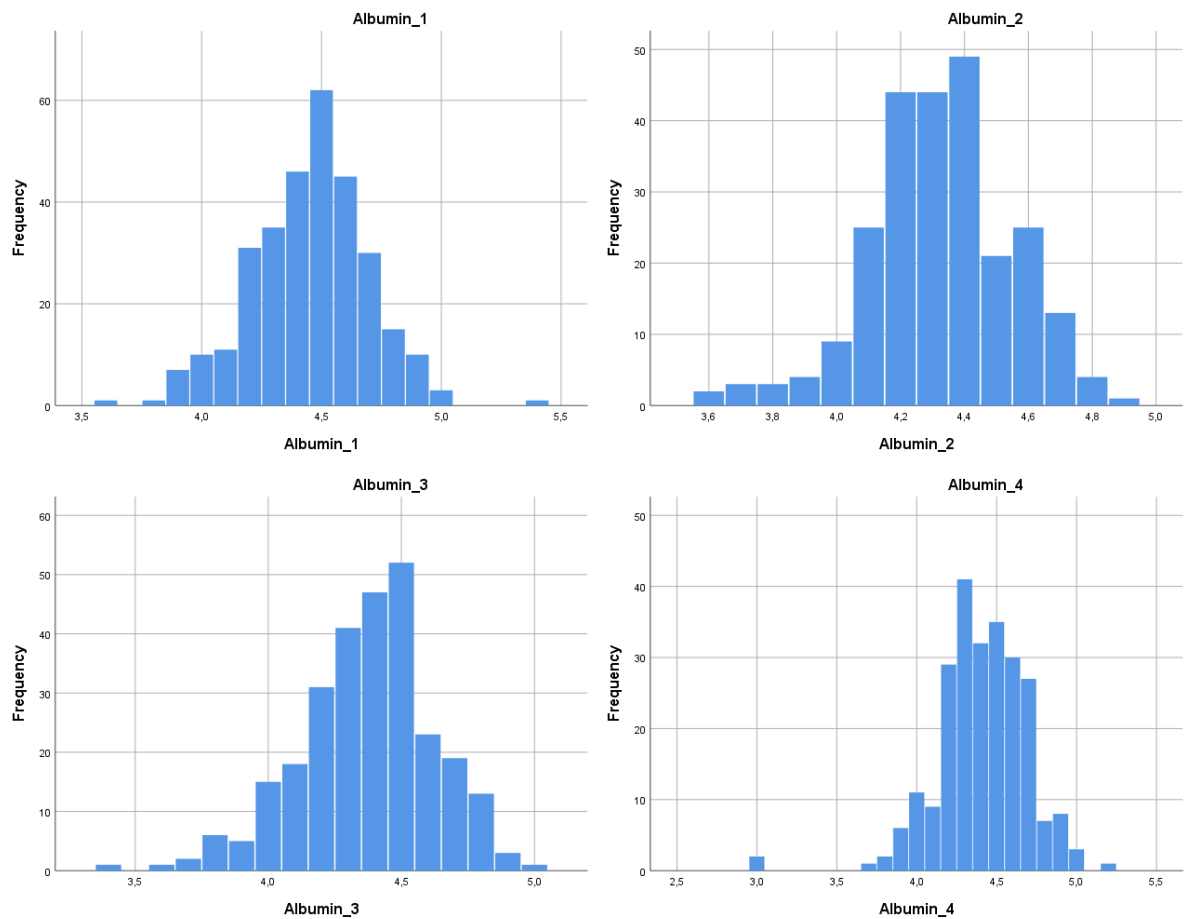


Figure 9.13 Results of the distribution of the albumin at the baseline (Albumin_1), at the end of RT course (Albumin_2), at the first (Albumin_3), and at the second follow-up (Albumin_4).

9.3.5 Fibrinogen

Fibrinogen levels were analyzed in 239 patients at baseline, in 247 patients at the end of radiotherapy, in 275 patients at the first, and in 242 patients at the second follow-up, respectively. The mean fibrinogen values were 315.59 ± 62.58 mg/dl, 318.01 ± 58.35 mg/dl, 323.04 ± 55.37 mg/dl, and $323,22 \pm 56,40$ mg/dl, respectively. The distribution of the fibrinogen results is displayed in Figure 9.14.

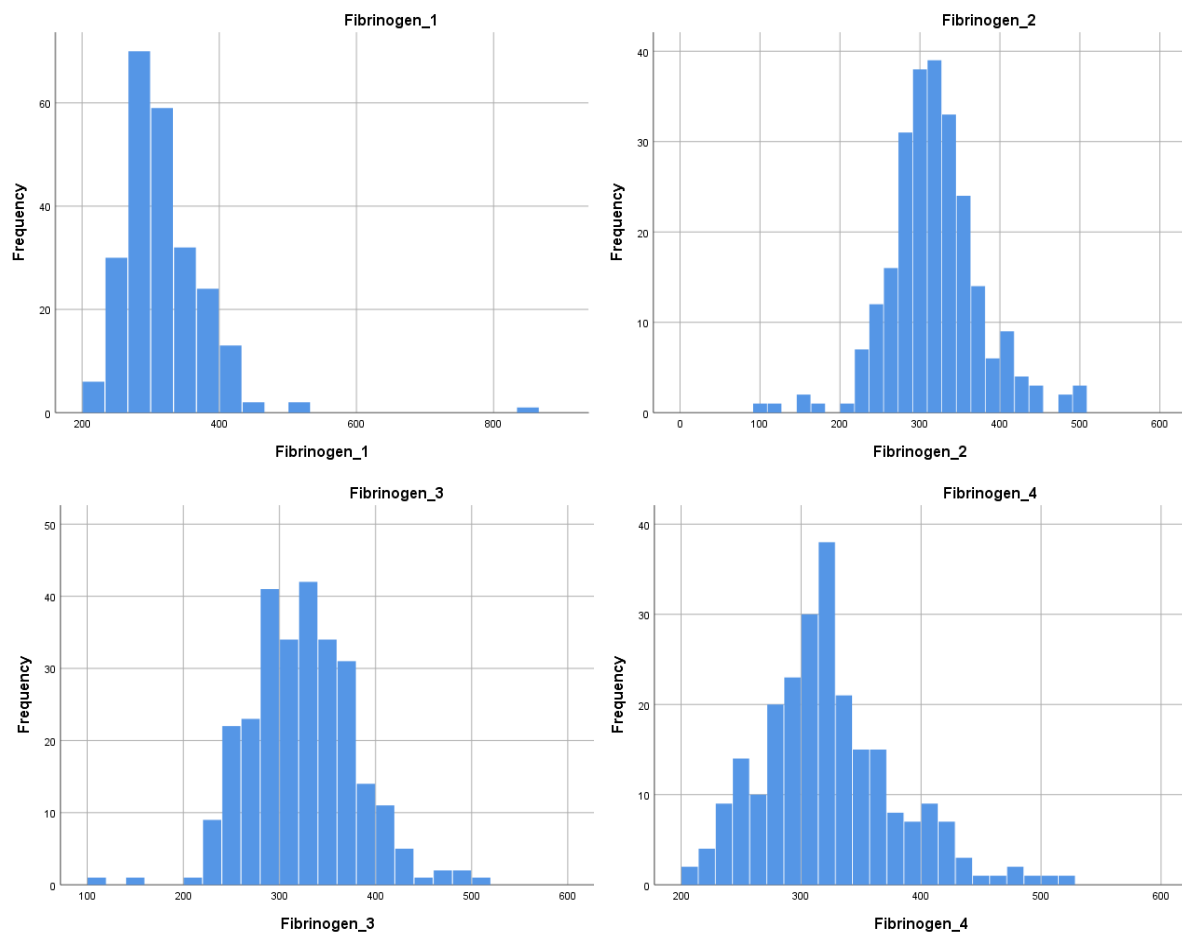


Figure 9.14 Results of the distribution of the fibrinogen at the baseline (Fibrinogen_1), at the end of RT course (Fibrinogen_2), at the first (Fibrinogen_3), and at the second follow-up (Fibrinogen_4).

9.3.6 Cholesterol

Cholesterol levels were evaluated in 308 patients at baseline, in 248 patients at the end of radiotherapy, in 278 patients at the first, and in 245 patients at the second follow-up, respectively. The mean cholesterol values were 193.10 ± 44.780 mg/dl, 182.67 ± 42.359 mg/dl, 191.15 ± 44.588 mg/dl, and 183.98 ± 45.491 mg/dl, respectively. The distribution of the cholesterol results is displayed in Figure 9.15.

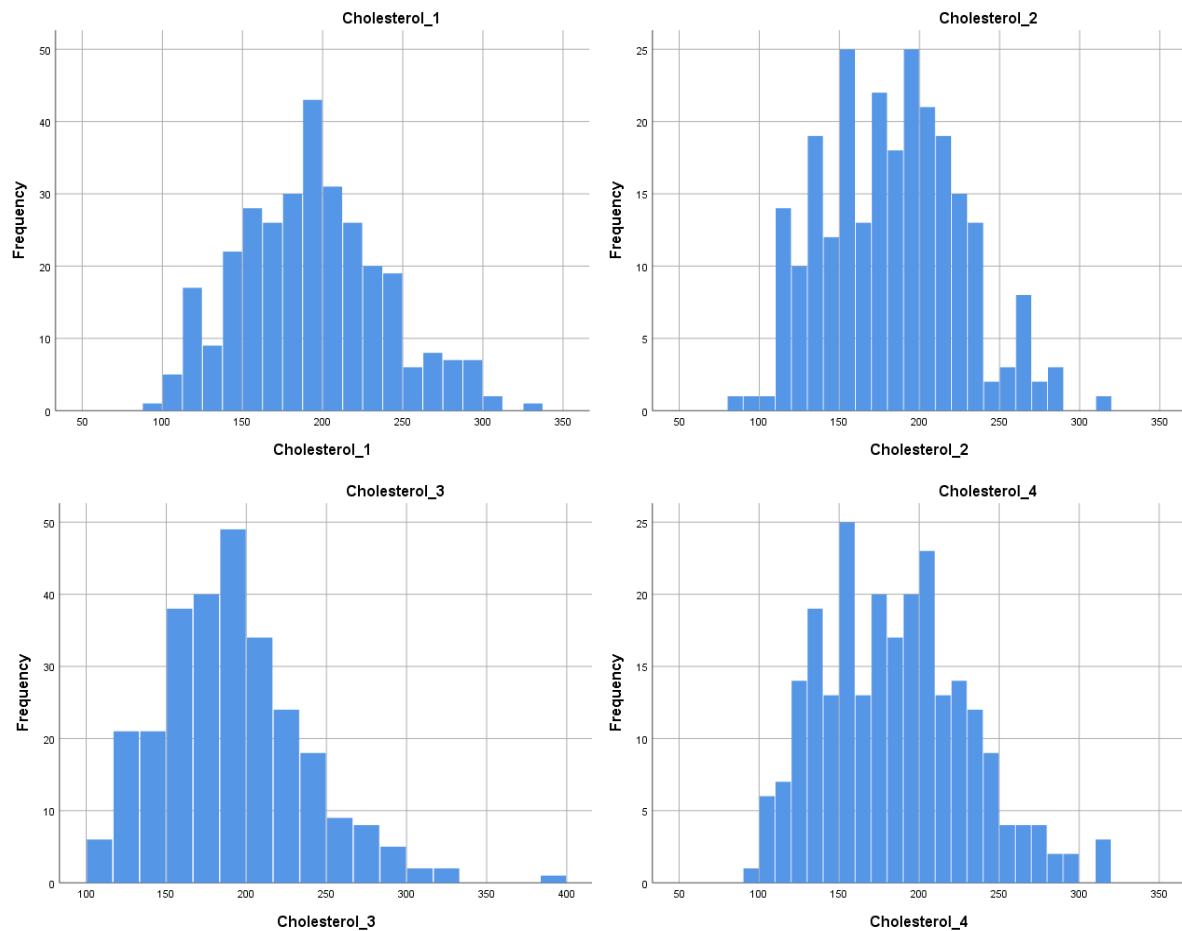


Figure 9.15 Results of the distribution of the cholesterol at the baseline (Cholesterol_1), at the end of RT course (Cholesterol_2), at the first (Cholesterol_3), and at the second follow-up (Cholesterol_4).

9.4 Cellular senescence measured by telomere length

9.4.1 Relative telomere length

Relative telomere length (RTL) was evaluated in 257 patients at baseline, in 219 patients at the end of radiotherapy, in 210 patients at the first, and in 142 patients at the second follow-up, respectively. The mean RTL values were 0.65 ± 0.34 kb, 0.62 ± 0.31 kb, 0.67 ± 0.43 kb, and 0.55 ± 0.26 kb, respectively. The distribution of the RTL results is displayed in Figure 9.16.

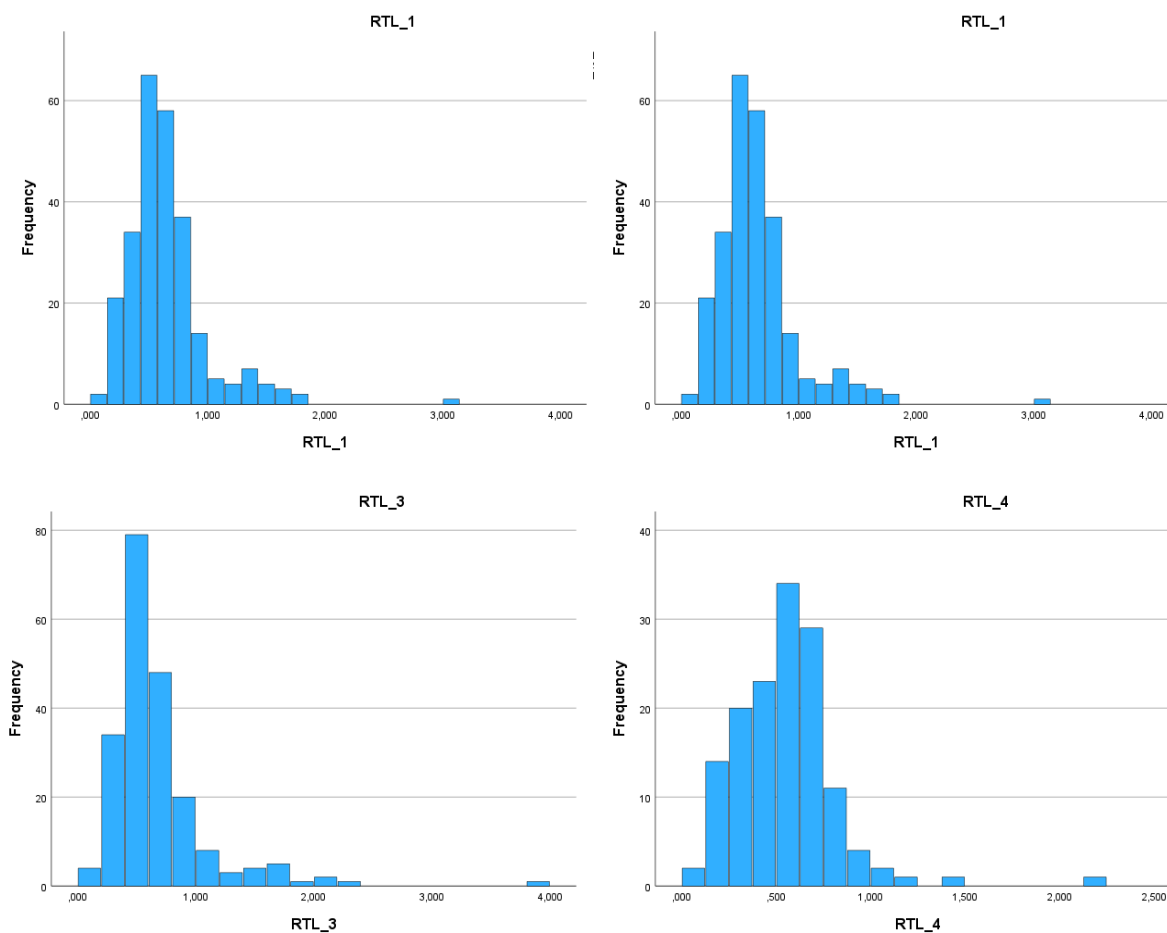


Figure 9.16 Results of the distribution of the RTL at the baseline (RTL_1), at the end of RT course (RTL_2), at the first (RTL_3), and at the second follow-up (RTL_4)

9.1 Association between biochemical and clinical age-related parameters

The correlation analysis revealed a significant positive correlation between higher pretherapeutic NLR and higher GDS score (correlation coefficient 0,15, $p=0.015$) suggesting an association between the elevated inflammatory parameters and worse mood state. Also, higher initial NLR was associated with the higher comorbidity burden measured with CCI on the baseline (correlation coefficient 0.148, $p=0.013$).

Pretherapeutic higher PLR significantly correlated with higher MNA at the baseline (correlation coefficient=0.180, $p=0.003$). Concerning CRP level, there was no significant association between pretherapeutic CRP levels and any of the clinical parameters measured with the tools of CGA.

Furthermore, the albumin level negatively correlated with the GDS at the baseline (correlation coefficient=-0.126, $p=0.043$). Higher blood cholesterol significantly correlated with a better social situation assessed with SOS (correlation coefficient=0.129, $p=0.032$). Additionally, lower pretherapeutic cholesterol correlated with a longer time in TUG (correlation coefficient=-0.203, $p=0.001$) as well as with higher initial comorbidity status measured with CCI (correlation coefficient=-0.351, $p<0.001$).

In addition, a higher pretherapeutic fibrinogen level correlated with higher IADL score (correlation coefficient=0.155, $p=0.025$) as well as with longer time needed for the completion of TUG (correlation coefficient=0.156, $p=0.027$). Moreover, initial MNA negatively correlated with pretherapeutic RTL (correlation coefficient -0.185, $p=0.005$; Figure 9.2).

		CRP_1	Cholesterol_1	Fibrinogen_1	Albumin_1	NLR_1	PLR_1	RTL_1
MMSE_1	Correlation Coefficient	0,002	-0,082	0,038	0,018	-0,068	-0,070	-,068
	Sig. (2-tailed)	0,973	0,175	0,525	0,794	0,260	0,245	,297
	N	277	277	277	210	278	278	235
SOS_1	Correlation Coefficient	0,080	-0,060	,129*	-0,073	-0,073	-0,018	-,111
	Sig. (2-tailed)	0,188	0,318	0,032	0,292	0,224	0,766	,092
	N	275	275	275	209	276	276	233
IADL_1	Correlation Coefficient	-0,090	0,056	0,019	,155*	0,013	0,043	-,066
	Sig. (2-tailed)	0,136	0,357	0,759	0,025	0,824	0,477	,313
	N	276	276	276	209	277	277	234

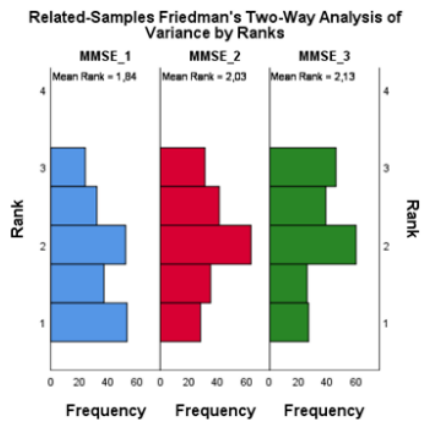
		CRP_1	Cholesterol_1	Fibrinogen_1	Albumin_1	NLR_1	PLR_1	RTL_1
GDS_1	Correlation Coefficient	0,092	-,126*	-0,019	-0,002	,150*	0,095	,010
	Sig. (2-tailed)	0,138	0,043	0,766	0,976	0,015	0,127	,885
	N	259	259	259	192	261	261	219
TUG_1	Correlation Coefficient	0,082	-0,071	-,203**	,156*	0,083	0,046	-,100
	Sig. (2-tailed)	0,181	0,246	0,001	0,027	0,175	0,450	,132
	N	269	269	269	203	270	270	227
MNA_1	Correlation Coefficient	-0,041	-0,034	0,086	-0,034	0,069	,180**	-,185**
	Sig. (2-tailed)	0,502	0,574	0,159	0,627	0,257	0,003	,005
	N	270	269	269	203	270	270	227
ADL_1	Correlation Coefficient	-0,037	0,096	0,062	-0,073	0,048	0,086	-,011
	Sig. (2-tailed)	0,545	0,111	0,308	0,295	0,423	0,156	,870
	N	276	276	276	209	277	277	234
CCI_1	Correlation Coefficient	0,087	0,011	-,351**	0,063	,148*	-0,048	,042
	Sig. (2-tailed)	0,149	0,861	0,000	0,362	0,013	0,423	,519
	N	278	278	278	210	280	280	236

Table 9.2 Rho-Spearman correlations between the clinical parameters measured with GA tools on the baseline: Mini-Mental State Examination (MMSE_1), Assessment of Social Situation (SOS_1), Instrumental Activities of Daily Living (IADL_1), Geriatric Depression Scale (GDS_1), Timed Up&Go (TUG_1) Mini Nutritional Assessment (MNA_1), Activities of daily living (ADL_1), Charlson comorbidity Index (CCI_1) and pretherapeutic laboratory parameters: C-reactive protein (CRP_1), cholesterol (Cholesterol_1), fibrinogen (Fibrinogen_1), albumin (Albumin_1), neutrophil-to-lymphocyte ratio (NLR_1), platelet-to-lymphocyte ratio (PLR_1) and relative telomere length (RTL_1)

9.2 Influence of radiotherapy on clinical conditions measured with GA tools

9.2.1 Changes in cognitive function measured with MMSE

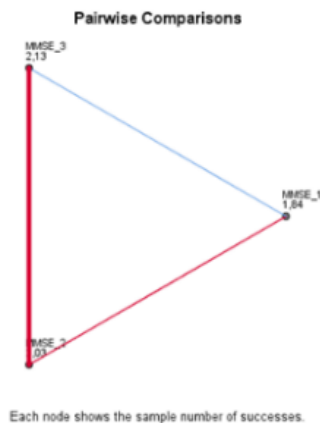
During the observation period, variance analysis revealed a significant increase in the results of the MMSE ($p=0.002$, Table 9.3).



Total N	198
Test Statistic	12,837
Degree Of Freedom	2
Asymptotic Sig. (2-sided test)	,002

Table 9.3 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary Figure for MMSE results

In addition, pairwise comparisons showed a significant improvement in cognitive function at the second follow-up when compared to the baseline ($p=0.004$, Table 9.4)

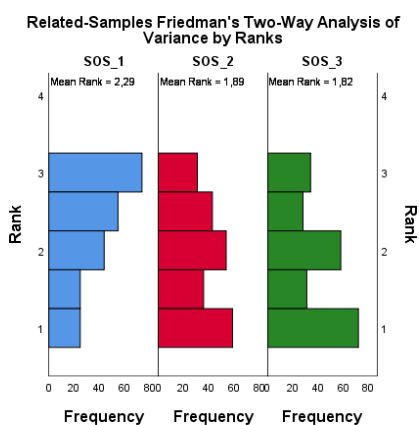


Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
MMSE_1- MMSE_2	-,189	,101	-1,884	,060
MMSE_1- MMSE_3	-,288	,101	-2,864	,004
MMSE_2- MMSE_3	-,098	,101	-,980	,327

Table 9.4 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for MMSE results. A significant difference was detected between baseline (MMSE_1) and second follow-up (MMSE_3)

9.2.2 Changes in social situation

During the observation period, a significant decrease in the results of the SOS was observed ($p < 0.001$, Table 9.5) suggesting a negative influence of RT for PCa on the social situation.

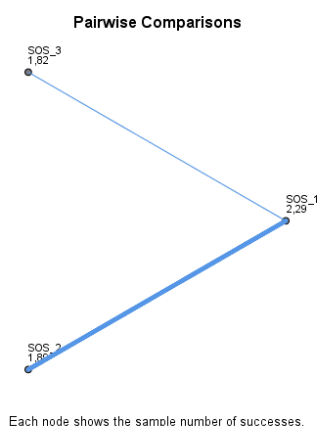


Total N	223
Test Statistic	35,803
Degree Of Freedom	2
Asymptotic Sig. (2-sided test)	,000

Table 9.5 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for SOS results

In addition, pairwise comparisons showed a significant decline in the results of the SOS at the first follow-up when compared to the baseline ($p < 0.001$, Table 9.6) as well as a significant

decline in social situation between the second follow-up and baseline ($p < 0.001$). A significant difference between the first and second follow-up investigation was not detected ($p = 0.478$).

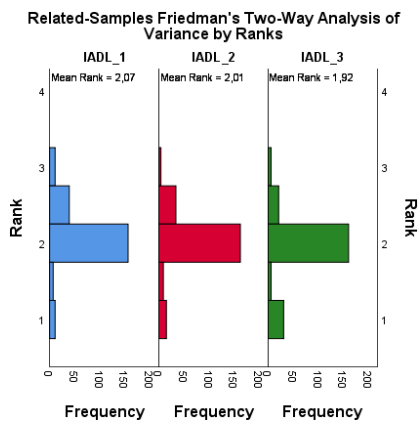


Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test	Sig.
SOS_3- SOS_2	,067	,095	,710	,478
SOS_3- SOS_1	,464	,095	4,901	,000
SOS_2- SOS_1	,397	,095	4,191	,000

Table 9.6 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for SOS results. A significant difference was detected between baseline (SOS_1) and first follow-up (SOS_2) as well as between baseline (SOS_1) and second follow-up (SOS_3)

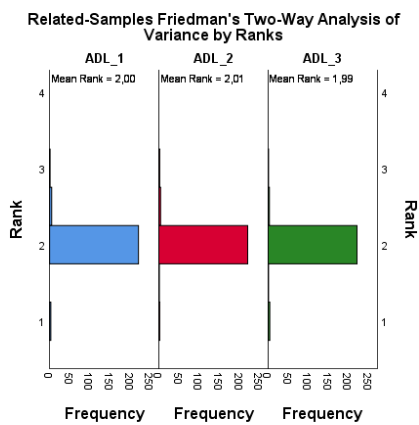
9.2.3 Changes in activities of daily living measured with ADL and IADL

During the observation period, a significant difference in result distribution with a tendency to the functional decline could be detected for IADL ($p = 0.005$, Table 9.7), however, there was no significant changes in IADL in pairwise comparisons ($p > 0.05$ for all comparisons, Table 9.9). There was no significant change in the ADLs measured at three points of time in the study ($p = 0.674$, Table 9.8)



Total N	224
Test Statistic	10,551
Degree Of Freedom	2
Asymptotic Sig. (2-sided test)	,005

Table 9.7 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for IADL results



Total N	230
Test Statistic	,788a
Degree Of Freedom	2
Asymptotic Sig. (2-sided test)	,674

Table 9.8 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for ADL results

Pairwise Comparisons



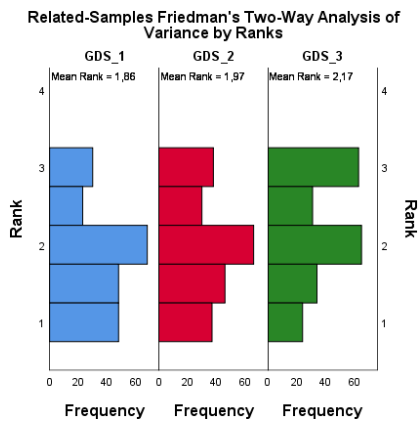
Each node shows the sample number of successes.

Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
IADL_3- IADL_2	,085	,094	,898	,369
IADL_3- IADL_1	,150	,094	1,583	,113
IADL_2- IADL_1	,065	,094	,685	,493

Table 9.9 Pairwise comparisons of Related-Samples Friedman’s Two-Way Analysis of Variance for IADL results. No significant difference was detected between baseline (IADL_1) and first follow-up (IADL_2) and second follow-up (IADL_3)

9.2.4 Changes in mood measured with GDS

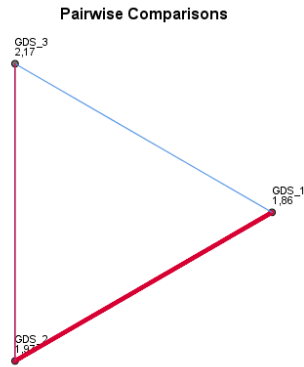
During the observation period, a significant increase in the results of the GDS was observed ($p < 0.001$, Table 9.10) suggesting a worsening of the mood in our patients.



Total N	217
Test Statistic	16,283
Degree Of Freedom	2
Asymptotic Sig.(2-sided test)	,000

Table 9.10 Related-Samples Friedman’s Two-Way Analysis of Variance by Ranks Summary for GDS results

In addition, pairwise comparisons showed a significant increase in the results of the GDS at the second follow-up when compared to the baseline ($p=0.001$, Table 9.11) implying a decline in a mood state as well as a significant mood worsening between the first and the second follow-up ($p=0.033$). A significant difference between the baseline and the first follow-up investigation was not detected ($p=0.259$).



Each node shows the sample number of successes.

Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
GDS_1- GDS_2	-,108	,096	-1,128	,259
GDS_1- GDS_3	-,313	,096	-3,264	,001
GDS_2- GDS_3	-,205	,096	-2,136	,033

Table 9.11 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for GDS results. A significant difference was detected between baseline (GDS_1) and second follow-up (GDS_2) as well as between first (GDS_2) and second follow-up (GDS_3)

9.2.5 Changes in mobility measured with TUG

During the observation period, there was no overall significant change in the mobility measured with TUG in all three assessments ($p=0.099$, Table 9.12)

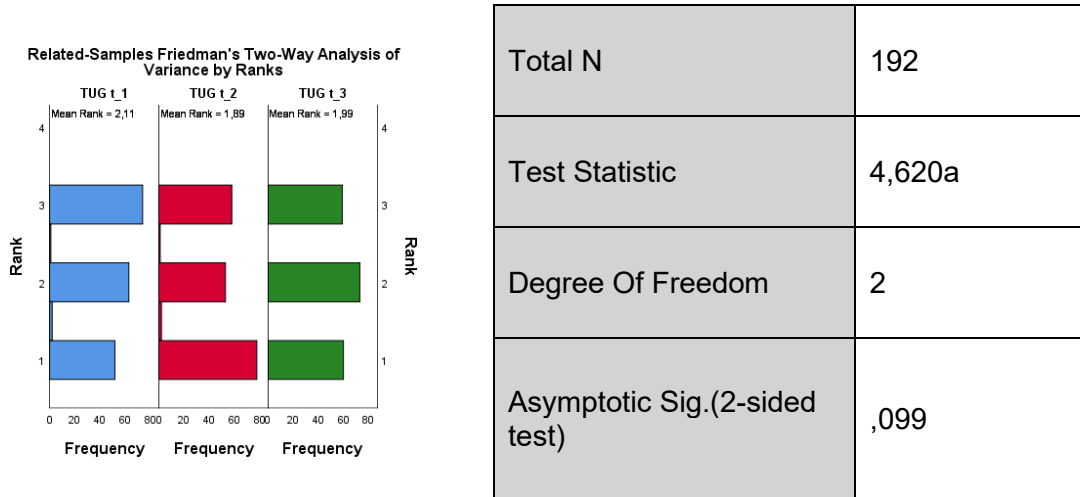


Table 9.12 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for TUG results

However, a pairwise comparison revealed a significant improvement in TUG in the first follow-up comparing to the baseline ($p=0.032$, Table 9.13). A significant difference could not be detected in the second follow-up when compared to the baseline ($p=0.251$) and first follow-up ($p=0.320$).

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
TUG_2-TUG_3	-,102	,102	-,995	,320
TUG 2-TUG_1	,219	,102	2,143	,032
TUG 3-TUG_1	,117	,102	1,148	,251

Table 9.13 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for TUG results. A significant difference was detected between baseline (TUG_1) and first follow-up (TUG_2). There was no statistically significant difference between the baseline (TUG_1) and second follow-up (TUG_3) as well as between first (TUG_2) and second follow-up (TUG_3)

9.2.6 Changes in nutritional status measured with MNA

During the observation period, a significant difference in the results of the MNA was observed ($p < 0.001$, Table 9.14.).

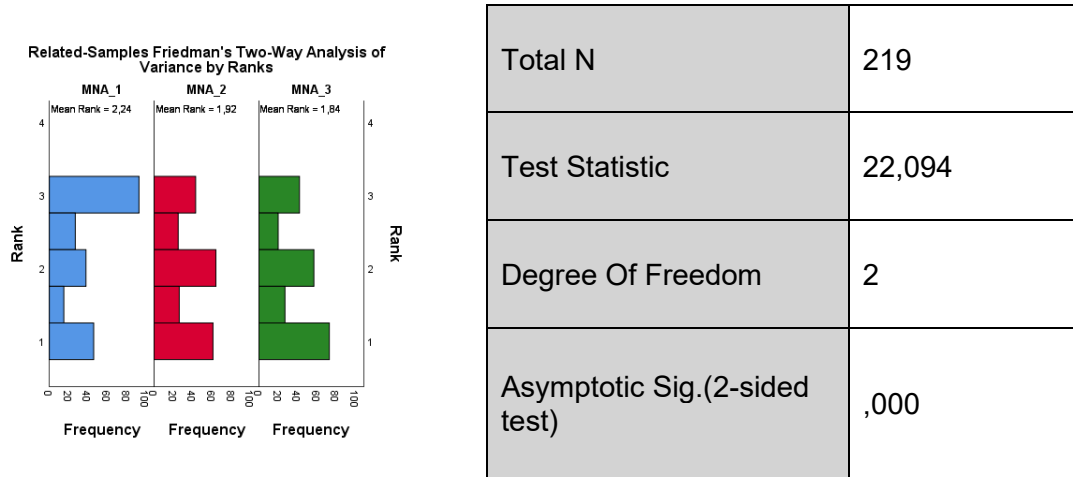
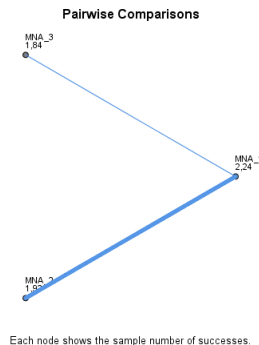


Table 9.14 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for MNA results

In addition, pairwise comparisons showed a significant decline in the results of the MNA at the first and second follow-up when compared to the baseline ($p = 0.001$, $p < 0.001$, respectively). A significant difference between the first and second follow-up investigation was not detected ($p = 0.445$, Table 9.15).

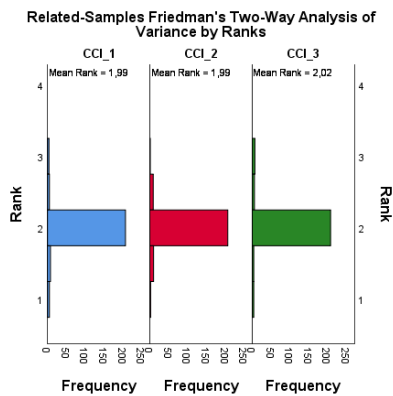


Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
MNA_3- MNA_2	,073	,096	,765	,445
MNA_3- MNA_1	,400	,096	4,181	,000
MNA_2- MNA_1	,326	,096	3,416	,001

Table 9.15 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for MNA results. A significant difference was detected between baseline (MNA_1) and second follow-up (MNA_2) as well as between the baseline (MNA_1) and second follow-up (MNA_3).

9.2.7 Changes in comorbidities measure with CCI

During the observation period, there was no significant change in the comorbidity status measured with CCI in all three assessments ($p=0.481$, Table 9.16)



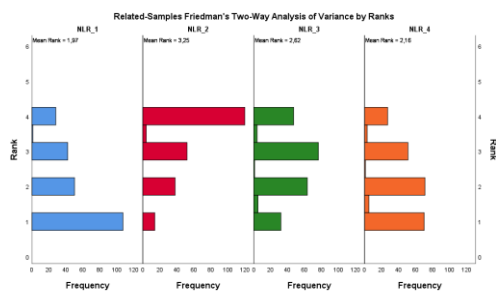
Total N	229
Test Statistic	1,463a
Degree Of Freedom	2
Asymptotic Sig. (2-sided test)	,481

Table 9.16 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for CCI results

9.3 Influence of radiotherapy on chronic inflammation

9.3.1 Neutrophil to lymphocyte ratio (NLR)

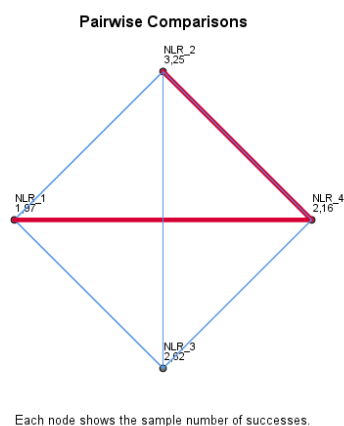
During the observation period, variance analysis revealed a significant difference in the results of the NLR ($p<0.001$, Table 9.17).



Total N	228
Test Statistic	133,065
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,000

Table 9.17 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for NLR results

In addition, pairwise comparisons showed a significant increase in the results of the NLR at the end of RT course and in the first follow-up when compared to the baseline ($p < 0.001$, for both comparisons, Table 9.18) as well as a significant decrease of NLR between in the first and second follow-up when compared to the end of the RT course ($p < 0.001$ for both comparisons). Moreover, a significant decrease in NLR could be detected between the first and second follow-up ($p < 0.001$). A significant difference between the baseline and the second follow-up was not detected ($p = 0.103$).

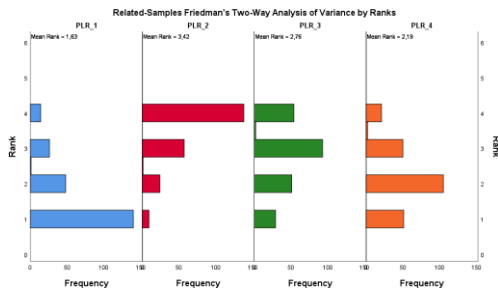


Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
NLR_1- NLR_4	-,197	,121	-1,632	,103
NLR_1- NLR_3	-,656	,121	-5,423	,000
NLR_1- NLR_2	-1,279	,121	-10,574	,000
NLR_4- NLR_3	,458	,121	3,791	,000
NLR_4- NLR_2	1,081	,121	8,941	,000
NLR_3- NLR_2	,623	,121	5,151	,000

Table 9.18 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for neutrophils/lymphocytes ratio). A significant difference could be detected between the baseline (NLR_1) and all following laboratory controls (NLR_2, NLR_3 and NLR_4) as well as between at the end of RT (NLR_2) and both follow-ups (NLR_3 and NLR_4), and between the first (NLR_3) and second (NLR_4) follow-up

9.3.2 Platelet to lymphocyte ratio (PLR)

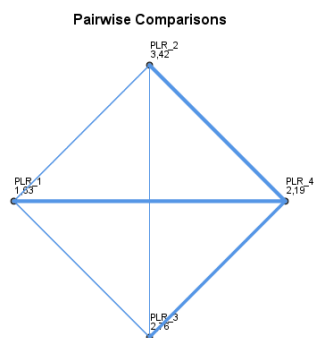
During the observation period, variance analysis revealed a significant difference in the results of the PLR ($p < 0.001$, Table 9.19).



Total N	228
Test Statistic	133,065
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,000

Table 9.19 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for PLR results

In addition, pairwise comparisons showed a significant increase in the results of the PLR at the end of RT course, in the first, and second follow-up when compared to the baseline ($p < 0.001$ for all comparisons Table 9.20) There was also a significant decrease of PLR between in the first and second follow-up when compared to the end of the RT course ($p < 0.001$ for both comparisons) as well as a significant decrease in PLR between the first and second follow-up ($p < 0.001$).



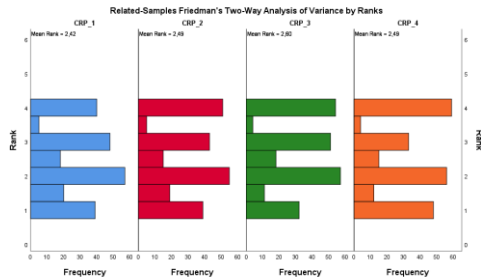
Each node shows the sample number of successes.

Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
PLR_1- PLR_4	-,566	,121	-4,687	,000
PLR_1- PLR_3	-1,138	,121	-9,429	,000
PLR_1- PLR_2	-1,790	,121	-14,840	,000
PLR_4- PLR_3	,572	,121	4,741	,000
PLR_4- PLR_2	1,225	,121	10,153	,000
PLR_3- PLR_2	,653	,121	5,411	,000

Table 9.20 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for platelets/lymphocytes ratio. A significant difference could be detected between the baseline (PLR_1) and all following laboratory controls (PLR_2, PLR_3 and PLR_4) as well as between at the end of RT (PLR_2) and both follow-ups (PLR_3 and PLR_4), and between the first (PLR_3) and second (PLR_4) follow-up

9.3.3 C-reactive protein (CRP)

During the observation period, variance analysis revealed no significant differences in the results of the CRP ($p=0.455$, Table 9.21).

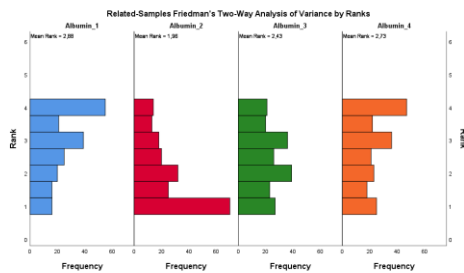


Total N	227
Test Statistic	2,612a
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,455

Table 9.21 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for CRP results

9.3.4 Albumin

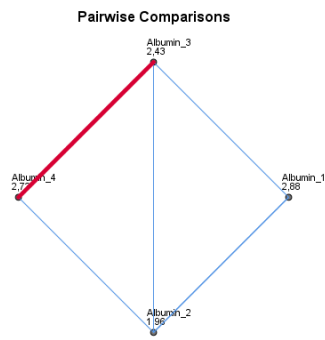
During the observation period, variance analysis revealed a significant difference in the results of the albumin level ($p=0.000$, Table 9.22).



Total N	192
Test Statistic	64,522
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,000

Table 9.22 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for albumin results

In addition, pairwise comparisons showed a significant decline in the results of albumin level at the end of RT course, and in the first follow-up when compared to the baseline ($p=0<001$ and $p=0.001$, respectively, Table 9.23) There was also a significant recovery in albumin levels between in the first and second follow-up when compared to the end of the RT course ($p<0.001$ for both comparisons) as well as an increase in albumin between the first and second follow-up ($p=0.024$) A significant difference between the baseline and the second follow-up could not be detected ($p=0.244$).



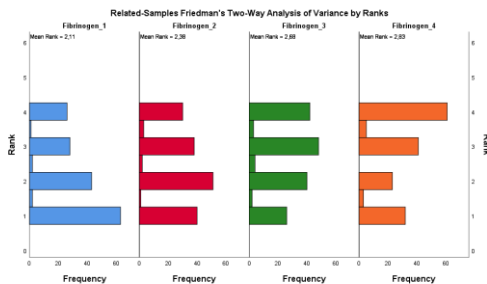
Each node shows the sample number of successes.

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Albumin_2-Albumin_3	-,466	,132	-3,538	,000
Albumin_2-Albumin_4	-,763	,132	-5,791	,000
Albumin_2-Albumin_1	,917	,132	6,957	,000
Albumin_3-Albumin_4	-,297	,132	-2,253	,024
Albumin_3-Albumin_1	,451	,132	3,419	,001
Albumin_4-Albumin_1	,154	,132	1,166	,244

Table 9.23 Pairwise comparisons of Related-Samples Friedman’s Two-Way Analysis of Variance for albumin). A significant difference could be detected between the baseline (Albumin_1) and the end of RT course, and first follow-up (Albumin_2, Albumin_3) as well as between at the end of RT (Albumin_2) and both follow-ups (Albumin_3 and Albumin_4), and between the first (Albumin_3) and second (Albumin_4) follow-up

9.3.5 Fibrinogen

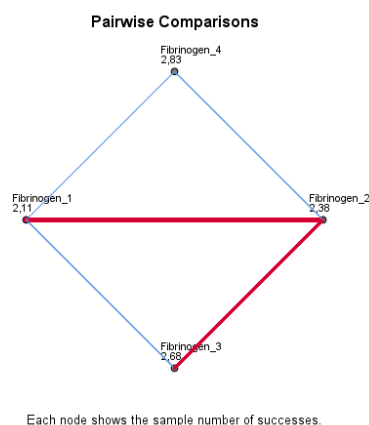
During the observation period, variance analysis revealed a significant difference in the results of the fibrinogen level ($p < 0.001$, Table 9.24).



Total N	165
Test Statistic	30,394
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,000

Table 9.24 Related-Samples Friedman’s Two-Way Analysis of Variance by Ranks Summary for fibrinogen results

In addition, pairwise comparisons showed a significant increase in the results of fibrinogen level in the first and second follow-up when compared to the baseline ($p=0<001$ for both comparisons, Table 9.25), as well as a significant increase of fibrinogen between the end of RT and first and second follow-up ($p=0.039$ and $p=0.02$, respectively). There also a nearly significant increase in fibrinogen level between the baseline and the RT of the RT course ($p=0.58$). A significant difference in fibrinogen level could not be found between the first and second follow-up ($p=0.277$).

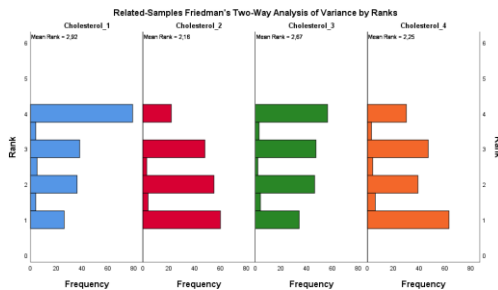


Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Fibrinogen_1- Fibrinogen_2	-,270	,142	-1,897	,058
Fibrinogen_1- Fibrinogen_3	-,564	,142	-3,966	,000
Fibrinogen_1- Fibrinogen_4	-,718	,142	-5,053	,000
Fibrinogen_2- Fibrinogen_3	-,294	,142	-2,068	,039
Fibrinogen_2- Fibrinogen_4	-,448	,142	-3,155	,002
Fibrinogen_3- Fibrinogen_4	-,155	,142	-1,087	,277

Table 9.25 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for fibrinogen values. A significant difference could be detected between the baseline (Fibrinogen_1) and both follow-ups (Fibrinogen_3 and Fibrinogen_4) as well as between at the end of RT (Fibrinogen_2) and both follow-ups (Fibrinogen_3 and Fibrinogen_4)

9.3.6 Cholesterol

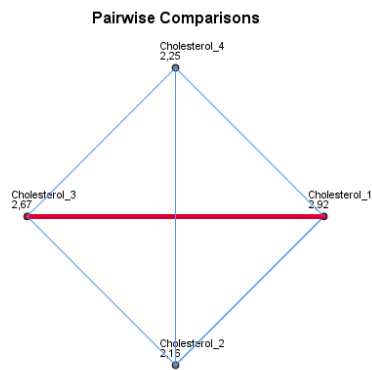
During the observation period, variance analysis revealed a significant difference in the results of the cholesterol level ($p < 0.001$, Table 9.26).



Total N	192
Test Statistic	44,389
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,000

Table 9.26 Related-Samples Friedman’s Two-Way Analysis of Variance by Ranks Summary for cholesterol results

In addition, pairwise comparisons showed a significant decline in the results of cholesterol level at the end of RT and at second follow-up when compared to the baseline ($p < 0.001$ for both comparisons, Table 9.27) as well as nearly significant decrease between of cholesterol between the baseline and first follow-up ($p = 0.058$). There was also a significant decrease on cholesterol level between the first and second follow-up ($p < 0.001$). Additionally, there was a significant increase of cholesterol between the end of RT and the first follow-up ($p < 0.001$) There was no significant difference between the end of the RT and second follow-up ($p = 0.527$).



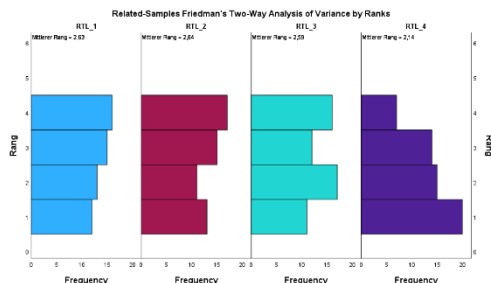
Each node shows the sample number of successes.

Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Cholesterol_2- Cholesterol_4	-,083	,132	-,632	,527
Cholesterol_2- Cholesterol_3	-,505	,132	-3,834	,000
Cholesterol_2- Cholesterol_1	,755	,132	5,732	,000
Cholesterol_4- Cholesterol_3	,422	,132	3,202	,001
Cholesterol_4- Cholesterol_1	,672	,132	5,099	,000
Cholesterol_3- Cholesterol_1	,250	,132	1,897	,058

Table 9.27 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for cholesterol. A significant difference could be detected between the baseline (Cholesterol_1) and the end of RT course, and second follow-up (Cholesterol_2 and Cholesterol_4) as well as between at the end of RT (Cholesterol_2) and first follow-up (Cholesterol_3), and between the first (Cholesterol_3) and second (Cholesterol_4) follow-up

9.4 Influence of radiotherapy on telomere length

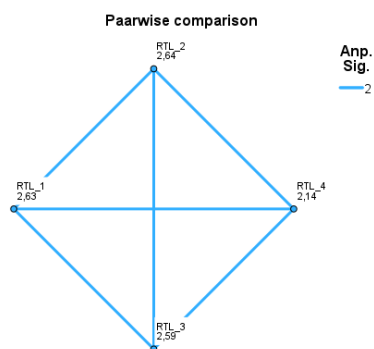
During the observation period, variance analysis revealed no overall significant difference in the results of the relative telomere length (RTL) ($p > 0.05$, Table 9.28).



Total N	56
Test Statistic	5,76
Degree Of Freedom	3
Asymptotic Sig. (2-sided test)	,124

Table 9.28 Related-Samples Friedman's Two-Way Analysis of Variance by Ranks Summary for RTL results

In addition, pairwise comparisons showed a significant decrease in RTL in second follow-up when compared to the baseline ($p = 0.048$) and to the end of RT ($p = 0.40$; Table 9.29), as well as a nearly significant decrease of PLR between the first and second follow-up ($p = 0.067$)



Each node shows the sample number of successes.

Sample 1- Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
RTL_4-RTL_3	0,446	0,244	1,830	0,067
RTL_4-RTL1	0,482	0,244	1,976	0,048
RTL_4-RTL_2	0,500	0,244	2,049	0,040
RTL_3-RTL_1	0,036	0,244	0,146	0,884
RTL_3-RTL_2	0,054	0,244	0,220	0,826
RTL_1-RTL_2	-0,018	0,244	-0,073	0,942

Table 9.29 Pairwise comparisons of Related-Samples Friedman's Two-Way Analysis of Variance for RTL. A significant difference could be detected between the baseline (RTL_1) and second follow-up (RTL_4) as well as between at the end of RT (RTL_2) and second follow-up (RTL_4).

10 Discussion

The aim of the present dissertation was to examine the influence of curative radiation therapy for prostate cancer on ageing-related biochemical, molecular, and clinical alterations. The analyses focussed on investigating whether curative radiation therapy administered to a small body area affects the ageing process and whether individuals treated with radiotherapy are at an elevated risk of accelerated ageing as a result of the cancer treatment they receive.

Most published papers addressing the problem of accelerated ageing after cancer therapy primarily concentrate on cohorts of paediatric patients with a very long follow up time. Given that the aggressive paediatric malignancies frequently require multimodal, intensive cancer treatment, it is challenging to distinguish between the effects of the different therapy modalities. Additionally, findings from cohorts of childhood cancer survivors cannot be translated to the changes observed in adults, given the significant biological differences between these patient groups regarding the physical and functional development of body systems, as well as the different repair and recovery potential between the two groups.

As the majority of malignant diseases occur in adults, with 50% of them in patients aged 65 years and older, there is a need for research on the influence of cancer therapy on ageing in patients in whom the ageing process is already advanced (162). Despite careful consideration of all clinical parameters, cancer therapy may disrupt metabolic balance and lead to deterioration in objectively measured and subjectively reported well-being and health. Therefore, choosing a cohort of potentially frail patients could help answer questions about the dynamics of the ageing process.

The present study was performed on a homogenous study cohort including 314 patients aged 65-86 who had been treated with curative radiation therapy for localized prostate cancer. Our findings indicate that RT significantly contributes to the activation of the inflammatory process and cellular senescence as measured with telomere length. Additionally, we observed that RT has a significant impact on health status, as assessed through the domains of a CGA.

10.1 Clinical alterations measured with tools of CGA

The majority of GA results indicate an adverse effect of the administered cancer therapy on health domains measured with CGA tools. The underlying reasons for these negative changes are complex, however, the measurable alterations observed over a time span of 16-18 months suggest an accelerated ageing process resulting from the medical interventions received.

10.1.1 Cognitive alterations

The influence of cancer treatment on cognitive capabilities has been an area of interest in previous research on cancer survivors' populations, yielding conflicting results. While certain cross-sectional and prospective studies failed to demonstrate an association between cancer therapy and cognitive impairment, other studies indicate that the prevalence of cancer therapy-related cognitive dysfunction ranges from 15 to 60% (163–165). Cancer therapy can also indirectly contribute to memory worsening by therapy-induced fatigue, altered glucose and lipid metabolism, worsened cardiovascular function, haematological changes, therapy-induced

chronic inflammation as well as treatment-associated psychological stress and anxiety. Chemotherapy-related cognitive difficulties impacting concentration and memory frequently arise during systemic therapy. This has led to the introduction of the term “chemo-brain”, that has been investigated in numerous trials(166–168).

Cognitive decline has frequently been described as a protracted side effect in patients obtaining high-volume cranial irradiation. Nevertheless, changes in memory have been documented in patients receiving non-cranial irradiation suggesting the activation of mechanisms that affect brain function possibly due to metabolic alterations. Therefore, RT may lead to decline in cognitive function for patients undergoing treatment in areas other than the cranial region(169,170).

In our study cohort, we noted no significant changes in cognition after the completion of RT as measured by MMSE. However, we detected an improvement in cognitive function at the clinical control appointment conducted 15 months after the completion of the radiation course when compared to the baseline assessment performed prior to the initiation of RT.

However, the majority of patients in our study cohort underwent neoadjuvant ADT administered before and during RT. Thus, a significant proportion of patients experienced androgen deprivation at the first and second memory assessment but not at the third assessment. It is established that treatments affecting sexual hormonal pathways sexual hormones pathways are associated with cognitive decline in breast and prostate cancer patients. For example, Ginty and colleagues presented convincing evidence highlighting the detrimental effects of ADT on cognitive function in prostate cancer patients (171). Given the negative impact of ADT on neurocognition, the discontinuation of ADT treatment in most patients may have contributed to an improvement of cognitive function.

Moreover, research indicates that physical activity and exercises enhance memory function. In our clinic, all patients are advised to implement healthy habits in their daily lives, and health-promoting behaviours such as regular exercise could have positively influenced cognitive function (172,173). As a significant percentage of our patients experienced weight gain associated with ADT, it is plausible that the termination of the ADT might have facilitated to return to their initial body weight after therapy that supported the patients to resume physical activity.

10.1.2 Social situation

In our study cohort, the summary score on the Nicolaus Scale for Social Situation applied to examine social situation decreased between decreased from the baseline assessment to the follow-up assessments at 3 months and 15 months after completion of radiation therapy indicating a decline in social situation.

The Nicolaus Scale for Social situation comprises four domains related to social life: close family relationships, activities, housing situation, and economic circumstances. In the surveys, the economic and household situation of the patients remained unchanged. This is because the study was performed on a geriatric patient cohort, the majority of whom had long-term settlements and received stable financial support from the government.

Therefore, the domains that underwent alterations were those linked to social contacts and activities. Since oncological therapy involves—and clinical check-ups associated with considerable travel time, especially for patients living in rural areas, the social situation of cancer patients may deteriorate during and after therapy. Additionally, therapy-related toxicity may pose an obstacle for social contacts and activities. The deterioration in social situation from baseline to the control 3 months after RT could largely attributed to the occurrence of radiation – induced toxicity, particularly genitourinary urgency that may lead patients prefer the comfort of their homes avoiding excessive physical stress. Furthermore, many patients reported ADT-connected toxicities as a limiting factor for initiating social contacts.

There is a significant correlation between alterations in social situation and depression(174). Thus, a decline in social and individual activities could also have been caused by mood changes as described in the subsequent part of the discussion. Furthermore, the onset of the Covid-19 pandemic might have had a subtle impact on the results in this domain of the CGA. However, a vast majority of our study participants were recruited during the pandemic, and the control appointments took place when Covid-19 restrictions had already been eased.

A pooled analysis of data form various studies showed that 45% of cancer patients experience significant social difficulties that encompass feelings of social isolation, reduced social activities, difficulties in meeting both work-related and not work-related obligations (175). Wright and colleagues documented the social problems covering areas such as managing at home, access to health and welfare services, finances, employment, legal matters, relationships, sexuality and body image, and recreation (176). Knox and colleagues also revealed a substantial impact of cancer diagnosis and treatment on social consequences, particularly the increased risk of social isolation. In view the numerous alterations in several domains of the social situation (177), it should be increasingly considered to involve social workers into the comprehensive cancer therapy and aftercare.

10.1.3 Activities of daily living and mobility

10.1.3.1 ADL / IADL

Elderly people constitute a high percentage of cancer patients and many of them are eligible for an aggressive therapy in curative intention. Despite assessing the performance status of cancer patients as good, geriatric patients exhibit diminished metabolic and physiological capacities. Therefore, this patient group is at increased risk of developing severe treatment-related toxicity, decline in overall health, and a substantial reduction in their quality of life. This on turn may result in higher dependency on external help in performing the ADLs. According to previous studies, approximately 33%-50% of adults with cancer face challenges or need help in carrying out basic and instrumental ADLs (178). In a meta-analysis performed by Neo, the most frequently affected basic ADLs were personal hygiene, walking and transfers, while the instrumental ADLs most commonly affected included housework, shopping, and transportation (178).

As maintaining of the independence is one of the goals in geriatric patients, there is a growing body of studies analysing the influence of cancer therapy on the activities of daily living and mobility in elderly patients. A meta-analysis performed by Neo revealed that about one-third of

adults with cancer display difficulties in carrying out ADLs and about a half needs assistance in performing IADLs(178).

To date, there is a limited number of studies that specifically focus on the influence of cancer therapy on the dynamics of patients' independence. A study of Rier showed that approximately 80% of geriatric patients receiving curative cancer treatment were able to maintain their IADL, whereas only 57% patients undergoing palliative therapy were able to sustain their IADL (179). A study of Hoppe revealed that 16,7% of older patients receiving systemic therapy experienced a functional decline after the therapy(180). Furthermore, a functional decline has been observed in patients with breast and prostate cancer after chemotherapy or hormone deprivation therapy(181,182).

However, data on the influence of the RT on functional status are sparse. Ursem et al. reported a gradual lowering of the ADL score in patients undergoing RT for prostate cancer (183). Reduced functionality was also reported in patients obtaining thoracic RT. However, the effects of RT on heart and lung function cannot be separated from other components influencing patients' ability to perform the ADLs. Nevertheless, RT could lead to the activation of subclinical inflammatory process potentially resulting in a decrease in observed strength and reduced ability to carry out ADLs.

In our study cohort, we did not observe significant alterations in the capability to perform basic ADL. This might be explained by a high baseline ADL score achieved by most patients at baseline and the relatively moderate toxicity associated with RT for prostate cancer.

In contrast, our results show a slight decline concerning the instrumental ADL during the observation time. This finding could be explained by a greater involvement of patients' families in addressing the daily requirements encompassed in IADLs.

10.1.3.2 Mobility

In our study, we observed a significant shorter time for the TUG at the control appointment 3 months after the RT in comparison to the time needed at the pretherapeutic assessment. In addition, comparisons between the first and second follow-up examination, as well as between the baseline and the second follow-up examination did not show a significant difference in the time needed in TUG assessment. These results are in contrast to previous studies investigating mobility and muscle strength in cancer patients undergoing cancer directed therapy.

For instance, McMcrary et al. described an association between chemotherapy-induced polyneuropathy and mobility deficits in a group of 100 patients (184). Furthermore, Clay et al detected a negative effect of ADT on physical function and walking speed (185). Alibhai et al. reported a decline of physical function measured with grip strength and 6MWT in prostate cancer patients receiving ADT, however, significant changes in the TUG score were not detected(186).

Nevertheless, there is currently no study on the influence of RT on mobility. The improvement in the TUG observed in our study, from baseline to the assessment three months after RT,

could potentially be attributed to changes in stool and urinary habits resulting from radiation-induced side effects. However, further research is needed to confirm or refute our findings.

10.1.4 Depression

Due to the psychological stress and substantial toxicity commonly associated with cancer diagnosis and treatment, cancer patients are at high risk of developing depression. The prevalence of depression in cancer patients is estimated to be up to three times higher than that in the general population (187). For instance, a meta-analysis of Watts showed a high prevalence of pre-treatment, in-treatment and post-treatment depression and anxiety in prostate carcinoma patients (188). In a trial performed by Chhatre et al., median depression scores increased at 6, 12 and 24 months in prostate cancer patients undergoing AS, RPE, and RT. Furthermore, depression was associated with a regret score concerning treatment decisions (189). An additional study by g et al. showed that a shared decision-making during therapy planning might have a protective effect against mood alterations (190).

Furthermore, administration of ADT has been linked with the development of depression (191,192). ADT may lead to persistent erectile disorders and heat flushes which may strongly negatively influence quality of life (193). Furthermore, administration of ADT may cause weight gain and loss of muscle mass, this, in turn, can alternate patients' self-perception and worsen the mood(194). However, the latency time from the initiation of ADT and begin of depression is unknown, similarly, it is not easy to estimate the persistent activity of completed ADT.

The GDS analysis in our study showed a significant worsening of mood between the initiation of RT and the control appointment 3 months after radiation therapy. Moreover, a further significant worsening was found 15 months after completion of radiation therapy when compared to the assessment 3 months after RT.

In our cohort, most patients received neoadjuvant ADT starting 6 months before the start of radiation therapy. The gradual increase in GDS scores within our cohort can therefore be explained by a combination of factors, including the effects of ADT treatment and its side effects, acute and late toxicity induced by radiation therapy, and alterations in everyday habits.

10.1.5 Nutritional assessment

Cancer and cancer treatment can induce malnutrition. Symptoms associated with cancer, such as loss of appetite, pain, bloating, gastrointestinal impairment, nausea, and emesis can lead to reduced food intake and weight loss. Cancer therapy often causes alterations in taste, nausea, fatigue, and difficulties in chewing and swallowing contributing to a further decrease of body muscle and fat mass(195,196). Additionally, factors such as severe health decline, psychological problems, and excessive medication can alter eating habits (197). Therefore, close attention should be paid to the nutritional status of patients before the initiation of cancer treatment, particularly intensive curative treatment modalities (198).

Qualitative and quantitative inappropriate intake of nutrients may result in the loss of fat and non-fat body tissue and lead to sarcopenia and development of a frail body phenotype. This in turn may lead to the self-perceived decline of muscle strength, generalized muscle weakness and reported self-assessed general health condition.

In our study, the nutritional status was assessed using the mini nutritional assessment (MNA) which includes questions about health issues influencing weight, current diet and medications intake, measurement of the circumference of arm and calf as well as the analysis patients' perception of their own health. A small number of patients was classified as malnourished, however, the majority exhibited a normal nutritional status. Although the mean value of the score was in the normal value

However, a significant decrease in the MNA score was detected between the baseline and two reassessments 3 and 15 months after radiation therapy, respectively. This decline in scores which still remains above the malnutrition cut-off, may be attributed to muscle loss which was frequently mentioned by patients during follow-up appointments. In addition, treatment-related toxicity could increase the number of taken medications as well as negatively influence the self-perceived health status leading to a decrease in MNA score. Pre-radiation therapy instructions, emphasizing a balanced diet and adequate hydration, could positively influence patients' nutritional decisions after completion of therapy.

10.1.6 Charlson Comorbidity Index

Given that the average age of prostate cancer diagnosis is 67 years, it is very likely that a vast majority of patients suffers from at least one comorbidity (199,200). Age related diseases may adversely affect the performance status of geriatric patients and need to be strongly considered when choosing an appropriate therapy (201).

The development of new diseases during oncologic therapy can be classified into two categories: those arising from predisposing factors, for example the occurrence of another malignancy shortly after the first cancer diagnosis, and those resulting from a depletion of metabolic reserve during cancer therapy.

Nevertheless, comorbidity burden has been associated with the progression of ageing processes. Chronic diseases such as congestive heart failure, history of myocardial infarction, arthritis, peripheral vascular disease, diabetes, hypertension, chronic obstructive lung disease, and depression have been associated with frailty among elderly. An elevation of the comorbidity burden in the course of a malignant disease due to occurrence of new metastases may therefore contribute to developing a frail phenotype and accelerate the biological ageing.

In our study, we did not detect a significant change in the comorbidity index during the observation time. Although our study showed no changes in comorbidity status, a more extended follow-up emphasizing the association between comorbidity status and major endpoints will provide further insight into the prognostic value of CCI.

10.2 **Biochemical parameters of chronic inflammation**

The observed values of the biochemical markers of ageing as well as their dynamics from the baseline, through RT, and during follow-up provide valuable insights into the role of radiation treatment for the initiation of an inflammatory response.

10.2.1 C-reactive protein

CRP represents an indicator of inflammation, with heightened CRP levels commonly observed during acute inflammation caused by infection, trauma, or other factors. In addition, elevated CRP levels are also observed in individuals suffering from chronic diseases such as diabetes mellitus, coronary disease, arterial hypertension or chronic renal disease indicating a chronic inflammatory response (202–205). High CRP levels have been associated with worse physical performance, decreased cognitive function, and poorer survival (104,206–208). For instance, in a cohort of high-functioning elderly patients, elevated levels of CRP have been identified as an independent risk factor associated with an over 2-fold increased risk of death(104). Therefore, the association between chronic inflammation and premature ageing continues to be a subject of many studies.

Increased CRP levels reflect a high metabolic activity and turnover and can also be observed in the course of radiation therapy, particularly in cases involving large tumour volumes or concurrent chemotherapy (209,210).

In our study cohort, we did not observe any significant dynamics in the CRP level between the baseline and other observation points. Although some patients showed a higher CRP level which was not caused by an infection or injury, RT did not significantly influence the CRP levels.

10.2.2 Fibrinogen

Fibrinogen, a 340-kDa glycoprotein, is one of the most important coagulation factors and also displays a proinflammatory activity. There is a body of evidence suggesting a pivotal role of fibrinogen in acute as well as in chronic inflammatory reaction (211). An increased expression of fibrinogen has been observed in several malignant and non-malignant diseases such as multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, bacterial infection, colitis, lung and kidney fibrosis, and Duchenne muscular dystrophy (211).

In addition, increased fibrinogen expression has been demonstrated in various tumours, influencing tumour growth, progression, angiogenesis, and the metastatic spread of malignant cells. The elevated levels of fibrinogen detected in cancer patients may result from tumour-associated cytokines or increased fibrinogen synthesis by the tumour cells (212).

An increase of fibrinogen levels has also been observed in ageing individuals, correlating with the ageing process and age-related conditions. Welstead and other authors described an association between elevated fibrinogen levels and frailty (213,214). Further investigations have also linked higher fibrinogen levels with the occurrence of frailty or comorbidities during long-term follow-ups (215,216).

Although the data regarding the influence of radiation therapy on fibrinogen synthesis is sparse, ionizing radiation along with infection or physical injury remains a significant trigger for the inflammation process and the release of inflammatory cytokines.

In our study, patients exhibited a marginally significant increase in blood fibrinogen levels during the course of radiotherapy. In addition, we detected a significant increase in fibrinogen levels at the follow-up examinations 3 and 15 months after radiation therapy when compared

to baseline. These results suggest that radiation therapy has an effect on triggering a chronic inflammatory process that persists beyond the completion of RT over an extended observation period. These results support the hypothesis that RT could contribute to an acceleration of ageing by initiating a systemic inflammatory process.

10.2.3 Albumin and Cholesterol

Low serum cholesterol and albumin levels have been proposed as indicators of subclinical chronic inflammation and/or dysregulation in inflammatory processes that contribute to an “ageing” phenotype and have been linked with functional decline (102,217–219). Additionally, hypoalbuminemia has been associated with a higher risk of all-cause mortality. Even in the group of patients with normal albumin levels (35-50 g/L) (107,220), investigators found a graded increase in all-cause mortality from patients with highest normal compared with lowest normal values (107).

10.2.3.1 Albumin

Albumin is a blood serum protein, which is decreased due to nutritional deficiencies, malabsorption, or as a consequence of acute or chronic inflammatory diseases (217). Acute and chronic inflammatory diseases can result in a loss or increased turnover of serum proteins, particularly by altering hepatic protein metabolism and inducing capillary leakage. Eckart and colleagues associated elevated inflammatory parameters with hypoalbuminemia in patients with acute illness (221). In chronic inflammatory diseases such as chronic renal failure, elevated inflammatory parameters have also been associated with hypoalbuminemia (222). The presence of hypoalbuminemia in cancer patients has been correlated with an unfavourable prognosis, indicating that a deficiency in serum proteins is linked to impaired recovery capabilities (223).

A decline in serum albumin during advanced age was observed in both genders and this finding was unrelated to the overall health status (224). Among hospitalized elderly individuals, up to 90% of patients were reported to have hypoalbuminemia (225) indicating that hypoalbuminemia is a component of the physiological ageing process.

Hypoalbuminemia was associated with sarcopenia in elderly patient. In numerous publications, lower serum albumin levels were found in individuals who displayed clinical signs sarcopenia (226) Other research has linked hypoalbuminemia not only with sarcopenia but also with frailty (227).

Thus, reduced serum albumin levels may be connected to an accelerated ageing process, leading to limited compensatory capacity and unfavourable outcomes in severe oncological and non-oncological conditions.

In our cohort, we detected a decline of serum albumin levels from the baseline assessment to the evaluation at the completion of radiation therapy. This indicates that radiation therapy induces an activation of inflammatory processes. The notable increase in albumin levels post-radiation therapy underscores the capacity for the metabolic reserve in our patients to renew. However, a significant difference persisted between the first measurement and the assessment three months after radiation therapy. A further recovery became apparent 15 months post-radiation resulting in a insignificant distinction between the baseline and this

subsequent blood evaluation. This observation suggests that the reduction in albumin levels is transient and potentially modifiable.

Until now, there has been no study analysing the impact of radiation therapy on serum albumin levels. Findings from our study cohort imply that RT may play a role in triggering the inflammatory process in prostate cancer patients, leading to a moderate reduction in metabolic reserve.

10.2.3.2 Cholesterol

The cholesterol levels observed in our cohort showed a significant decline during the course of RT, followed by a significant recovery between the end of RT and the first follow-up. Furthermore, there was a significant decrease in cholesterol levels between the first and second follow-ups, along with an overall significant reduction in blood cholesterol from baseline to 15 months after completion of RT. We suppose that, similarly to the decline in albumin levels, RT triggers an inflammatory process, excessive utilization of body fat reserves, and only partial compensation for these processes in the elderly organism. Unlike the albumin level, the decrease in serum cholesterol appears not to be transient, as there was a significant drop in cholesterol levels between 3 and 15 months post- completion of RT.

The decline in cholesterol levels observed in our cohort suggests a radiation-therapy induced reduction in metabolic reserves, possibly driven by inflammatory processes triggered by RT and therefore accelerated occurrence of ageing symptoms. Supporting this hypothesis, a cross-sectional study found that high blood cholesterol levels were associated with a lower risk of four frailty subtypes (228) Additionally, in a study conducted by Manieri et al., significantly lower cholesterol levels were observed in individuals with ageing-related conditions such as cognitive impairment, poorer somatic health, higher disability, and a higher level of malnutrition (229) These findings support our hypothesis regarding a link between biochemical changes induced by radiation therapy and the acceleration of ageing processes.

10.2.4 NLR and PLR

NLR and PLR represent markers of chronic inflammation. Higher PLR and NLR scores are found in patients with heart failure, autoimmune diseases such as lupus and other inflammatory mediated conditions (230–232).

Increased NLR and PLR also frequently indicate an underlying subclinical chronic inflammation linked to metabolic syndrome and cardiovascular diseases. In previous studies, an elevated NLR has been associated with the prevalence of components of metabolic syndrome (233). In addition, an elevated PLR has been recognized as an indicator of more severe coronary artery disease in patients experiencing stable angina pectoris (234).

Additionally, elevated PRL and NLR have been correlated with physiological ageing as well as with age-related conditions. For instance, increased NLR levels were found in a population study in a collective of elderly individuals (235). In addition, elevated NLR and PLR levels have been correlated with a lower grip strength, and sarcopenia (236–240) as well as with cognitive decline and frailty. Furthermore, elevated NLR and PLR in postmenopausal women have been

correlated with lower bone (241). The data from these studies confirm the valuable role of PLR and NLR in monitoring age-related conditions.

Additionally, numerous studies showed also a prognostic role of PLR and NLR on treatment outcome in patients with cancer (155,242). In the studies analysing the role of PLR and NLR in malignancies, the elevated values of these parameters were associated with the secretory activity of cancer affecting coagulation as well as with the infiltration of cancer tissue with lymphocytes (243,244). In the most studies, the baseline values of NLR and PLR were analysed in order to predict the outcome in the patients.

However, data on the dynamics of PLR and NLR in the course of oncologic therapy and follow-up are sparse. In a previous study, a negative prognostic value of persistent elevated PLR and NLR levels 24-36 months after breast cancer treatment has been detected (245). However, the influence of different treatment modalities on PLR and NLR levels has not yet been analysed.

In our study we detected a significant increase of NLR from the baseline assessment to the end of the therapy course. Subsequently, a significant decline in NLR was evident.

In terms of PLR, we noted a significant increase from the initiation of the therapy to the end of the therapy course. After the completion of RT, the PLR decreased, however, at the second follow-up assessment, the PLR remained significantly higher compared to baseline.

The observed dynamics of PLR and NLR may reflect the different influence of RT on blood components. Lymphocytes are acknowledged as the most radiosensitive cells with up to 93% of patients receiving irradiation experiencing lymphopenia (246). The impact of RT on lymphocytes is not only associated with bone marrow volume, but also with the volume of blood and lymphatics within the radiation (239,247). Neutrophils seem to be less sensitive to radiation compared to lymphocytes. Platelets reduction is also observed in patients receiving radiation therapy (248); however, the use of IMRT showed a milder drop in thrombocytes compared to 3D conformal RT (249).

Since our patients underwent irradiation in a small body area and the bone marrow exhibits a high regenerative capacity, particularly over the long term, our results indicate that RT leads to the onset of inflammatory processes and the sustenance of minimal intrinsic inflammation levels thereafter. This supports the notion of radiation therapy potentially influencing the ageing process through inflammatory mechanisms.

10.3 Telomere length

In our cohort, we could observe a significant telomere attrition 15 months after RT compared to both baseline and the assessment conducted at the end of RT. Additionally, a significant shortening of telomere length was detected between the follow-up assessments at 3 and 15 months post-treatment. Furthermore, although not statistically significant, there was a marginal increase in telomere length measured 3 months after the radiation therapy compared to both baseline and the completion of the radiation therapy course.

The shortening of telomeres throughout lifespan and its relationship with ageing has extensively been described in the literature. Cellular senescence results in a progressive

reduction in telomere length leading to impaired tissue and organ functions commonly observed in ageing organisms. Accelerated telomere attrition is observed in people 70 years and older (250) however, a deceleration of this process in physically healthy people over 90 years suggests a potential predisposition for maintaining telomere length and preserving physical condition in certain long-living individuals (251). Telomere attrition has been well described in several longitudinal studies. For instance, Crocco and colleagues described a decrease of about 13.64% in leucocytes telomere length over a 7-years observation period(250).

Telomere shortening can be accelerated by environmental factors such as psychological and physiological stress, cigarette smoking, obesity, and high homocysteine blood level (252). Furthermore, accelerated ageing was described in studies including childhood cancers survivors which suggest an influence of cancer therapy on ageing (253). Several studies described a correlation between cancer therapy and telomere shortening (253,254). However, the quality of data is heterogenous as many studies have only included small patients' groups. In the studies analysing the impact of chemotherapy, there have been mixed findings, with some reporting no association while others indicate telomere shortening.

However, there are studies describing contrasting effects of external noxes on the telomere length. A large observational study conducted in workers directly engaged in cleaning the contaminated areas around Chernobyl power plant after the nuclear catastrophe from 1986 revealed a significant longer telomere in one group of the workers (255). The study describes that worker dealing with dirtier tasks connected to a higher exposure to radiation, had longer telomeres than workers responsible for tasks related to lower radiation exposure (255). The explanation of this phenomenon could be the activation of telomerase in the most exposed workers resulting with higher observed mean telomere length. However, the authors point out the unknown impact of other factors such as extensive alcohol and cigarette consume as well as chronic psychic stress which could also influence the obtained results. Furthermore, among the cancer patients, there is some evidence suggesting a lengthening of telomeres in the course of the anti-cancer therapy (256). In a cross-sectional study including patients with ovarian cancer treated with surgery and cis-platin based chemotherapy, telomeres were observed to be longer after therapy compared to baseline (257). In contrast, a longitudinal study conducted by Maeda et al. examined telomere shortening in 25 patients aged 52-83 undergoing radiation therapy alone, showing no overall association (258). However, decrease in the proportion of short telomeres was detected with higher doses.

There is also a row of studies describing the interaction between chronic inflammation and telomere length. A study performed on patients with depression revealed a significant correlation between elevated CRP values and telomere shortening (259). The relationship between chronic inflammation and telomere shortening is being described as a two-sided process by some authors. Most papers suggest a negative influence of chronic inflammation on telomere length, whereas a small body of evidence suggests the activation of chronic inflammation through shortened telomeres and impaired cell function (260).

To date, the results regarding the influence of external noxes on telomere shortening remain inconclusive. Our results suggest a moderate effect of radiation therapy on telomere recovery immediately following treatment, which did not reach statistical significance in our study cohort. However, the most intriguing observation is the prolonged, negative effect of ionizing radiation

on telomere length 15 months after treatment, indicating the activation of mechanisms leading to telomere attrition, potentially through the activation of chronic inflammatory processes.

10.4 Correlations between laboratory and clinical parameters

In our study, we detected several associations between age-related biomarkers and scores reached in various components of comprehensive geriatric assessment.

For instance, an elevated NLR and decreased albumin levels were linked to a diminished mood status measured with GDS indicating an influence of the inflammatory status and metabolic reserve on mood.

Furthermore, a pretherapeutic lower cholesterol level and an elevated fibrinogen level were associated with a longer time needed for the completion of the tasks of the TUG supporting the influence of sarcopenia and chronic inflammation on patient mobility.

In contrast, a higher baseline cholesterol level significantly correlated with a better social situation suggesting a greater metabolic reserve that enables patients to maintain social contacts and pursue their hobbies.

In our analyses, we also detected a significant correlation between an elevated NLR and an increased burden of comorbidities. This relationship can be attributed to the inflammatory background of many of the conditions assessed by the CCI, such as cardiovascular diseases, chronic soft tissue ailments, pulmonary disorders, and malignancies.

We also observed a significant negative relationship between telomere length and nutritional status suggesting a pre-existing telomere erosion caused possibly by unhealthy nutritional habits, extensive pharmacy, recently experienced acute illness or worse general body condition manifested by worse self-perceived health status.

The correlations observed between clinical and biochemical age-related parameters could contribute to identification of biologically older patients. However, future studies are necessary to confirm our findings.

10.5 Strengths and limitations

To the best of our knowledge, this study represents the first analysing the influence of small-volume prostate cancer radiation therapy on clinical, biochemical and molecular ageing-related parameters. Major strengths of our study are its prospective design as well as the inclusion of such a large and homogeneous patient cohort resulting in a high level of scientific significance.

To date, no previous studies on ageing have been performed including a comparable number of participants who obtained the same treatment regimen.

Regarding radiation treatment for prostate cancer, nearly all patients received conventionally fractionated RT with the same single fraction dose of 2 Gy and total radiation dose ranging from 70 to 78 Gy. Patients treated with hypofractionated RT received an equivalent

radiobiologic radiation dose ranging from 68,4 to 72 Gy. Target volumes were defined according to current international guidelines, in addition, definition of set up margins as well as daily imaging were performed according to institutional internal guidelines. Furthermore, the planning procedure was performed by the same team of planning radiation technologist and physicist and volumetric modulated arc radiation therapy was applied in all patients.

Furthermore, the clinical assessments and reassessments were performed by a group of four radiation oncologists trained in the same manner what implies a high quality and homogeneity of the obtained clinical data. The comprehensive geriatric assessment conducted encompassed included all crucial health domains, and the laboratory analyses focused on key haematological, biochemical and molecular parameters related to aging. Therefore, the data obtained enable a comprehensive analysis of changes in health status within the described patient group.

The selected observation period following the completion of RT also allows a proper interpretation of the ageing alternations triggered by the treatment, as the 18-month timeframe is suitable for detecting significant changes in molecular, biochemical, and clinical parameters compared to those occurring naturally through ageing.

Nevertheless, a few limitations of our study have to be taken into account. There may be a moderate selection bias in the study cohort that results from the preselection of the patients with prostate cancer in our region conducted by the urologist, who were referring the patients for the further treatment. For instance, patients with a strongly reduced general performance and patients with a limited life expectancy due to their advanced comorbidities were not referred to the RT at all and probably obtained ADT as the single treatment.

Another potential drawback of our study is the longitudinal design with only one observed patients' cohort. A Matched Pair Case-Control Study could possibly allow for a comparison between the dynamics of natural ageing and accelerated ageing in patients obtaining RT with or without ADT. Similarly, we lack the opportunity to compare our results with a group of patients undergoing exclusively surgical treatment or ADT for prostate cancer. Furthermore, attempting to construct a matching control group without malignancy could result in a strong selection bias and deliver unreliable data regarding patients' health. Additionally, conducting an observational study involving prostate cancer patients who do not receive appropriate cancer therapy would lead to a high selection bias and lack ethical justification.

In addition, a total of 64 patients was lost between the baseline second follow-up up. Nevertheless, the remaining observation cohort, consisting of over 200 patients, still meets the required number of individuals to maintain the significance level of our results.

In summary, the size and homogeneity of our study cohort, as well as the prospective, observational design and the high quality of collected data, render our results highly significant and reliable.

11 Conclusions

The results obtained in the present study indicate that curative radiation therapy significantly affects the ageing process. Most of the clinical alterations identified reveal a significant negative impact of RT on the ageing process. Furthermore, our results indicate that the locally administered radiation therapy leads to the initiation of an inflammatory process within the body contributing to a reduction in metabolic reserve. We also detected a protracted shortening of telomeres suggesting that RT triggers ageing-processes through the enhancement of cellular senescence.

In addition, biochemical parameters were significantly associated with ageing-related clinical conditions suggesting that laboratory markers could be used for the identification of fragile patients. However, additional studies are necessary before firm conclusions regarding the relationship between clinical conditions and biochemical parameters can be drawn.

Nevertheless, it is essential to consider the impact of radiation therapy on accelerated ageing when deciding on the optimal cancer treatment, particularly for patients with compromised health status or those for whom there are medically equivalent alternatives.

12 Bibliography

1. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Vol. 48, *Age and Ageing*. Oxford University Press; 2019. p. 16–31.
2. Osteosarcopenia A case of geroscience.
3. Azzolino D, Spolidoro GCI, Saporiti E, Luchetti C, Agostoni C, Cesari M. Musculoskeletal Changes Across the Lifespan: Nutrition and the Life-Course Approach to Prevention. Vol. 8, *Frontiers in Medicine*. Frontiers Media S.A.; 2021.
4. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ, Ilich JZ. Aging human body: Changes in bone, muscle and body fat with consequent changes in nutrient intake. Vol. 234, *Journal of Endocrinology*. BioScientifica Ltd.; 2017. p. R37–51.
5. Riggs BL, Melton LJ, O'fallon WM. Drug Therapy for Vertebral Fractures in Osteoporosis: Evidence That Decreases in Bone Turnover and Increases in Bone Mass Both Determine Antifracture Efficacy. Vol. 18. 1996.
6. *The Effects of Medications on Bone*. 2007.
7. Xu L, Zhao Q, Li K, Zhang Y, Wang C, Hind K, et al. The Role of Sex Hormones on Bone Mineral Density, Marrow Adiposity, and Muscle Adiposity in Middle-Aged and Older Men. *Front Endocrinol (Lausanne)*. 2022 Feb 21;13.
8. Daley MJ, Spinks WL. *Sports Medicine* 29: 1-12, Jan 2000. Vol. 29, *Sports Med*. 2000.
9. Shafrin J, Sullivan J, Goldman DP, Gill TM. The association between observed mobility and quality of life in the near elderly. *PLoS One*. 2017 Aug 1;12(8).
10. Bergland A, Jørgensen L, Emaus N, Strand BH. Mobility as a predictor of all-cause mortality in older men and women: 11.8 year follow-up in the Tromsø study. *BMC Health Serv Res*. 2017 Jan 10;17(1).
11. Terry RD, Katzman R. Life span and synapses: will there be a primary senile dementia? *Neurobiol Aging*. 2001 May;22(3):347–8.
12. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Vol. 29, *Clinics in Geriatric Medicine*. 2013. p. 737–52.
13. Terry RD, Katzman R. Life span and synapses: will there be a primary senile dementia? [Internet]. 2001. Available from: www.elsevier.com/locate/neuaging
14. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal Magnetic Resonance Imaging Studies of Older Adults: A Shrinking Brain. 2003.
15. Dickstein DL, Kabaso D, Rocher AB, Luebke JI, Wearne SL, Hof PR. Changes in the structural complexity of the aged brain.
16. Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, et al. β -amyloid imaging and memory in non-demented individuals: Evidence for preclinical Alzheimer's disease. *Brain*. 2007 Nov;130(11):2837–44.

17. Rodrigue KM, Kennedy KM, Park DC. Beta-amyloid deposition and the aging brain. Vol. 19, *Neuropsychology Review*. 2009. p. 436–50.
18. Jack CR, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain*. 2008;131(3):665–80.
19. Salat DH, Kaye JA, Janowsky JS. Prefrontal Gray and White Matter Volumes in Healthy Aging and Alzheimer Disease [Internet]. Vol. 56, *Arch Neurol*. 1999. Available from: <https://jamanetwork.com/>
20. Rogalski E, Stebbins GT, Barnes CA, Murphy CM, Stoub TR, George S, et al. Age-related changes in parahippocampal white matter integrity: A diffusion tensor imaging study. *Neuropsychologia*. 2012 Jul;50(8):1759–65.
21. Van Der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. Vol. 76, *Neurology in Practice*. 2005.
22. General risk factors for dementia A systematic evidence review.
23. Summary of the evidence on modifiable risk factors for cognitive decline and dementia A population-based perspective Elsevier Enhanced Reader.
24. Yin J, Lassale C, Steptoe A, Cadar D. Exploring the bidirectional associations between loneliness and cognitive functioning over 10 years: The English longitudinal study of ageing. *Int J Epidemiol*. 2019 Dec 1;48(6):1937–48.
25. *Psychiatric Disorders in the Elderly*.
26. Sood A, Singh P, Gargi P. Psychiatric morbidity in non-psychiatric geriatric inpatients. *Indian J Psychiatry*. 2006;48(1):56.
27. *The Impact of Depression on Quality of Life of the Elderly Elsevier Enhanced Reader*.
28. Vaughan L, Leng X, La Monte MJ, Tindle HA, Cochrane BB, Shumaker SA. Functional independence in late-life: Maintaining physical functioning in older adulthood predicts daily life function after age 80. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*. 2016 Mar 1;71:S79–86.
29. KATZ S. Assessing Self-maintenance: Activities of Daily Living, Mobility, and Instrumental Activities of Daily Living. *J Am Geriatr Soc*. 1983 Dec;31(12):721–7.
30. Farias ST, Park LQ, Harvey DJ, Simon C, Reed BR, Carmichael O, et al. Everyday cognition in older adults: Associations with neuropsychological performance and structural brain imaging. *Journal of the International Neuropsychological Society*. 2013;19(4):430–41.
31. Chu NM, Sison S, Muzaale AD, Haugen CE, Garonzik-Wang JM, Brennan DC, et al. Functional independence, access to kidney transplantation and waitlist mortality. *Nephrology Dialysis Transplantation*. 2020 May 1;35(5):870–7.
32. Sands LP, Yaffe K, Lui LY, Stewart A, Eng C, Covinsky K. The Effects of Acute Illness on ADL Decline Over 1 Year in Frail Older Adults With and Without Cognitive Impairment [Internet]. Vol. 57, *Journal of Gerontology*. 2002. Available from: <https://academic.oup.com/biomedgerontology/article/57/7/M449/553461>

33. Tomioka K, Kurumatani N, Hosoi H. Association between social participation and instrumental activities of daily living among community-dwelling older adults. *J Epidemiol.* 2016;26(10):553–61.
34. Mamikonian-Zarpas A, Laganá L. The Relationship between Older Adults' Risk for a Future Fall and Difficulty Performing Activities of Daily Living. *J Aging Gerontol* [Internet]. 2015 Mar 24;3(1):8–16. Available from: <http://savvysciencepublisher.com/jms/index.php/jag/article/view/242>
35. Beltz S, Gloystein S, Litschko T, Laag S, van den Berg N. Multivariate analysis of independent determinants of ADL/IADL and quality of life in the elderly. *BMC Geriatr.* 2022 Dec 1;22(1).
36. Poverty Among the Population Aged 65 and Older [Internet]. Available from: <https://crsreports.congress.gov>
37. Department of Economic and Social Affairs programme on ageing The focal point on ageing in the United Nations system social.un.org/ageing [@UN4Ageing](https://twitter.com/UN4Ageing).
38. Khan N, Khan S, Tan Swee Leng O, Booi Chen T, Gale Vergara R. Explore the Factors that Influence Elderly Poverty. *IBIMA Publishing Journal of Southeast Asian Research* [Internet]. 2017;2017:13. Available from: <http://www.ibimapublishing.com/journals/JSAR/jsar.html>
39. Khan N, Khan S, Tan Swee Leng O, Booi Chen T, Gale Vergara R. Explore the Factors that Influence Elderly Poverty. *IBIMA Publishing Journal of Southeast Asian Research* [Internet]. 2017;2017:13. Available from: <http://www.ibimapublishing.com/journals/JSAR/jsar.html>
40. Almeida APSC, Nunes BP, Duro SMS, Facchini LA. Socioeconomic determinants of access to health services among older adults: a systematic review. *Rev Saude Publica.* 2017;51.
41. Guthmuller S. Loneliness among older adults in Europe: The relative importance of early and later life conditions. *PLoS One.* 2022 May 18;17(5):e0267562.
42. Guthmuller S. Loneliness among older adults in Europe: The relative importance of early and later life conditions. *PLoS One.* 2022 May 1;17(5 May).
43. James Alexander Crewdson. The Effect of Loneliness in the Elderly Population: A Review. *Healthy Aging Clin Care Elder.* 2016 Mar 7;8:1–8.
44. Beridze G, Ayala A, Ribeiro O, Fernández-Mayoralas G, Rodríguez-Blázquez C, Rodríguez-Rodríguez V, et al. Are loneliness and social isolation associated with quality of life in older adults? Insights from Northern and Southern Europe. *Int J Environ Res Public Health.* 2020 Nov 2;17(22):1–15.
45. Aylaz R, Aktürk Ü, Erci B, Öztürk H, Aslan H. Relationship between depression and loneliness in elderly and examination of influential factors. *Arch Gerontol Geriatr.* 2012 Nov;55(3):548–54.

46. Zhang CQ, Chung PK, Zhang R, Schüz B. Socioeconomic Inequalities in Older Adults' Health: The Roles of Neighborhood and Individual-Level Psychosocial and Behavioral Resources. *Front Public Health*. 2019 Oct 25;7.
47. Read S, Grundy E, Foverskov E. Socio-economic position and subjective health and well-being among older people in Europe: A systematic narrative review. Vol. 20, *Aging and Mental Health*. Routledge; 2016. p. 529–42.
48. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *Journal of Clinical Oncology*. 2014 Aug 20;32(24):2595–603.
49. Antonio M, Saldaña J, Carmona-Bayonas A, Navarro V, Tebé C, Nadal M, et al. Geriatric Assessment Predicts Survival and Competing Mortality in Elderly Patients with Early Colorectal Cancer: Can It Help in Adjuvant Therapy Decision-Making? *Oncologist*. 2017 Aug 1;22(8):934–43.
50. Freyer G, Geay JF, Touzet S, Provencal J, Weber B, Jacquin JP, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Annals of Oncology*. 2005 Nov;16(11):1795–800.
51. Biesma B, Wymenga ANM, Vincent A, Dalesio O, Smit HJM, Stigt JA, et al. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin–gemcitabine or carboplatin–paclitaxel: NVALT-3 a phase III study. *Annals of Oncology*. 2011 Jul;22(7):1520–7.
52. Hamaker ME, Vos AG, Smorenburg CH, Rooij SE, Munster BC. The Value of Geriatric Assessments in Predicting Treatment Tolerance and All-Cause Mortality in Older Patients With Cancer. *Oncologist*. 2012 Nov 1;17(11):1439–49.
53. Pilnik NG, Ibero M M, Carri D, Mareca O. Influence of some clinical parameters in the tolerance to treatment in elderly patients with advanced lung cancer. *Journal of Clinical Oncology*. 2010 May 20;28(15_suppl):e19600–e19600.
54. Loh KP, Soto-Perez-de-Celis E, Hsu T, de Glas NA, Battisti NML, Baldini C, et al. What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper. *J Oncol Pract*. 2018 Feb;14(2):85–94.
55. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. *Cell*. 2013 Jun;153(6):1194–217.
56. Schmauck-Medina T, Molière A, Lautrup S, Zhang J, Chlopicki S, Madsen HB, et al. New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary. *Aging*. 2022 Aug 31;14(16):6829–39.
57. Maldonado E, Morales-Pison S, Urbina F, Solari A. Aging Hallmarks and the Role of Oxidative Stress. *Antioxidants*. 2023 Mar 6;12(3):651.

58. Narita M, Nuñez S, Heard E, Narita M, Lin AW, Hearn SA, et al. Rb-Mediated Heterochromatin Formation and Silencing of E2F Target Genes during Cellular Senescence. *Cell*. 2003 Jun;113(6):703–16.
59. Miller KN, Dasgupta N, Liu T, Adams PD, Vizioli MG. Cytoplasmic chromatin fragments—from mechanisms to therapeutic potential. *Elife*. 2021 Jan 29;10.
60. Moujaber O, Fishbein F, Omran N, Liang Y, Colmegna I, Presley JF, et al. Cellular senescence is associated with reorganization of the microtubule cytoskeleton. *Cellular and Molecular Life Sciences*. 2019 Mar 1;76(6):1169–83.
61. Das UN. “Cell Membrane Theory of Senescence” and the Role of Bioactive Lipids in Aging, and Aging Associated Diseases and Their Therapeutic Implications. *Biomolecules*. 2021 Feb 8;11(2):241.
62. Srivastava S. The Mitochondrial Basis of Aging and Age-Related Disorders. *Genes (Basel)*. 2017 Dec 19;8(12):398.
63. Giorgi C, Marchi S, Simoes ICM, Ren Z, Morciano G, Perrone M, et al. Mitochondria and Reactive Oxygen Species in Aging and Age-Related Diseases. In 2018. p. 209–344.
64. Liu J, Hetzer MW. Nuclear pore complex maintenance and implications for age-related diseases. *Trends Cell Biol*. 2022 Mar;32(3):216–27.
65. Rocha A, Dalgarno A, Neretti N. The functional impact of nuclear reorganization in cellular senescence. *Brief Funct Genomics*. 2022 Jan 25;21(1):24–34.
66. Barascu A, Le Chalony C, Pennarun G, Genet D, Zaarour N, Bertrand P. Oxidative stress alters nuclear shape through lamins dysregulation. *Nucleus*. 2012 Sep 27;3(5):411–7.
67. Gonzalo S. DNA Damage and Lamins. In 2014. p. 377–99.
68. Taimen P, Pflieger K, Shimi T, Möller D, Ben-Harush K, Erdos MR, et al. A progeria mutation reveals functions for lamin A in nuclear assembly, architecture, and chromosome organization. *Proceedings of the National Academy of Sciences*. 2009 Dec 8;106(49):20788–93.
69. Kaushik S, Tasset I, Arias E, Pampliega O, Wong E, Martinez-Vicente M, et al. Autophagy and the hallmarks of aging. *Ageing Res Rev*. 2021 Dec;72:101468.
70. Nechushtai L, Frenkel D, Pinkas-Kramarski R. Autophagy in Parkinson’s Disease. *Biomolecules*. 2023 Sep 22;13(10):1435.
71. Kanno H, Handa K, Murakami T, Aizawa T, Ozawa H. Chaperone-Mediated Autophagy in Neurodegenerative Diseases and Acute Neurological Insults in the Central Nervous System. *Cells*. 2022 Apr 2;11(7):1205.
72. Funderburk SF, Marcellino BK, Yue Z. Cell “Self-Eating” (Autophagy) Mechanism in Alzheimer’s Disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*. 2010 Jan 25;77(1):59–68.
73. Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res*. 1965 Mar;37(3):614–36.

74. Meyne J, Ratliff RL, Moyzis RK. Conservation of the human telomere sequence (TTAGGG)_n among vertebrates. *Proceedings of the National Academy of Sciences*. 1989 Sep;86(18):7049–53.
75. Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, et al. A highly conserved repetitive DNA sequence, (TTAGGG)_n, present at the telomeres of human chromosomes. *Proceedings of the National Academy of Sciences*. 1988 Sep;85(18):6622–6.
76. Shin JS, Hong A, Solomon MJ, Soon Lee C. The role of telomeres and telomerase in the pathology of human cancer and aging. *Pathology*. 2006 Apr;38(2):103–13.
77. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature*. 1990 May;345(6274):458–60.
78. Starkweather AR, Alhaeeri AA, Montpetit A, Brumelle J, Filler K, Montpetit M, et al. An Integrative Review of Factors Associated with Telomere Length and Implications for Biobehavioral Research. *Nurs Res*. 2014 Jan;63(1):36–50.
79. Bendix L, Thinggaard M, Fenger M, Kolvraa S, Avlund K, Linneberg A, et al. Longitudinal Changes in Leukocyte Telomere Length and Mortality in Humans. *The Journals of Gerontology: Series A*. 2014 Feb;69A(2):231–9.
80. Vaziri H, Dragowska W, Allsopp RC, Thomas TE, Harley CB, Lansdorp PM. Evidence for a mitotic clock in human hematopoietic stem cells: loss of telomeric DNA with age. *Proceedings of the National Academy of Sciences*. 1994 Oct 11;91(21):9857–60.
81. Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. *Mech Ageing Dev*. 2019 Jan;177:37–45.
82. Fathi E, Charoudeh HN, Sanaat Z, Farahzadi R. Telomere shortening as a hallmark of stem cell senescence. *Stem Cell Investig*. 2019 Mar;6:7–7.
83. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. *The Lancet*. 2003 Feb;361(9355):393–5.
84. Boonekamp JJ, Simons MJP, Hemerik L, Verhulst S. Telomere length behaves as biomarker of somatic redundancy rather than biological age. *Aging Cell*. 2013 Apr 22;12(2):330–2.
85. Zhu X, Han W, Xue W, Zou Y, Xie C, Du J, et al. The association between telomere length and cancer risk in population studies. *Sci Rep*. 2016 Feb 26;6(1):22243.
86. Schneider C V., Schneider KM, Teumer A, Rudolph KL, Hartmann D, Rader DJ, et al. Association of Telomere Length With Risk of Disease and Mortality. *JAMA Intern Med*. 2022 Mar 1;182(3):291.
87. Hägg S, Zhan Y, Karlsson R, Gerritsen L, Ploner A, van der Lee SJ, et al. Short telomere length is associated with impaired cognitive performance in European ancestry cohorts. *Transl Psychiatry*. 2017 Apr 18;7(4):e1100–e1100.

88. Montiel Rojas D, Nilsson A, Ponsot E, Brummer RJ, Fairweather-Tait S, Jennings A, et al. Short Telomere Length Is Related to Limitations in Physical Function in Elderly European Adults. *Front Physiol*. 2018 Aug 10;9.
89. Ayoub A, Raynaud C, Heride C, Revaud D, Sabatier L. Telomeres: Hallmarks of radiosensitivity. *Biochimie*. 2008 Jan;90(1):60–72.
90. Semeraro MD, Almer G, Renner W, Gruber HJ, Herrmann M. Telomere length in leucocytes and solid tissues of young and aged rats. *Aging*. 2022 Feb 28;14(4):1713–28.
91. Daniali L, Benetos A, Susser E, Kark JD, Labat C, Kimura M, et al. Telomeres shorten at equivalent rates in somatic tissues of adults. *Nat Commun*. 2013 Mar 19;4(1):1597.
92. Ariffin H, Azanan MS, Abd Ghafar SS, Oh L, Lau KH, Thirunavakarasu T, et al. Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging. *Cancer*. 2017 Nov 27;123(21):4207–14.
93. Vatanen A, Hou M, Huang T, Söder O, Jahnukainen T, Kurimo M, et al. Clinical and biological markers of premature aging after autologous SCT in childhood cancer. *Bone Marrow Transplant*. 2017 Apr 9;52(4):600–5.
94. Feng J, Funk WD, Wang SS, Weinrich SL, Avilion AA, Chiu CP, et al. The RNA Component of Human Telomerase. *Science* (1979). 1995 Sep;269(5228):1236–41.
95. Shawi M, Autexier C. Telomerase, senescence and ageing. *Mech Ageing Dev*. 2008 Jan;129(1–2):3–10.
96. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Telomere dysfunction in ageing and age-related diseases. *Nat Cell Biol*. 2022 Feb 14;24(2):135–47.
97. Tominaga K, Suzuki HI. TGF- β Signaling in Cellular Senescence and Aging-Related Pathology. *Int J Mol Sci*. 2019 Oct 10;20(20):5002.
98. Schulz S, Schagdarsurengin U, Suss T, Müller-Werdan U, Werdan K, Gläser C. Relation between the tumor necrosis factor-alpha (TNF-alpha) gene and protein expression, and clinical, biochemical, and genetic markers: age, body mass index and uric acid are independent predictors for an elevated TNF-alpha plasma level in a complex risk model. *Eur Cytokine Netw*. 2004;15(2):105–11.
99. Forsey RJ, Thompson JM, Ernerudh J, Hurst TL, Strindhall J, Johansson B, et al. Plasma cytokine profiles in elderly humans. *Mech Ageing Dev*. 2003 Apr;124(4):487–93.
100. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, Nadrowski P, Chudek J, Slusarczyk P, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immunity & Ageing*. 2016 Dec 3;13(1):21.
101. Akriou D, Perlepe G, Kirgou P, Gourgoulis KI, Malli F. Pathophysiological Aspects of Aging in Venous Thromboembolism: An Update. *Medicina (B Aires)*. 2022 Aug 10;58(8):1078.
102. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. *J Cell Mol Med*. 2009 Sep 29;13(9b):3103–9.

103. Ferrucci L, Penninx BWJH, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, et al. Change in Muscle Strength Explains Accelerated Decline of Physical Function in Older Women With High Interleukin-6 Serum Levels. *J Am Geriatr Soc.* 2002 Dec 9;50(12):1947–54.
104. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, et al. Associations of elevated Interleukin-6 and C-Reactive protein levels with mortality in the elderly**Access the “Journal Club” discussion of this paper at <http://www.elsevier.com/locate/ajmselect/>. *Am J Med.* 1999 May;106(5):506–12.
105. Giovannini S, Onder G, Liperoti R, Russo A, Carter C, Capoluongo E, et al. Interleukin-6, C-Reactive Protein, and Tumor Necrosis Factor-Alpha as Predictors of Mortality in Frail, Community-Living Elderly Individuals. *J Am Geriatr Soc.* 2011 Sep 24;59(9):1679–85.
106. Alley DE, Crimmins E, Bandeen-Roche K, Guralnik J, Ferrucci L. Three-Year Change in Inflammatory Markers in Elderly People and Mortality: The Invecchiare in Chianti Study. *J Am Geriatr Soc.* 2007 Nov 29;55(11):1801–7.
107. Corti MC. Serum Albumin Level and Physical Disability as Predictors of Mortality in Older Persons. *JAMA: The Journal of the American Medical Association.* 1994 Oct 5;272(13):1036.
108. Li X, Ma L. From biological aging to functional decline: Insights into chronic inflammation and intrinsic capacity. *Ageing Res Rev.* 2024 Jan;93:102175.
109. Brinkley TE, Leng X, Miller ME, Kitman DW, Pahor M, Berry MJ, et al. Chronic Inflammation Is Associated With Low Physical Function in Older Adults Across Multiple Comorbidities. *J Gerontol A Biol Sci Med Sci.* 2009 Apr 1;64A(4):455–61.
110. Reuben DB, Cheh AI, Harris TB, Ferrucci L, Rowe JW, Tracy RP, et al. Peripheral Blood Markers of Inflammation Predict Mortality and Functional Decline in High-Functioning Community-Dwelling Older Persons. *J Am Geriatr Soc.* 2002 Apr 8;50(4):638–44.
111. Salanitro AH, Ritchie CS, Hovater M, Roth DL, Sawyer P, Locher JL, et al. Inflammatory biomarkers as predictors of hospitalization and death in community-dwelling older adults. *Arch Gerontol Geriatr.* 2012 May;54(3):e387–91.
112. Zhang D, Mobley EM, Manini TM, Leeuwenburgh C, Anton SD, Washington CJ, et al. Frailty and risk of mortality in older cancer survivors and adults without a cancer history: Evidence from the National Health and Nutrition Examination Survey, 1999-2014. *Cancer.* 2022 Aug 24;128(15):2978–87.
113. Esbenshade AJ, Lu L, Friedman DL, Oeffinger KC, Armstrong GT, Krull KR, et al. Accumulation of Chronic Disease Among Survivors of Childhood Cancer Predicts Early Mortality. *Journal of Clinical Oncology.* 2023 Jul 10;41(20):3629–41.
114. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. *New England Journal of Medicine.* 2006 Oct 12;355(15):1572–82.

115. Ness KK, Plana JC, Joshi VM, Luepker R V., Durand JB, Green DM, et al. Exercise Intolerance, Mortality, and Organ System Impairment in Adult Survivors of Childhood Cancer. *Journal of Clinical Oncology*. 2020 Jan 1;38(1):29–42.
116. Ness KK, Partin MR, Howell CR, Krull KR, Brinkman TM, Armstrong GT, et al. Progression of frailty in young adult survivors of childhood cancer: St. Jude Lifetime Cohort. *Journal of Clinical Oncology*. 2019 May 20;37(15_suppl):10057–10057.
117. Phillips NS, Duke ES, Schofield HLT, Ullrich NJ. Neurotoxic Effects of Childhood Cancer Therapy and Its Potential Neurocognitive Impact. *Journal of Clinical Oncology*. 2021 Jun 1;39(16):1752–65.
118. Deisenroth A, Söntgerath R, Schuster AJ, von Busch C, Huber G, Eckert K, et al. Muscle strength and quality of life in patients with childhood cancer at early phase of primary treatment. *Pediatr Hematol Oncol*. 2016 Aug 17;33(6):393–407.
119. Kojima G, Liljas A, Iliffe S. Frailty syndrome: implications and challenges for health care policy. *Risk Manag Healthc Policy*. 2019 Feb;Volume 12:23–30.
120. Armenian SH, Gibson CJ, Rockne RC, Ness KK. Premature Aging in Young Cancer Survivors. *JNCI: Journal of the National Cancer Institute*. 2019 Mar 1;111(3):226–32.
121. Alfano CM, Peng J, Andridge RR, Lindgren ME, Povoski SP, Lipari AM, et al. Inflammatory Cytokines and Comorbidity Development in Breast Cancer Survivors Versus Noncancer Controls: Evidence for Accelerated Aging? *Journal of Clinical Oncology*. 2017 Jan 10;35(2):149–56.
122. Landier W, Armenian S, Bhatia S. Late Effects of Childhood Cancer and Its Treatment. *Pediatr Clin North Am*. 2015 Feb;62(1):275–300.
123. Salerno EA, Saint-Maurice PF, Willis EA, Moore SC, DiPietro L, Matthews CE. Ambulatory Function and Mortality among Cancer Survivors in the NIH-AARP Diet and Health Study. *Cancer Epidemiology, Biomarkers & Prevention*. 2021 Apr 1;30(4):690–8.
124. Nekhlyudov L, Campbell GB, Schmitz KH, Brooks GA, Kumar AJ, Ganz PA, et al. Cancer-related impairments and functional limitations among long-term cancer survivors: Gaps and opportunities for clinical practice. *Cancer*. 2022 Jan 15;128(2):222–9.
125. Országhová Z, Mego M, Chovanec M. Long-Term Cognitive Dysfunction in Cancer Survivors. *Front Mol Biosci*. 2021 Dec 14;8.
126. Glare PA, Davies PS, Finlay E, Gulati A, Lemanne D, Moryl N, et al. Pain in Cancer Survivors. *Journal of Clinical Oncology*. 2014 Jun 1;32(16):1739–47.
127. Ahmad TA, Gopal DP, Chelala C, Dayem Ullah AZ, Taylor SJ. Multimorbidity in people living with and beyond cancer: a scoping review. *Am J Cancer Res*. 2023;13(9):4346–65.
128. Holmqvist AS, Chen Y, Hageman L, Landier W, Wu J, Francisco LF, et al. Severe, life-threatening, and fatal chronic health conditions after allogeneic blood or marrow transplantation in childhood. *Cancer*. 2023 Feb 15;129(4):624–33.

129. Alfano CM, Peng J, Andridge RR, Lindgren ME, Povoski SP, Lipari AM, et al. Inflammatory Cytokines and Comorbidity Development in Breast Cancer Survivors Versus Noncancer Controls: Evidence for Accelerated Aging? *Journal of Clinical Oncology*. 2017 Jan 10;35(2):149–56.
130. Cupit-Link MC, Kirkland JL, Ness KK, Armstrong GT, Tchkonja T, LeBrasseur NK, et al. Biology of premature ageing in survivors of cancer. *ESMO Open*. 2017;2(5):e000250.
131. Latoch E, Konończuk K, Konstantynowicz-Nowicka K, Muszyńska-Roslan K, Sztolsztener K, Chabowski A, et al. Asymptomatic Survivors of Childhood Acute Lymphoblastic Leukemia Demonstrate a Biological Profile of Inflamm-Aging Early in Life. *Cancers (Basel)*. 2022 May 20;14(10):2522.
132. Walsh KM. Telomere Attrition in Childhood Cancer Survivors. *Clinical Cancer Research*. 2020 May 15;26(10):2281–3.
133. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov 12;68(6):394–424.
134. Leslie SW, Soon-Sutton TL, R I A, Sajjad H, Skelton WP. *Prostate Cancer*. 2024.
135. *Krebserkrankungen - STATISTIK AUSTRIA - Die Informationsmanager*.
136. Graham LS, Lin JK, Lage DE, Kessler ER, Parikh RB, Morgans AK. Management of Prostate Cancer in Older Adults. *American Society of Clinical Oncology Educational Book*. 2023 May;(43).
137. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic Incidence and Duration of Prostate Cancer. *Am J Epidemiol*. 1998 Oct 15;148(8):775–85.
138. N. Mottet (Chair) PC (Vice chair), RCN van den BEBEP (European PCCU. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer.
139. Health Commission of the PRC N. National guidelines for diagnosis and treatment of prostate cancer 2022 in China (English version). *Chinese Journal of Cancer Research*. 2022;34(3):270–88.
140. Walter LC, Covinsky KE. Cancer Screening in Elderly Patients. *JAMA*. 2001 Jun 6;285(21):2750.
141. Hamaker ME, Vos AG, Smorenburg CH, Rooij SE, Munster BC. The Value of Geriatric Assessments in Predicting Treatment Tolerance and All-Cause Mortality in Older Patients With Cancer. *Oncologist*. 2012 Nov 1;17(11):1439–49.
142. Li D, Soto-Perez-de-Celis E, Hurria A. Geriatric Assessment and Tools for Predicting Treatment Toxicity in Older Adults With Cancer. *The Cancer Journal*. 2017 Jul;23(4):206–10.
143. Terret C, Albrand G, Droz JP. Geriatric Assessment in Elderly Patients with Prostate Cancer. *Clin Prostate Cancer*. 2004 Mar;2(4):236–40.
144. Shevach JW, Weiner AB, Kasimer RN, Miller CH, Morgans AK. Risk Assessment and Considerations for Proper Management of Elderly Men with Advanced Prostate Cancer: A Systematic Review. *Eur Urol Oncol*. 2020 Aug;3(4):400–9.

145. Graham LS, Lin JK, Lage DE, Kessler ER, Parikh RB, Morgans AK. Management of Prostate Cancer in Older Adults. American Society of Clinical Oncology Educational Book. 2023 May;(43).
146. KATZ S. Assessing Self-maintenance: Activities of Daily Living, Mobility, and Instrumental Activities of Daily Living. J Am Geriatr Soc. 1983 Dec;31(12):721–7.
147. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179–86.
148. Podsiadlo D, Richardson S. The Timed “Up & Go”: A Test of Basic Functional Mobility for Frail Elderly Persons. J Am Geriatr Soc. 1991 Feb;39(2):142–8.
149. Guigoz Y, Vellas B. The Mini Nutritional Assessment (MNA) for Grading the Nutritional State of Elderly Patients: Presentation of the MNA, History and Validation. In: Mini Nutritional Assessment (MNA): Research and Practice in the Elderly. Basel: KARGER; 1999. p. 3–12.
150. Nikolaus T SLNBM et al. Soziale Aspekte bei Diagnostik und Therapie hochbetagter Patienten. Erste Erfahrungen mit einem neu entwickelten Fragebogen im Rahmen des geriatrischen Assessment. Z Gerontol. 1994;7:240–5.
151. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state.” J Psychiatr Res. 1975 Nov;12(3):189–98.
152. Yesavage JA, Sheikh JI. 9/Geriatric Depression Scale (GDS). Clin Gerontol. 1986 Nov 18;5(1–2):165–73.
153. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987 Jan;40(5):373–83.
154. Mathur K, Kurbanova N, Qayyum R. Platelet-lymphocyte ratio (PLR) and all-cause mortality in general population: insights from national health and nutrition education survey. Platelets. 2019 Nov 17;30(8):1036–41.
155. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, et al. Prognostic Value of PLR in Various Cancers: A Meta-Analysis. PLoS One. 2014 Jun 26;9(6):e101119.
156. Fest J, Ruiters TR, Groot Koerkamp B, Rizopoulos D, Ikram MA, van Eijck CHJ, et al. The neutrophil-to-lymphocyte ratio is associated with mortality in the general population: The Rotterdam Study. Eur J Epidemiol. 2019 May 19;34(5):463–70.
157. Kanapuru B, Ershler WB. Inflammation, Coagulation, and the Pathway to Frailty. Am J Med. 2009 Jul;122(7):605–13.
158. Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med. 2003 Feb;114(3):180–7.
159. Reuben DB, Cheh AI, Harris TB, Ferrucci L, Rowe JW, Tracy RP, et al. Peripheral Blood Markers of Inflammation Predict Mortality and Functional Decline in High-Functioning Community-Dwelling Older Persons. J Am Geriatr Soc. 2002 Apr 8;50(4):638–44.

160. Pieper CF, Rao KMK, Currie MS, Harris TB, Cohen HJ. Age, Functional Status, and Racial Differences in Plasma D-Dimer Levels in Community-Dwelling Elderly Persons. *J Gerontol A Biol Sci Med Sci*. 2000 Nov 1;55(11):M649–57.
161. Cawthon RM. Telomere measurement by quantitative PCR. *Nucleic Acids Res*. 2002 May 15;30(10):47e–47.
162. Van Herck Y, Feyaerts A, Alibhai S, Papamichael D, Decoster L, Lambrechts Y, et al. Is cancer biology different in older patients? *Lancet Healthy Longev*. 2021 Oct;2(10):e663–77.
163. RUZICH M, RYAN B, OWEN C, DELAHUNTY A, STUART-HARRIS R. Prospective evaluation of cognitive function in patients with early breast cancer receiving adjuvant chemotherapy. *Asia Pac J Clin Oncol*. 2007 Sep 24;3(3):125–33.
164. Du XL, Xia R, Hardy D. Relationship Between Chemotherapy Use and Cognitive Impairments in Older Women With Breast Cancer. *Am J Clin Oncol*. 2010 Dec;33(6):533–43.
165. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer*. 2007 Mar;7(3):192–201.
166. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA. ‘Chemobrain’ in breast carcinoma? *Cancer*. 2004 Aug 21;101(3):466–75.
167. Sales MVC, Suemoto CK, Apolinario D, Serrao ValeriaT, Andrade CS, Conceição DM, et al. Effects of Adjuvant Chemotherapy on Cognitive Function of Patients With Early-stage Colorectal Cancer. *Clin Colorectal Cancer*. 2019 Mar;18(1):19–27.
168. Wefel JS, Vidrine DJ, Marani SK, Swartz RJ, Veramonti TL, Meyers CA, et al. A prospective study of cognitive function in men with non-seminomatous germ cell tumors. *Psychooncology*. 2014 Jun 16;23(6):626–33.
169. Noal S, Levy C, Hardouin A, Rieux C, Heutte N, Ségura C, et al. One-Year Longitudinal Study of Fatigue, Cognitive Functions, and Quality of Life After Adjuvant Radiotherapy for Breast Cancer. *International Journal of Radiation Oncology*Biophysics*. 2011 Nov;81(3):795–803.
170. Hill-Kayser C. Patient-Reports of Fatigue and Cognitive Changes in Cancer Survivors. *Gerontol Geriatr Med*. 2018 Aug 7;4(1):1–5.
171. McGinty HL, Phillips KM, Jim HSL, Cessna JM, Asvat Y, Cases MG, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Supportive Care in Cancer*. 2014 Aug 25;22(8):2271–80.
172. Livingston PM, Salmon J, Courneya KS, Gaskin CJ, Craike M, Botti M, et al. Efficacy of a referral and physical activity program for survivors of prostate cancer [ENGAGE]: Rationale and design for a cluster randomised controlled trial. *BMC Cancer*. 2011 Dec 13;11(1):237.
173. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen

- Suppression Therapy for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial. *Journal of Clinical Oncology*. 2010 Jan 10;28(2):340–7.
174. Gonzalez-Saenz de Tejada M, Bilbao A, Baré M, Briones E, Sarasqueta C, Quintana JM, et al. Association between social support, functional status, and change in health-related quality of life and changes in anxiety and depression in colorectal cancer patients. *Psychooncology*. 2017 Sep;26(9):1263–9.
 175. van Roij J, Brom L, Youssef-El Soud M, van de Poll-Franse L, Raijmakers NJH. Social consequences of advanced cancer in patients and their informal caregivers: a qualitative study. *Supportive Care in Cancer*. 2019 Apr 13;27(4):1187–95.
 176. Wright P, Smith A, Booth L, Winterbottom A, Kiely M, Velikova G, et al. Psychosocial difficulties, deprivation and cancer: three questionnaire studies involving 609 cancer patients. *Br J Cancer*. 2005 Sep 6;93(6):622–6.
 177. Knox MK, Hales S, Nissim R, Jung J, Lo C, Zimmermann C, et al. Lost and stranded: the experience of younger adults with advanced cancer. *Supportive Care in Cancer*. 2017 Feb 27;25(2):399–407.
 178. Neo J, Fettes L, Gao W, Higginson IJ, Maddocks M. Disability in activities of daily living among adults with cancer: A systematic review and meta-analysis. *Cancer Treat Rev*. 2017 Dec;61:94–106.
 179. Rier HN, Meinardi MC, van Rosmalen J, Westerweel PE, de Jongh E, Kitzen JJEM, et al. Association Between Geriatric Assessment and Post-Chemotherapy Functional Status in Older Patients with Cancer. *Oncologist*. 2022 Nov 3;27(11):e878–88.
 180. Hoppe S, Rainfray M, Fonck M, Hoppenreys L, Blanc JF, Ceccaldi J, et al. Functional Decline in Older Patients With Cancer Receiving First-Line Chemotherapy. *Journal of Clinical Oncology*. 2013 Nov 1;31(31):3877–82.
 181. Bylow K, Dale W, Mustian K, Stadler WM, Rodin M, Hall W, et al. Falls and Physical Performance Deficits in Older Patients With Prostate Cancer Undergoing Androgen Deprivation Therapy. *Urology*. 2008 Aug;72(2):422–7.
 182. Kenis C, Decoster L, Bastin J, Bode H, Van Puyvelde K, De Grève J, et al. Functional decline in older patients with cancer receiving chemotherapy: A multicenter prospective study. *J Geriatr Oncol*. 2017 May;8(3):196–205.
 183. Ursem C, Diaz-Ramirez LG, Boscardin J, Lee S. Changes in functional status associated with radiation for prostate cancer in older veterans. *J Geriatr Oncol*. 2021 Jun;12(5):808–12.
 184. McCrary JM, Goldstein D, Wyld D, Henderson R, Lewis CR, Park SB. Mobility in survivors with chemotherapy-induced peripheral neuropathy and utility of the 6-min walk test. *Journal of Cancer Survivorship*. 2019 Aug 6;13(4):495–502.
 185. Clay CA, Perera S, Wagner JM, Miller ME, Nelson JB, Greenspan SL. Physical Function in Men With Prostate Cancer on Androgen Deprivation Therapy. *Phys Ther*. 2007 Oct 1;87(10):1325–33.

186. Alibhai SMH, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, et al. Impact of Androgen-Deprivation Therapy on Physical Function and Quality of Life in Men With Nonmetastatic Prostate Cancer. *Journal of Clinical Oncology*. 2010 Dec 1;28(34):5038–45.
187. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. *J Affect Disord*. 2012 Dec;141(2–3):343–51.
188. Watts S, Leydon G, Birch B, Prescott P, Lai L, Eardley S, et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. *BMJ Open*. 2014 Mar;4(3):e003901.
189. Chhatre S, Gallo JJ, Guzzo T, Morales KH, Newman DK, Vapiwala N, et al. Trajectory of Depression among Prostate Cancer Patients: A Secondary Analysis of a Randomized Controlled Trial. *Cancers (Basel)*. 2023 Apr 2;15(7):2124.
190. Meissner VH, Simson BW, Dinkel A, Schiele S, Ankerst DP, Lunger L, et al. Treatment decision regret in long-term survivors after radical prostatectomy: a longitudinal study. *BJU Int*. 2023 May 6;131(5):623–30.
191. Dinh KT, Reznor G, Muralidhar V, Mahal BA, Nezoslosky MD, Choueiri TK, et al. Association of Androgen Deprivation Therapy With Depression in Localized Prostate Cancer. *Journal of Clinical Oncology*. 2016 Jun 1;34(16):1905–12.
192. Tsao PA, Ross RD, Bohnert ASB, Mukherjee B, Caram ME V. Depression, Anxiety, and Patterns of Mental Health Care Among Men With Prostate Cancer Receiving Androgen Deprivation Therapy. *Oncologist*. 2022 Apr 5;27(4):314–22.
193. Sharifi N. Androgen Deprivation Therapy for Prostate Cancer. *JAMA*. 2005 Jul 13;294(2):238.
194. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in Body Composition during Androgen Deprivation Therapy for Prostate Cancer. *J Clin Endocrinol Metab*. 2002 Feb;87(2):599–603.
195. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. *European Journal of Oncology Nursing*. 2005 Jan;9:S51–63.
196. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. *The Lancet*. 2023 Mar;401(10380):951–66.
197. Zanetti M, Veronese N, Riso S, Boccardi V, Bolli C, Cintoni M, et al. Polypharmacy and malnutrition in older people: A narrative review. *Nutrition*. 2023 Nov;115:112134.
198. Bossi P, De Luca R, Ciani O, D’Angelo E, Caccialanza R. Malnutrition management in oncology: An expert view on controversial issues and future perspectives. *Front Oncol*. 2022 Oct 5;12.
199. Fowler H, Belot A, Ellis L, Maringe C, Luque-Fernandez MA, Njagi EN, et al. Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. *BMC Cancer*. 2020 Dec 28;20(1):2.

200. Jefferson M, Drake RR, Lilly M, Savage SJ, Price ST, Hughes Halbert C. Co-morbidities in a Retrospective Cohort of Prostate Cancer Patients. *Ethn Dis.* 2020 Apr 2;30(Suppl 1):185–92.
201. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin.* 2016 Jul 17;66(4):337–50.
202. Hage FG. Hypertension and C-reactive protein. *Hypertension Research.* 2012 Oct 9;35(10):969–71.
203. Li J, Chen J, Lan H yao, Tang Y. Role of C-Reactive Protein in Kidney Diseases. *Kidney Diseases.* 2023;9(2):73–81.
204. Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, et al. C-Reactive Protein as a Predictor for Incident Diabetes Mellitus Among Middle-aged Men. *Arch Intern Med.* 2003 Jan 13;163(1):93.
205. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. *The Egyptian Heart Journal.* 2015 Jun;67(2):89–97.
206. Watanabe Y, Kitamura K, Nakamura K, Sanpei K, Wakasugi M, Yokoseki A, et al. Elevated C-Reactive Protein Is Associated with Cognitive Decline in Outpatients of a General Hospital: The Project in Sado for Total Health (PROST). *Dement Geriatr Cogn Dis Extra.* 2016 Jan 19;6(1):10–9.
207. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-Reactive Protein Is an Important Biomarker for Prognosis Tumor Recurrence and Treatment Response in Adult Solid Tumors: A Systematic Review. *PLoS One.* 2015 Dec 30;10(12):e0143080.
208. Cesari M, Penninx BWJH, Pahor M, Lauretani F, Corsi AM, Williams GR, et al. Inflammatory Markers and Physical Performance in Older Persons: The InCHIANTI Study. *J Gerontol A Biol Sci Med Sci.* 2004 Mar 1;59(3):M242–8.
209. Kiprian D, Czarkowska-Paczek B, Wyczalkowska-Tomasik A, Fuksiewicz M, Kotowicz B, Paczek L. Radiotherapy and radiochemotherapy increase serum levels of pro-inflammatory interleukin-6 and C-reactive protein in patients with head and neck cancers. *Transl Cancer Res.* 2018 Feb 1;7(1):41–7.
210. Cengiz M, Akbulut S, Atahan IL, Grigsby PW. Acute phase response during radiotherapy. *International Journal of Radiation Oncology*Biography*Physics.* 2001 Mar;49(4):1093–6.
211. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. *Semin Immunopathol.* 2012 Jan 31;34(1):43–62.
212. SAHNI A, SIMPSON-HAIDARIS PJ, SAHNI SK, VADAY GG, FRANCIS CW. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). *Journal of Thrombosis and Haemostasis.* 2008 Jan;6(1):176–83.
213. Welstead M, Muniz-Terrera G, Russ TC, Corley J, Taylor AM, Gale CR, et al. Inflammation as a risk factor for the development of frailty in the Lothian Birth Cohort 1936. *Exp Gerontol.* 2020 Oct;139:111055.

214. Navarro-Martínez R, Serrano-Carrascosa M, Buigues C, Fernández-Garrido J, Sánchez-Martínez V, Castelló-Domenech AB, et al. Frailty syndrome is associated with changes in peripheral inflammatory markers in prostate cancer patients undergoing androgen deprivation therapy. *Urologic Oncology: Seminars and Original Investigations*. 2019 Dec;37(12):976–87.
215. Walker KA, Walston J, Gottesman RF, Kucharska-Newton A, Palta P, Windham BG. Midlife Systemic Inflammation Is Associated With Frailty in Later Life: The ARIC Study. *The Journals of Gerontology: Series A*. 2019 Feb 15;74(3):343–9.
216. Pérez-Tasigchana RF, León-Muñoz LM, Lopez-García E, Gutiérrez-Fisac JL, Laclaustra M, Rodríguez-Artalejo F, et al. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age Ageing*. 2017 Sep 1;46(5):807–12.
217. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *Journal of Parenteral and Enteral Nutrition*. 2019 Feb 4;43(2):181–93.
218. Feingold KR GC. The Effect of Inflammation and Infection on Lipids and Lipoproteins. 2022.
219. Schalk BWM, Visser M, Deeg DJH, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. *Age Ageing*. 2004 May;33(3):266–72.
220. Jellinge ME, Henriksen DP, Hallas P, Brabrand M. Hypoalbuminemia Is a Strong Predictor of 30-Day All-Cause Mortality in Acutely Admitted Medical Patients: A Prospective, Observational, Cohort Study. *PLoS One*. 2014 Aug 22;9(8):e105983.
221. Eckart A, Struja T, Kutz A, Baumgartner A, Baumgartner T, Zurfluh S, et al. Relationship of Nutritional Status, Inflammation, and Serum Albumin Levels During Acute Illness: A Prospective Study. *Am J Med*. 2020 Jun;133(6):713-722.e7.
222. Don BR, Kaysen G. POOR NUTRITIONAL STATUS AND INFLAMMATION: Serum Albumin: Relationship to Inflammation and Nutrition. *Semin Dial*. 2004 Nov 9;17(6):432–7.
223. An S, Shim H, Kim K, Kim B, Bang HJ, Do H, et al. Pretreatment inflammatory markers predicting treatment outcomes in colorectal cancer. *Ann Coloproctol*. 2022 Apr 30;38(2):97–108.
224. Klonoff-Cohen H, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the healthy elderly. *J Clin Epidemiol*. 1992 Mar;45(3):207–12.
225. Brock F, Bettinelli LA, Dobner T, Stobbe JC, Pomatti G, Telles CT. Prevalence of hypoalbuminemia and nutritional issues in hospitalized elders. *Rev Lat Am Enfermagem*. 2016;24(0).
226. Silva-Fhon JR, Rojas-Huayta VM, Aparco-Balboa JP, Céspedes-Panduro B, Partezani-Rodrigues RA. Sarcopenia y albúmina sanguínea: revisión sistemática con metaanálisis. *Biomédica*. 2021 Sep 22;41(3):590–603.

227. Picca A, Coelho-Junior HJ, Calvani R, Marzetti E, Vetrano DL. Biomarkers shared by frailty and sarcopenia in older adults: A systematic review and meta-analysis. *Ageing Res Rev.* 2022 Jan;73:101530.
228. Yin M, Zhang X, Zheng X, Chen C, Tang H, Yu Z, et al. Cholesterol alone or in combination is associated with frailty among community-dwelling older adults: A cross-sectional study. *Exp Gerontol.* 2023 Sep;180:112254.
229. Ranieri Renzo Rozzini Simone Franzo P. Serum Cholesterol Levels as a Measure of Frailty in Elderly Patients. *Exp Aging Res.* 1998 Mar;24(2):169–79.
230. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. *Arq Bras Cardiol.* 2015;
231. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol.* 2016 May 3;26(3):372–6.
232. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy.* 2001;102(1):5–14.
233. Hashemi Moghanjoughi P, Neshat S, Rezaei A, Heshmat-Ghahdarijani K. Is the Neutrophil-to-Lymphocyte Ratio an Exceptional Indicator for Metabolic Syndrome Disease and Outcomes? *Endocrine Practice.* 2022 Mar;28(3):342–8.
234. Yuksel M, Yildiz A, Oylumlu M, Akyuz A, Aydin M, Kaya H, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity. *The Anatolian Journal of Cardiology.* 2015 Aug 21;15(8):640–7.
235. Li J, Chen Q, Luo X, Hong J, Pan K, Lin X, et al. Neutrophil-to-Lymphocyte Ratio Positively Correlates to Age in Healthy Population. *J Clin Lab Anal.* 2015 Nov 2;29(6):437–43.
236. Dillon K, Goodman ZT, Kaur SS, Levin B, McIntosh R. Neutrophil-to-Lymphocyte Ratio Amplifies the Effects of Aging on Decrements in Grip Strength and Its Functional Neural Underpinnings. *The Journals of Gerontology: Series A.* 2023 Jun 1;78(6):882–9.
237. Li S, Chen X, Gao M, Zhang X, Han P, Cao L, et al. The neutrophil-to-lymphocyte ratio is associated with mild cognitive impairment in community-dwelling older women aged over 70 years: a population-based cross-sectional study. *Front Aging Neurosci.* 2023 Sep 14;15.
238. Liaw FY, Huang CF, Chen WL, Wu LW, Peng TC, Chang YW, et al. Higher Platelet-to-Lymphocyte Ratio Increased the Risk of Sarcopenia in the Community-Dwelling Older Adults. *Sci Rep.* 2017 Nov 30;7(1):16609.
239. Wang X, Wang P, Zhao Z, Mao Q, Yu J, Li M. A review of radiation-induced lymphopenia in patients with esophageal cancer: an immunological perspective for radiotherapy. *Ther Adv Med Oncol.* 2020 Jan 26;12:175883592092682.

240. Xu W, Liang Y, Lin Z. Association Between Neutrophil–Lymphocyte Ratio and Frailty: The Chinese Longitudinal Healthy Longevity Survey. *Front Med (Lausanne)*. 2022 Jan 3;8.
241. Yolaçan H, Guler S. Inverse Correlation Between Bone Mineral Density and Systemic Immune Inflammation Index in Postmenopausal Turkish Women. *Cureus*. 2023 Apr 12;
242. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. *Sci Rep*. 2019 Dec 1;9(1).
243. Han S, Liu Y, Li Q, Li Z, Hou H, Wu A. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. *BMC Cancer*. 2015 Dec 4;15(1):617.
244. Lin RJ, Afshar-Kharghan V, Schafer AI. Paraneoplastic thrombocytosis: the secrets of tumor self-promotion. *Blood*. 2014 Jul 10;124(2):184–7.
245. Kim JY, Jung EJ, Kim JM, Lee HS, Kwag SJ, Park JH, et al. Dynamic changes of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicts breast cancer prognosis. *BMC Cancer*. 2020 Dec 7;20(1):1206.
246. Standish LJ, Torkelson C, Hamill FA, Yim D, Fitzpatrick A, Olsen M, et al. Immune Defects in Breast Cancer Patients after Radiotherapy NIH Public Access. Vol. 6, *J Soc Integr Oncol*. 2008.
247. Pinkawa M, Djukic V, Klotz J, Petz D, Piroth MD, Holy R, et al. Hematologic changes during prostate cancer radiation therapy are dependent on the treatment volume. *Future Oncology*. 2014 Apr;10(5):835–43.
248. Button LN, DeWolf WC, Newburger PE, Jacobson MS, Kevy SV. The effects of irradiation on blood components. *Transfusion (Paris)*. 1981 Jul 8;21(4):419–26.
249. Miszczyk M, Majewski W. Hematologic toxicity of conformal radiotherapy and intensity modulated radiotherapy in prostate and bladder cancer patients. *Asian Pacific Journal of Cancer Prevention*. 2018 Oct 1;19(10):2803–6.
250. Crocco P, De Rango F, Dato S, Rose G, Passarino G. Telomere length as a function of age at population level parallels human survival curves. *Aging*. 2021 Jan 15;13(1):204–18.
251. Vaupel JW, Carey JR, Christensen K, Johnson TE, Yashin AI, Holm N V., et al. Biodemographic Trajectories of Longevity. *Science (1979)*. 1998 May 8;280(5365):855–60.
252. Liu P, Zhang Y, Ma L. Telomere length and associated factors in older adults with hypertension. *Journal of International Medical Research*. 2019 Nov 30;47(11):5465–74.
253. Cupit-Link MC, Kirkland JL, Ness KK, Armstrong GT, Tchkonina T, LeBrasseur NK, et al. Biology of premature ageing in survivors of cancer. *ESMO Open*. 2017;2(5):e000250.
254. Sanoff HK, Deal AM, Krishnamurthy J, Torrice C, Dillon P, Sorrentino J, et al. Effect of Cytotoxic Chemotherapy on Markers of Molecular Age in Patients With Breast Cancer. *JNCI: Journal of the National Cancer Institute*. 2014 Apr;106(4).

255. Reste J, Zvigule G, Zvagule T, Kurjane N, Eglite M, Gabruseva N, et al. Telomere length in Chernobyl accident recovery workers in the late period after the disaster. *J Radiat Res.* 2014 Nov 1;55(6):1089–100.
256. Gallicchio L, Gadalla SM, Murphy JD, Simonds NI. The Effect of Cancer Treatments on Telomere Length: A Systematic Review of the Literature. *JNCI: Journal of the National Cancer Institute.* 2018 Oct 1;110(10):1048–58.
257. Idei T, Sakamoto H, Yamamoto T. Terminal Restriction Fragments of Telomere are Detectable in Plasma and Their Length Correlates with Clinical Status of Ovarian Cancer Patients. *Journal of International Medical Research.* 2002 Jun 25;30(3):244–50.
258. Maeda T, Nakamura K, Atsumi K, Hirakawa M, Ueda Y, Makino N. Radiation-associated changes in the length of telomeres in peripheral leukocytes from inpatients with cancer. *Int J Radiat Biol.* 2013 Feb 23;89(2):106–9.
259. Shin D, Shin J, Lee KW. Effects of Inflammation and Depression on Telomere Length in Young Adults in the United States. *J Clin Med.* 2019 May 19;8(5):711.
260. Liu S, Nong W, Ji L, Zhuge X, Wei H, Luo M, et al. The regulatory feedback of inflammatory signaling and telomere/telomerase complex dysfunction in chronic inflammatory diseases. *Exp Gerontol.* 2023 Apr;174:112132.

13 Appendix

13.1 Activities of Daily Living (ADL)

	Punkte
Essen	
• Unabhängig, isst selbständig, benutzt Geschirr und Besteck	10
• Braucht etwas Hilfe, z.B. Fleisch oder Brot schneiden	5
• Nicht selbständig, auch wenn o.g. Hilfe gewährt wird	0
Bett/(Roll-)Stuhltransfer	
• Unabhängig in allen Phasen der Tätigkeit	15
• Geringe Hilfen oder Beaufsichtigung erforderlich	10
• Erhebliche Hilfe beim Transfer, Lagewechsel, Liegen/Sitz selbständig	5
• Nicht selbständig, auch wenn o.g. Hilfe gewährt wird	0
Waschen	
• Unabhängig beim Waschen von Gesicht, Händen; Kämmen, Zähneputzen	5
• Nicht selbständig bei o.g. Tätigkeit	0
Toilettenbenutzung	
• Unabhängig in allen Phasen der Tätigkeit (incl. Reinigung)	10
• Benötigt Hilfe, z.B. wg. unzureich. Gleichgewichtes od. bei Kleidung/Reinig.	5
• Nicht selbständig, auch wenn o.g. Hilfe gewährt wird	0
Baden	
• Unabhängig bei Voll- oder Duschbad in allen Phasen der Tätigkeit	5
• Nicht selbständig bei o.g. Tätigkeit	0
Gehen auf Flurebene bzw. Rollstuhlfahren	
• Unabhängig beim Gehen über 50 m, Hilfsmittel erlaubt, nicht Gehwagen	15
• Geringe Hilfe oder Überwachung erforderlich, kann mit Hilfsm. 50 m gehen	10
• Nicht selbständig beim Gehen, kann aber Rollstuhl selbständig bedienen, auch um Ecken und an einen Tisch heranfahren, Strecke mind. 50 m	5
• Nicht selbständig beim Gehen oder Rollstuhlfahren	0
Treppensteigen	
• Unabhängig bei der Bewältigung einer Treppe (mehrere Stufen)	10
• benötigt Hilfe oder Überwachung beim Treppensteigen	5
• Nicht selbständig, kann auch mit Hilfe nicht Treppe steigen	0
An- und Auskleiden	
• Unabhängig beim An- und Auskleiden (ggf. auch Korsett oder Bruchband)	10
• Benötigt Hilfe, kann aber 50% der Tätigkeit selbständig durchführen	5
• Nicht selbständig, auch wenn o.g. Hilfe gewährt wird	0
Stuhlkontrolle	
• Ständig kontinent	10
• Gelegentlich inkontinent, maximal einmal/Woche	5
• Häufiger/ständig inkontinent	0
Urinkontrolle	
• Ständig kontinent, ggf. unabhängig bei Versorgung eines DK/Cystofix	10
• Gelegentlich inkontinent, max. einmal/Tag, Hilfe bei ext. Hamableitung	5
• Häufiger/ ständig inkontinent	0

13.2 Instrumental Activities of Daily Living (IADL)

Erweitertes Assessment: IADL

Telefon:

Benutzt Telefon aus eigener Initiative 1
Wählt einige bekannte Nummern 1
Nimmt ab, wählt nicht selbständig 1
Benutzt das Telefon überhaupt nicht 0

Einkaufen:

Kauft selbständig die meisten benötigten
Sachen ein 1
Tätigt wenige Einkäufe 0
Benötigt bei jedem Einkauf Begleitung 0
Unfähig zum Einkaufen 0

Kochen:

Plant und kocht erforderliche Mahlzeiten
selbständig 1
Kocht erforderliche Mahlzeiten nur nach
Vorbereitung durch Drittpersonen 0
Kocht selbständig, hält aber benötigte
Diät nicht ein 0
Benötigt vorbereitete und servierte Mahlzeiten
..... 0

Haushalt:

Hält Haushalt instand oder benötigt zweitweise
Hilfe bei schweren Arbeiten 1
Führt selbständig kleine Hausarbeiten aus 1
Führt selbständig kleine Hausarbeiten aus,
kann aber die Wohnung nicht rein halten 1
Benötigt Hilfe in allen Haushaltsverrichtungen
..... 1
Nimmt überhaupt nicht teil an tgl. Verrichtungen
im Haushalt 0

Wäsche:

Wäscht sämtliche eigene Wäsche 1
Wäscht kleine Sachen 1
Gesamte Wäsche muß|auswärts versorgt
werden 0

Transportmittel:

Benutzt unabhängig öffentliche Verkehrsmittel,
eigenes Auto 1
Bestellt und benutzt selbständig Taxi, benutzt
aber keine öffentlichen Verkehrsmittel 1
Benutzt öffentliche Verkehrsmittel in
Begleitung 1
Beschränkte Fahrten in Taxi oder Auto in
Begleitung 0
Reist überhaupt nicht 0

Medikamente:

Nimmt Medikamente in genauer Dosierung und
zum korrekten Zeitpunkt eigenverantwortlich
..... 1
Nimmt vorbereitete Medikamente korrekt 0
Kann korrekte Einnahme von Medikamenten
nicht handhaben 0

Geldhaushalt:

Regelt finanzielle Geschäfte selbständig
(Budget, Schecks, Einzahlungen, Gang zur
Bank) 1
Erledigt täglich kleine Ausgaben. Benötigt
Hilfe bei Einzahlungen, Bankgeschäften 1
Ist nicht mehr fähig mit Geld umzugehen 0

Dieser Bogen ist retrospektiv erhoben und die rein subjektive Einschätzung des Probanden
Gesamtpunktzahl: _____/8

13.3 Timed "Up & Go" (TUG)

Timed "Up & Go"

Handlungsanleitung

Der Proband sitzt auf einem Stuhl mit Armlehne (Sitzhöhe ca. 46 cm). Er darf gegebenenfalls ein Hilfsmittel (z.B. Stock) benutzen. Die Arme liegen locker auf den Armstützen und der Rücken liegt der Rücklehne des Stuhles an. Beim Erreichen dieser Position hilft der Untersucher nicht mit. Nach Aufforderung soll der Proband mit einem normalen und sicheren Gang bis zu einer Linie laufen, die in drei Metern Entfernung vor dem Stuhl auf dem Boden angezeichnet ist, sich dort umdrehen, wieder zurück zum Stuhl gehen und sich in die Ausgangsposition begeben. Die dafür benötigte Zeit wird in Sekunden notiert; es ist keine Stoppuhr vorgeschrieben. Vor der eigentlichen Zeitmessung kann der Proband den Bewegungsablauf üben. Der Untersucher kann den Bewegungsablauf einmal demonstrieren.

Patient hat _____ Sekunden gebraucht

Patient hat keine Gehhilfe benutzt: _____

Patient hat Gehhilfe benutzt _____ und zwar: _____

13.4 Mini Nutritional Assessment (MNA)

		Einteilung	Punkte
1	Hat der Patient einen verminderten Appetit? Hat er während der letzten 3 Monate wegen Appetitverlust, Verdauungsproblemen, Schwierigkeiten beim Kauen oder Schlucken weniger gegessen (Anorexie)?	0 = schwere Anorexie 1 = leichte Anorexie 2 = keine Anorexie	
2	Gewichtsverlust in den letzten 3 Monaten	0 = Gewichtsverlust > 3 kg 1 = weiß es nicht 2 = Gewichtsverlust zwischen 1 und 3 kg 3 = kein Gewichtsverlust	
3	Mobilität / Beweglichkeit	0 = vom Bett zum Stuhl 1 = in der Wohnung mobil 2 = verlässt die Wohnung	
4	Akute Krankheit oder psychischer Stress während oder letzten 3 Monate?	0 = ja 2 = nein	
5	Psychische Situation	0 = schwere Demenz oder Depression 1 = leichte Demenz oder Depression 2 = keine Probleme	
6	Körpermassenindex (Body Mass Index, BMI) (Körpergewicht / (Körpergröße) ² , in kg/m ²)	0 = BMI < 19 1 = 19 ≤ BMI < 21 2 = 21 ≤ BMI < 23 3 = BMI ≥ 23	
Ergebnis Vor-Anamnese (Teil I)			
7	Wohnsituation: Lebt der Patient unabhängig zu Hause?	0 = nein 1 = ja	
8	Medikamentenkonsum: Nimmt der Patient mehr als 3 Medikamente (pro Tag)?	0 = nein 1 = ja	
9	Hautprobleme: Schorf oder Druckgeschwüre?	0 = nein 1 = ja	
10	Mahlzeiten: Wieviele Hauptmahlzeiten isst der Patient pro Tag? (Frühstück, Mittag- und Abendessen)?	0 = 1 Mahlzeit 1 = 2 Mahlzeiten 2 = 3 Mahlzeiten	
11	Lebensmittelauswahl: Isst der Patient • mindestens einmal pro Tag Milchprodukte? ja nein • mindestens ein- bis zweimal pro Woche Hülsenfrüchte oder Eier? ja nein	0,0 = wenn 0 oder 1 mal «ja» 0,5 = wenn 2 mal «ja» 1,0 = wenn 3 mal «ja»	

	<ul style="list-style-type: none"> jeden Tag Fleisch, Fisch oder Geflügel 	ja nein	
12	Isst der Patient mindestens zweimal pro Tag Obst oder Gemüse?	0 = nein 1 = ja	
13	Wieviel trinkt der Patient pro Tag? (Wasser, Saft, Kaffee, Tee, Wein, Bier...)	0,0 = weniger als 3 Gläser / Tassen 0,5 = 3 bis 5 Gläser / Tassen 1,0 = mehr als 5 Gläser / Tassen	
14	Essensaufnahme mit / ohne Hilfe	0 = braucht Hilfe beim Essen 1 = isst ohne Hilfe, aber mit Schwierigkeiten 2 = isst ohne Hilfe, keine Schwierigkeiten	
15	Glaubt der Patient, dass er gut ernährt ist?	0 = schwerwiegende Unter-/Mangelernährung 1 = weiß es nicht oder leichte Unter-/Mangelernährung 2 = gut ernährt	
16	Im Vergleich mit gleichaltrigen Personen schätzt der Patient seinen Gesundheitszustand folgendermaßen ein:	0,0 = schlechter 0,5 = weiß es nicht 1,0 = gleich gut 2,0 = besser	
17	Oberarmumfang (OAU in cm)	0,0 = OAU < 21 0,5 = 21 ≤ OAU ≤ 22 1,0 = OAU > 22	
18	Wadenumfang (WU in cm)	0 = WU < 31 1 = WU ≥ 31	
	Ergebnis Teil 1		
	Ergebnis Teil 2		
	Gesamtsumme		

≥ 24 Punkte: unauffällig

17-23,5 Punkte : Risiko für Unterernährung

< 17 Punkte: Unterernährung

13.5 Social Status and Support Survey (SOS)

Soziale Situation (SoS) n. Nikolaus

Teil 1: Soziale Kontakte und Unterstützung (Kon)

1. Wie leben Sie?

schon lange allein	1
seit kurzem allein (< 1 Jahr)	0
bei Familienangehörigen oder mit rüstigem Partner	1
mit Lebenspartner, der selbst Hilfe braucht	0

2. Haben Sie Personen (auch professionelle Helfer), auf die Sie sich verlassen und die Ihnen zu Hause regelmäßig helfen können? (Aufzählen)

Bezugsperson(en) vorhanden	1
keine Bezugspersonen vorhanden (weiter Frage 5)	0

3. Wie oft sehen Sie diese Person(en)?

mehrmals täglich/jeden Tag	1
einmal in der Woche	1
selten (ein- bis zweimal im Monat)	0
(fast) nie	0

4. Wie ist Ihr Verhältnis zu o.g. Person(en)?

Beziehung harmonisch und vertrauensvoll	1
Beziehung teilweise konfliktbeladen und gespannt	0

5. Wie haben sich in letzter Zeit Ihre Kontakte entwickelt?

habe neue Bekannte gewonnen	1
keine Veränderung	1
einige Kontakte habe ich aufgeben müssen	0
habe nahezu alle wichtigen Kontakte verloren (z.B. Lebenspartner verstorben)	0

6. Sind Sie mit diesem Zustand zufrieden?

fühle mich rundum gut versorgt	1
es geht so, man muß zufrieden sein	0
fühle mich einsam und im Stich gelassen	0

Zwischensumme Kon : _____

Teil 2: Soziale Aktivitäten (Akt)

1. Welchen Beruf haben Sie ausgeübt? _____
2. Welche Hobbies (Handarbeit, handwerkli. Tätigkeit, Basteln, Musizieren, Gartenarbeit, Briefmarken o.ä. sammeln etc.) oder Interessen (Vorträge, Ausflüge, Theater, Sport, Bücher lesen, Kirchengang, Seniorentreff, Enkel hüten etc.) haben Sie, die Sie noch regelmäßig betreiben? (Aufzählen)

Hobbies/Interessen vorhanden	1
keine Hobbies/Interessen	0

3. Haben Sie ein Haustier?

ja	1
nein	0

4. Wie oft verlassen Sie Ihre Wohnung? (Einkaufen, Erledigungen, Spaziergehen, (Arzt-) Besuche, Garten usw.)

täglich	1
mindestens ein- bis zweimal in der Woche	1
seltener als einmal pro Woche	0
(fast) nie	0

5. Wie haben sich in letzter Zeit Ihre Interessen entwickelt?

Habe noch neue Pläne und Interessen	1
unverändert	1
habe einige Interessen aufgeben müssen	0
habe (fast) alle Interessen verloren	0

6. Sind Sie mit diesem Zustand zufrieden?

voll und ganz, fühle mich nicht beeinträchtigt	1
fühle mich schon eingeschränkt, muß zufrieden sein	0
nein, bin durch Alter/Krankheit stark behindert	0

Zwischensumme Akt: _____

Teil 3: Wohnsituation (Wohn)

1. Treppen	Wohnung im Erdgeschoß oder Lift im Haus Viele Treppen, erster Stock oder höher	1 0
2. Komfort	Wohnung eingeschossig, geräumig und rollstuhlgängig beengte Verhältnisse, Türschwellen, viele Teppiche mehrere Wohnebenen, nicht rollstuhlgeeignet	1 0 0
3. Heizung	Gut und bequem heizbar (Öl- oder Gaszentralheizung) schlecht und mühsam heizbar (Kohle- oder Ölöfen)	1 0
4. Wasser	Warmes Wasser in Küche und/oder Bad Kein warmes Wasser vorhanden	1 0
5. Bad/WC	Innerhalb der Wohnung, rollstuhlgeeignet klein, nicht rollstuhlgängig, außerhalb der Wohnung	1 0
6. Telefon	vorhanden nicht vorhanden	1 0
7. Beleuchtung	Treppenhaus und Flure hell, genügend Lichtschalter Treppenhaus und Flure schummrig beleuchtet wenig Lichtschalter	1 0 0
8. Einkaufen	alle Geschäfte des tgl. Bedarfs leicht erreichbar nur Bäcker/Metzger in der Nähe alle Geschäfte weiter entfernt	1 0 0
9. Nahverkehr	Haltestelle in der Nähe (<1km) nächste Haltestelle weiter entfernt	1 0
10. Wohndauer	wohnt schon lange Zeit in der Wohnung (>5 Jahre) hat innerhalb der ltz. 5 Jahre Wohnung bezogen	1 0
11. Fühlen Sie sich in Ihrer Wohnung und der Wohngegend wohl?	bin mit der Wohnsituation sehr zufrieden geht so, muß zufrieden sein bin unzufrieden	1 0 0

Zwischensumme Wohn: _____

Teil 4: Ökonomische Verhältnisse (Ökon)

1. Wieviel Geld steht Ihnen monatlich zur Verfügung? _____

2. Kommen Sie mit Ihrem Geld gut über die Runden?

ja	1
nur wenig	0
nein	0

3. Haben Sie Ersparnisse, Vermögen (eigenes Haus)? (Aufzählen)

ja, ausreichend	1
nur wenig	0
nein	0

4. Regeln Sie Ihre Finanzen selbst?

ja	1
nein	0

Zwischensumme Ökon: _____

Die GESAMTPUNKTZAHL ergibt sich aus: Punkte Kon _____

+ Punkte Akt _____

+ Punkte Wohn _____

+ Punkte Ökon _____

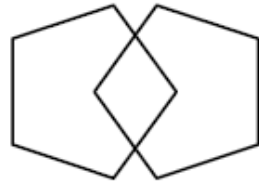
Gesamtsumme = _____

13.6 Mini Mental State Examination (MMSE)

Mini-Mental State Examination (MMSE)

- (0 / 1) 1. Was für ein Datum ist heute?
(0 / 1) 2. Welche Jahreszeit?
(0 / 1) 3. Welches Jahr haben wir?
(0 / 1) 4. Welcher Wochentag ist heute?
(0 / 1) 5. Welcher Monat?
- (0 / 1) 6. Wo sind wir jetzt ? welches Bundesland?
(0 / 1) 7. welcher Landkreis/welche Stadt?
(0 / 1) 8. welche Stadt/welcher Stadtteil?
(0 / 1) 9. welches Krankenhaus?
(0 / 1) 10. welche Station/welches Stockwerk?
- (0 / 1) 11. Bitte merken Sie sich: Apfel
(0 / 1) 12. Pfennig
(0 / 1) 13. Tisch
Anzahl der Versuche:
- Ziehen Sie von 100 jeweils 7 ab oder buchstabieren Sie Stuhl rückwärts:
- (0 / 1) 14. 93 L
(0 / 1) 15. 86 H
(0 / 1) 16. 79 U
(0 / 1) 17. 72 T
(0 / 1) 18. 65 S
- Was waren die Dinge, die Sie sich vorher gemerkt haben ?
- (0 / 1) 19. Apfel
(0 / 1) 20. Pfennig
(0 / 1) 21. Tisch
- (0 / 1) 22. Was ist das? Uhr
(0 / 1) 23. Bleistift/Kugelschreiber
(0 / 1) 24. Sprechen Sie nach: "Kein wenn und oder aber."
- Machen Sie bitte folgendes:
- (0 / 1) 25. Nehmen Sie bitte das Blatt in die Hand,
(0 / 1) 26. Falten Sie es in der Mitte und
(0 / 1) 27. Lassen Sie es auf den Boden fallen
- (0 / 1) 28. Lesen Sie und machen Sie es bitte ("Augen zu !")
(0 / 1) 29. Schreiben Sie bitte einen Satz (mind. Subjekt und Prädikat)
(0 / 1) 30. Kopieren Sie bitte die Zeichnung (zwei Fünfecke)

Augen zu!



13.7 Geriatric Depression Scale (GDS)

Geriatrische Depressions-Skala (GDS)

1. Sind Sie grundsätzlich mit Ihrem Leben zufrieden? Ja Nein
2. Haben Sie viele Ihrer Aktivitäten und Interessen aufgegeben? Ja Nein
3. Haben Sie das Gefühl, Ihr Leben sei unausgefüllt? Ja Nein
4. Ist Ihnen oft langweilig? Ja Nein
5. Sind Sie die meiste Zeit guter Laune? Ja Nein
6. Haben Sie Angst, daß Ihnen etwas Schlimmes zustoßen wird? Ja Nein
7. Fühlen Sie sich die meiste Zeit glücklich? Ja Nein
8. Fühlen Sie sich oft hilflos? Ja Nein
9. Bleiben Sie lieber zu Hause, anstatt auszugehen und Neues zu unternehmen? Ja Nein
10. Glauben Sie, mehr Probleme mit dem Gedächtnis zu haben als die meisten anderen? Ja Nein Ja Nein
11. Finden Sie, es sei schön, jetzt zu leben? Ja Nein
12. Kommen Sie sich in Ihrem jetzigen Zustand ziemlich wertlos vor? Ja Nein
13. Fühlen Sie sich voller Energie? Ja Nein
14. Finden Sie, daß Ihre Situation hoffnungslos ist? Ja Nein
15. Glauben Sie, daß es den meisten Leuten besser geht als Ihnen? Ja Nein

Summe: _____

13.8 Charlson Comorbidity Index (CCI)

Charlson Komorbiditäts-Index

Erkrankung	Bewertung	Punkte
Herzinfarkt ¹	1	
Herzinsuffizienz ²	1	
periphere arterielle Verschlusskrankheit ³	1	
cerebrovaskuläre Erkrankungen ⁴	1	
Demenz ⁵	1	
Chronische Lungenerkrankung ⁶	1	
Kollagenose ⁷	1	
Ulkuskrankheit ⁸	1	
Leichte Lebererkrankung ⁹	1	
Diabetes mellitus (ohne Endorganschäden) ¹⁰	1	
Hemiplegie	2	
Mäßig schwere und schwere Nierenerkrankung ¹¹	2	
Diabetes mellitus mit Endorganschäden ¹²	2	
Tumorerkrankung ¹³	2	
Leukämie ¹⁴	2	
Lymphom ¹⁵	2	
Mäßig schwere und schwere Lebererkrankung ¹⁶	3	
Metastasierter solider Tumor	6	
AIDS	6	
Summe		

¹ Patienten mit Hospitalisierung wegen elektrokardiographisch und/oder enzymatisch nachgewiesenem Herzinfarkt

² Patienten mit nächtlicher oder durch Anstrengung induzierte Dyspnoe mit Besserung der Symptomatik unter Therapie

³ Patienten mit claudicatio intermittens, nach peripherer Bypass-Versorgung, mit akutem arteriellem Verschluss oder Gangrän sowie nicht versorgtem abdominellen oder thorakalen Aortenaneurysma >6cm

⁴ Patienten mit TIA oder Apoplex ohne schwerwiegenden Residuen

⁵ Patienten mit chronischem kognitiven Defizit

⁶ Patienten mit pulmonal bedingter Dyspnoe bei leichter oder mäßig schwerer Belastung ohne Therapie oder

Patienten mit anfallsweiser Dyspnoe (Asthma)

⁷ Polymyalgie rheumatica, Lupus erythematodes, schwere rheumatoide Arthritis, Polymyositis

⁸ Patienten die bereits einmal wegen Ulcera behandelt wurden

⁹ Leberzirrhose ohne portale Hypertonie

¹⁰ Patienten mit Diab. mell. und medikamentöser Therapie

¹¹ Dialysepflichtigkeit oder Kreatinin >3mg/dl

¹² oder zurückliegender Krankenhausaufnahmen wegen hyperosmolarem Koma oder Ketoazidose

¹³ Sämtliche solide Tumore ohne Metastasennachweis innerhalb der letzten fünf Jahre

¹⁴ Akute und chronische Leukosen

¹⁵ Hodgkin und Non-Hodgkin-Lymphome, multiples Myelom

¹⁶ Leberzirrhose mit portaler Hypertonie ohne stattgehabte Blutung und Patienten mit Varizenblutung in der Anamnese