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DOUTORAMENTO
GERONTOLOGIA E GERIATRIA

Avaliação geriátrica de pessoas idosas propostas para Radioterapia

Geriatric evaluation of older adults proposed for Radiotherapy

Edna Darlene Rodrigues Pinto

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UNIVERSIDADE DO PORTO – INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DE AVEIRO

Edna Darlene Rodrigues Pinto

Avaliação geriátrica de pessoas idosas propostas para Radioterapia

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Orientadora:

Professora Doutora Laetitia Costa Teixeira
Professora Auxiliar
Instituto de Ciências Biomédicas Abel Salazar

Coorientadores:

Professora Doutora Escarlata López
Professora Associada
GenesisCare Espanha

Doutor Paulo Almeida
Médico especialista em Medicina Interna com a Competência em Geriatria
Unidade de Saúde Local de São João, E.P.E

"Não mudamos com a idade na estrutura do que somos.

Apenas, como na música, somo-lo noutro tom."

"We do not change with age in the core of our being—

we simply, like music, find ourselves in a different key."

Vergílio Ferreira, 1987

Livro Conta-Corrente V volume.

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ABBREVIATIONS

ADL	Activities of Daily Living
3D	Three dimensional
AdHOC	Aged in Home Care
ART	Adaptative radiotherapy
ASCO	American Society of Clinical Oncology
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AUP	Actual utilisation percentage
BMI	Body mass index
CA-OUP	Optimal comorbidity-adjusted EBRT utilisation rate
CARG	Cancer and Aging Research Group
CES	Comissão de Ética para a Saúde
CETI	Comissão de Ética
CGA	Global Geriatric Assessment
CHT	Chemotherapy
CI	Confidence interval
CINTESIS	Center for Health Technology and Services Research
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CNS	Central nervous system
CT	Computed Tomography
DC	Disease control
DIBH	Deep Inspiration Breath Hold
DIRAC	DIrectory of RAdiotherapy Centres
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group Performance Status
EFS	Edmonton Frail Scale
EIT	European Institute of Innovation & Technology
EORTC	European Organisation for Research and Treatment of Cancer
ESS	Exton-Smith Scale
ESTRO	European SocieTy for Radiotherapy and Oncology
ESTRO - HERO	HERO project (Health Economics in Radiation Oncology) from ESTRO (European SocieTy for Radiotherapy and Oncology)
EUROPA trial	ExclUsive endocRine Therapy Or Radiation theraPy for Women Aged ≥70 Years Early Stage Breast Cancer
FCT	Foundation for Science and Technology
FDA	Food and Drugs Administration
G8	Geriatric-8
GDS	Geriatric Depression Scale
GFI	Groningen Frailty Indicator
GLOBOCAN	Global Cancer Observatory
HNC	Head and Neck Cancer
HR	Hazard ratio
HT	Hormone therapy
IADL	Instrumental Activities of Daily Living
IAEA	International Atomic Energy Agency
IBM	International Business Machines
ICBAS	Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IGRG	International Geriatric Radiotherapy Group
IPO-P	Instituto Português de Oncologia do Porto
LC	Local control
LIVELUNG trial	LIVELUNG - Impact of CGA in Patients Diagnosed With Localized NSCLC Treated With SBRT
mFI	modified frailty index
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
MPI	Multidimensional Prognostic Index
MRI	Magnetic Resonance Imaging
MV	Megavoltage Unit / RT machines
NCCN	National Comprehensive Cancer Network
NEGERMI	Geriatrics Study Group of the Portuguese Society of Internal Medicine
NSCLC	non-small cell lung cancer
NSW	New South Wales, Australia
ONCO-MPI	Onco-Multidimensional Prognostic Index
OR	Odds ratio
OS	overall survival
OUP	Optimal Utilisation Proportion
PRORAD trial	Prostate Cancer Patients Treated With Radiotherapy
PT	Portugal
QOL	Quality of Life
QUARTS	RadioTherapy for Cancer: QUAnification of Infrastructure and Staffing Needs
RISE	Health Research Network
RO	Radiation Oncologists
ROC	Receiver operating characteristic
RON	Registo Oncológico Portugues / Portuguese National Cancer Registry
RORENO	Cancer registry of northern region of Portugal
RT	Radiotherapy
RTT	Radiation therapist
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
SEER	Surveillance, Epidemiology, and End Results Program
SIOG	International Society of Geriatric Oncology
SPMSQ	Short Portable Mental Status Questionnaire
SPSS	Statistical Package for Social Sciences
SRS	Radiosurgery
TRST	Triage Risk Screening Tool
ULSJ	Unidade Local de São João, E.P.E. previously named Centro Hospitalar Universitário São João
VES-13	Vulnerable Elders Survey

RESUMO

De acordo com os estudos publicados previamente, espera-se que em 2045 a população idosa com 70 anos ou mais corresponda a cerca de 60% de todos os novos casos de cancro. No entanto, a evidência que sustenta as opções terapêuticas nesta população é limitada. Uma vez que a Radioterapia (RT) está indicada em cerca de metade dos novos casos de cancro, independentemente da idade, torna-se imperativo contribuir para a investigação da população idosa e as indicações para RT.

O objetivo geral deste projeto foi aprofundar o conhecimento sobre os conceitos da Geriatria Oncológica e promover a sua aplicação prática no contexto da Radioterapia, fortalecendo a integração destas áreas para melhorar a prestação de cuidados das pessoas idosas com cancro.

Com base no racional da Geriatria Oncológica, o processo de avaliação da pessoa idosa com cancro inicia-se com o rastreio de fragilidade, seguido de uma eventual Avaliação Geriátrica Global (CGA). Nesse sentido, esta tese inclui vários estudos que foram desenvolvidos com esse foco. Realizou-se uma revisão da literatura com o objetivo de explorar a relação entre a fragilidade e os resultados terapêuticos da RT. No decurso da preparação desta revisão da literatura, constatou-se a existência de dados de acesso aberto que permitiam o cálculo das necessidades futuras de RT, pelo que foi elaborado um estudo com esse objetivo. Perante as publicações internacionais que referiam uma subutilização da RT na população idosa, foi realizado um estudo dessa utilização com base nos dados do Registo Oncológico Nacional Português. Dada a elevada incidência de cancro na população idosa, considerou-se pertinente avaliar os conhecimentos de Geriatria Oncológica dos Radioncologistas, através da realização de um questionário. Adicionalmente, foi desenhado um estudo realizado com pessoas idosas a realizar RT, com os objetivos de validar uma ferramenta de prognóstico baseada em domínios do CGA – Onco-Multidimensional Prognostic Index (Onco-MPI) e de avaliar a qualidade de vida (QoL) durante e 1 ano após a RT.

Para a concretização deste projeto de investigação foram utilizadas várias metodologias, nomeadamente, revisão da literatura, inquéritos dirigidos a Radioncologistas, análise de dados de registos oncológicos e um estudo de coorte envolvendo 227 doentes idosos em dois centros oncológicos portugueses. A população estudada na coorte foi constituída por idosos com idade igual ou superior a 70 anos submetidos a RT, tendo sido recolhidos dados sobre o estado funcional, dados de saúde e QoL.

De acordo com a revisão da literatura, existem alguns resultados que mostram uma relação entre a fragilidade, perfis de toxicidade à RT menos favoráveis e tratamentos de RT incompletos. No entanto, a RT é um tratamento localizado que apresenta um perfil de toxicidade restrito à localização do tratamento. Esta natureza localizada da RT, associada a uma precisão crescente, graças ao desenvolvimento tecnológico recente, pode proporcionar uma oportunidade única para oferecer tratamentos oncológicos a idosos frágeis. Esta vantagem decorre do facto dos idosos frágeis apresentarem uma reserva funcional insuficiente para tolerar o stress de outros tratamentos oncológicos, como as terapêuticas sistémicas ou a cirurgia.

Com base na nossa projeção das necessidades futuras de RT em Portugal, estima-se um aumento de 18% na procura de RT até 2040, para todas as idades e tipos de cancro. Este aumento associa-se a uma necessidade de aquisição de equipamentos de RT adicionais e de formação/ contratação de profissionais especializados para satisfazer a procura crescente. Esta projeção sugere que, sem um investimento significativo em infraestruturas e sem o aumento do número de profissionais de saúde, Portugal poderá ter dificuldades em prestar cuidados oncológicos adequados nas próximas décadas.

Uma parte importante deste projeto de investigação envolveu a avaliação do conhecimento dos Radioncologistas relativos à geriatria oncológica. O inquérito realizado revelou que, embora a maioria dos Radioncologistas reconhecesse o número crescente da população idosa com cancro, apenas uma pequena percentagem avalia a fragilidade por rotina. Cerca de 98% dos inquiridos expressaram uma forte necessidade de formação adicional em geriatria oncológica, evidenciando uma lacuna significativa na sua capacidade de lidar com os desafios únicos das pessoas idosas.

A análise dos dados do Registo Oncológico Nacional Português permitiu comparar a utilização real da RT com as recomendações internacionais definidas para os vários tipos de cancro. Os resultados revelaram uma subutilização substancial da RT, particularmente na população idosa. Estes resultados sublinham a diferença entre os cuidados recomendados e os cuidados prestados na vida real, identificando oportunidades para melhorar a acessibilidade ao tratamento de RT para a população idosa.

Pretendeu-se validar o Índice de Prognóstico Onco-Multidimensional (Onco-MPI) como uma ferramenta para prever o risco de mortalidade aos 12 meses em doentes

oncológicos idosos submetidos a RT. Foi analisada uma coorte de 227 doentes e o Onco-MPI apresentou uma relação entre a sobrevivência aos 12 meses, de acordo com as categorias de baixo, médio e alto risco. Apesar das limitações destes resultados preliminares, o mesmo sugere que a incorporação na prática clínica de ferramentas como o Onco-MPI pode melhorar o planeamento e os resultados do tratamento oncológico.

Por último, os dados da avaliação da QoL durante e um ano após a RT revelaram que a redução do propósito de vida, problemas de mobilidade e maior rigidez articular foram prevalentes, particularmente em mulheres e nos doentes com pior estado funcional. Estes resultados apontam para a necessidade de incorporar a QoL nos protocolos de avaliação do impacto da RT, de forma a implementar estratégias dirigidas que visem a manutenção da QoL.

No geral, esta tese sublinha a natureza complexa do tratamento das pessoas idosas com cancro. Destaca a importância crítica de incorporar as avaliações da fragilidade e da QoL na tomada de decisões de RT para antecipar e gerir as necessidades particulares desta população. Existe uma clara necessidade de melhorar a formação dos Radioncologistas em geriatria oncológica e um apelo urgente a investimentos em infraestruturas de RT. A integração na prática clínica de ferramentas como o Onco-MPI pode permitir a personalização da RT, com um impacto positivo nos resultados clínicos e na qualidade de vida. Estes resultados sustentam uma abordagem personalizada e centrada na pessoa idosa, que obrigará a mudanças na prática clínica e nas políticas de saúde tendo em vista o bem-estar das pessoas idosas com cancro.

ABSTRACT

According to previously published studies, it is expected that by 2045 the older population aged 70 and over will account for about 60% of all new cancer cases. However, the evidence supporting therapeutic options in this population is limited. Since Radiotherapy (RT) is indicated in about half of new cancer cases, regardless of age, it is imperative to contribute to the research of the older population and RT indications.

The general objective of this project was to deepen the knowledge about the concepts of Geriatric Oncology and promote its practical application in the context of Radiotherapy, strengthening the integration of these areas to improve the provision of care for older people with cancer.

Based on the rationale of Geriatric Oncology, the process of evaluating the older person with cancer begins with frailty screening, followed by a possible Global Geriatric Assessment (CGA). In this sense, this thesis includes several studies that have been developed with this focus. A literature review was carried out with the objective of exploring the relationship between frailty and the therapeutic results of RT. During the preparation of this literature review, it was found that there were open access data that allowed the calculation of future RT needs, so a study was prepared for this purpose. In view of the international publications that reported an underuse of RT in the older population, a study of this use was carried out based on data from the Portuguese National Cancer Registry. Given the high incidence of cancer in the older population, it was considered pertinent to evaluate the knowledge of Geriatric Oncology of Radiation Oncologists, through a questionnaire. Additionally, a study was designed with older people undergoing RT, with the objectives of validating a prognostic tool based on CGA domains – Onco-Multidimensional Prognostic Index (Onco-MPI) and assessing quality of life during (QoL) and 1 year after RT.

To carry out this research project, several methodologies were used, namely, literature review, surveys addressed to Radiation Oncologists, analysis of data from cancer registries, and a cohort study involving 227 older patients in two Portuguese cancer centres. The cohort study population consisted of older people aged 70 years or older who underwent RT, and data on functional status, health data and QoL were collected.

According to the literature review, there are some results that show a relationship between frailty, less favourable RT toxicity profiles, and incomplete RT treatments.

However, RT is a localized treatment that has a toxicity profile restricted to this location. This localized nature of RT, and the most recent techniques that allow an improved accuracy, can provide a unique opportunity to offer oncology treatments to frail older adults. This advantage stems from insufficient functional reserve to tolerate the stress of other oncological treatments, such as systemic therapies or surgery.

Based on our projection of future RT needs in Portugal, it is estimated that there will be an 18% increase in demand for RT by 2040, for all ages and types of cancer. This increase is associated with a need to purchase additional RT equipment and to train/hire specialized professionals to meet the growing demand. This projection suggests that, without significant investment in infrastructure and an increase in the number of health professionals, Portugal may struggle to provide adequate cancer care in the coming decades.

An important part of this research involved the assessment of the knowledge of radiation oncologists about geriatric oncology. The survey revealed that, although most radiation oncologists recognized the growing number of older people with cancer, only a small percentage routinely assess frailty. About 98% of respondents expressed a strong need for additional training in geriatric oncology, highlighting a significant gap in their ability to deal with the unique challenges of older people.

The analysis of data from the Portuguese National Cancer Registry allowed us to compare the actual use of RT with international recommendations for the various types of cancer. The results revealed a substantial underutilization of RT, particularly in the older population. These results underline the difference between recommended care and real-life care, identifying opportunities to improve accessibility to RT treatment for the older population.

This study also aimed to validate the Onco-Multidimensional Prognostic Index (Onco-MPI) as a tool to predict the risk of mortality at 12 months in older cancer patients undergoing RT. A cohort of 227 patients was analysed and Onco-MPI showed a relationship between survival at 12 months, according to the low, medium and high-risk categories. Despite the limitations of these preliminary results, it suggests that the incorporation of tools such as Onco-MPI into clinical practice can improve cancer treatment planning and outcomes.

Finally, data from the assessment of QoL during and one year after RT revealed that reduced life purpose, mobility problems and greater joint stiffness were prevalent, particularly in women and patients with worse functional status. These results point

to the need to incorporate QoL assessments in the evaluation of the impact of RT, to implement targeted strategies aimed at maintaining QoL.

Overall, this thesis highlights the complex nature of the treatment of older people with cancer. It highlights the critical importance of incorporating frailty and QoL assessments into RT decision-making to anticipate and manage the particular needs of this population. There is a clear need to improve the training of Radiation Oncologists in geriatric oncology and an urgent call for investments in RT infrastructure. The integration of tools such as Onco-MPI into clinical practice can allow the personalization of RT, with a positive impact on clinical outcomes and quality of life. These results support a personalized, older person-centred approach, which will require changes in clinical practice and health policies for the well-being of older people with cancer.

LIST OF PAPERS

This research project is divided into four studies, which share a focus on radiotherapy and older people with cancer. These four studies resulted in six papers, submitted to international peer-reviewed journals. The publications referred to in the table below are listed according to the order of presentation throughout this thesis.

Study	Paper
Study 1. Research context	Rodrigues, E.D., Gonsalves, D., Teixeira, L., López Ramírez, E.. Frailty—the missing constraint in radiotherapy treatment planning for older adults. *Aging Clinical and Experimental Research* **34**, 2295–2304 (2022). https://doi.org/10.1007/s40520-022-02200-1
	Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L. The future needs of external beam radiotherapy in Portugal until 2040. *Clinical Oncology*, Volume **36**, Issue 11, e421 - e428 (2024). https://doi.org/10.1016/j.clon.2024.07.011
Study 2. Use of radiotherapy by older adults in Portugal	Rodrigues, E.D., Bento, M.J., Calisto, R., Rodrigues, J., Almeida, P., López Ramírez, E., Teixeira, L. Utilisation Patterns of Radiotherapy Among Older Patients: Insights from Portuguese National Cancer Registry Data. *Journal of Cancer Policy. In Press, Journal Pre-proof.* https://doi.org/10.1016/j.jcpo.2024.100522
Study 3. Radiation Oncologists' knowledge of geriatric oncology	Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L. An evaluation of Portuguese Radiation Oncologists Knowledge and Practice in relation to Geriatric Oncology. *Journal of Radiotherapy in Practice* (artigo submetido em Agosto de 2024)
Study 4. Validation of Onco-MPI and Quality of Life changes in Portuguese older adults undergoing Radiotherapy	Rodrigues, E.D., v.d. Elzen, C., Alves, A., Moura, M.J., Soares, E., Almeida, P., López Ramírez, E., Teixeira, L. *Validation of the Onco-MPI Prognosis Tool: Interim analysis of a Study of Older Cancer Patients Undergoing Radiotherapy in Portugal. xxxx*
	Rodrigues, E.D., v.d. Elzen, C., Alves, A., Almeida, P., López Ramírez, E., Teixeira, L. Quality of Life Outcomes in Older Cancer Patients Undergoing Radiotherapy: A Longitudinal Study Using the EORTC QLQ-ELD14 Module. *Supportive Care in Cancer* (submetido em Outubro de 2024)

LIST OF ORAL COMMUNICATIONS AND POSTERS

During this research project, posters and oral communications were presented at national and international conferences, with peer review. The results presented in the form of poster and oral communication are listed below, according to the study in which they were developed, by type of presentation and in chronological order.

Study	Research Output
Study 1	POSTER • Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L., Radiotherapy needs by Portuguese older adults in 2040 – a GLOBOCAN analysis, GSA 2023, 8/11/2023, Tampa, Flórida, Estados Unidos da América. • Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L., The future needs of External Beam Radiotherapy in Portugal until 2040, ESTRO 2024, 3/05/2024, Glasgow, Escócia. ORAL COMMUNICATION • Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L.. Radioterapia: assegurar o acesso universal em Portugal até 2040. XX CNATARP, promovido pela ATARP – Associação Portuguesa dos Técnicos de Radiologia, Radioterapia e Medicina Nuclear, 3 e 4 de novembro de 2023, Coimbra, Portugal.
Study 2	POSTER • Rodrigues, E.D., Bento, M.J., Calisto, R., Rodrigues, J., Almeida, P., López Ramírez, E., Teixeira, L. The Radiotherapy use by older cancer patients in Portugal - 2018 national cancer registry data, GSA 2023, 8/11/2023, Tampa, Flórida, Estados Unidos da América. ORAL COMMUNICATION • Almeida, P., Rodrigues, E.D., Bento, M.J., Calisto, R., Rodrigues, J., López, E., Teixeira, L. A utilização da Radioterapia por pessoas idosas em Portugal – dados do registo oncológico nacional. 6ª Reunião do Núcleo de Estudos de Geriatria, 26 a 27 de outubro de 2023, Figueira da Foz, Portugal.
Study 3	POSTER • Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L. What Are the Knowledge and Practices on Geriatric Oncology Among Portuguese Radiation Oncologists? - Survey Findings, ESTRO 2025, Vienna, Austria (submetido em Novembro de 2024).

Study 4	POSTER • Rodrigues, E.D., v.d. Elzen, C., Alves, A., Moura, M.J., Soares, E., Almeida, P., López Ramírez, E., Teixeira, L., Caracterização da População Idosa Admitida em Dois Serviços de Radioterapia da Zona Norte, 42º Congresso Português de Geriatria e Gerontologia, 23/11/2022, Lisboa. • Alves, A., v.d. Elzen, C., Moura, M.J., Pinto, M.G., Casalta-Lopes, J., Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L. Assessment of Late Toxicity in Older Patients Undergoing Radiotherapy: A Descriptive Analysis, ESTRO 2024, 3/05/2024, Glasgow, Escócia. ORAL COMMUNICATION • Alves, A., v.d. Elzen, C., Moura, M.J., Pinto, M.G., Casalta-Lopes, J., Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L. Avaliação da toxicidade da Radioterapia na população idosa, a realidade de um centro hospitalar. 16º Congresso Nacional do Idoso – Geriatria 2023, 22 e 23 de junho de 2023, Porto, Portugal.
	POSTER • Rodrigues, E.D., Alves, A., Aires, F., Moura, M.J., Soares, E., Almeida, P., López Ramírez, E., Teixeira, L. Avaliação da qualidade de vida das pessoas idosas a realizar radioterapia, Encontros da Primavera 2023, 23/03/2023, Évora. • Rodrigues, E.D., Aires, F., Sá, C., v.d. Elzen, C., Alves, A., Moura, M.J., Soares, E., López Ramírez, E., Teixeira, L. Association between activities of daily living and quality of life in older people undergoing RT, ESTRO 2023, 12/05/2023, Viena, Austria. • v.d. Elzen, C., Alves, A., Moura, M.J., Pinto, G., Rodrigues, E.D., Almeida, P., López Ramírez, E., Teixeira, L., Cancer in the older patients: the 1-year impact of radiotherapy in quality of life, ESTRO 2024, 3/05/2024, Glasgow, Escócia. • Rodrigues, E.D., Moura, M.J., Soares, E., Almeida, P., López Ramírez, E., Teixeira, L., Assessing the quality of life in older persons with cancer: during radiotherapy and one-year post-treatment, Faone-year Radiologists and Radiation Oncologists 2024, 27/09/2024, Dublin, Irlanda. ORAL COMMUNICATION • E.D. Rodrigues; C Elzen; A. Alves; M.J. Moura; E. Soares; P. Almeida; E. López; L. Teixeira, Assessing the quality of life in older persons with cancer undergoing radiotherapy, during and one-year post-treatment, Multinational Association of Supportive Care in Cancer (MASCC) 2024, 27/06/2024, Lille, França.

GENERAL INTRODUCTION

Due to close contact with family members diagnosed with cancer at advanced ages, the researcher developed an early interest in oncology and geriatrics. This personal experience revealed the particularities of healthcare and inspired the pursuit of an integrated master's in medicine. Upon its completion, the researcher deepened her understanding of various aspects of medicine, solidifying a preference for oncology. The presence of the technological component and the innovative aspect of Radiation Oncology, combined with its growing relevance in the older population, particularly given the increasing incidence of cancer in this age group, were the main reasons for choosing this specialty.

During specialty training, the student became aware of the insufficient integration of geriatric components in oncology decisions, which was the main reason to start the Doctoral Programme in Gerontology and Geriatrics. Throughout medical training, the student developed several research projects, some of which involved older patients, aged 70 years or over. In the later years of training, clinical practice was particularly focused on the care of older patients referred for radiotherapy. This older population presented several challenges such as cognitive impairment, coordination of care for nursing home residents, and managing pre-existing comorbidities, among others. Most of these cases were referred for radiotherapy due to the impossibility or refusal of surgery or chemotherapy.

This reality highlights an emerging challenge, underscoring the importance of preparing Radiotherapy Services for the increasing demand from older population. Based on this gap, the researcher formulated hypotheses aimed at addressing the need for tailored care for this growing population. The future demand will require a collaboration with other professionals to provide holistic management of the older person with cancer, either with curative or palliative intent. Recognizing the insufficient exploration of older people topics during both pre- and post-graduate training, the student viewed this research project as a unique opportunity to enhance academic knowledge, achieve professional fulfilment, and contribute to the personalisation of care, particularly for older adults with cancer referred for radiotherapy treatment.

Fully aware of the dedication required for this challenge, the researcher paused clinical activities to focus exclusively on the development of this project, made possible by the FCT/CINTESIS Doctoral Grant.

This project, entitled "GERIATRIC EVALUATION OF OLDER ADULTS PROPOSED FOR RADIOTHERAPY" aims to strengthen knowledge in geriatric oncology and apply it within Radiation Oncology. The focus of this project was defined based on need of a multidisciplinary approach in the geriatric oncology setting, where oncologists should improve their knowledge about geriatric assessment, while geriatricians should increase their familiarity about oncology treatments.

The following general objectives were defined for this research project:

Assess External Beam RT utilization among older adults aged 70 years or over, using data from the Portuguese National Cancer Registry. It is imperative to gain a more detailed understanding of the national reality regarding the influx of older adults into Radiotherapy Services. The aim is to provide this data to the relevant authorities so that they can take adjustment measures regarding future needs, in line with projected ageing trends.

Examine the knowledge of geriatric oncology among Portuguese radiation oncologists, with the objective of assessing their current application of this knowledge in the clinical practice. It is intended that, through the evaluation of its current use, professionals will be made more aware of its importance.

Validate the Onco-Multidimensional Prognostic Index (Onco-MPI) to the Portuguese older population undergoing RT. This tool is a geriatric assessment-based tool that has been developed and validated to predict mortality risk in older adults with cancer. As it uses geriatric assessment domains to predict one-year survival, hopefully it can be incorporated into therapeutic decision-making algorithms.

Analyse changes in the QoL of older adults with cancer treated with RT using the EORTC QLQ-ELD14 questionnaire. This survey aims to assess the ability of the older adults to cope with cancer, and the way the disease may affect them.

Thesis outline:

This thesis is structured in four main parts, each addressing a specific aspect of the research and its broader context.

The first section includes the essential preliminary segments, such as acknowledgments, abstracts (in Portuguese and English), lists of research outputs of this research project such as articles, communications and posters, as well as a general introduction that prepares the reader for the context of the project, briefly outlining its objectives.

Part I - Conceptual and Methodological Framework lays the groundwork for the research. It begins with Chapter 1, which provides the conceptual framework exploring the theoretical basis of the study, emphasizing the importance of a multidisciplinary approach in the context of geriatric oncology. Chapter 2 outlines the methodological framework, detailing the research design, the tools and techniques used for data collection and analysis, ensuring the accuracy and validity of the research approach.

Part II - Research Results represents the main results of this research project, presented in six chapters. Chapter 3 discusses the role of frailty as a crucial but often overlooked factor in the planning of radiation therapy treatment for the older population. Chapter 4 focuses on forecasting the future demand for external beam radiotherapy in Portugal until 2040, using forecasting methods to provide valuable information for health care planning. Chapter 5 explores patterns in the use of radiotherapy among older patients, drawing on data from the Portuguese National Cancer Registry to identify trends and gaps in care. Chapter 6 assesses the knowledge and practices of Portuguese radiation oncologists in relation to geriatric oncology, highlighting areas for improvement in training and awareness. Chapter 7 examines the validation of the ONCO-MPI prognostic tool for older adults undergoing radiotherapy in Portugal, evaluating its usefulness to improve clinical decision-making. Chapter 8 assesses the quality of life of older cancer patients during radiation therapy and one year after treatment, providing critical insights into patient-centred care outcomes.

Part III - Discussion and Conclusions integrates the results presented in Part II in a broader context, reflecting on their implications for clinical practice, health policies and future research. The conclusions chapter cites the key messages of

the thesis and offers recommendations for improving the care provided to older adults with cancer, along with suggestions for further study.

Finally, **Part IV - Appendices** includes supplementary materials, such as relevant documentation supporting the thesis.

PART I - CONCEPTUAL AND METHODOLOGICAL FRAMEWORK



CHAPTER 1. CONCEPTUAL FRAMEWORK

1.1 Cancer

Nowadays, worldwide cancer is the third leading cause of death, reduced lifespan, and burden of disease. Regarding the lifetime lived with disability, cancer is the fourth cause linked to it. Consequently, is well recognized that cancer as a significant impact on both mortality and morbidity. Recently, the 2021 report from Institute for Health Metrics and Evaluation states that worldwide around 23 million new cancer cases were registered. The mortality linked to these new cancer cases was accounted to be almost 10 million deaths and the morbidity translated into 252 million years of healthy lifespan lost (InstituteHealthMetrics&Evaluation, 2021).

In 2045 in Europe is expected that older adults aged 70 years or over will account to about 60% of all new cancer cases. This projection occurs in a scenario where European population is assumed to reach 713 million in 2045, in contrast to 747 million in 2022. However, the older population aged 70 or over is expected to be 150 million in 2045, in comparison with 104 million in 2022. This growth in older population will translate into a rise of new cancer cases, projected to be 3 million in 2045, as opposed to 2 million in 2022 (Observatory, 2024). In Portugal, 69,567 new cancer cases and 33,762 cancer-related deaths were reported by the Global Cancer Observatory in 2022 (GLOBOCAN, 2022).

The ageing of the population brings multiple challenges in relation to the complex interplay between normal ageing processes and acquired diseases.

The normal ageing processes translate into a decline of function in several organs. This change in renal, hepatic, and bone marrow function can be associated with increased risk of experiencing chemotherapy toxicity. There is also an increase in fat mass and a decline in lean mass, which is associated with a raised risk of toxicity to systemic treatments. Furthermore, the presence of comorbidities and polypharmacy increases the risk of side effects and drug interactions (Arenas et al., 2018; Hounsome et al., 2017).

The access to cancer treatments can be jeopardized by age, because the organ function reduction turns treatment decisions more complex and can even result in an omission of cancer treatments (Kravchenko et al., 2015). Also, age itself does not correlate with functional capacity, so in the absence of an individualized

geriatric assessment, cancer treatments may be omitted in healthy older adults with cancer (Rogers et al., 2015).

This discrimination based on age is recognized by World Health Organization as Ageism, that defined it as "*stereotyping and discrimination against individuals or groups on the basis of their age*". Ageism has been shown to correlate with negative effects on health outcomes, as reported in 95.5% of the studies in a systematic review that included over 7 million participants (Chang et al., 2020). However, a more recent review focusing on ageism in cancer patients concludes that the literature on this phenomenon within this specific population remains limited (Krasovitsky et al., 2023).

This individualized geriatric assessment aims to improve the understanding of functional capacity of each older adult, evaluate frailty and other geriatric syndromes, but also, to implement prehabilitation interventions. Once completed, this evaluation allows healthcare providers to adapt the cancer treatment to the functional capacity and avoid the decision making based solely on age (Hurria, 2009).

1.2 Radiotherapy

Radiotherapy (RT) is one of the most important cancer treatment modalities alongside with surgery and systemic treatments (such as chemotherapy, immunotherapy, and hormone therapy). The most common type of radiation used in the treatment of cancer is external beam radiation. It involves positioning a radioactive source outside the patient's body, with the energy carefully directed and shaped to reach the area where the tumour is located. In contrast, brachytherapy involves placing radioactive sources directly in or near the tumour. These radioactive sources naturally decay over time, delivering high doses of radiation to a localized region (SEER_Training, 2023).

Within the scope of this thesis, RT refers to treatment with external beam radiation, and does not refer to data regarding the indication, use, and future needs of brachytherapy.

The cancer treatment modalities can be used in combination separately based on the clinical context defined by cancer location, staging and patient's characteristics and preferences. Surgery is one of the oldest methods of treating tumours and involves the physical removal of the tumour mass. RT is used frequently after

surgery, to reduce the risk of recurrence, aiming to irradicate any remaining cancer cells that were not visible, or when complete tumour removal would result in unacceptable morbidity, requiring radiation to target the remaining tumour mass (Mee et al., 2023).

The anticancer effect of systemic treatments relies on drug distribution and metabolism. Frail patients who may have compromised drug metabolism and distribution due to a reduced organ capacity, are at higher risk of toxicity. This increased risk of toxicity from systemic treatments occurs due to a combination of age-related changes in various organ systems. It is found that there is an increased risk of myelosuppression due to decreased haematopoietic reserve. On the other hand, mucositis and diarrhoea may be more frequent due to the reduced proliferation of stem cells. There is also an increase in the potential for cardiotoxicity, due to the reduction of cardiomyocytes. There is an increased risk of pulmonary toxicity, due to the impairment of respiratory reserve. Finally, decreased brain volume and circulation increases susceptibility to neurotoxicity. This increase the risk of drug-related side effects is linked to pharmacokinetics changes caused by well-known age-related physiological changes. The drugs absorption may be impaired due to reduced gastric secretion, motility and absorption surface, as well as decreased digestive organs circulation. The drugs distribution is also altered, due to changes in body composition, such as increased fat and reduced intracellular water, reducing the effectiveness of water-soluble drugs while prolonging the effects of fat-soluble drugs. Reduced liver size, hepatic blood flow and enzyme activity delay the metabolism of systemic treatments. Finally, decreased renal function, including lower glomerular filtration and tubular excretion, delays drug clearance, increasing the risks of toxicity (Feliu et al., 2018).

Furthermore, patients taking more than 5 drugs are also at an increased risk of drug interactions and toxicity. For older patients with functional disabilities, the cancer treatment selection must take into consideration the balance between effective cancer control, manageable side-effect, and maintaining QoL (NIH-NIC, 2019).

Around half of all cancer cases may be recommended to performed RT at some point of their cancer journey. RT is a local treatment that uses radiation to destroy cancer cells, aiming to target the tumour while avoiding the irradiation of surrounding healthy tissues. Considering the localized and precise nature of RT, this cancer treatment modality may be relevant for those patients that prefer

options that preserve the organ or are considered ineligible to more invasive treatments or with contraindications for systemic treatment. For those patients, RT will not replace the benefits of other cancer modalities but will be able to contribute to QoL maintenance since it is able to control symptoms such as active haemorrhage and cancer related pain (Dohm et al., 2021).

RT is delivered using machines that are under continuous research aiming to achieve technological advancements. Recent technological achievements have enhanced RT precision, offering a personalized and precise treatment.

Precise targeting is a reality thanks to specialized RT planning software that incorporates advanced imaging techniques, such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), to accurately identify the tumour's location and define its boundaries. RT planning is a personalized process where radiation beams are selected to match the tumour's size and shape. A combination of radiation beams allows that the dose delivered to the tumour to be around 100% and sharply decrease to nearly 0% a few millimetres away. This process aims to find the best RT plan that allows an optimal coverage of tumour's area while limiting the exposure of healthy tissues to radiation. Also, RT schedules aim to take advantage of the different response to radiation between healthy tissues and tumour cells. RT usually is delivered in small doses over several weeks, because tumour cells cannot repair the radiation damage as healthy tissues. Also, the machines used to deliver RT feature advance imaging techniques that allow for daily monitoring of the tumour's location before treatment, ensuring that radiation beams are directed at the tumour area. This allows to evaluate the tumour response and adjust RT to anatomical changes, defining new boundaries and limiting the healthy tissues exposure to radiation (Agency, 2023).

Tailoring cancer treatments to specific needs and conditions of older adults has been reported to be an important factor that may improve cancer outcomes and QoL. The need to personalize cancer treatment in older adults has been highlighted by geriatric oncology interest groups, such as International Society of Geriatric Oncology (SIOG) and Cancer and Aging Research Group (CARG) (Mohile et al., 2015).

Some studies have reported improved QoL when cancer treatments were adjusted to meet the needs of older population. One of these studies, concluded that older women with hormone receptor-positive, low-risk breast cancer reported better QoL with RT alone compared to those receiving hormonal treatment or chemotherapy.

Local control was not compromised by the use of RT alone (Ward et al., 2019). Further evidence will be available once the results from the ongoing EUROPA clinical trial (NCT04134598) are released (*ExclUsive endocRine Therapy Or Radiation theraPy for Women Aged ≥70 Years Early Stage Breast Cancer (EUROPA)*, 2024). A more favourable QoL profile, especially in urinary and sexual domains, was also reported in older men with prostate cancer who underwent RT in comparison to those who performed radical prostatectomy. However, they reported less favourable QoL outcomes regarding bowel function (Wang et al., 2020). The QoL profile is currently under investigation in the PRORAD study (NCT05645237). Health-related QoL data in older men with prostate cancer who underwent different RT modalities are being collect to understand the long term impact of RT on QoL (*HRQOL in Prostate Cancer Patients Treated With Radiotherapy (PRORAD)*, 2024).

Furthermore, RT, specifically stereotactic body radiotherapy (SBRT) is first treatment option for older adults with non-small cell lung cancer (NSCLC), who suffer from other severe comorbidities and reduced lung function, which pose a high risk of surgical complications (Schneider et al., 2018). Further data concerning the impact of appropriate geriatric evaluation, conducted through CGA, combined with SBRT for NSCLC, on QoL and survival outcomes is under investigation in the LIVELUNG study (NCT05919641) (*LIVELUNG - Impact of CGA in Patients Diagnosed With Localized NSCLC Treated With SBRT (LIVELUNG)*, 2024).

1.3 Clinical trials for older adults with cancer

As previously stated, older adults comprise the majority of cancer patients. However, within clinical trials their representation is well below the cancer incidence. Namely, for the trials approved by the Food and Drugs Administration (FDA), only 36% of all participants were aged 65 or over, in contrast with 60% of cancer incidence in this age group in the United States. This underrepresentation is even more evident for the patients aged 70 and 75. The cancer incidence was 46% and 31% whereas the clinical trials representation was 20% and 9%, for those aged 70 and 75, respectively (Scher & Hurria, 2012).

For the oldest subgroups, an analysis of clinical trials that led to cancer treatments approved by FDA between 2005 and 2015, showed that persons aged 80 or over, represented 16% of new cancer cases. However, they only accounted for 4% of the population included in these trials. Unfortunately, these disparities in

representation of age groups according to their incidence, compromises the translation of evidence produced by clinical trials into real world scenarios (Singh et al., 2017).

International organisations such as American Society of Clinical Oncology (ASCO) and the FDA are aware of this fact and have already published recommendations to promote the reporting of age-specific data regarding the toxicity profiles of cancer treatments (Singh et al., 2018). BrintzenhofeSzoc et al. published a systematic review that analysed the percentage of studies that report toxicity patterns and treatment outcomes stratified by age groups. They focused their analysis on chemotherapy papers published between 2016 and 2017 and found that treatment efficacy was reported by age in less than 40% and that side effects only in 9% of the studies (BrintzenhofeSzoc et al., 2020).

Taking into consideration that age should not be the only criteria to make decisions in geriatric oncology, designing clinical trials that include CGA as tool to evaluate and stratify outcomes, can improve the knowledge about the heterogeneous ageing population that undergo cancer treatments. Also, CGA allows the identification of frail patients and the designing of treatment arms that include tailored treatments for patients that require prehabilitation or treatment adjustments. There are several trials that incorporate CGA in their design, and hopefully their outcomes will help to validate the hypothesis that cancer outcomes improve when patients are correctly stratified by their health status and frailty is identified (Bumanlag et al., 2022).

1.4 Frailty

In cancer setting, frailty can translate into several health problems, such as a decline in heart and lung function, sarcopenia, malnutrition and increased risk of falls. The route of frailty in cancer patients is difficult to identify because it is influenced by multiple factors such as cancer related problems, treatment toxicity, multimorbidity, polypharmacy and senescence. Regardless of the underlying condition, frailty is defined by Dent et al. as a *"condition characterised by decreased physiological capacity and increased vulnerability to stress",* that can be correctly identified through a CGA (Dent et al., 2019). Due to different frailty assessment models, the literature regarding the prevalence of frailty among older cancer

patients is limited. Handforth et al., found that the prevalence of frailty ranged from 6% to 86%, in the studies included in their analysis (Handforth et al., 2015).

1.4.1 Comprehensive Geriatric Assessment (CGA)

Identifying frailty is a cornerstone of providing care to older adults with cancer. This identification and tailored interventions must be carried out through CGA. CGA is more than an evaluation performed by a geriatric doctor, it may involve assessments by multiple specialist doctors, nurses and other health professionals. Furthermore, focus on other issues than diseases, such as functional and cognitive disabilities, nutritional status, and social risks and environmental problems that also play a role in overall patient's well-being.

CGA has focus that goes beyond the disease itself, including clinical, emotional, nutritional, and functional status, cognitive function, social support and environmental factors. As a result of CGA, a list of bio-phyco-social problems is created, and several interventions are delineated taking into consideration the personal goals of the older person. CGA is more than an assessment, since it involves the management of the problems uncovered (Welsh et al., 2014). Furthermore, CGA surpasses the guess of a very experienced physician based solely on age concerning functional status of an older adult with cancer (Tucci et al., 2009).

The Geriatrics Study Group of the Portuguese Society of Internal Medicine (NEGERMI) plays a crucial role in the development and valorisation of geriatrics in Portugal. NEGERMI's activities centre on several key objectives aimed at improving the care and quality of life (QoL) of the older through scientific and educational practices. NEGERMI has the priority to gather consensus and create protocols tailored to older populations. These efforts are fundamental for the standardisation of care and the adoption of best practices based on scientific evidence. To this end, it has published national recommendations regarding the tools to be used for each domain of CGA, as described below (GERMI, 2013).

1. Katz Index of Independence in Activities of Daily Living (ADL): Assesses the older person's ability to carry out basic daily activities, including bathing, dressing, toileting, transferring, maintaining continence and eating (Katz et al., 1970).

2. Lawson & Brody Instrumental Activities of Daily Living (IADL) Scale: Assesses the older person's autonomy in carrying out more complex activities needed to live

independently in the community, such as using the telephone, shopping, preparing meals, housekeeping, laundry, transport, managing medication and dealing with finances (Lawton & Brody, 1969).

3. Holden functional walking classification: The walking autonomy is assessed by evaluating the type of assistance or supervision needed while walking on different surfaces (Holden et al., 1984).

4. Yesavage Geriatric Depression Scale (GDS) - Short Form: Depression screening instrument focused on the cognitive and behavioural aspects typically affected by depression in the older population (Sheikh & Yesavage, 1988).

5. Mini Mental State Examination (MMSE): Questionnaire summarising cognitive functions, covering orientation, immediate and recent memory, attention and calculation, language and constructive capacity (Pfeiffer, 1975).

6. Mini Nutritional Assessment (MNA): Detects the presence or risk of malnutrition without requiring laboratory parameters. It includes an initial screening (6 questions) and a detailed assessment (12 additional questions, if necessary) (Kaiser et al., 2009).

Internationally, CGA is also recommended by SIOG, a non-profit association focused on geriatric oncology and accounts with contributions from healthcare professionals in more than 80 countries. In the context of treating older cancer patients, the CGA allows impairments detection not identified in the routine clinical history or physical examination. In addition, it has the ability to predict serious treatment-related toxicity, allows survival estimation for various tumour locations. CGA results can influence the choice and intensity of cancer treatment. The consensus published by SIOG recommends that the following domains should be assessed in the CGA: functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition and the presence of geriatric syndromes. The authors of the consensus do not recommend a specific tool for assessing each domain, recognising that various tools and models for implementing the CGA are available (Wildiers et al., 2014).

Several studies have been exploring the impact of CGA in cancer-specific and patient-reported outcomes. One such study, conducted as a clinical trial, focused on frail older patients with colorectal cancer, found that CGA-based interventions improved chemotherapy completion rates, decreased dose reductions, and

improved quality of life, including mobility and disease burden, compared with standard of care (Lund et al., 2021). Another randomized controlled trial reported potential benefits of CGA for quality of life. It included 61 patients aged 70 years and older who were diagnosed with stage 2–4 gastrointestinal, genitourinary, or breast cancer within 6 weeks of starting chemotherapy. This study was able to demonstrate the feasibility of recruiting and retaining older people with cancer for a geriatric evaluation and management study, especially for those who survived at least six months after the intervention (Puts et al., 2018).

Currently, evidence on the role of CGA in radiation oncology is not as vast as for medical oncology. The limited data, often based on small studies, and has not consistently shown CGA to be a reliable predictor of treatment tolerability or toxicity. Nevertheless, the results from one prospective study that enrolled 85 older patients (above 75 years) with inoperable, locally advanced non-squamous-cell lung cancer were enrolled in demonstrated that CGA and the Vulnerable Elders Survey (VES-13) are independent prognostic tools. Based on this evaluation the patients fit for concurrent chemoradiotherapy were correctly identified, which significantly improved survival outcomes but was associated with higher toxicity risks in patients with higher VES-13 scores (Antonio et al., 2018).

1.4.2 Multidimensional Prognostic Index (MPI)

Efforts has been made to standardize CGA and create protocols of assessment that provide measurable outcomes. Piloto et al., developed the Multidimensional Prognostic Index (MPI), based on CGA of hospitalised older patients that allows to predict one-year mortality (Pilotto et al., 2008).

The authors studied the CGA domains that influence the risk of mortality and created a mortality risk model that defined scores for each factor. The domains found to influence 1-year mortality are described below:

Activities of Daily Living (ADLs): This domain assesses independence in six essential activities, such as bathing, dressing and transferring.

Instrumental Activities of Daily Living (IADL): This domain assesses more complex daily tasks that require greater cognitive and physical abilities, including managing finances and using transport.

Cognitive Status (Short Portable Mental Status Questionnaire, SPMSQ): Cognitive function is assessed through a 10-item questionnaire that measures orientation, memory and other cognitive abilities (Pfeiffer et al., 1984).

Comorbidity (Cumulative Illness Rating Scale, CIRS): This domain examines the severity of co-existing medical conditions in 13 systems, such as cardiovascular and respiratory diseases. The CIRS provides two scores: the Comorbidity Index (CIRS-CI), which reflects the number of significant pathologies, and the Severity Index (CIRS-SI), which indicates the overall severity of the illnesses (Bernard S Linn et al., 1968).

Nutritional Status (Mini Nutritional Assessment, MNA): Nutritional health is assessed through measures such as body mass index and dietary intake (Kaiser et al., 2009).

Risk of pressure ulcers (Exton-Smith Scale, ESS): This domain assesses the risk of developing pressure ulcers by evaluating physical and mental condition, activity, mobility and incontinence (Norton et al., 2002).

Medication use: The number of medications taken by the patient is recorded, reflecting polypharmacy and potential medication-related problems.

Social Support: This domain examines the patient's social environment, including household structure and support services.

The scores from the eight domains are added up and divided by 8, to calculate the MPI score, that ranges from 0 to 1. The MPI score is then categorised into three 1-year mortality risk levels: low (≤0.33), moderate (0.34-0.66) and severe (>0.66). The MPI can be a useful toll guiding clinical decisions and predicting 1-year mortality risk based on CGA domains.

The relevance of MPI has been shown in several clinical contexts. The outcomes in patients with cancer, community acquired pneumonia and heart failure could be predicted based on MPI scores (Giantin et al., 2018; Pata et al., 2021; Pilotto et al., 2009; Pilotto et al., 2010). Also, based on predictive relevance of MPI, other authors have been developing and validating other MPI formats such as telephone-administered and self-administered versions (C. Custodero et al., 2021; Pilotto et al., 2019).

1.4.3 Oncology Multidimensional Prognostic Index (Onco-MPI)

Considering MPI great potential to be a suitable tool for supporting decision-making in geriatric oncology, Brunello et al. developed the Oncology Multidimensional Prognostic Index (Onco-MPI). Similarly to MPI, Onco-MPI takes into consideration CGA domains to predict 1-year mortality risk in older adults with cancer (Brunello et al., 2016).

Patients aged 70 years or over, with a confirmed diagnosis of cancer and who underwent CGA and attended the Geriatric Oncology Programme at the Instituto Oncologico Veneto in Padua, Italy, between September 2004 and June 2011, were included in the development and validation of Onco-MPI.

Based on a multivariable Cox proportional hazard model of the CGA domains and cancer characteristics, the factors impacting 1-year mortality, and respective weights were defined.

The patients included in the Onco-MPI development cohort were followed up every 3-6 months, with an average follow-up time of 2.5 years.

A comparison between the predicted and observed deaths within 1 year of follow up was carried out using the Hosmer-Lemeshow test. Results suggested that the Onco-MPI has a reliable performance in predicting the risk of 1-year mortality, and the calculated p-value for the development cohort was 0.854 (D'Agostino & Nam, 2004). Furthermore, a comparison of pairs of patients to assess if Onco-MPI predicts correctly who will have a longer survival was performed using a concordance index (c-index). If this index is 0.5 means that Onco-MPI has a poor prediction power while 1.0 means that it allows a perfect mortality prediction. For the development cohort, the c-index was 0.869 (95% CI: 0.841-0.897), showing a high predictive accuracy (Pencina & D'Agostino, 2004).

1.5 Quality of life as key outcome in cancer care of older adults

Undoubtedly, it is important that cancer treatment decisions align with the preferences of older adults with cancer and that QoL is considered a key outcome by healthcare providers. Defining QoL is complex, as it involves several domains such as physical health, cognitive function, independence, and social relationships. Achieving the right balance between these domains is essential for ensuring life satisfaction and overall well-being (Florian et al., 2018).

Maslow's Hierarchy of Needs, a psychology theory, proposes a framework for understanding human needs. According to Maslow, when they are met, a person can experience life satisfaction and overall well-being. At the base of the pyramid are basic needs, including food, warmth and shelter. Once these needs are satisfied, individuals can pursue higher levels of needs such as safety, social relationships, self-esteem and, finally, self-actualisation, which involves realising one's full potential. In a very simplified way, this theory may be translated into older adults with cancer. Their basic needs can include physical health and cognitive functioning. Once these basic needs are met, older adults can then pursue social interactions, hobbies and finding a sense of purpose (Maslow, 1943).

Furthermore, the priorities regarding QoL and survival can be different between each person dealing with cancer. Also, there is published data that states that older adults more frequently prioritize QoL over survival (Florian et al., 2018).

Seghers et al. studied the QoL of older adults with cancer in the two years previous to the assesstment. Based on the interviews with 63 older adults aged 70 or over, indicators of QoL included cognition preservation, contact with family, independence and staying in their own home (Seghers et al., 2022).

The main factors affecting QoL were explored in another study, carried out in a French university hospital. The authors interviewed 102 cancer patients over the age of 74. Older adults identified as the main factors affecting QoL, the importance of maintaining close relationships with family and friends, having autonomy in decision-making and mobility, being in good health, avoiding pain and not facing problems related to family members (Matelot et al., 2021).

EORTC QLQ-ELD14: Quality of life evaluation tool

The SIOG working group published that QoL must be a core component of all aspects of care for the older cancer patient and that treatment decisions should not be made solely based on age. Instead, these decisions should focus on individual needs and utilising QoL tools such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and ELD-14 in conjunction with comprehensive geriatric assessment. Regular QoL assessments must be performed with the input of a multidisciplinary team (Scotte et al., 2018).
The EORTC established 70 years old to be the cut-off age for 'older patients' and developed the EORTC QLQ-ELD14 questionnaire to 'measure health-related QoL in older patients' with cancer (Wheelwright et al.). The EORTC QLQ-ELD14

questionnaire, aims to ‘assess the ability of the older adults to cope with cancer, and the way the disease may affect them. The EORTC QLQ-ELD14 module contains 14 items with four response levels, including age-specific scales related to each item such as mobility, joint stiffness, family support, worries about others and worries about the future, maintenance of purpose, and burden of illness. For questions evaluating symptoms, higher scores indicate worse mobility and more joint stiffness, higher worries about others or the future, and higher burden of illness. On the other hand, for questions focusing on functional domains, a lower score reflects lower family support and purpose (Wheelwright et al., 2013). This module was already validated to the Portuguese population by Cipriano et al (Cipriano et al., 2021).

The importance of the proposed research

As mentioned previously, is it expected that cancer incidence in the older population will continue to increase in the future. This increase will require that cancer treatment proposals are adjusted to the specific needs of this population. As previously stated, older adults with cancer may present several comorbidities and geriatric syndromes that adds complexity to the decision-making process and that can translate into increased risk of side effects to systemic cancer treatments. Given its localised nature, RT can play an important role in providing a way to control cancer related symptoms and providing QoL. However, there is limited published research about older adults that undergone RT.

Research problem/ questions

1. Importance of frailty assessment in radiotherapy decisions:

In general, frailty is not assessed or incorporated into cancer treatment decisions, particularly in relation to RT decisions. A systematic and timely frailty evaluation, based on CGA, is needed to better understand the health status of an older adult with cancer, rather than focusing solely on age.

2. Future needs for radiotherapy:

The planning and allocation of resources to radiotherapy services must consider the cancer incidence expectations for the next decades. Considering the future rise in cancer incidence due to ageing, it is important to provide up-to-date data regarding the RT needs to allow policy makers to plan the future of cancer care.

3. Use of radiotherapy among older adults:

The published data about the use of radiotherapy among older adults with cancer is limited. Knowing the usage profile provides opportunities to address potential challenges faced by this population.

4. Knowledge of geriatric oncology among radiation oncology professionals:

Facing the rising number of older adults with cancer, it is important that the healthcare professionals are aware of the specific needs of this population. Assessing the knowledge about geriatric oncology among radiation consultants and residents allows to identify ways to improve it.

5. Validation of the Onco-MPI tool:

Prognosis tools that are based on CGA domains can provide valuable information for the decision-making process regarding cancer treatments in older adults. One such tool, Onco-MPI, developed to predict 1-year survival, has not yet been validated in radiotherapy setting or among Portuguese cancer patients. So, validating its predictive value of this context would offer useful information for the decision-making process.

6. Quality of life of older adults undergoing radiotherapy:

While RT can have curative effects that improve the QoL of older adults with cancer, it may impair QoL. Data on the QoL of older adults in the RT setting has not been extensively covered in the literature. Measuring QoL using tool that were developed specifically to this population is essential to better understand how RT affects their QoL.

Research objectives

The general objective of this project was to deepen the knowledge about the concepts of Geriatric Oncology and promote its practical application in the context of Radiotherapy, strengthening the integration of these areas to improve the provision of care for older people with cancer.

Additionally, the following secondary objectives were defined:

1. To emphasise the importance of frailty assessment

Aim: To summarise the available evidence exploring how frailty correlates with RT outcomes in older adults with cancer and explore how it can contribute to the personalisation RT.

2. To estimate future RT needs:

Aim: To update data regarding future RT demand up to 2040 for the Portuguese population, to provide information to policymakers that allows for adequate planning of the resources needed to meet this demand.

3. To describe the use of radiotherapy by older adults:

Aim: To increase knowledge about RT use among Portuguese older population through the analysis of Portuguese cancer registry data concerning how many cancer patients aged 70 or over underwent RT.

4. To investigate knowledge of geriatric oncology:

Aim: To understand the current knowledge of geriatric oncology among Portuguese radiation oncologists, with the of identifying knowledge gaps and preferred training methods to address them.

5. To validate the Onco-MPI tool:

Aim: To perform a geriatric evaluation by applying the Onco-MPI domains and assessing its accuracy in predicting one-year survival through a follow up of the included participants.

6. To assess quality of life using the EORTC QLQ-ELD 14 survey:

Aim: To assess the QoL of older adults with cancer who underwent RT by applying the EORTC QLQ-ELD 14 survey and studying factors associated with poor QoL outcomes.

CHAPTER 2. METHODOLOGICAL FRAMEWORK

As previously mentioned in the previous chapter, this thesis has several research objectives, namely, i) conduct a descriptive literature review that contextualize this research; ii) assess RT utilization among older adults aged 70 years or over, using data from the Portuguese National Cancer Registry; iii) examine the understanding of geriatric oncology among Portuguese radiation oncologists; iv) validate the Onco-Multidimensional Prognostic Index (Onco-MPI) to the Portuguese older population undergoing RT; v) analyse changes in the QoL of older adults with cancer treated with RT using the EORTC QLQ-ELD14 questionnaire. To meet these objectives, four studies were developed that involved diverse populations, procedures, and methodologies. Within this chapter, these details will be described for each study, as summarized on Table 2.1.

Table 2.1 - Summary of the studies that comprises this research thesis, focusing on populations and methodologies covered.

Study		Population	Methodology
Study 1. Research context	Frailty and Radiotherapy	• Not applicable	• Narrative review • Pubmed • Keywords: frailty AND cancer AND radiotherapy.
	Future needs for external beam radiotherapy (EBRT)	•Not applicable •Aggregated data from Global Cancer Observatory.	•Extracted the new cancer cases in Portugal for 2040. •Calculated the optimal number of EBRT courses and machines accordingly with ESTRO/HERO guidelines. •Calculated staff needs accordingly with IAEA guidelines.
Study 2. Use of radiotherapy by older adults in Portugal		•Not applicable •Aggregated data from Portuguese National Cancer Registry (RON)	•Cancer cases from January to June 2018 were analysed. •Optimal Utilization Proportions (OUP) of EBRT were derived from European ESTRO/HERO. •Actual utilization percentages (AUP) were extracted from RON.
Study 3. Radiation Oncologists' knowledge of geriatric oncology		•Specialists / Consultants and Residents in Radiation Oncology (RO)	•A pretested 22-item online survey on RO' geriatric oncology knowledge was disseminated.
Study 4. Validation of Onco-MPI and Quality of Life Changes in Portuguese Older Adults Undergoing Radiotherapy	Validation of the Onco-MPI prognosis tool	•Older adults ≥70y/o •Curative or palliative RT	•Patients across two cancer centres in Portugal were included. •Variables included age, sex, BMI, ADL, IADL, ECOG performance status, MMSE, education level, caregiver information, comorbidities, medications, cancer stage, and treatment details.
	Quality of life of older adults undergoing radiotherapy	•Older adults ≥70y/o •Curative or palliative RT •Without cognitive impairment	•QoL assessed by EORTC QLQ-ELD14 tool. •QoL evaluated during RT, in person. •Follow-up interviews were conducted via telephone 1 year after the first evaluation.

2.1 Ethical approval

Ethical approval was requested from the institutional and hospital ethics committees after defining the population and methodology of the various studies. The authorizations obtained are detailed in the Table 2.2.

Table 2.2 – Outline of the ethical approvals obtained from institutional and hospital ethics committees.

Study	Ethical approval
Study 1. Research context	• Not applicable
Study 2. Use of radiotherapy by older adults in Portugal	• Research Ethics Committee from Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto (reference 2021CE/P026 (P366/CETI/ICBAS). • Health Research Ethics Committee from Instituto Português de Oncologia do Porto- IPO Porto, Portugal (reference CES 59/022).
Study 3. Radiation Oncologists' knowledge of geriatric oncology	• Research Ethics Committee from Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto (reference 2021/CE/P026 (P366/CETI/ICBAS).
Study 4. Validation of Onco-MPI and Quality of Life Changes in Portuguese Older Adults Undergoing Radiotherapy	• Health Research Ethics Committee from Instituto Português de Oncologia do Porto (IPO-P), (reference IPO-P CES 263/021). • Health Research Ethics Committee from Unidade Local de São João (ULSJ) (reference CES ULSJ 138-21).

2.2 Study 1. Research context

The study 1 focused on a descriptive literature review that provided context to this research. It focused on the relationship between frailty and RT. During this literature review, a special attention was noted into the GLOBOCAN database regarding future needs of RT, and an additional analysis was performed. This study translated into two papers, entitled "Frailty—the missing constraint in radiotherapy treatment planning for older adults" and "The future needs of external beam radiotherapy in Portugal until 2040".

2.2.1 Frailty and Radiotherapy

This narrative review was based on observational studies in relation to the absence of experimental ones. The Pubmed was searched using the following key search words: frailty AND cancer AND radiotherapy. We found additional papers needed to complement certain topics in Google Scholar. All the duplicates were removed, and abstracts were reviewed. We excluded the papers that do not include frailty evaluation or screening.

2.2.2 Future needs for external beam radiotherapy (RT)

The data were collected online in the Global Cancer Observatory (GCO) website, https://gco.iarc.fr/en, on 26th July 2023 and transferred to an Excel sheet. It was obtained as aggregate data from GCO accordingly with the following settings:

a) Cancer tomorrow
b) Exploration by cancer type
c) Incidence cases
d) Population: Portugal
e) Timeline: 2020 and 2040
f) Both sexes
g) All age groups

The tumour location data from the GCO online database was initially categorized using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). It was subsequently reorganized according to cancer types defined in the HERO project (Health Economics in Radiation Oncology) from ESTRO (European SocieTy for Radiotherapy and Oncology) (ESTRO-HERO) that establishes optimal utilization proportions (Borras et al., 2015). The cancer types were classified as

follows: breast, prostate, colon, lung/trachea/bronchi, rectum/anal canal, head and neck, stomach, bladder, cervix, brain and CNS, kidney, uterus, leukaemia, pancreas, ovary, liver, myeloma, lymphoma, oesophagus, gallbladder and biliary tract, melanoma, testis, unknown primary, vulva, vagina, and thyroid gland. Additionally, non-melanoma skin cancers were excluded from the analysis in line with ESTRO-HERO methodology.

2.2.2.1 Analyses of the data

The GCO data regarding new cancer cases in 2020 was analysed and the estimative for 2040 for patients of all ages living in Portugal were obtained from the same source (Sung et al., 2021). For the most frequent cancer sites the optimal radiotherapy (RT) utilisation percentage are published (Borras et al., 2015). Based on the GCO estimate for new cancer cases in Portugal for 2040 it was calculated the optimal number of RT courses. The OUP is the proportion of new cancer cases that should receive RT at least once. In line with the International Atomic Energy Agency (IAEA) - DIrectory of RAdiotherapy Centres (DIRAC) and ESTRO/HERO guidelines we estimated the number of RT machines / Megavoltage (MV) units needed. Also, the authors followed the IAEA staffing guidelines.

To quantify the future needs of external beam RT until 2040 to avail this information to policy makers and provide useful data for future planning of RT departments, the following calculations were performed:

A. Optimal number of RT courses per cancer site

Based on the GCO incidence data for 2020 and 2040, it is possible to estimate the optimal number of RT courses per cancer site, accordingly with the data published by ESTRO-HERO Project:

$$Optimal\ radiotherapy\ utilisation\ percentage \times New\ cancer\ cases$$

The percentage change in optimal RT courses between 2020 and 2040 was calculate through:

$$\frac{(2040\ optimal\ EBRT\ courses - 2020\ optimal\ EBRT\ courses)}{2020\ optimal\ EBRT\ courses} \times 100$$

B. Optimal number of MV units needed until 2040

The authors translated these optimal number of RT courses and fractions into the number of MV units needed. Within the published results from ESTRO-HERO project, the optimal RT OUP for Portugal was published. That way, according with the total cancers excluding non-melanoma skin cancers incidence available in GCO, the authors calculated the optimal RT courses for each percentage. The ESTRO-HERO guidelines recommended a range from 400 to 450 patients per year for each MV unit, which is in line with the former 450 patients recommended by QUARTS (Dunscombe et al., 2014; Slotman et al., 2005).

To obtain the number of MV units needed the following formula was used:

$$\frac{Optimal\ EBRT\ courses}{400\ or\ 450\ patients\ per\ year}$$

The extra MV units needed were calculated based on the IAEA directory of RT centres, that states that Portugal had 56 MV units available in 2021 (*DIrectory of RAdiotherapy Centres*, 2022).

The number of the additional MV units was calculated through:

$$Number\ of\ MV\ units\ needed\ in\ 2040 - 56\ MV\ units\ available\ in\ 2021$$

C. Optimal staff requirements for the additional MV units needed until 2040

To provide full access to RT, there is need to staff properly the RT departments for every MV unit installed. The IAEA staffing guidelines states that is needed one radiation oncologist for every 250-300 patients/year, one medical physicist per 300-400 patients/year and one radiation therapist for every 100-150 patients/year (Rosenblatt, 2014). The estimate assumed that current MV units comply with these recommendations. These estimated staff requirements exclude the replace of retired or resigned employees.

According to these guidelines, the optimal staff to cover 2040 demand was calculated by:

$$\frac{Mean\ value\ of\ patients\ by\ each\ MV\ units\ per\ year}{Mean\ value\ of\ patients\ by\ staff\ category\ per\ year} \times additional\ MV\ units$$

2.3 Study 2 - Use of radiotherapy by older adults in Portugal

The study 2 centred on the use of RT utilization among older adults aged 70 years or over, based on data from the Portuguese National Cancer Registry known as Registo Oncológico Nacional (RON). The paper entitled "Utilisation Patterns of Radiotherapy Among Older Patients: Insights from Portuguese National Cancer Registry Data" was produced based on this study.

2.3.1 Research participants:

The research team requested data to RON. The data request was completed by RON professionals in November 2022 and was provided to the research team as aggregated data, focusing on the following information:

a) Identify the patients who received a novel cancer diagnosis between January and June 2018.
b) Create categories by age groups, specifically: <70, 70-74, 75-79, 80-84, and 85 years and older.
c) Create categories by location accordingly with the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).
d) For each category, identify the number of new cancer cases and the number of patients that underwent RT treatments.

In the dataset provided by RON, tumour location was categorized using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). However, it was then organized according to cancer locations defined in the ESTRO-HERO literature to determine optimal utilization proportions (Borras et al., 2015). Based on that publication, the cancer locations were classified as follows: breast, prostate, colon, lung / trachea / bronchi, rectum / anal canal, head and neck, stomach, bladder, cervix, brain and central nervous system (CNS), kidney, uterus, leukaemia, pancreas, ovary, liver, myeloma, lymphoma, oesophagus, gallbladder and biliary tract, melanoma, testis, unknown primary, vulva, vagina, and thyroid gland. Also, the non-melanoma skin cancers were excluded from the analysis according to ESTRO-HERO methodology.

Age groups were defined as <70, 70-74, 75-79, 80-84, and 85 years and older, to compare RT utilisation patterns between them. The number of older persons with cancer that underwent RT were included regardless the aim of the treatment, curative or palliative.

2.3.2 Analyses of the data

The OUP of RT for each cancer location, it is defined by ESTRO-HERO task force as "the proportion of new cancer cases that should receive RT treatment at least once in the course of their disease" (Borras et al., 2018).

To compare the optimal utilization with the actual proportion of cancer patients that receive RT, the following calculations were performed.

A. Evidence-based optimal use of RT courses per cancer location

The evidence-based OUP of RT per cancer location, that translates into the number of cancer cases that would receive RT in an optimal scenario, was estimated according with the data published by ESTRO-HERO project (Borras et al., 2015):

$$Optimal\ radiotherapy\ utilisation\ percentage\ \times cancer\ cases\ reported\ in\ RON$$

B. Actual utilisation percentage

The actual utilisation percentage (AUP) of RT, was calculated by:

$$\frac{Number\ of\ patients\ who\ underwent\ EBRT\ per\ cancer\ location}{Number\ of\ new\ cancer\ cases\ per\ cancer\ location} \times 100$$

C. Actual utilisation percentage of RT relative to the evidence-based optimal use per cancer location

The research team calculated the actual use of RT compared to the recommended optimal use, based on evidence, for each cancer type, using the formula below:

$$\frac{Number\ of\ patients\ who\ underwent\ RT}{Number\ of\ patients\ with\ indication\ for\ EBRT\ per\ OUP} \times 100$$

The comparison between the age groups was performed using a descriptive analysis. Variation in RT utilization patterns based on age and tumour location were explored.

D. Comparison between AUP and Optimal Comorbidity Adjusted RT Utilisation Rate

Based on published data on optimal comorbidity-adjusted RT utilization rates for lung, rectal, prostate, cervix, and breast cancers extracted from a cohort from New South Wales, Australia (NSW) cohort, the authors compared these rates with the actual RT utilization data from Portugal. The comparison was performed by age groups, namely, all ages, 70-79 and 80 years or over. Also, it was compared the Portuguese AUP with the Australian AUP data.

The analysis used in this study was descriptive in nature and performed using Microsoft Excel.

2.4 Study 3 - Radiation Oncologists' knowledge of geriatric oncology

The study 3 was designed to provide insights about the understanding of geriatric oncology among Portuguese radiation oncologists (RO). This study analysed data from a survey distributed to radiation oncologists. The paper named "An evaluation of Portuguese Radiation Oncologists Knowledge and Practice in relation to Geriatric Oncology" details the findings of this survey.

2.4.1 Survey

A survey assessing RO's perspectives in geriatric oncology was developed based on literature review and investigator consensus (Leifer et al., 2019). Some questions found in the literature were adapted to the Portuguese reality and to the absence of geriatrics as a stablished specialty in the country. This 22-item online survey underwent a pretest with 10 individuals from Unidade Local de São João's Radiotherapy Department to ensure consistency and content clarity.

The study targeted RO, specialists/consultants and residents, actively involved in cancer patient care in Portugal. The entire eligible cohort comprised 43 residents and 172 specialists/consultants, who were registered on Portuguese Medical Council statistics database. The online survey was distributed to several RT department directors by email and presented during in-person meetings across five Portuguese RT departments. The responses were obtained between November 2021 and April 2022. The survey was designed to be completed in less than 10 minutes and no financial incentives were provided for survey completion.

An online survey was created using Google Forms linked to ICBAS institutional email account and shared through a link. Participants accessed this link via email forwarded by department directors or shared during project presentation at RT departments meetings in person. When they accessed the link, the survey above was displayed. They were then able to give their consent to participate and proceed to the questions. Each participant could complete the survey only once and individually.

The survey covered RO characteristics (gender, age, professional details, cancer type experience), institutional factors (type, geriatric assessment availability), geriatric knowledge (training, older age definition), patient management (age-related treatment variations, informal/formal geriatric assessments, frailty screening), awareness of international recommendations for older cancer patients,

and future training needs. The frailty screening tools identified in the survey included Geriatric-8 (G8), VES-13, and Triage Risk Screening Tool once an abnormal result on these have been stablished as associated with functional decline and poorer survival (Loh et al., 2018). The inquiry about International Geriatric Radiotherapy Group (IGRG), was added based on its focus on older patients. This group was founded in 2012 by 15 radiotherapy institutions in the United States and Europe and aims to improve radiotherapy techniques for older cancer patients, enhancing their chances of cure and quality of life (Popescu et al., 2019).

The data, which includes participants' consent, professional background, training, clinical practices, use of international guidelines, and methods for improving their knowledge, was automatically compiled into an Excel worksheet. This worksheet was automatically available on Google Drive and was not coded.

The final version was distributed and is presented in Part IV, Table 4.1.

2.4.2 Analyses of the data

We conducted descriptive analyses on responses obtained from this survey. Also, the pattern of responses was compared between specialists/consultants and residents. The survey confidence level and margin of error were calculated according to Serdar et al (Serdar et al., 2021).

We employed independent proportions analysis to compare frailty screening and CGA utilisation rates between residents and specialists/consultants. IBM® SPSS® Statistics version 27 and Microsoft Office 365 Apps for Enterprise - Excel® were employed for conducting both descriptive and statistical analyses.

Statistical significance was considered to differences with a P-value below 0.05.

2.5 Study 4. Validation of Onco-MPI and Quality of Life Changes in Portuguese Older Adults Undergoing Radiotherapy

The study 4 was developed to validate the Onco-Multidimensional Prognostic Index (Onco-MPI) to the Portuguese older population undergoing RT. It also aimed to analyse changes in the QoL of older adults with cancer treated with RT using the EORTC QLQ-ELD14 questionnaire. An interim analysis of the prognostic role of Onco-MPI is comprised in the paper "Validation of the Onco-MPI Prognosis Tool: Interim analysis of a Study of Older Cancer Patients Undergoing Radiotherapy in Portugal". The QoL analysis is presented in the paper "Quality of Life Outcomes in Older Cancer Patients Undergoing Radiotherapy: A Longitudinal Study Using the EORTC QLQ-ELD14 Module".

2.5.1 Procedure

Between April 2022 and February 2023, the participants were recruited in the radiotherapy departments of the ULSJ and IPO-P. Through the RT research liaison at each institution, older persons aged 70 or over who were diagnosed with cancer and undergoing RT treatment, whether for palliative or curative purposes, were identified.

The RT research liaison had a form that linked each patient's name and medical file number with a study code. This study code consisted of the last three digits of the institution's postal code followed by the sequence number of the patient's entry into the study.

The objectives and design of the study were explained to the older person who met the inclusion criteria by professionals from the RT departments. If the older person agreed to be contacted by the researcher, this was noted on a specific form and communicated to the researcher. The researcher reviewed the list when visiting the departments and, in collaboration with the RT technicians, conducted the interviews before or after the RT treatment to minimize disruption to the department routine.

The variables that are required to compute the Onco-MPI and the first QoL assessment were collected in person on a day when the patient was already visiting the RT department for a scheduled appointment. The older person was given the option to complete the questionnaire on their own or have the questions asked orally by the researcher, who would then note the responses.

In this first interview, they were asked for their telephone number and explained that they would be contacted to repeat the quality-of-life questionnaire. About a year after the end of the RT treatment, the researcher asked the RT research liaison for information about the vital status of the participants, to contact those who had not died during this period.

The final QoL assessment was conducted over the phone, with the researcher asking the questions orally and registering the responses.

2.5.2 Validation of the Onco-MPI prognosis tool

Brunello et al. developed the Onco-MPI that takes into consideration CGA domains to predict 1-year mortality risk in older adults with cancer (Brunello et al., 2016). The basic ADL were assessed using the Katz scale (Katz et al., 1970), and IADL using the Lawton and Brody one (Lawton & Brody, 1969). Performance status was classified by Eastern Cooperative Oncology Group Performance Status (ECOG-PS)(Oken et al., 1982), and cognitive function by MMSE (Pfeiffer, 1975). All of these scales/classifications were used in their Portuguese versions, accordingly with NEGERMI (GERMI, 2013).

Number of severe comorbidities were classified accordingly with Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (B. S. Linn et al., 1968). The cancer stage was classified accordingly with The Eighth Edition American Joint Committee on Cancer Staging Manual(Amin et al., 2017). The age, sex, ADL, IADL, ECOG-PS, MMSE, education level, and caregiver information were assessed during an in-person interview on one of the days the patient attended the department for RT. The weight and height needed to calculate BMI, number of severe comorbidities, number of drugs, cancer stage, tumour location, RT intent, and previous/concomitant cancer treatments were extracted from electronic medical records.

Reflecting the time gap between cancer diagnosis and RT, and considering the prognostic nature of this tool, efforts were made to collect the status of patients either previously or at the time of diagnosis. For example, if a patient experienced weight loss since diagnosis, medical records were assessed to determine their normal weight before cancer treatment. Additionally, patients were directly asked if their performance status was better or worse before their cancer diagnosis.

The inclusion criteria for participation in the Onco-MPI validation study were as follows: persons aged 70 years or older, diagnosed with cancer of any type and at

any stage, undergoing RT treatment for curative or palliative purposes, and capable of understanding and consenting to participation in the study. The exclusion criteria were the presence of sensory deficits that prevented the completion of study procedures, a very poor general health status or severe treatment-related toxicity, where participation in the study would impose a physical and emotional burden for the patient.

The table 2.3 lists the variables that are required to compute the Onco-MPI, following the method outlined by Brunello et al (Brunello et al., 2016).

Table 2.3 - Variables that are required to compute the Onco-MPI, following the method outlined by Brunello et al.

Variable	Type	Details	Purpose
Sex	Categoric	female male	Descriptive analysis Computing Onco-MPI
Age	Continuous*		Descriptive analysis Computing Onco-MPI
Age		70-74 years 75-84 years 85 years and older	Descriptive analysis
Body Mass Index (BMI) kg/m^2 $= \frac{Weight}{Height^2}$	Continuous*		Descriptive analysis Computing Onco-MPI
BMI	Categoric (Cacador et al., 2021)	BMI <22: underweight BMI 22-27: normal weight BMI >27: overweight	Descriptive analysis
Activities of Daily Living (ADL)	Continuous*		Computing Onco-MPI
Activities of Daily Living (ADL)	Categoric (Katz et al., 1970)	0= Total dependence 1= Extensive assistance required 2= Limited assistance required 3= Minimal help needed 4= Independent	Descriptive analysis

Instrumental Activities of Daily Living (IADL)	Continuous*		Computing Onco-MPI
Instrumental Activities of Daily Living (IADL)	Categoric (Lawton & Brody, 1969)	0= Total dependence 1= Extensive assistance required 2= Limited assistance required 3= Minimal help needed 4= Independent	Descriptive analysis
ECOG Performance Status	Categoric (Oken et al., 1982)	0= Fully active 1= Restricted in physically strenuous activities 2= Ambulatory and capable of all self-care 3= Capable of only limited self-care 4 = Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	Descriptive analysis
ECOG Performance Status	Continuous*		Computing Onco-MPI
Education	Categoric	0 = Illiterate 1= 1 to 11 years 2= More than 11 years	Descriptive analysis
Cognitive impairment adjusted to education	Categoric (GERMI, 2013)	Illiterate MMSE≤15 1 to 11 years of education MMSE≤22 More than 11 years of education MMSE≤27	Descriptive analysis
Cognitive impairment not adjusted to education	Categoric	MMSE < 24	Computing Onco-MPI
Caregiver	Categoric	Needed Not needed	Descriptive analysis Computing Onco-MPI
Number of severe comorbidities	Continuous*		Computing Onco-MPI

classified accordingly with CIRS-G			
Number of drugs	Continuous*		Computing Onco-MPI
Polypharmacy	Categoric	Yes: 5 or more drugs No: less than 5 drugs	Descriptive analysis
Under cancer treatment	Categoric	Yes No	Descriptive analysis
Cancer location	Categoric	Breast Colorectal Lung Prostate Other genitourinary Other	Descriptive analysis Computing Onco-MPI
Cancer stage	Categoric	I II III IV	Descriptive analysis Computing Onco-MPI
RT intent	Categoric	Curative Palliative	Descriptive analysis
Previous/concomitant hormone therapy	Categoric	Yes No	Descriptive analysis
Previous surgery	Categoric	Yes No	Descriptive analysis

* These variables were considered continuous to compute the Onco-MPI accordingly with the authors recommendations.

2.5.2.1 Analyses of the data

The Onco-MPI was computed utilizing the variables and its estimated domain weights, following the method outlined by Brunello et al. The Onco-MPI score predicts one-year mortality in older cancer patients by categorizing them into three risk levels: low, moderate, and high. This score is calculated using a validated algorithm that integrates various domains from the CGA, including age, sex, BMI, and the presence of a caregiver. It also considers ADL, IADL, ECOG-PS, MMSE, CIRS-G, and the number of medications. Additionally, the model incorporates cancer sites and stages to refine the risk assessment (Brunello et al., 2016), as described in Table 2.4.

Table 2.4 - Estimated domain weights of each variable, as defined by Brunello et al.

Domains Onco MPI (Di)	**Category**	Weights for Onco-MPI (Si)
Age (>=70 years)	Continuous	**0,04730**
Sex	Female	**0,00000**
	Male	**0,01706**
BMI (Kg/m2)	Continuous	**-0,09782**
ADL	Continuous	**-0,07717**
IADL	Continuous	**0,04983**
ECOG Performance status	Continuous	**0,70607**
N°of comorbidites (severe) CIRS	Continuous	**-0,12960**
Cancer stage	1	**0,00000**
	2	**1,11712**
	3	**0,74957**
	4	**1,80828**
Tumour site	Other	**0,00000**
	Breast	**-1,93081**
	Colorectal	**-1,03025**
	Lung	**0,36265**
	Prostate	**-1,57998**
	Other geniturinary	**0,19956**
MMSE	< 24	**0,00000**
	≥ 24	**0,06270**
Number of drugs	Continuous	**-0,01218**
Caregiver	No	**0,00000**
	Yes	**0,21035**
Raw onco-MPI (R)	R= $\sum(Si \times Di)$	
Normalization formula for onco-MPI	$\frac{(R + 2.371)}{8.034}$	
Cut-offs (Recursive partition and amalgamation method)	Low	0 - 0.46
	Medium	0.47 - 0.63
	High	0.64 - 1.00

A descriptive analysis of the validation cohort was performed using IBM® SPSS® Statistics version 27. This analysis included a comparison between the original cohort and the validation cohort. Follow-up time was defined as the period from the interview to death from any cause, or up to 12 months after the interview if the patient was still alive.

Kaplan-Meier survival curves were generated using IBM® SPSS® Statistics version 27 to compare survival rates between the original and validation cohorts. Overlapping

survival curves were created to facilitate this comparison. Univariate analysis was performed using Cox regression in IBM® SPSS® Statistics version 27.

Area under the curve (AUC) based on the receiver operating characteristic (ROC) curve was used to measure the diagnostic accuracy of the original Onco-MPI and were calculated using MedCalc® 20.218, MedCalc® Software Ltd, following the method described by DeLong et al (DeLong et al., 1988).

2.5.3 Quality of life of older adults undergoing radiotherapy

As the QoL study population was the same as the Onco-MPI validation study, the inclusion criteria were identical. Regarding the exclusion criteria, the same criteria applied, with the addition that patients with cognitive impairment detected by MMSE were excluded.

During the first phase of face-to-face interviews, 232 participants were recruited. Twenty-eight patients with cognitive impairment detected through the MMSE were excluded from the analysis. Due to incomplete clinical records, 5 patients were also excluded, resulting in 199 participants included in the quality-of-life analysis during RT treatments. Out of these 199 participants, 30 died during the first year of follow-up and 67 could not be contacted by telephone. Therefore, 102 participants had their quality of life assessed twice, during and one year after RT treatments.

The QoL was assessed using the EORTC-ELD14, a module developed by the European Organisation of Research and Treatment of Cancer Quality of Life Group to evaluate QoL in older cancer patients. The QLQ-ELD14 includes five multi-item scales assessing mobility, worries about others, future concerns, maintaining purpose, and burden of illness, plus two single items on joint stiffness and family support. Scoring follows the QLQ-C30 method, with scores ranging from 0 to 100, where higher scores on functional scales and family support indicate better functioning, and higher scores on symptom scales indicate more severe symptoms. The QoL domains were scored into the raw score and linear transformation, according to the EORTC QLQ ELD 14 manual (Wheelwright et al., 2013). This module was previously validated to Portuguese population by Cipriano et al (Cipriano et al., 2021). The Portuguese and English versions of this module are presented in Part IV, Table 4.2.

Different questions refer to different QoL domains, and for some there is only a single question, as shown in Table 2.5.

Table 2.5 – Labelling of each question into a specific quality-of-life domain evaluated by EORTC-ELD14, namely, maintaining purpose, family support, mobility, worries about others, future worries, burden of illness and joint stiffness.

		Number of items (n)	Item range	QLQ-ELD14 item numbers (I1, I2, …, In)
Functional scale/items				
Maintaining Purpose	MP	2	3	41, 42
Family Support	FS	1	3	35
Symptom scales/items				
Mobility	MO	3	3	31, 33, 34
Worries about Others	WO	2	3	36, 37
Future Worries	FU	3	3	38 - 40
Burden of Illness	BU	2	3	43, 44
Joint Stiffnes	JS	1	3	32

2.5.3.1 Analyses of the data

QoL scoring was performed according to the EORTC manual (Wheelwright et al., 2013)

a. Raw score

For each single-item domain, the score represents the raw score of that item. For multi-item scales, it was calculated the average score of the relevant items using the formula provided below.

$$\textit{Raw Score} = \mathrm{RS} = \{(\mathrm{I1} + \mathrm{I2} + \ldots + \mathrm{In}) \div \mathrm{n}\}$$

b. Linear Transformation

To calculate the Score S, the raw was transformed into a score ranging 0 to 100 using the formula provided, applicable to both the functional and symptom scales/items.

$$\text{Scales: } S = \{(\mathrm{RS} - 1)\ \text{range}\} \times 100$$

A comparison of patient characteristics at initial and follow-up interviews was performed.

A box plot analysis was performed to compare the distribution of QoL linear scores at two different time points: during RT and one year after completing RT, to visualize the distribution, median, interquartile range, and potential outliers.

For the patients interviewed twice, the paired samples t-test was conducted in SPSS to compare the means of related QoL domains during RT and 1 year after, employing a significance level of $\alpha = 0.05$.

To analyse changes in the prevalence of moderate to severe functional problems and symptoms (scored as “quite a bit” and “very much”) during RT compared to one-year post-treatment, a descriptive analysis of the prevalence of moderate to severe cases was performed, followed by Wilcoxon-test for each problem or symptom.

Considering a difference of ≥10 points on the linear transformation scale as clinically significant, the patients were stratified into two groups according to clinically significant differences in QoL between the periods during and post RT (Osoba et al., 1998). These groups were delineated as follows: those experiencing clinically significant decline in QoL and the other group with the remaining patients.

A comparison was performed between frequencies of significant decline across the subgroups such as age groups, sex, school years, BMI, caregiver, ADL, IADL, two or more CIRS-G grade 3 or 4 comorbidities, polypharmacy (≥5 drugs), tumour locations, RT intent, previous or concomitant chemotherapy (CHT), concomitant hormone therapy (HT), and previous surgery. We used crosstabs and Chi-square (χ^2) tests to compare frequencies, and the results were statistically significant with $p<0.05$.

PART II - RESEARCH RESULTS



CHAPTER 3. FRAILTY - THE MISSING CONSTRAINT IN RADIOTHERAPY TREATMENT PLANNING FOR OLDER ADULTS

Edna Darlene Rodrigues [1,2,3]*, Daniela Gonsalves [4], Laetitia Teixeira[1,2]

Escarlata López Ramírez [5]

[1] Departamento de Estudo de Populações, ICBAS – Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Rua de Jorge Viterbo Ferreira, n° 228, 4050-313, Porto, Portugal, Portugal

[2] CINTESIS - Center for Health Technology and Services Research, Rua Dr. Plácido da Costa, s/n 4200-450, Porto, Portugal, Portugal;

[3] EIT Health Ageing PhD School

[4] GenesisCare en Madrid, Hospital San Francisco de Asís, Calle de Joaquín Costa, 28, 28002 Madrid, Spain

[5] GenesisCare en Madrid, Hospital Vithas La Milagrosa, Calle de Modesto Lafuente, 14, 28010 Madrid, Spain

ORCID

Edna Darlene Rodrigues 0000-0001-8170-3952

Laetitia Teixeira 0000-0002-9276-3683

Escarlata López Ramírez 0000-0001-6099-2855

*** Corresponding author**: Edna Darlene Rodrigues, up201610921@g.uporto.pt

+These authors contributed equally to this work.

Abstract

Current demographic changes translate into an increased frequency of cancer in older adults. Available data shows that about 45-55% of the new cancer patients will need RT treatments, with an expected increase of 20-30% in the future. To provide the best cancer care it is mandatory to assess frailty, offer appropriate curative treatments to patients and personalise them for the frail. Based on published data, the median prevalence of frailty in older population is about 42%. Recently the free radical theory of frailty has been proposed stating that oxidative damage is more prevalent in frail patients. In parallel, RT is one of the most frequent cancer treatments offered to older adults and is a source of external free radicals. RT dose constraints correlate with toxicity rates, so we open the question whether frailty should be considered when defining these constraints. Thus, for this paper, we will highlight the importance of frailty evaluation for RT treatment decisions and outcomes.

Keywords:

Frailty, radiotherapy, dose constraints, free radicals.

Introduction

In Europe, cancer accounts for more than 3.7 million new cases and 1.9 million deaths each year, being the second leading cause of death and morbidity. In particular, about half of these cancer cases occur in older adults (WHO, 2022).

It is undeniable that ageing is related to changes in multiple organs/systems. In addition, an older person with cancer has another health problems that may interfere with cancer outcomes (Sawhney et al., 2005).

We are in the era of personalised cancer care, based on molecular markers and targeted therapies. For older adults, comprehensive geriatric assessment (CGA) is the cornerstone of personalization (Extermann, 2017).

The challenge of ageing older patients with cancer diagnosis is not a recent concern. In 1993, a publication by "Europe Against Cancer" program stated that older patients "are not receiving the same standard of specialised oncological care as younger patients". Furthermore, the authors highlighted the need for research that replaces subjective opinions with objective frailty assessment instruments, namely CGA. Almost 30 years later, we still have much room for improvement in cancer care and multiple evidence gaps related to cancer treatment in older adults (Monfardini et al., 1993b).

Moreover, the age definition of older adult is a recurring discussion. Japan has the oldest population in the world. In 2006, Orimo et al reviewed the definition of older adults, analysing data from surveys on public attitudes and older adults requiring nursing care, long-term epidemiological, clinical, and pathological studies. The authors recommended the change of older adults' definition to the 75 y/o or over (Orimo, 2006). Nevertheless, for older adults with cancer, chronological age is a poor predictor of cancer tolerance and outcomes (Anita O'Donovan & Michelle Leech, 2020).

Frailty is evaluated by means of CGA and is defined as "a state of increased vulnerability to stressors that results from decreased physiological reserves". The median prevalence of frailty in older cancer patients is stated to be 42% (Handforth et al., 2015).

Cancer treatments include surgery, chemotherapy (CHT), immunotherapy, and radiotherapy (RT), each applied alone or in combination, according to the type and stage of cancer.

Based on the definition of frailty "a state of increased vulnerability to stressors", should we aim to further reduce the radiation dose reaching the organs at risk around the tumour (Fried et al., 2004)?

This could be a strong premise to offer to frail patients less invasive treatments, such as high-precision RT.

It should be noted that there is a lack of evidence related to frail patients undergoing RT and their need for personalized treatment options.

This narrative review is based on observational studies in relation to the absence of experimental ones. The research method is illustrated in Figure 3.1. The Pubmed was searched using the following key search words: frailty AND cancer AND radiotherapy. We found additional papers needed to complement certain topics in Google Scholar. All the duplicates were removed, and abstracts were reviewed. We excluded the papers that do not include frailty evaluation or screening.

Thus, for this paper, we will highlight the importance of frailty evaluation for RT treatment decisions and outcomes.

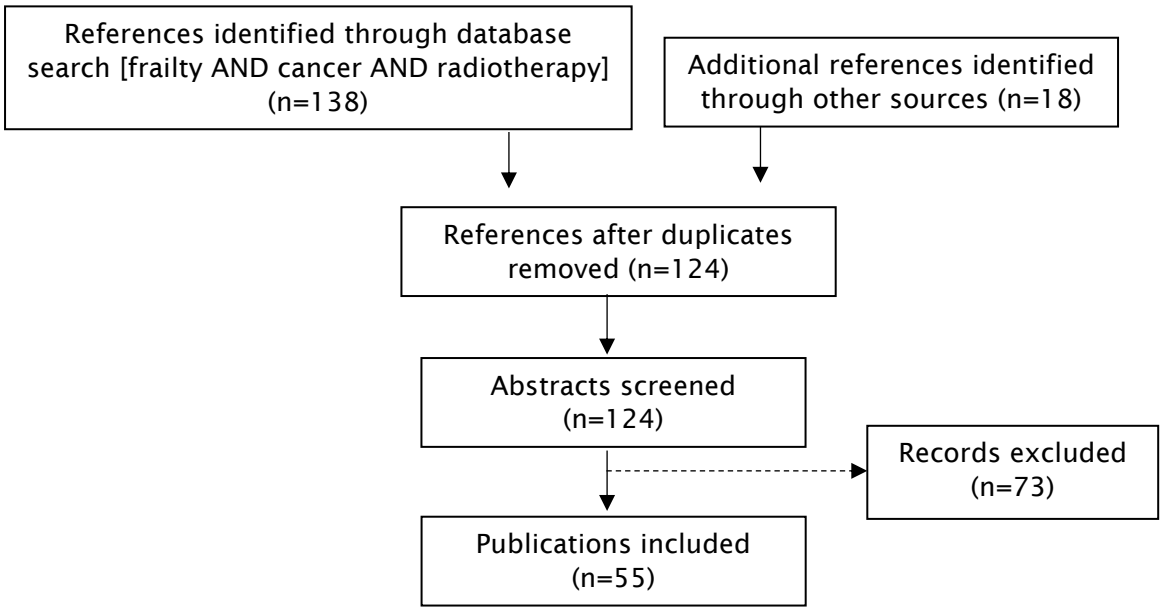


Figure 3.1- Flow chart of the research methodology.

Cancer and radiotherapy burden

The current demographic change translates into an increased incidence of cancer in older adults. In Europe, for all cancers, including non-melanoma skin cancers, in 2020, there were 2.08 million people aged 70 y/o or over, and it is expected to reach 3.06 million by 2040 (GLOBOCAN, 2021; Sung et al., 2021).

The economic burden of cancer, consisting of direct, informal care, and indirect costs, for Europe-27 in 2018 was about 199 billion euros (378 euros per capita). For a 50% increase in incidence, the cost almost doubled between 1995 and 2018 (Hofmarcher et al., 2020).

RT is one of the most frequent cancer treatments offered to older adults, in combination with surgery, chemotherapy and/or immunotherapy.

Data from Moffitt Cancer Centre published in 2010, related to cancer treatments in nonagenarians, show that RT was the second most frequent modality after surgery, 16% and 37%, respectively (Extermann et al., 2010).

Available data show that about 45-55% of the new cancer patients will need RT treatments, with an expected increase of 20-30% soon, based on current demographic changes. Thus, in Europe, for 2040, about 1.5 million people over 70 are expected to need RT treatments, but could reach 2.5 million in the extreme scenario (Slotman et al., 2005).

Data published in 2020, based on 12 European countries, related to expenditure for RT as a percentage of cancer care and healthcare budget were 4.3%-12.3% and 0.24%-0.67%, respectively (Lievens, Defourny, et al., 2020). The total operational costs of RT in Europe are estimated to be about 5.8 billion euros per year (Zubizarreta et al., 2017).

Real world RT use may have a discrepancy from the prediction based on cancer care guideline, particularly for older patients. Based on the Surveillance, Epidemiology and End Results-Medicare dataset in patients aged ≥66 years, the frequency of cancer care according to guidelines reduces as age increases for the majority of cancer patients included (Fang et al., 2017).

Why is frailty evaluation important in the context of radiotherapy?

We are ageing, but at our own pace, each with unique physical and mental capacities and varying degrees of declines. Often older people are seen as a burden

to society based on the assumption of frailty and dependence as a hallmark of ageing. This fact translates into discrimination in public policies and healthcare services. There is an urgent need to address anti-ageing attitudes and provide personalised approach to the needs of older people (Organization, 2021).

Briefly, the changes of ageing are characterised by a reduction in cardiac, pulmonary, renal, and bone marrow functional reserve, increased risk of gastrointestinal mucosal damage, decline in memory, cognition, and hormonal levels, and altered muscle and body composition. In this context, tolerance to cancer therapy may be reduced and, simultaneously, older adults may face an increased risk of developing treatment toxicity (Sawhney et al., 2005).

Due to these changes, frailty should be evaluated. In a very busy oncology practice, it can be performed in a 2-step process: first, a geriatric screening to identify the patients at risk of frailty, second, a CGA to personalise the treatment proposal (Extermann, 2017).

The evidence provided by a systematic review shows that after a geriatric evaluation the treatment plan was altered in a median of 28% of patients, in most cases to a less intensive option. In addition, this evaluation allowed identification of social, nutritional and polypharmacy issues. In the end, a positive effect on treatment completion and treatment-related toxicity/complications was observed in 75% and 55% of the included studies, respectively (Hamaker et al., 2018).

The information derived from the geriatric assessment may allow radiation oncology professionals to develop a personalised approach to RT, taking into account social frailty to treatment schedules and implement technical measures to reduce doses to healthy tissues in patients with proven reduced organ reserve (A. O'Donovan & M. Leech, 2020).

A thorough understanding of an older person’s comorbidities, social context, and personal expectations are necessary to make the right healthcare choices. In the absence of this assessment, the management of older patients remains a challenge and may result in under or overtreatment. There are data for locally advanced prostate cancer showing that for every 10-year increase in age the likelihood of receiving radical treatment was more than halved (Sehl et al., 2005).

It is stated elsewhere that comorbidities increase with age because of normal organ function decline (Arenas et al., 2018; Hounsome et al., 2017). Thus, treatment

decisions for older cancer patients can be challenging and some curative decisions may be omitted in this context (Kravchenko et al., 2015). Age itself is seen as a factor in reluctance to curative treatments even for older patients with preserved physical and mental functions, based on the misconception of low tolerance (Rogers et al., 2015).

To provide the best care it is mandatory to assess frailty, offer curative treatments to suit patients and personalise them for the frail. Frailty is a systemic condition defined by Dent et al as "an age-related clinical condition, typically with deterioration in the physiological capacity of several organ systems, that is characterised by an increase susceptibility to sudden, disproportionate functional decline following stressor events". It is important to highlight that frailty should not become a new ageism factor to reduce access to cancer treatments (Dent et al., 2019). Frailty represents a major challenge even for geriatricians, who are seen as the most qualified physicians to deal with older adults needs (Pilotto et al., 2020).

As shown in Figure 3.2, there are concomitant factors influencing frailty in cancer patients. Frailty is the sum of concomitant factors. Senescence or inflammaging can be clinically translated in cardiopulmonary function as a decline in maximal oxygen consumption, in muscle function as sarcopenia and loss of strength and power, and in metabolism as lower energy uptake and malnutrition. Multimorbidity and polypharmacy may present as congestive heart failure with low cardiopulmonary reserve, or osteoarthritis with sarcopenia and weakness, or diabetic neuropathy with impaired proprioception and risk of falling, and drug interaction with intestinal side-effect and weight loss. Cancer-related issues may be linked to anaemia and weakness, immunosuppression and fatigue, and tumour pain and sarcopenia. Lastly, treatment-related issues are determined by treatment toxicity such as intestinal mucositis and weight loss, need for frequent hospital visits and fatigue, and other symptoms specific to each type of cancer treatment. (Goede et al., 2021).

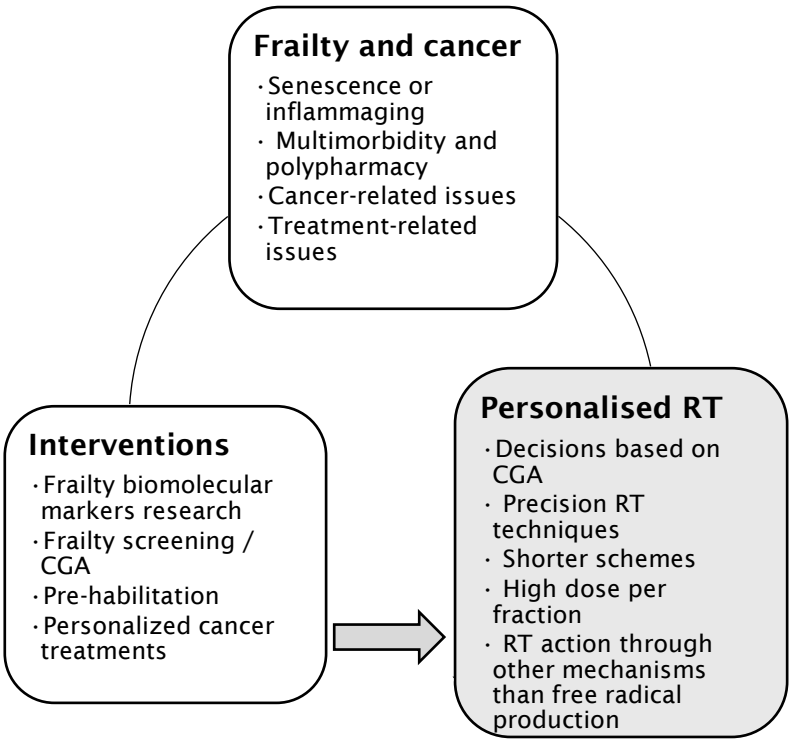


Figure 3.2 - Frailty is the sum of concomitant factors. To manage frailty and provide the best cancer care, there are several interventions to be implemented. Personalized cancer treatment will be based on the previous evaluation and aim to cure the cancer but with reduced toxicity. Specifically for radiotherapy treatment, such toxicity can be reduced by choosing sophisticated techniques with higher dose per fraction and shorter treatment schemes, which allow exploring other mechanisms of action besides the production of free radicals. CGA – Comprehensive geriatric assessment

Thus, it is very important to know how many older cancer patients are frail. The available data is controversial because there are multiple models of frailty evaluation. Handforth et al reviewed published data up to 2015, and found 22 studies, all evaluated cognition and function, with a median prevalence of frailty of 42% (range 6% - 86%) (Handforth et al., 2015).

For older patients, there are logistical problems to take into consideration when deciding RT treatment schedules. Hypofractioned regimens (fewer treatments with higher daily doses) may reduce treatment time and improve treatment compliance. Delivery of higher daily doses aims to improve the accuracy of RT, through techniques such as stereotactic body RT or brachytherapy. These accurate techniques may also have a more favourable toxicity profile, delivering very high doses to the tumour and with abrupt reduction to nearby healthy tissues (Somasundar et al., 2018).

Therefore, it is important to offer frail patients less invasive treatments, such as high-precision RT.

In the palliative scenario, older patients also have specific needs. Adaptations to improve comfort during immobilisation/positioning and shorter treatment courses to reduce the burden of travel, are reasons in favour of choosing single fraction or hypofractionated regimens (O'Donovan & Morris, 2020).

Rationale and evidence related to frailty and radiotherapy

It is well reported in the literature that radiation has effects on important ageing mechanisms, such as cellular senescence, inflammation, macromolecular/organelle dysfunction, and stem cell and progenitor dysfunction (Sedrak et al., 2021).

There is evidence that shows a significant increase in age accelerating epigenetic changes in early-stage breast cancer patients following cancer treatments with RT and/or CHT (Sehl et al., 2020).

Additionally, cerebrovascular disease was diagnosed in 63% of participants from Childhood Brain Tumours survivors, about 20 years after brain RT (Remes et al., 2020).

RT delivered at conventional fractionated schedules generates a significant amount of free radicals, which can interfere in the redox metabolism for minutes, hours, days, and even years after exposure (Spitz & Hauer-Jensen, 2014). Could this external source of free radicals play an important role in frail older adults undergoing RT treatments?

Viña et al proposed the free radical frailty theory, that states “that frailty is associated with oxidative damage to tissues and to macromolecules”. Furthermore, the authors highlight that the oxidative stress and free radicals play an important role in the process of developing frailty. In contrast, ageing is not associated with that oxidative damage. Animal studies performed by the Vinã et al research group show that oxidative stress impacts health time but not lifespan. Data from Toledo Frailty Study related to parameters of oxidative stress in people aged 65 to 90 y/o, corroborate that oxidation is unrelated to age. Moreover, lipid peroxidation and protein oxidation were higher for frail persons compared with age matched controls, which allows the conclusion that frailty is related to oxidative stress. (Viña, 2019)

Thus, we can raise the question: for frail/pre-frail patients, with limited functional reserve, should we adopt RT techniques and schedules that allow lower free radical production?

The RT treatment planning integrates a very accurate process. First, the patient performs a tomography to characterize the individual anatomy. Second, the radiation oncologist and the radiation therapist draw the organs on a computer. Using software, we define the organs to be irradiated, and which organs need to be protected. For example, in a breast cancer patient, we draw the whole breast as the target volume and the heart and lungs as the organs at risk. For each organ at risk, radiation dose constraints are defined. A dose constraint is defined as "a restriction on the prospective doses to individuals, which may result from a defined source, for use at the planning stage in radiation protection whenever optimisation is involved" (OFFICE, 2019). Focusing on the heart as an organ at risk, if less than 10% of the heart volume receives less than 25Gy, it is stated in the literature that there is less than 1% risk of cardiac mortality in 15 years after RT treatment (Gagliardi et al., 2010).

In the case of a frail patient proposed for breast RT, should we aim to irradiate less heart volume, based on the correlation between frailty and increased oxidative damage?

This opens the door to the use of new RT techniques and fractionations in frail patients. These allow treating the tumour while avoiding the surrounding normal tissues, like Deep Inspiration Breath Hold (DIBH) and hypofractionated treatments schemes (such as 5 fractions for early breast cancer). Regarding other cancer sites, there are high precision RT techniques available, such as Stereotactic Body Radiotherapy (SBRT) for lung, radiosurgery (SRS) for brain, rectal spacers for prostate, and protons for various sites (O'Donovan et al., 2022).

Every effort should be made to reduce the radiation dose reaching healthy tissues, especially for older patients with reduced organ reserve. One of the promising technologies, currently collecting data from pre-clinical experimental models, is FLASH RT defined as a single ultra-high dose rate >=40Gy/s. This new technology can reduce treatment time and dose to healthy tissue and is associated with reduced reactive oxygen species production (Lin et al., 2021).

It is known that host factors can impact normal tissue tolerance, as stated by Emami et al, including age, comorbid conditions, host response to radiation, smoking and performance status (Emami, 2013).

Even with comorbidities, it is stated in the literature that older cancer patients show good tolerance to modern RT techniques and in some cases, RT alone can achieve cancer cure (Popescu et al., 2019).

Frailty as predictor of radiotoxicity and other outcomes is a controversial topic. Published data regarding this issue are summarized in Table 3.1.

In a cohort study, frailty or vulnerability assessed by Geriatric-8 (G-8), Vulnerable Elders Survey-13 (VES-13), or Fried phenotype, were associated with higher rates of radiotoxicity, with an area under the curve of 0.86, 0.79, and 0.61, respectively (Runzer-Colmenares et al., 2017).

Another prospective study that examined the role of the Edmonton Frail Scale as a predictor of radiotoxicity in older patients showed no statistical correlation (Keenan et al., 2017).

Data related to head and neck cancer patients, show that frailty (evaluated by CGA, Groningen Frailty Indicator, and G-8) and restriction in geriatric domains were not associated with acute radiation-induced toxicity (Bras et al., 2021).

For patients with early stage non-squamous cell lung cancer treated with SBRT, the modified frailty index (mFI) was associated with a shorter 3-year overall survival compared with fit ones (37.3% vs 74.7%; p=0,003), but the increase in mortality was more likely to be linked to other causes unrelated to lung cancer (Franco et al., 2018). Another study, states that for this group of patients, frailty (evaluated by mFI) was a significant predictor of reduced overall survival (HR = 1.98 95% CI 1.02-3.85, p=0,04) (Raghavan et al., 2018).

Data from a Greek RT department show that for patients aged 75 or over, treated with curative or palliative RT, VES-13 > 3 was associated with a 2.12 times higher frequency of incomplete RT course, and this frequency was 3.34 times higher if the score was > 7 (Spyropoulou et al., 2014).

Regarding urological cancer patients undergoing initial surgery or radiotherapy, the frail patients (classified based on the CGA) had a higher risk of cancer-related

hospitalisations compared with fit ones (OR=6.79 95% CI 1.42-32.51) (Monfardini et al., 2017).

Table 3.1 – Summary of the studies that evaluated the implications of frailty in the context of Radiotherapy. CGA – Comprehensive geriatric assessment; CIRS-G - Cumulative Illness Rating Scale Geriatrics; DC – Disease control; EFS - Edmonton Frail Scale; G-8 - Geriatric-8; GFI- Groningen Frailty Indicator; HNC – Head and neck cancers; HR – Hazard ratio; LC- local control; mFI- modified frailty index; NSCLC – Non-squamous cell lung cancer; OR – Odds ratio; OS – overall survival; RT- Radiotherapy; SBRT – Stereotactic body radiotherapy; VES-13 - Vulnerable Elders Survey-13.

Study	Population	Intervention/ Comparison	Frailty evaluation	Outcomes	Main message
Runzer-Colmenares [2017] (41)	Cohort study: patients with cancer with medical recommendation of radiotherapy. 181 patients (mean age: 78.1 years, all males).	Relation between frailty and radiotoxicity	Before RT, frailty was measured using Fried phenotype, and vulnerability using VES-13 and G-8 scales.	Frailty or vulnerability evaluated by G-8, VES-13, or Fried phenotype, were associated with higher rates of radiotoxicity, with an area under the curve of 0.86, 0.79, and 0.61, respectively.	The authors found an association between frailty/vulnerability and the development of radiotoxicity.
Keenan [2017] (42)	Prospective study. 63 patients (> 70 y/o) undergoing radical radiotherapy for any malignant diagnosis.	EFS	EFS	There was a relation between EFS category and age ($p = 0.001$) but not with Grade 3+ toxicity ($p = 0.350$) The grade 3+ toxicity was correlated with Radiotherapy dose ($p = 0.005$).	There was no statistical correlation between EFS score and the presence of grade 3+ RT toxicity.

Bras [2021] (43)	Prospective study. 259 newly diagnosed HNC patients undergoing curative treatment. Mean age was 67.4 ± 10.8 y/o.	Association between frailty screening and CGA on short term adverse events	GA, GFI and (G8)	Number of deficit domains of CGA (OR = 1.71, 95%CI = 1.14-2.56), GFI (OR = 2.54, 95%CI = 1.02-6.31) and G8 (OR=5.59, 95%CI = 2.14-14.60) were associated with postoperative complications, but not with radiation-induced toxicity.	Frailty and restrictions in geriatric domains were associated with postoperative complications, but not with radiation-induced acute toxicity in curatively treated HNC patients.
Franco [2018] (44)	Retrospective study. 139 patients with stage I/II NSCLC treated with SBRT. Median age was 74 years [Interquartile Range 66, 80].	Evaluate a mFI in predicting OS and non-cancer death.	mFI score: non-frail (0-1) frail (>/=2)	Frailty was associated with a lower 3-year OS (37.3% vs. 74.7%; p=0.003) and 3-year cumulative incidence of non-cancer death (36.7% vs. 12.5%; p=0.02. Frailty remained significant in the multivariate model [OS HR for mFI >/=2: 2.25 (1.14-4.44); p=0.02].	Frailty is associated with lower OS in older patients with early-stage NSCLC treated with SBRT, yet frail patients survived a median 2.5 years, and were more likely to die of causes unrelated to the primary lung cancer, suggesting SBRT should be considered even in older patients deemed unfit for surgery.

Raghavan [2018] (45)	Retrospective study. 140 patients with early-stage NSCLC treated with SBRT. 73% of the patient had >70 y/o.	Assess the relationship between frailty (mFI) and OS and tumour control.	mFI of 8 variables: non-frail (mFI </= 2) frail (mFI > 2)	OS was significantly lower in frail than non-frail patients (P = 0.01) with 3-year OS of 59.3% versus 82.0%. LC and DC were significantly lower in frail than non-frail patients (3y-LC: 85.3% vs. 97.0%; p = 0.02; 3y-DC 80.6% vs. 93.4%, p= 0.03).	Frailty is associated with reduced OS in early-stage NSCLC patients treated with SBRT. Characterizing frailty using an mFI before treatment could help guide treatment decision making and patient counselling.
Spyropoulou [2014] (46)	Prospective study. 230 older patients (>75y/o) who received radical or palliative radiotherapy.	Evaluate the impact of VES-13 in RT adherence.	VES-13	17.8% of the patients did not complete radiotherapy. A VES-13 score >3 was associated with 2.14 times higher probability of not completing radiotherapy, whereas in patients with scores >7 this probability was 3.34 times higher.	Patients with higher VES-13 scores had increased probability of not completing radiotherapy. It was independent of other factors, such as age, sex, comorbidities, type of radiotherapy, and presence of side effects.

Monfardini [2017] (47)	Multicentric prospective cohort study. Enrolled 295 patients (aged 70+ years) with prostate cancer treated with radiotherapy (72%) and/or surgery.	To access the role of CGA in cancer care.	Frailty was defined based on CGA, using the Balducci's criteria.	60% of the patients were vulnerable or frail. 40% had at least one CIRS-G grade 3 or 4 comorbidities. For these, only 34% were seen by a specialist.	Future care plans should be improved to incorporate geriatric principles into cancer treatment decisions. These should aim for a better management of comorbidities.

Insights from real world clinical experience

Based on the available clinical data and the personal experience of radiation oncologists, radiotherapy is an important tool in fighting cancer in older patients. There is room to improvement, mostly in the assessment of the geriatric patient and in supporting interventions and adjustment of available technologies to improve the accuracy of RT and reduce toxicity (Cree et al., 2019).

In addition, radiation oncologists should be prepared for the specific needs of older patients, including effectively improving communication. In this population, it is important to ask directly about information needs, have an honest balance between realism and hope, recognize that older patients have other goals other than survival, and learn techniques to reduce miscommunication (Fakhreddine et al., 2017).

Furthermore, it is important to offer support to those patients in frail or pre-frail stages. Preliminary data and recommendations already exist for the implementation of pre-habilitation programs for these patients, namely Prehab4cancer - Manchester. This intervention aims to shorten recovery time after cancer treatments, reduce peri-operative complications and improve compliance with non-surgical treatments. Their preliminary data show 80% acceptability and 95% adherence, demonstrating high acceptability for older patients, refuting the idea that this population has low adherence to exercise interventions (Moore et al., 2021).

Moreover, a clinical trial designed by Viña et al, shows that exercise is an effective way to fight frailty, and “56% of the patients were less frail than when they started the exercise and the number of visits to primary care fell by 45% in the exercise intervention group.” (Viña, 2019)

Regarding RT, there is evidence that shorter treatment schemes are well tolerated and are associated with non-inferior cancer outcomes compared with standard ones and are a logical alternative for frail older patients. Available data includes RT treatments for glioblastoma (15 fractions), early breast cancer (5 fractions), prostate cancer (5 to 20 fractions), early-stage non-squamous cell lung cancer (1 to 5 fractions), and resectable locally advanced rectal cancer (5 fractions) (O’Donovan et al., 2022).

Research outlook

This narrative review aims to open the discussion related to RT treatments for older frail cancer patients and to highlight the importance of frailty evaluation in RT setting. Nevertheless, it has some limitations related to the observational nature of the reported studies. Additionally, the population included in those studies was heterogenous regarding cancer type, geriatric/frailty evaluation, and cancer treatments.

There is no robust evidence linking frailty and personalisation of cancer/radiotherapy treatments. Thus, future research opportunities in the field of geriatric oncology and specifically for radiotherapy are endless.

The impact of deficits identified through CGA on cancer outcomes and treatment tolerance should be further studied in future clinical trials (Cree et al., 2019). As shown in figure 3.2, there are interventions that can be implemented to improve frailty management in cancer patients.

We await the results of a promising clinical trial that randomised cancer patients proposed to CHT + - RT, to CGA or conventional care, based on the results of the G-8 frailty screening tool. Quality of life is the primary endpoint and plasma samples will be collected for search on prognostic biomarkers (Mahmoud et al., 2021).

More research projects aimed at finding new biomolecular markers for frailty are needed to provide the possibility of conducting optimal treatment selection trials based on them (Popescu et al., 2019).

The definition of physiologic and pathologic ageing is unclear. The balance between oxidative eustress and oxidative damage may play an important role and provide research opportunities in the future (Polidori & Mecocci, 2022).

Currently, older adults represent a significant percentage of patients in RT departments, but they are underrepresented in clinical trials.

Radiation oncologists should be trained to screen for frailty in their patients. A RT-specific frailty tool to be applied periodically should be developed to detect changes during RT treatments.

The Multidimensional Prognostic Index (MPI) was developed based on the CGA and provides a quantitative risk score. This score allows predicting the risk of

morbidity, mortality, hospitalization, institutionalization in community-dwelling older adults. Recently, there was the need to validate the MPI administered by telephone in an Italian population due to pandemic restrictions (Carlo Custodero et al., 2021). Validation of this tool to evaluate score fluctuations during and after RT, could be a research opportunity.

Data provided by a systematic review identify the most important factors for older adults to accept treatment: convenience and success rates, seeing a need for treatment, trust in the physician and following his/her recommendations. Declining cancer treatment was motivated by concerns about the discomfort of treatments, fear of side effects, and transportation difficulties. Thus, future trials should include assessment of these factors and implement measures to improve treatment adherence (Puts et al., 2015).

RT as a localized treatment present its toxicity profile highly dependent on the tumour site. Efforts should be made to improve knowledge of each cancer site, which will allow prediction of toxicity patterns based on factor specific to older adults. This localised nature of RT may provide a unique opportunity to offer cancer treatments to frail older adults with low functional reserve to cope with the greater stress of other cancer therapies such as CHT or surgery. As VanderWalde states “we can choose to accept the changing demographics of cancer care, or we can continue to study our treatments in a minority of our patients without knowing if they will benefit the patients we treat the most; the choice is ours” (VanderWalde et al., 2017).

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CHAPTER 4. THE FUTURE NEEDS OF EXTERNAL BEAM RADIOTHERAPY IN PORTUGAL UNTIL 2040

Edna Darlene Rodrigues [1,2]*, Paulo Almeida [3], Escarlata López Ramírez [4], Laetitia Teixeira[1,2]

[1]Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.

[2] CINTESIS – Center for Health Technology and Services Research/ RISE - Health Research Network, Porto, Portugal.

[3] Internal Medicine Department, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal.

[4] Radiation Oncology Department, GenesisCare, Malaga, Spain.

ORCID

Edna Darlene Rodrigues: 0000-0001-8170-3952
Paulo Almeida: 0000-0002-4879-559X
Escarlata López Ramírez: 0000-0001-6099-2855
Laetitia Teixeira: 0000-0002-9276-3683

Abstract

Introduction: External beam radiotherapy (EBRT) is essential to offer an effective cancer treatment, but it needs to be accessible, well-timed, and high-quality. There is a global lack of radiotherapy infrastructure and investment that compromises the cancer outcomes.

Purpose: The authors aim to quantify the future needs of EBRT until 2040 to cover the future demand.

Methods: Based on the Global Cancer Observatory estimate for new cancer cases in Portugal for 2040 it was calculated the optimal number of EBRT courses. The OUP is the proportion of new cancer cases that should receive EBRT at least once. In line with the International Atomic Energy Agency (IAEA) DIrectory of RAdiotherapy Centres and European SocieTy for Radiotherapy and Oncology - Health Economics in Radiation Oncology guidelines, we estimated the number of EBRT machines / Megavoltage (MV) units needed. Also, the authors followed the IAEA staffing guidelines.

Results: The calculated median increase in the optimal number of EBRT courses for the year 2040 was found to be 18% when compared to the requirements in 2020. The projected number of optimal EBRT courses for 2040 was estimated to be approximately 34.000. Consequently, a range of 18 to 30 new EBRT machines/ MV units will need to be installed to adequately address the growing demand. To meet this demand, it is anticipated that a total of 28 to 46 radiation oncologists, 22 to 36 medical physicists, and 61 to 102 radiation therapists will be required.

Conclusion:

The deficit of EBRT machines / MV units in Portugal will require a change in the cancer related – policies and an investment to offer full access to EBRT treatments.

Introduction:

In Europe, cancer is the second leading cause of death and morbidity. It accounts for more than 3.7 million new cases and 1.9 million deaths each year (*Cancer - Impact*, 2023). In Portugal, the same trend is seen, with 28 544 cancer deaths, around 25% of all deaths (*Causas de morte - Cause of deaths 2019*, 2019).

Radiotherapy (RT) is essential to offer an effective cancer treatment, but it needs to be accessible, well-timed, and high-quality. There is a global lack of RT infrastructure and investment that compromises the cancer outcomes (Atun et al., 2015).

The HERO project (Health Economics in Radiation Oncology) from ESTRO (European SocieTy for Radiotherapy and Oncology) aims to "provide solid data to the RT community to engage with governments, funders and decision makers, and advocate for better funding for RT, better resource planning and ultimately better care for cancer patients". The ESTRO-HERO task force provides evidence-based recommendations regarding provision, accessibility, needs and costs of radiotherapy. Also, provides economic evaluation models for radiation oncology (*Health Economics in Radiation Oncology*, 2023).

Focusing on the Optimal Utilisation Proportion (OUP) for each cancer site, it is defined by the task force as "the proportion of new cancer cases that should receive external radiotherapy treatment at least once in the course of their disease" (Borras et al., 2018).

This OUP was obtained from a decision analytic model, designed by the Australian Collaboration for Cancer Outcomes Research and Evaluation (CCORE), where the indications for radiotherapy for each cancer site were derived from evidence-based treatment guidelines by tumour site and stage at diagnosis (Barton et al., 2014).

In Portugal, the OUP external beam RT (EBRT) for all cancers excluding non-melanoma skin cancers ranges between 49.7% and 51.1%, accordingly with the ESTRO-HERO data (Borras et al., 2015). In 2040, accordingly with Global Cancer Observatory (GCO) data, around 34,000 cancer patients will require EBRT (Sung et al., 2021).

The International Atomic Energy Agency (IAEA) provides a DIrectory of RAdiotherapy Centres (DIRAC) with the registry of RT machines from more than 7.000 centres worldwide, including EBRT machines, better described within the

DIRAC as Megavoltage (MV) units. DIRAC considers a MV unit as either a Radionuclide Teletherapy Unit or an Electron Accelerator which are medical devices used to deliver EBRT. Portugal has 24 RT centres and 56 MV units registered and only 17 MV units with less than 10 years from installation (*Maps of Equipment age - DIrectory of RAdiotherapy Centres*, 2022).

Portugal exhibits a mixed profile compared to the median values of 28 European countries in the HERO database concerning oncology infrastructure and technology. The country falls below the median for MV units per million inhabitants, MV units equipped with IMRT and IGRT, simulators per department, and courses per department, indicating areas for potential improvement in equipment availability and the adoption of advanced technologies. In contrast, Portugal aligns with the median for MV units per department and simulators per MV unit, showing average performance in these aspects. Notably, Portugal surpasses the median for simulators equipped with 3D imaging, highlighting a strength in advanced imaging capabilities. Additionally, Portugal aligns with the median in terms of the number of RT courses per treatment machine. However, it falls below the median for RT courses per radiation oncologist and per medical physicist or dosimetrist, suggesting a higher workload for these professionals. Conversely, Portugal is above the median for RT courses per radiation therapist (RTT) or nurse, indicating relatively better staffing levels in this area. Overall, while Portugal shows strength in advanced imaging, there are clear opportunities for enhancing equipment availability and professional staffing to meet European standards (Grau et al., 2014; Lievens et al., 2015).

The authors aim to quantify the future needs of external beam radiotherapy (EBRT) until 2040 to avail this information to policy makers and provide useful data for future planning of RT departments.

Methods:

Based on the GCO estimate for new cancer cases in Portugal for 2040 it was calculated the optimal number of EBRT courses. The OUP is the proportion of new cancer cases that should receive EBRT at least once. In line with the IAEA/DIRAC and ESTRO/HERO guidelines we estimated the number of EBRT machines / Megavoltage (MV) units needed. Also, the authors followed the IAEA staffing guidelines.

Optimal number of EBRT courses per cancer site

The GCO data regarding new cancer cases in 2020 was analysed and the estimative for 2040 for patients of all ages living in Portugal were obtained (Sung et al., 2021). For the most frequent cancer sites the optimal radiotherapy utilisation percentage are published (Borras et al., 2015). Based on the GCO incidence data for 2020 and 2040, it is possible to estimate the optimal number of EBRT courses per cancer site, accordingly with the data published by ESTRO-HERO Project:

$$Optimal\ radiotherapy\ utilisation\ percentage\ \times New\ cancer\ cases$$

The percentage change in optimal EBRT courses between 2020 and 2040 was calculate through:

$$\frac{(2040\ optimal\ EBRT\ courses - 2020\ optimal\ EBRT\ courses)}{2020\ optimal\ EBRT\ courses} \times 100$$

Optimal number of MV units needed until 2040

The authors translated these optimal number of EBRT courses and fractions into the number of MV units needed. Within the published results from ESTRO-HERO project, the optimal RT OUP for Portugal was published. That way, according with the total cancers excluding non-melanoma skin cancers incidence available in GCO, the authors calculated the optimal EBRT courses for each percentage. The ESTRO-HERO guidelines recommended a range from 400 to 450 patients per year for each

MV unit, which is in line with the former 450 patients recommended by QUARTS (Dunscombe et al., 2014; Slotman et al., 2005).

To obtain the number of MV units needed the following formula was used:

$$\frac{Optimal\ EBRT\ courses}{400\ or\ 450\ patients\ per\ year}$$

The extra MV units needed were calculated based on the IAEA directory of RT centres, that states that Portugal had 56 MV units available in 2021 (*DIrectory of RAdiotherapy Centres*, 2022).

The number of the additional MV units was calculated trough:

$$Number\ of\ MV\ units\ needed\ in\ 2040 - 56\ MV\ units\ available\ in\ 2021$$

Optimal staff requirements for the additional MV units needed until 2040

To provide full access to RT, there is need to staff properly the RT departments for every MV unit installed. The IAEA staffing guidelines states that is needed one radiation oncologist for every 250-300 patients/year, one medical physicist per 300-400 patients/year and one radiation therapist for every 100-150 patients/year (Rosenblatt, 2014). The estimate assumed that current MV units comply with these recommendations. These estimated staff requirements exclude the replace of retired or resigned employees.

According to these guidelines, the optimal staff to cover 2040 demand was calculated by:

$$\frac{Mean\ value\ of\ patients\ by\ each\ MV\ units\ per\ year}{Mean\ value\ of\ patients\ by\ staff\ category\ per\ year} \times additional\ MV\ units$$

Results:

In the Figure 4.1, we provide a visual summary of the key findings from our study. The diagram illustrates the main results regarding new cancer patients in 2040, the additional MV units, and staff required.

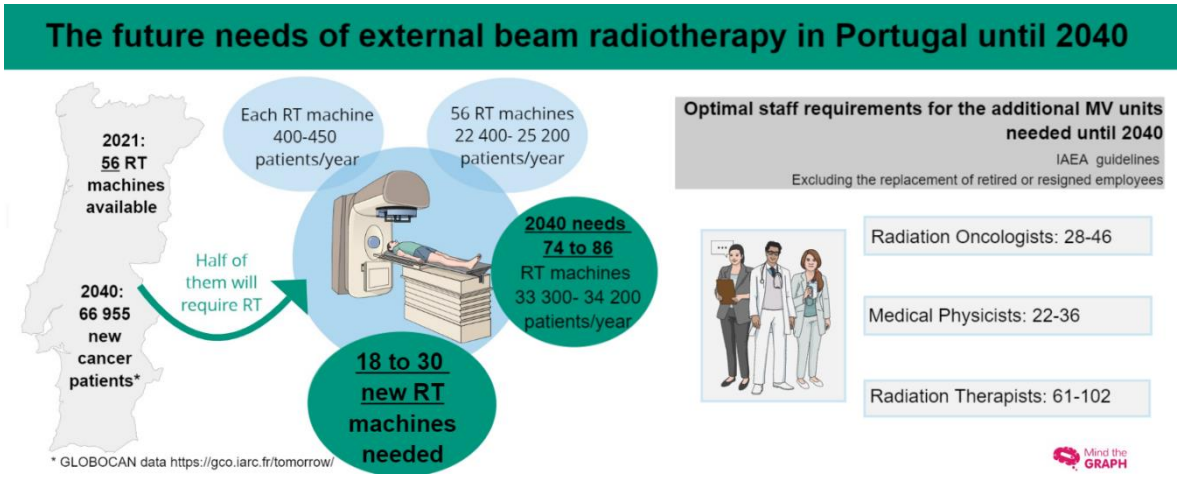


Figure 4.1 - The figure shows the future needs for external beam radiotherapy (EBRT) in Portugal by 2040. It estimates that 18 to 30 more RT machines will be required to meet the rising number of cancer patients. Additionally, 28-46 Radiation Oncologists, 22-36 Medical Physicists, and 61-102 Radiation Therapists will be needed to support this increase, according to international guidelines.

The data related to the optimal number of EBRT courses, and the estimated percentage change are shown on Table 4.1.

Table 4.1 – Portugal: Optimal number of radiotherapy courses and fractions per cancer site for which the optimal percentage is available in the literature. It includes new cancer cases (excluding non-melanoma skin cancers) for all ages. Based on Global Cancer Observatory data the authors estimated the expected changes in radiotherapy needs for 2040 (DIrectory of RAdiotherapy Centres, 2022; Sung et al., 2021).

		2020		**2040**		
Cancer site	Optimal radiotherapy proportion	New cases GLOBOCAN	EBRT optimal courses	New cases GLOBOCAN	EBRT optimal courses	Percentage change (2020 to 2040)
Bladder	0.47	2,608	1,226	3,305	1,553	27%
Brain	0.80	1,105	884	1,236	989	12%
Breast	0.87	7,041	6,126	7,100	6,177	1%
Cervix	0.71	865	614	817	580	-6%
Colon	0.04	5,367	215	6,617	265	23%
Gallbladder	0.17	143	24	182	31	27%
Head and neck	0.74	2,658	1,967	2,844	2,105	7%
Kidney	0.15	1,191	179	1,400	210	18%
Leukaemia	0.04	1,547	62	1,884	75	22%
Lung	0.78	5,415	4,224	6,448	5,029	19%
Lymphoma	0.73	2,331	1,702	2,633	1,922	13%
Melanoma	0.21	1,071	225	1,163	244	9%
Myeloma	0.45	886	399	1,105	497	25%
Oesophagus	0.71	683	485	790	561	16%
Ovary	0.04	561	22	616	25	10%
Pancreas	0.49	1,792	878	2,264	1,109	26%
Prostate	0.58	6,759	3,920	8,216	4,765	22%
Rectum	0.60	4,954	2,972	5,989	3,593	21%
Stomach	0.27	2,950	797	3,608	974	22%
Testis	0.15	244	37	213	32	-13%
Thyroid	0.04	1,698	68	1,563	63	-8%
Unknown primary	0.61	1,227	748	1,506	919	23%
Uterus	0.32	1,238	396	1,376	440	11%
Vagina	0.94	49	46	60	56	22%
Vulva	0.39	200	78	249	97	25%
Other	0.19	1,130	215	1,328	252	18%
TOTAL			28,507		32,565	
				Overall median change		**18%**

Optimal number of EBRT courses per cancer site

Based on the OUP and the number of GCO new cancer cases for 2020 and 2040 for Portugal, the number of optimal EBRT courses was calculated. For example, in the optimal scenario around 47% of the bladder cancer patients are expected to perform EBRT. That way, for 3.305 new bladder cancer cases in 2040, the expected optimal EBRT courses are 1.553. Which translates in 27% increase in the optimal number of EBRT courses in comparison with 2020 EBRT needs. On the other hand, for cervix cancer the 2040 optimal EBRT courses are estimated to decrease 6% in comparison with 2020 needs, in relation to a reduction in new cervix cancer cases according to 2040 GCO estimative. Overall, for all cancer cases in Portugal (excluding non-melanoma skin cancers), the median increase in the optimal number of EBRT courses in 2040 was calculated to be 18%, in comparison to 2020 needs.

Optimal number of MV units needed until 2040

The number of MV units needed for 2030 and 2040 was calculated, as shown in Table 4.2 regarding 2040, the GCO estimates 66955 new cancer cases (excluding non-melanoma skin cancers), which translates into a range of 33.277 to 34.214 optimal EBRT courses. In the scenario where each MV unit treats 450 patients per year and the OUP per new cancer cases is 49.7%, to cover EBRT demand 74 MV units will be needed. Based on the 56 MV units available in Portugal in 2021, an extra 18 ones need to be installed to cover EBRT demand. In the other hand, for the scenario where each MV unit treats 400 patients per year and the percentage of EBRT utilisation per new cancer cases is 51,1%, to cover EBRT demand, 86 MV units will be needed. Based on the 56 MV units available in Portugal in 2021, an extra 30 MV units needs to be gradually installed to cover RT demand. So, a range between 18 and 30 additional MV units are required to be installed to provide full access to EBRT until 2040.

Table 4.2 - Portugal - Number of MV units needed based on the guidelines published by ESTRO-HERO that estimates 400-450 patients per year for each MV unit (Grau et al., 2014; Lievens et al., 2015). The authors calculated the needs for these two scenarios. Also, the estimated MV units needed were calculated for the Portuguese Optimal Utilization Proportion (OPU) minimum and maximum, as stated in the ESTRO-HERO publication (Borras et al., 2015). The extra MV units needed were calculated based on the IAEA - DIRAC that states that there were 56 RT machines installed in 2021 (Dunscombe et al., 2014). In DIRAC, a MV unit is either a Radionuclide Teletherapy Unit or an Electron Accelerator.

				Optimal number of RT Courses		Optimal MV units 1: (Scenario 450 patients/year/unit)				Optimal MV units 2: (Scenario 400 patients/year/unit)			
	All cancers (excl. non-melanoma skin cancer)	OUP min	OUP max	By OUP min	By OUP max	RT machines needed by OUP min	Extra MV units needed	RT machines needed by OUP max	Extra MV units needed	RT machines needed by OUP min	Extra MV units needed	RT machines needed by OUP max	Extra MV units needed
2020	57,742	49.7%	51.1%	28,698	29,506	64	NA	66	NA	72	NA	74	NA
2030	63,339	49.7%	51.1%	31,479	32,366	70	14	72	16	79	23	81	25
2040	**66,955**	**49.7%**	**51.1%**	**33,277**	**34,214**	**74**	**18**	**76**	**20**	**83**	**27**	**86**	**30**

Table 4.3 - Optimal staff requirements for the additional Megavoltage (MV) units, according to IAEA staffing guidelines, based on the assumption that current MV units comply with these recommendations (Slotman et al., 2005). These estimated staff requirements exclude the replace of retired or resigned employees.

	IAEA staffing guidelines (patients/year)	Mean value	Staff proportion for every 425 patients treated by each RT machine	Scenario 18 additional RT machines until 2040	Scenario 30 additional RT machines until 2040
Radiation oncologist	250-300	275	1.55	28	46
Medical physicist	300-400	350	1.21	22	36
Radiation therapist	100-150	125	3.40	61	102

Optimal staff requirements for the additional MV units needed until 2040

The Table 4.3 shows the optimal staff requirements for the additional MV units, according to IAEA staffing guidelines. The authors considered the two marginal scenarios from the range between 18 to 30 additional MV units until 2040. For the 18 additional MV units, there will be needed 28 radiation oncologists, 22 medical physicists, and 61 radiation therapists. On the other hand, for the 30 additional MV units, there will be needed 46 radiation oncologists, 36 medical physicists, and 102 radiation therapists.

Discussion

Based on the GCO estimate for new cancer cases in Portugal (excluding non-melanoma skin cancers) for 2040, around 34.000 EBRT courses will be needed to cover EBRT demand. It is expected an 18% increase for all tumour sites until 2040. The estimated increase in the number of EBRT courses between 2020 and 2040. So, a range between 18 and 30 additional MV units could be required to cover EBRT needs until 2040 for Portuguese population.

Undoubtedly, RT will continue to play an important role in cancer treatments as it has been for more than a century, facing the expected raise in the cancer incidence rate (Baumann & Bacchus, 2020). However, in Portugal this increase will take place at the expense of 24% of population will be aged 70 years old or over (*Projeções de População Residente 2018-2080* 2020). This group of patients needs comprehensive geriatric evaluation once frailty can be present in 42% of them. For these frail older patients, EBRT as a non-invasive cancer treatment, can be the most suitable option, increasing even further the EBRT demand (Oncology, 2023; Rodrigues et al., 2022).

The estimated increase in the demand of EBRT courses until 2040 can be translated into an average investment of €12 million per year, based on the cost-accounting model published by ESTRO-HERO project. This model can help policy makers to estimate EBRT costs, including the staff, machines, resources, and support personnel, with an estimated cost of €3,518 per each EBRT course (Defourny et al., 2019).

Of course, estimating EBRT costs is complex. Nowadays there is a trend to reduce the number of fractions per treatment course, achieving the same clinical outcomes

and acceptable toxicity patterns. But the reduction of treatment fractions incorporates complexity to EBRT treatment planning and increases the time spent by each professional involved in the process. For example, for bone metastasis, a 30 Gy in 10 fractions requires around 7 hours to be planned and delivered, but a 24Gy in 3 fractions of stereotactic ablative body radiotherapy (SABR) requires 11 hours. The estimated cost for 30Gy in 10 fractions and 24Gy in 3 fractions SABR is €1.494 and €3.226, respectively (Spencer et al., 2022).

Nevertheless, the first European cost-effectiveness analysis states that moderately hypofractionated RT is cost saving in comparison to conventional RT, when all expenses are considered. The calculated cost included diagnostic test and procedures, inpatient stays, medical visits, and transportation. The significant savings were due transportation with the remaining costs comparable between both groups. Also, the Quality Adjusted Life Years were marginally higher for moderately hypofractionated RT (Zhou et al., 2022).

Also, a Hungarian cost-effectiveness analysis of intensity-modulated RT with normal and hypofractionated schemes for the treatment of localised prostate cancer revealed that RT access improved by 10% with moderate hypofractionation for prostate cancer (Zemplenyi et al., 2018).

To provide shorter RT treatments, reduce acute and late toxicity, and make possible combinations with new systemic treatments, it is imperative that the purchased MV units incorporate novel technologies such as stereotactic body (SBRT) or adaptative (ART) radiotherapy and accurate positioning systems such as Surface Guided Radiotherapy (SGRT). The ESTRO-HERO project has a novel framework aiming “defining and assessing the value of radiotherapy innovations, to support clinical implementation and equitable access, within a sustainable healthcare system”. It is based on the concept of value-based healthcare, defined as the health outcomes (that matter most to patients) achieved per dollar spent over the total cycle of care. Soon, there will be robust evidence to support RT equipment purchase linked to the best patient outcomes that will help to navigate within the fast-paced RT technology market (Lievens et al., 2021).

Indeed, there is a need to additional investment worldwide to provide full access to RT, although this investment depends on the income level of the country (Zubizarreta et al., 2017).

The installation of a MV unit involves a meticulous process, with a detailed evaluation of national and institutional needs, infrastructure readiness, and radiotherapy program formulation. This phase, being time-consuming, precedes the implementation stage, which includes staff training, equipment specification, facility planning, equipment delivery coordination, and treatment initiation. We are already behind schedule due to the extended time between needs identification and the initiation of patient treatment in this process. (Iżewska & Agency, 2008).

In Portugal, our results show that to provide full access to EBRT until 2040 could be needed to install 18 to 30 additional MV units. This lack of equipment has been highlighted by Portuguese Radiation Oncology College in the last decade. In 2015, they highlighted that Portugal needed around 60 MV units to offer full access to RT in that year (*Segunda Revisão Rede Nacional de Especialidade Hospitalar e de Referenciação de Radioterapia*, 2015). But, IAEA DIRAC shows that in 2021 there were 56 MV units available in Portugal (*DIrectory of RAdiotherapy Centres*, 2022).

Even Portugal has reached the goal of 5.5 MV units per million habitants, this does not translate into an improved availability to the cancer patients at national level. This reality is limited by the distribution of MV units in urban areas, that is not in line with the location of the cancer patients (*Segunda Revisão Rede Nacional de Especialidade Hospitalar e de Referenciação de Radioterapia*, 2015).

This deficit of MV units will continue in the future without a change in the cancer related - policies. Furthermore, the available data concerning 2016 provided by National Statistics Institute and Portuguese Radiation Oncology College, shows that there were 33 and 23 MV units in public sector and private/public-private partnerships, respectively. Based on the total 445,662 RT sessions performed in 2016, the number per machine was 11,460 and 2,934 for public sector and private/public-private partnerships, respectively (College, 2017; *Estatísticas da Saúde : 2016*, 2016). The Portuguese Radiation Oncology College emphasized in 2015 that some private RT departments had low levels of RT courses performed by MV unit. Also, in 2017 they reinforced the need to consider the private sector equipment already installed to offer RT treatments to all cancer patients, through the process of defining cancer referral networks (College, 2017). The Portuguese law allows signing contracts with private sector when the national healthcare system does not have the capacity to provide timely care, as states the 29th article of the Estatuto do Serviço Nacional de Saúde / Statute of the National Health Service, published in 2022 (*Statute of the National Health Service - Republic Diary*

No. 52/2022, 2022). Our results stating that there is a need to install 18 to 30 additional MV units, assume that all the MV units available are working at full capacity. So, if the policy makers continue to exclude private equipment from the national cancer referral networks, it will be needed to install more than 30 MV units in the national healthcare system's RT departments.

The most recent published survey from RT Portuguese staff shows that the ratio per MV unit was in line with the IAEA requirements. The ESTRO-HERO survey performed in 2013 states that in Portugal there were 90 radiation oncologists, 65 medical physics, 239 radiation therapists (Dunscombe et al., 2014). The report published by the Portuguese Radiation Oncology College states a total of 47 MV units in 2013, which translates into ratios above the IAEA guidelines (College, 2013). Nonetheless, the number of MV units have been below the required to cover the needs for the past decade.

Based on GLOBOCAN's projections for new cancer cases in 2040 and DIRAC data, the future need for additional MV units varies widely across Western European countries. Switzerland, Finland, and France are expected to see an increase of less than 20% in demand for new MV units by 2040. In contrast, Portugal, Greece, Malta, and the United Kingdom anticipate an increase of more than 60% in the demand for MV units (*DIrectory of RAdiotherapy Centres*, 2022; Sung et al., 2021).

Furthermore, the IAEA RT staffing calculator highlights the impact of novel RT techniques that will be used in a growing number of patients. For example, delivery a RT treatment with breathing control, reducing heart irradiation and toxicity, requires more working hours from staff. The imaging, planning and first setup is calculated to be 2 hours for the radiation oncologist, 4 hours for the medical physicist, and 2h30 for the radiation therapist. In comparison to RT with free breathing, 1h30, 50 minutes, and 2h30 will be spend by radiation oncologist, medical physicist, and radiation therapist, respectively (*Staffing in Radiotherapy: An Activity Based Approach*, 2015).

The RT workforce shortfall is already a reality in several countries. In the United Kingdom, the Royal College of Radiologists recognize that the rising cancer incidence considering the ageing population will translate into a staff crisis (Charlton & Hindocha, 2023). Worldwide, the median ratio of radiation oncologists presents a significant variation. The ratio shows that there is one radiation oncologist for every 400 cancer patients in high-income countries but in low-

income countries the number of cancer patients rises to 1.316. This ratio is below the 250-300 cancer patients recommended by IAEA guidelines. No data was reported regarding the ratio of medical physicists and radiation therapists (Trapani et al., 2021).

Oncologists of the future will need to adapt to technological and scientific advances while navigating resource limitations. This necessitates a shift in training to ensure that oncologists are not only clinically competent but also versatile in integrating innovations and addressing diverse healthcare contexts. As detailed in the editorial by O'Leary and Yeoh, the training of oncologists must evolve to include a more integrated approach, emphasizing cost-effective, evidence-based practices that align with local resources and priorities. This holistic development of oncologists is crucial for delivering the best possible health outcomes across different settings, ultimately improving global cancer care (O'Leary & Yeoh, 2022).

This study has the limitation of being based on data provided from various entities. Some of these databases are relying on information provided by RT departments, through surveys and frequent updates. There is a bias of incomplete information that can compromise the reliability of the results. It would be interesting to include the stage (early vs. advanced) of tumours requiring radiotherapy but unfortunately, this data was unavailable. Also, the future needs calculation model fails to incorporate the effect of hypofraction in RT access.

Conclusion

EBRT as a non-invasive cancer treatment, can be the most suitable option for an expected aged Portuguese population, increasing even further the EBRT demand in the future. Certainly, the deficit of MV units in Portugal will require a change in the cancer related – policies and an investment to offer full access to EBRT treatments. This investment must include a value-based healthcare analysis regarding novel technologies available. Also, measures must be taken to assure that staff requirements are meet in line with the expected complexity of the future RT treatments.

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CHAPTER 5. UTILISATION PATTERNS OF RADIOTHERAPY AMONG OLDER PATIENTS: INSIGHTS FROM PORTUGUESE NATIONAL CANCER REGISTRY DATA

Edna Darlene Rodrigues [1,2]*, Maria José Bento[3,4,5], Rita Calisto[3,4], Jéssica Rodrigues [3,4], Paulo Almeida [5], Escarlata López [6], Laetitia Teixeira[7,2]

[1] Department of Behavioral Sciences, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.

[2] CINTESIS – Center for Health Technology and Services Research, Porto, Portugal.

Maria José Bento

[3] Cancer Epidemiology Group, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto) / Porto Comprehensive Cancer Centre (Porto.CCC) & RISE@CI-IPOP (Health Research Network), Porto, Portugal;

[4] Department of Epidemiology, Portuguese Oncology Institute of Porto, Porto, Portugal;

[5] Internal Medicine Department, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal.

[6] Oncologia Radioterápica e Directora Médica GenesisCare Sur, Málaga, Espanha.

[7] Department of Population Studies, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal

*Corresponding author: up201610921@g.uporto.pt

ORCID

Edna Darlene Rodrigues: 0000-0001-8170-3952
Maria José Bento: 0000-0002-7690-9830
Rita Calisto: 0000-0002-5151-5245
Jéssica Rodrigues: 0000-0002-1571-5151
Paulo Almeida: 0000-0002-4879-559X
Escarlata López: 0000-0001-6099-2855
Laetitia Teixeira: 0000-0002-9276-3683

Abstract

Introduction: Radiation therapy (RT) will be required by millions of those aged 70 or older by 2040 based on European growth in cancer incidence among this age group.

Purpose: This study evaluates the use of external radiotherapy (EBRT) using data from the Portuguese National Cancer Registry (RON), analysing various cancer locations and age groups. A comparative analysis was conducted between actual EBRT utilization and comorbidity-adjusted optimal rates.

Methods: Based on RON's data, cancer diagnoses from January to June 2018 were analysed. Optimal Utilization Proportions (OUP) of EBRT were obtained from European SocieTy for Radiotherapy and Oncology (ESTRO), Health Economics in Radiation Oncology (HERO) project. Actual utilization percentages (AUP) were calculated using national cancer registry data, and a comparative analysis adjusting for comorbidities was conducted.

Results: For most cancer locations and age groups, the actual EBRT utilisation fell below the ESTRO-HERO recommendations, with potential untreated patients estimated at 22% of all new cancer cases across all age groups. Disparities were observed for older patients, such as breast cancer EBRT actual utilisation declining from 68% to 25% for patients aged under 70 and 85 or older, respectively. Also, cervix cancer patients aged 75 or older exhibited nearly 100% optimal EBRT utilisation. Conversely, older patients with bladder and colon cancer had significantly lower RT actual utilisation rates. Comorbidity-adjusted EBRT utilisation rates for lung, rectal, cervix, and breast cancers in patients aged 70-79 did not reached ESTRO-HERO task force recommended rates. The actual EBRT usage in Portugal failed to meet the comorbidity-adjusted optimal utilisation rate for all cancer locations and age groups. Nevertheless, Portuguese actual EBRT for rectal and prostate cancer, exceeded the actual rates in Australian cohort.

Conclusion: While EBRT is essential for older adults with cancer, disparities and suboptimal utilization highlight opportunities for improving cancer care provision.

Background

In Europe, comprising all cancers, including non-melanoma skin cancers, the total number of cases occurring in persons aged 70 years or older was 2.08 million in 2020. This figure is anticipated to rise to 3.06 million by 2040 (Sung et al., 2021). With an anticipated 20–30% rise in demand due to demographic changes, around 1.5 to 2.5 million older adults in Europe are expected to require external radiotherapy (EBRT) treatments by 2040 (Slotman et al., 2005).

EBRT offers advantages over surgery and chemotherapy due to its non-invasive nature, localized approach, minimal discomfort, and overall improvement in quality of life, ranking as the second most common modality after surgery in nonagenarians, as indicated by 2010 data from Moffitt Cancer Centre (Choi & Cho, 2016; Extermann et al., 2010).

Research indicates under-utilization of EBRT, especially among females, those residing over 100 km from the nearest RT facility, and individuals aged 60 or above, or 80 or above, with a Charlson comorbidity index of 1 or above, or requiring assistance with daily activities (Yap et al., 2020).

While acknowledging the limitations of evaluating EBRT usage through national cancer registries, they remain essential for estimating EBRT usage proportions (Jagsi et al., 2012; Walker et al., 2013).

The Portuguese National Cancer Registry (RON), established in 2018, consolidates data from public and private health institutions nationwide (Costa Miranda, 2021; Pontes L., 2001).

Despite the lack of comprehensive data on the completeness of RON, there is information available for the northern region of Portugal (RORENO), specifically for gastric cancer. The overall estimates for the completeness of gastric cancer registration ranged between 82.9% and 96.4%, depending on the worst- and best-case scenarios (Castro et al., 2012).

Evidence-based recommendations and resource planning for EBRT are provided by the European Society for Radiotherapy and Oncology (ESTRO), Health Economics in Radiation Oncology (HERO) project (*Health Economics in Radiation Oncology*, 2023).

Focusing on the Optimal Utilisation Proportion (OUP) of EBRT for each cancer location, it is defined by ESTRO-HERO task force as “the proportion of new cancer

cases that should receive EBRT treatment at least once in the course of their disease" (Borras et al., 2018). In Portugal, the OUP of EBRT for all cancers, excluding non-melanoma skin cancers, ranges between 49.7% and 51.1%, accordingly with the ESTRO-HERO data (Borras et al., 2015).

A recognized limitation of prior models designed to estimate OUP of EBRT has been the lack of high-quality population-based data to estimate the suitability for EBRT, particularly in cases where the omission of EBRT is considered due to restricted patient fitness or prognosis. To fill this gap, Mackenzie et al. developed an age- and comorbidity-adjusted OUP model for patients with breast, lung, rectal, prostate, and cervix cancers. This model allows to compare the comorbidity-adjusted-OUP to actual EBRT utilisation rates (Mackenzie et al., 2022; Mackenzie, Vajdic, Delaney, Comans, Agar, et al., 2023).

To calculate the comorbidity-adjusted-OUP, the comorbidities were evaluated through the C3 index score, a scoring system developed by Sarfati et al. This score is based on the analysis of hospital records of comorbid conditions within a 5-year period prior to cancer diagnosis or the index hospitalization at the time of diagnosis. Additionally, cancer locations were combined into five location groups, with the primary outcome being noncancer mortality (Sarfati et al., 2014).

In the age- and comorbidity-adjusted OUP model, patients were classified as medically unfit, and thus unsuitable candidates for EBRT, if their C3 score was bigger than 3, corresponding to a Charlson Comorbidity Index score of above 2 (Mackenzie et al., 2022; Mackenzie, Vajdic, Delaney, Comans, Agar, et al., 2023).

This study aims to assess EBRT utilization among older adults aged 70 years or over, using data from the Portuguese National Cancer Registry. A comparison with younger patients will also be conducted to provide a broader perspective. The main objectives of this study were to calculate evidence-based optimal EBRT use by cancer location and age groups, analyse actual EBRT utilization, and conduct a comparative analysis using Mackenzie et al.'s model.

Methods

An analysis of the 2018 national RON dataset was conducted, with a specific focus on the utilisation of EBRT. The registries included persons who received a novel cancer diagnosis within the temporal span of January to June 2018. Relevant details regarding RT treatment are incorporated into the RON by each institution. It should be noted that each hospital retrospectively feed the database, and that EBRT information was collected in November 2022. To comply with ESTRO-HERO OUP literature, the non-melanoma skin cancers were excluded from the analysis. Subsequently these patients were categorized into age groups, specifically: <70, 70-74, 75-79, 80-84, and 85 years and older. Furthermore, the RON cancer registries, categorized by location using International Classification of Diseases for Oncology, Third Edition (ICD-O-3), were organized based on cancer locations as defined in the ESTRO-HERO literature. (Borras et al., 2015). The cancer locations were defined as breast, prostate, colon, lung/trachea/bronchi, rectum/anal canal, head and neck, stomach, bladder, cervix, brain and CNS, kidney, uterus, leukaemia, pancreas, ovary, liver, myeloma, lymphoma, oesophagus, gallbladder and biliary tract, melanoma, testis, unknown primary, vulva, vagina, and thyroid gland.

Ethics approval

This study was approved by Research Ethics Committee from the School of Medicine and Biomedical Sciences, University of Porto, Portugal (reference 2021/CE/P026 (P366/CETI/ICBAS) and by Health Research Ethics Committee from Portuguese Oncology Institute of Porto - IPO Porto, Portugal (reference CES 59/022).

Evidence-based optimal use of EBRT courses per cancer location

The evidence-based OUP of EBRT, courses per cancer location was estimated according with the data published by ESTRO-HERO project (Borras et al., 2015):

$$Optimal\ radiotherapy\ utilisation\ percentage\ \times cancer\ cases\ reported\ in\ RON$$

Actual utilisation percentage

The actual utilisation percentage (AUP) of radiotherapy was calculated by:

$$\frac{Number\ of\ patients\ who\ underwent\ EBRT\ per\ cancer\ location}{Number\ of\ new\ cancer\ cases\ per\ cancer\ location} \times 100$$

Actual utilisation percentage of radiotherapy relative to the evidence-based optimal use per cancer location

The AUP of radiotherapy relative to the evidence-based OUP per cancer location was calculated through:

$$\frac{Number\ of\ patients\ who\ underwent\ RT}{Number\ of\ patients\ with\ indication\ for\ EBRT\ per\ OUP} \times 100$$

The comparison between the age groups will be performed using descriptive analysis techniques. The authors examined and presented differences in EBRT utilization patterns, highlighting any notable variations based on age.

Comparison between AUP and Optimal Comorbidity Adjusted Radiotherapy Utilisation Rate

Based on published data on optimal comorbidity-adjusted EBRT utilization rates for lung, rectal, prostate, cervix, and breast cancers from an Australian - New South Wales (NSW) cohort, the authors compared these rates with the actual EBRT utilization data from Portugal. The comparison was performed by age groups, namely, all ages, 70-79 and 80 years or over. Also, it was compared the Portuguese AUP with the Australian AUP data.

The analysis used in this study was descriptive in nature and conducted using Microsoft Excel.

Results

2018 national cancer registry data

According to the data derived from the RON, the database encompassed a total of 32,435 patients. Therefore, after excluding non-melanoma skin cancers, a total of 24.819 patients were considered as eligible cohort. Among these, 9.498 were aged 70 years old or over.

Evidence-based optimal use of EBRT courses per cancer location

Based on the OUP and the recorded number of new cancer cases registered in RON for the period between January and June 2018, the number of optimal EBRT courses was calculated. The data concerning all cancer locations and age groups is displayed in Table 5.1. To illustrate, for breast cancer, in the optimal scenario around 87% of patients are expected to perform EBRT. That way, for 3.530 new breast cancer cases aged below 70 y/o, the expected optimal EBRT courses are 3.071. On the other hand, for patients aged 70 y/o or over, for the 1.169 new cancer cases, 1.017 patients had indication for EBRT per OUP.

Actual utilisation of radiotherapy

Table 5.1 presents data on AUP for all cancer locations and age groups. Considering prostate cancer as an example, where the optimal use of EBRT should be 58% of all new cancer cases, the AUP of EBRT was 39% for both age groups. Focusing on liver cancer, as the ESTRO-HERO guidelines considerer the OUP as 0%, so the actual use of EBRT for this location exceeded the recommended percentage. However, except for vulva cancer patients aged 70 years or older, the actual utilisation for other cancer locations and age groups fell below the recommended levels. The estimated number of patients potentially untreated was 3.381 for those aged 0-69 years and 2.093 for those aged 70 years or older, around 22% of all new cancer cases.

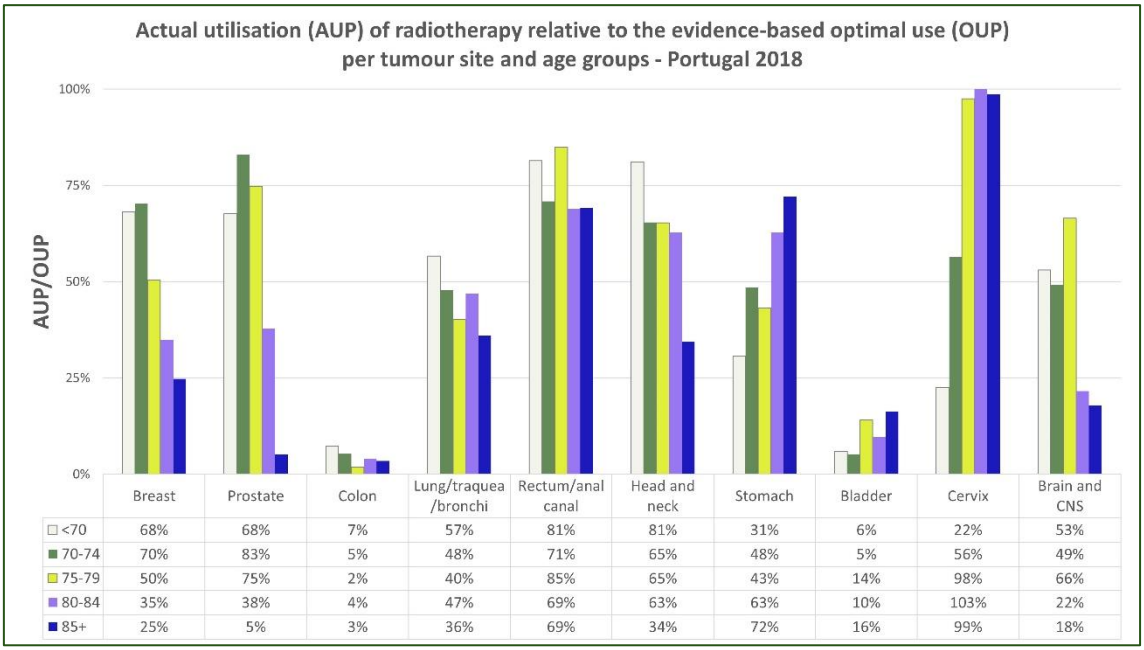
Table 5.1 Utilization of External Beam Radiotherapy (EBRT) Across Various Cancer Locations and Age Groups. This table presents the Optimal Utilization Percentage (OUP) of EBRT and actual utilization rates across different cancer types and age groups. For each cancer type, data is segmented by age groups: 0-69, 70-74, 75-79, 80-84, and 85+. The table includes total numbers of patients with an indication for EBRT, numbers of patients who underwent EBRT, actual utilization percentages (AUP), and the comparison of new cases across these age groups. The values are detailed for each cancer location, illustrating variations in EBRT utilization by age group.

							All age groups					0-69					70-74					75-79					85+				
CANCER LOCATION	Optimal RT Utilization Percentage (OUP)	TOTAL	TOTAL RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP	New cases	RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP	New cases	RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP	New cases	RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP	New cases	RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP	New cases	RT patients per OUP	Patients who underwent RT	AUP	AUP/OUP
Breast	87%	4699	4088	2586	55%	63%	3530	3071	2091	59%	68%	378	329	231	61%	70%	303	264	133	44%	50%	293	255	89	30%	35%	195	170	42	22%	25%
Prostate	58%	2925	1697	1144	39%	67%	1472	854	577	39%	68%	651	378	313	48%	83%	452	262	196	43%	75%	251	146	55	22%	38%	99	57	3	3%	5%
Colon	4%	2809	112	61	2%	54%	1337	53	39	3%	73%	472	19	10	2%	53%	405	16	3	1%	19%	375	15	6	2%	40%	220	9	3	1%	34%
Lung/ Trachea/ Bronchi	77%	1988	1531	793	40%	52%	1185	912	517	44%	57%	370	285	136	37%	48%	239	184	74	31%	40%	147	113	53	36%	47%	47	36	13	28%	36%
Rectum/ Anal Canal	60%	1298	779	607	47%	78%	702	421	343	49%	81%	200	120	85	43%	71%	159	95	81	51%	85%	155	93	64	41%	69%	82	49	34	41%	69%
Head And Neck	74%	1290	955	711	55%	74%	878	650	527	60%	81%	151	112	73	48%	65%	118	87	57	48%	65%	84	62	39	46%	63%	59	44	15	25%	34%
Stomach	27%	1261	340	139	11%	41%	677	183	56	8%	31%	199	54	26	13%	48%	189	51	22	12%	43%	124	33	21	17%	63%	72	19	14	19%	72%
Bladder	47%	1214	571	50	4%	9%	508	239	14	3%	6%	209	98	5	2%	5%	211	99	14	7%	14%	155	73	7	5%	10%	131	62	10	8%	16%
Cervix	71%	1169	830	211	18%	25%	1116	792	178	16%	22%	15	11	6	40%	56%	13	9	9	69%	98%	15	11	11	73%	103%	10	7	7	70%	99%
Brain And CNS	80%	715	572	298	42%	52%	516	413	219	42%	53%	99	79	39	39%	49%	64	51	34	53%	66%	29	23	5	17%	22%	7	6	1	14%	18%
Other	19%	1487	283	229	15%	81%	910	173	157	17%	91%	204	39	28	14%	72%	153	29	21	14%	72%	124	24	14	11%	59%	96	18	9	9%	49%
Kidney	15%	635	95	20	3%	21%	402	60	18	4%	30%	94	14	0	0%	0%	79	12	1	1%	8%	41	6	1	2%	16%	19	3	0	0%	0%
Uterus	38%	584	222	170	29%	77%	346	131	95	27%	72%	99	38	30	30%	80%	64	24	22	34%	90%	46	17	14	30%	80%	29	11	9	31%	82%
Leukaemia	4%	481	19	14	3%	73%	296	12	13	4%	110%	58	2	0	0%	0%	60	2	1	2%	42%	35	1	0	0%	0%	32	1	0	0%	0%
Pancreas	49%	398	195	37	9%	19%	236	116	27	11%	23%	83	41	4	5%	10%	47	23	5	11%	22%	23	11	1	4%	9%	9	4	0	0%	0%

Ovary	4%	253	10	6	2%	59%	179	7	5	3%	70%	27	1	0	0%	0%	28	1	0	0%	0%	15	1	1	7%	167 %	4	0	0	0%	0%
Liver	0%	247	0	25	10%	NA	162	0	17	10%	NA	46	0	5	11%	NA	22	0	2	9%	NA	12	0	1	8%	NA	5	0	0	0%	NA
Myeloma	45%	222	100	38	17%	38%	115	52	18	16%	35%	38	17	10	26%	58%	32	14	4	13%	28%	24	11	3	13%	28%	13	6	3	23%	51%
Lymphoma	73%	215	157	68	32%	43%	171	125	60	35%	48%	20	15	1	5%	7%	15	11	3	20%	27%	6	4	3	50%	68%	3	2	1	33%	46%
Oesophagus	71%	197	140	109	55%	78%	145	103	75	52%	73%	26	18	17	65%	92%	13	9	9	69%	98%	9	6	7	78%	110 %	4	3	1	25%	35%
Gallbladder And Biliary Tract	17%	187	32	15	8%	47%	90	15	8	9%	52%	46	8	5	11%	64%	32	5	2	6%	37%	15	3	0	0%	0%	4	1	0	0%	0%
Melanoma	21%	171	36	9	5%	25%	86	18	6	7%	33%	24	5	0	0%	0%	23	5	0	0%	0%	18	4	1	6%	26%	20	4	2	10%	48%
Testis	7%	126	9	6	5%	68%	119	8	4	3%	48%	1	0	0	0%	0%	1	0	0	0%	0%	2	0	1	50%	714 %	3	0	1	33%	476 %
Unknown Primary	61%	120	73	41	34%	56%	78	48	27	35%	57%	16	10	5	31%	51%	12	7	4	33%	55%	10	6	4	40%	66%	4	2	1	25%	41%
Vulva	39%	97	38	37	38%	98%	45	18	15	33%	85%	12	5	4	33%	85%	9	4	3	33%	85%	16	6	8	50%	128 %	15	6	7	47%	120 %
Vagina	94%	31	29	14	45%	48%	20	19	6	30%	32%	3	3	1	33%	35%	0	0	0	NA	NA	3	3	3	100 %	106 %	5	5	4	80%	85%
Thyroid Gland	4%	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA

Actual utilisation of radiotherapy relative to the evidence-based optimal use per cancer location

Figure 5.1 shows the proportion of actual versus optimal EBRT utilization, with 100% representing the ideal scenario, by age group. For breast, prostate, lung, brain, and central nervous system (CNS) cancers, ratios are similar for those under 70 and those aged 70-74, with significant differences in older age groups.



	Breast	Prostate	Colon	Lung/traquea /bronchi	Rectum/anal canal	Head and neck	Stomach	Bladder	Cervix	Brain and CNS
<70	68%	68%	7%	57%	81%	81%	31%	6%	22%	53%
70-74	70%	83%	5%	48%	71%	65%	48%	5%	56%	49%
75-79	50%	75%	2%	40%	85%	65%	43%	14%	98%	66%
80-84	35%	38%	4%	47%	69%	63%	63%	10%	103%	22%
85+	25%	5%	3%	36%	69%	34%	72%	16%	99%	18%

Figure 5.1 - This graph presents the actual utilization of radiotherapy in Portugal for 2018 across different tumour sites and age groups, compared to the evidence-based optimal usage (OUP). The data indicate that radiotherapy is less frequently used in older age groups, particularly for breast, prostate, and lung cancers. In contrast, younger patients (under 70) receive radiotherapy at levels closer to the recommended guidelines, while the oldest patients (85 and above) exhibit the most significant underutilization.

Figure 5.2 illustrates the proportion of actual versus optimal EBRT utilization for patients under 70 compared to those 70 and older, based on aggregate data. Table 5.1 presents the AUP and AUP/OUP for age groups <70, 70-74, 75-79, 80-84, and 85+. Utilization patterns vary by age group and cancer type.

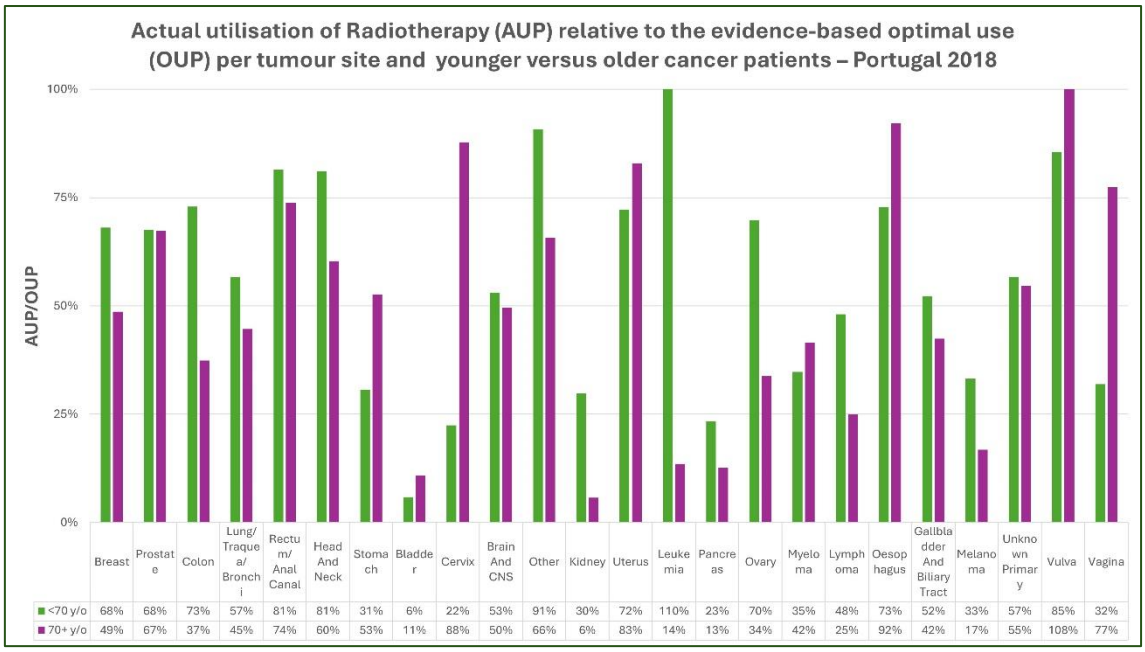


Figure 5.2 - Illustrates the proportion of actual versus optimal External Beam Radiotherapy (EBRT) utilization for patients under 70 compared to those 70 and older, based on aggregate data.

When comparing AUP relative to OUP, patients under 70 generally show higher AUP/OUP ratios for cancers like breast, colon, rectum, head and neck, kidney, leukaemia, ovary, lymphoma, and melanoma, though most ratios fall below 100%. In contrast, patients 70 or older have higher AUP/OUP ratios for cancers such as stomach, cervix, uterus, myeloma, oesophagus, testis, vulva, and vagina. Ratios for prostate, brain, CNS, and unknown primary cancers remain consistent across age groups.

For breast cancer, EBRT use is 68% of the optimal level for patients under 70 but drops to 25% for those aged 85+. Prostate cancer patients between 70-79 show a slight increase in EBRT use, likely as an alternative to surgery. Cervix cancer patients aged 75+ approach 100% of optimal EBRT utilization. In contrast, bladder and colon cancer patients have EBRT utilization rates well below the optimal level.

<u>Comparison between AUP and Optimal Comorbidity Adjusted Radiotherapy Utilisation Rate</u>

Notably, as shown on Table 5.2, the model presented by Mackenzie et al. elucidates that, for lung, rectal, cervix, and breast cancers, the optimal comorbidity-adjusted EBRT utilisation rate (CA-OUP) decreases 17%, 9%, 19%, and

7%, respectively, in patients aged 70-79 years when compared to the rates published by ESTRO-HERO task force. On the other hand, for prostate cancer, a marginal increase of 3% is observed within the same age group. For instance, while prostate cancer ESTRO-HERO task force states an OUP of 58%, the CA-OUP increases to 61% for those aged 70-79 years but decreases to 51% for those aged 80 and above when adjusted for comorbidities. Notably, the actual use of EBRT for the NSW population was below the recommended levels for all cancer locations and age groups, except for cervix cancer in patients aged 70-79 y/o. While a similar trend is observed in Portugal, for rectal and prostate cancer, the actual usage was higher in Portugal compared to NSW.

Table 5.2 - Comparison between Actual utilisation percentage (AUP) and Optimal Comorbidity Adjusted Radiotherapy Utilisation Rate for Portuguese (PT) and New South Wales (NSW) population. Lung cancer includes a small and b non-small cell lung cancer. This data shows a notable decline in Optimal Comorbidity Adjusted Radiotherapy Utilisation Percentage for lung, rectal, cervix, and breast cancers and a slight increase for prostate cancer for the age group 70-79 years in comparison with Optimal Radiotherapy Utilisation Percentage. The AUP was below the recommended for PT and NSW population except for cervix cancer patients aged ≥70 years.

	All ages				70–79 years			80+ years		
Cancer location	**Optimal Radiotherapy Utilisation Percentage [11]**	**Optimal Comorbidity Adjusted Radiotherapy Utilisation Percentage [12,13]**	**AUP – NSW**	**AUP – PT**	**Optimal Comorbidity Adjusted Radiotherapy Utilisation Percentage [12,13]**	**AUP-NSW**	**AUP-PT**	**Optimal Comorbidity Adjusted Radiotherapy Utilisation Percentage [12,13]**	**AUP-NSW**	**AUP-PT**
Lung cancer	77	58[a] / 62[b]	56[a] / 38[b]	40	54[a] / 60[b]	51[a] / 37[b]	34	49[a] / 49[b]	32[a] / 25[b]	34
Rectal cancer	60	53	37	46	51	35	45	43	27	41
Prostate cancer	58	63	21	39	61	33	46	51	16	17
Cervix cancer	71	62	46	18	52	75	54	40	56	72
Breast cancer	87	84	61	55	80	56	53	70	24	27

Discussion

In our study, we analysed 24,819 cancer registries, with 9,498 for patients aged 70 or older. EBRT utilization for Portuguese patients across all cancer types and age groups was below ESTRO-HERO recommendations, except for vulva cancer patients aged 70 and older. An estimated 3,381 patients aged 0-69 and 2,093 aged 70 or older, around 22% of new cancer cases, potentially lacked access to EBRT. Actual EBRT usage in Portugal was below CA-OUP for all age groups and cancer locations, although the AUP for rectal and prostate cancer surpassed that of the Australian cohort.

Our study, despite benefiting from RON's integration and data validation processes, has notable limitations. We lack specific timing information relative to diagnosis, which may affect utilization rates. Although this data is available in the RON database, it was not requested. Additionally, database entry may underrepresent some patients who received EBRT. The RON database classifies palliative EBRT when metastatic disease is present at diagnosis, which could introduce bias; thus, we did not stratify data based on EBRT purpose. Moreover, the RON database includes both EBRT and brachytherapy, potentially leading to overestimated EBRT rates.

Our findings reveal a significant theoretical deficit in EBRT access, consistent with ESTRO-HERO's report that over a quarter of European cancer patients requiring EBRT do not receive it. Portugal's current utilization of EBRT is approximately 50-60% of the optimal level, similar to Estonia and Albania. All other countries in the report show higher actual-to-optimal EBRT utilization rates (Lievens, Borras, et al., 2020).

Our study shows variable EBRT utilization patterns across age groups and cancer types, emphasizing its role as an alternative to surgery. These patterns align with Mackenzie et al., who found reduced EBRT use with increasing age for several cancers, but increased use for curative settings in prostate and cervix cancers (Mackenzie, Vajdic, Delaney, Comans, Morris, et al., 2023). Diver et al. also noted that older women with cervical cancer, often with more advanced disease, are more likely to receive radiation. This might explain why older Portuguese women with cervical cancer receive more radiation as they age (Diver et al., 2018).

The RON database lacks information about comorbidities and so we extrapolated the correction from the NSW data, to calculate the CA-OUP, assuming the distribution of comorbidities are similar. The comparison is also limited by the lack

of detailed cohort information as well as differences in follow-up periods and median ages at diagnosis. However, both Portuguese and NSW data show inferior AUP compared to CA-OUP. Also, the availability of EBRT is different, Australia's 224 EBRT machines are sufficient to meet 95% of its needs, whereas Portugal's 57 EBRT machines cover only 73% of its needs (*DIrectory of RAdiotherapy Centres*, 2022; Dunscombe et al., 2014; Sung et al., 2021).

Additionally, data from 2016 by the National Statistics Institute and the Portuguese Radiation Oncology College indicates there were 33 MV units in the public sector and 23 in private or public-private partnerships. With a total of 445,662 RT sessions performed in 2016, each machine handled 11,460 sessions in the public sector and 2,934 sessions in the private/public-private partnerships (College, 2017; *Estatísticas da Saúde : 2016*, 2016). Also, the distribution of MV units in Portugal, concentrated in urban areas, does not match patient distribution. Despite achieving the target of 5.5 MV units per million inhabitants, access remains inadequate. National healthcare billing practices in Portugal—€114 per simple treatments and €275 per complex treatments—do not appear to influence underutilization (Administration, 2023; *Segunda Revisão Rede Nacional de Especialidade Hospitalar e de Referenciação de Radioterapia*, 2015). This shortage of MV units will persist unless cancer-related policies are revised including better integration of private sector equipment.

Ageism and other factors may contribute to EBRT underutilization. Systematic reviews identify factors like convenience, success rates, and trust in physicians affecting treatment acceptance. Also, reluctance is tied to concerns about treatment discomfort, fear of side effects, and transportation issues (Puts et al., 2015). There is a need for more education in geriatric oncology (Lucinda Morris et al., 2017). Healthcare professionals must recognize that, for older adults with cancer, chronological age poorly predicts tolerance and outcomes. Treatment decisions should reflect this understanding (Anita O'Donovan & Michelle Leech, 2020).

Despite longstanding awareness of disparities in cancer care for older patients, significant gaps remain. The European Beating Cancer Plan calls for improved radiotherapy access and a European Cancer Dashboard to monitor inequalities. Improved access to EBRT could potentially save up to 1 million lives in Europe by 2035 (Monfardini et al., 1993a; Organization, 2022).

As cancer incidence rises and the older population grows, EBRT will remain a vital treatment option, especially for frail older patients, expected to be present in in 42% of older individuals. Given the non-invasive attributes of EBRT, it emerges as a particularly wise therapeutic option for these frail older patients, thereby further stressing the demand for EBRT. (Baumann & Bacchus, 2020; *Projeções de População Residente 2018-2080* 2020).

Advanced technologies like stereotactic body (SBRT) or adaptive (ART) radiotherapy, and accurate positioning systems such as Surface Guided Radiotherapy (SGRT) offer opportunities for safer, higher-quality treatments (Oncology, 2023; Rodrigues et al., 2022).

Conclusion

Our study found that access to EBRT is below ESTRO-HERO recommendations among cancer patients in Portugal, particularly in older populations. This underutilization of EBRT may be linked to comorbidities and the insufficient or uneven distribution of MV units, especially outside urban areas. Improving access to EBRT is essential to address the rising cancer incidence and enhance the quality of cancer care. As a non-invasive treatment, EBRT is a vital tool for improving the quality of life for frail older cancer patients.

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CHAPTER 6. AN EVALUATION OF PORTUGUESE RADIATION ONCOLOGISTS' KNOWLEDGE AND PRACTICE IN RELATION TO GERIATRIC ONCOLOGY

Edna Darlene Rodrigues [1,2]*, Paulo Almeida [3], Escarlata López Ramírez [4], Laetitia Teixeira[1,2]

[1]Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.

[2] CINTESIS – Center for Health Technology and Services Research/ RISE - Health Research Network, Porto, Portugal.

[3] Internal Medicine Department, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal.

[4] Radiation Oncology Department, GenesisCare, Malaga, Spain.

Abstract

Introduction:

Cancer is a major health concern in Portugal, especially among older adults, who represent nearly half of new cases. Radiation therapy (RT) is crucial in their treatment, emphasizing the need for improved education in geriatric oncology for radiation oncologists (RO).

Methods:

A pretested 22-item online survey on RO' geriatric oncology knowledge was disseminated.

Results: The analysis involved 52 respondents, including 13 residents (25%) and 39 consultants (75%); RO were asked to specify the age threshold they considered to define an older cancer patient. Their responses were as follows: 60 years (n=2, 3.8%), 65 years (n=7, 13.5%), 68 years (n=1, 1.9%), 70 years (n=29, 55.8%), 75 years (n=10, 19.2%), and 80 years (n=2, 3.8%). Forty-six respondents (88.5%) acknowledged an observed increase in the number of older cancer patients in RT departments. Twenty-nine participants (55.8%) reported that age was considered either most of the time or always in clinical decisions. Regarding frailty screening, it was performed by 15 participants (28.8%), while four participants (7.7%) stated that frailty was assessed during comprehensive geriatric assessment in another department. Of those implementing screening tools, nine (17.3%) utilized the G8 tool, and two respondents (3.8%) employed the Triage Risk Screening Tool - TRST tool. Most respondents reported a lack of awareness regarding specific guidelines for older cancer patients, and 98.1% expressed the need for enhanced training in geriatric oncology.

Conclusion:

The study highlights a critical need for improved training in geriatric oncology among RO professionals. Furthermore, the findings underscore the imperative for treatment decisions to reflect an understanding beyond chronological age, emphasizing the necessity of addressing this knowledge gap in clinical practice.

Highlights

- The analysis encompassed 52 respondents, primarily consisting of 75% RO consultants and 25% residents, falling short of the intended sample size.
- Findings, reported with a 90% confidence level and 10% margin of error, highlighted a predominantly female representation (56.6%) and a significant proportion (51.9%) working in university hospitals.
- Radiation oncologists' expertise spanned various cancer subtypes, with age significantly influencing clinical decision-making. Frailty assessment was underutilized.
- Despite limited awareness of guidelines specific to older cancer patients and sparse staff resources for comprehensive geriatric assessments, there was a recognized need for enhanced training in geriatric oncology among respondents.

Introduction

In the Portuguese context, cancer is the second major cause of both mortality and morbidity, accounting for 28,544 cancer-related deaths, approximately constituting 25% of the overall mortality (*Causas de morte - Cause of deaths 2019*, 2019). Notably, nearly half of these new cancer cases occur within the older adult population aged above 70 y/o or over (Costa Miranda, 2021). Approximately 45-55% of new cancer cases may require radiation therapy (RT), with an expected 20-30% increase due to demographic changes. RT is commonly used in older adults with cancer, often alongside surgery, chemotherapy, and/or immunotherapy (Borras et al., 2015).

Older cancer patients frequently formulate treatment decisions based upon a basis of trust in their healthcare providers, adhering to the recommendations offered by their physicians (Puts et al., 2015). Physicians, especially radiation oncologists (RO), should acknowledge that the predictive value of chronological age in assessing tolerance and outcomes for older adults with cancer is limited. In light of this recognition, treatment decisions must be informed by a understanding of the complex interplay of factors influencing the health and outcomes of this population (Anita O'Donovan & Michelle Leech, 2020). One of the most important concepts in this context is frailty, a multisystem syndrome characterized by diminished physiological reserves, mirroring alterations across tissues and organs. This phenomenon is intricately linked with geriatric syndromes, multimorbidity, and the physiological changes such as senescence, collectively reflecting aging's complexity (Thillainadesan et al., 2020).

There is a growing emphasis on personalized and patient-centred approaches. Within this context, the perspectives of RO on geriatric oncology play a critical role in shaping treatment strategies for older cancer patients. Despite the increasing recognition of the challenges associated with cancer in the geriatric population, a notable gap exists in the literature regarding the specific viewpoints of RO on geriatric oncology in the context of Portugal, where there is no specialized geriatric medical specialty.

Given the 2021 statistics indicating 172 (80%) registered consultants and 43 (20%) residents in radiation oncology across Portugal, training initiatives should be strategically tailored to meet the specific needs and availability of both residents and consultants (Administration, 2018, 2019, 2020, 2021; Council, 2022). The findings from this research can play a pivotal role in enhancing existing training

programs, ensuring that radiation oncologists, including both residents and experienced consultants, are adequately equipped to navigate the distinctive challenges inherent in the treatment of older cancer patients.

Moreover, given the critical role of RT in improving outcomes for older adults with cancer, there is a pronounced need for improved educational initiatives within the domain of geriatric oncology (Lucinda Morris et al., 2017; Terret & Droz, 2009). RO must anticipate and address the unique needs of older patients, with a focus on having access to frailty status, ideally assessed through a Comprehensive Geriatric Assessment (CGA). When such assessment is not available, RO must be familiar with frailty screening tools (Anita O'Donovan & Michelle Leech, 2020). Additionally, it is important to enhance communication by directly assessing information needs, balancing realism with hope, recognizing non-survival goals, and employing techniques to reduce miscommunication (Fakhreddine et al., 2017). This research aimed to examine the understanding of geriatric oncology among Portuguese radiation oncologists, with the objective of assessing their current knowledge in this field.

Methods

Ethics

This study was approved by Research Ethics Committee from the School of Medicine and Biomedical Sciences, University of Porto, Portugal (reference 2021/CE/P026 (P366/CETI/ICBAS). Informed consent was obtained for all the participants.

Development of the Survey Instrument

A 22-item online survey assessing RO's perspectives in geriatric oncology underwent a pretest with 10 individuals from Centro Hospitalar Universitário São João's Radiotherapy Department to ensure consistency and content clarity. This survey was developed based on literature review and investigator consensus. (Leifer et al., 2019). Some questions found in the literature were adapted to the Portuguese reality and to the absence of geriatrics as a stablished specialty in the country. After refining the pretest, the finalized survey was distributed. The final distributed version of the survey is available on supplementary data.

The questionnaire covered RO characteristics (gender, age, professional details, cancer type experience), institutional factors (type, geriatric assessment availability), geriatric knowledge (training, age categorization), patient management (age-related treatment variations, informal/formal geriatric assessments, frailty screening), awareness of international recommendations for older cancer patients, and future training needs. The question about the use of frailty screening tools included Geriatric-8 (G8), Vulnerable Elders Survey-13 (VES-13), and Triage Risk Screening Tool. These were selected based on previous publications that state that an abnormal result on these have been stablished as associated with functional decline and poorer survival (Loh et al., 2018). The authors aimed to increase awareness about International Geriatric Radiotherapy Group (IGRG), so a question asking about it was created. This group was founded in 2012 by 15 radiotherapy institutions in the United States and Europe and aims to improve radiotherapy techniques for older cancer patients, enhancing their chances of cure and quality of life (Popescu et al., 2019).

Participants

The study encompassed RO (consultants and residents) actively involved in cancer patient care in Portugal. The entire eligible cohort comprised 43 residents and 172 consultants, identified through the Portuguese Medical Council statistics database. The sample size was estimated to be 139, to 95% of confidence level and a margin of error of 5%. The online survey was distributed to department directors and presented during in-person meetings across five Portuguese radiotherapy departments. The responses were obtained between November 2021 and April 2022. No financial incentives were provided for survey completion, and based on pilot testing, the survey was designed to be completed in less than 10 minutes.

Data Analysis

We conducted summary descriptive analyses on responses obtained from this survey. Also, the pattern of responses was compared between consultants and residents. The survey confidence level and margin of error were calculated according to Serdar et al (Serdar et al., 2021).

We employed crosstab analysis to compare frailty screening and CGA utilisation rates between residents and consultants. IBM® SPSS® Statistics version 27 and Microsoft Office 365 Apps for Enterprise - Excel® were employed for conducting both descriptive and statistical analyses.

Statistical significance was considered to differences with a P-value below 0.05.

Results

In this analysis, 52 respondents were included, comprising 13 residents (25%) and 39 consultants (75%) in RO. The estimated sample size of 139 was not met and the outcomes of this study are reported with a confidence level of 90% and a margin of error of 10%. Of the total respondents, 31 (56.6%) were female, and 27 (51.9%) worked at a university hospital. Consultant expertise covered various cancer subtypes: genitourinary (n=15, 28.8%), breast (n=15, 28.8%), gastrointestinal (n=13, 25%), head and neck (n=13, 25%), lung (n=11, 21.2%), central nervous system (n=7, 13.5%), haematology (n=9, 17.3%), gynaecology (n=6, 11.5%), and skin/sarcomas (n=6, 11.5%).

In relation to pre-graduate training in geriatrics within the context of RO, four participants (7.7%) reported having received such training. Post-graduate training in geriatrics was reported by one respondent (1.9%). Seven respondents (13.5%) indicated the presence of a designated professional for geriatric oncology within their respective hospitals. However, only six participants (11.5%) affirmed the availability of staff resources for the implementation of a comprehensive geriatric assessment.

More than half of the RO considered 70 years old as the threshold for defining an older cancer patient, as illustrated in Figure 6.1.

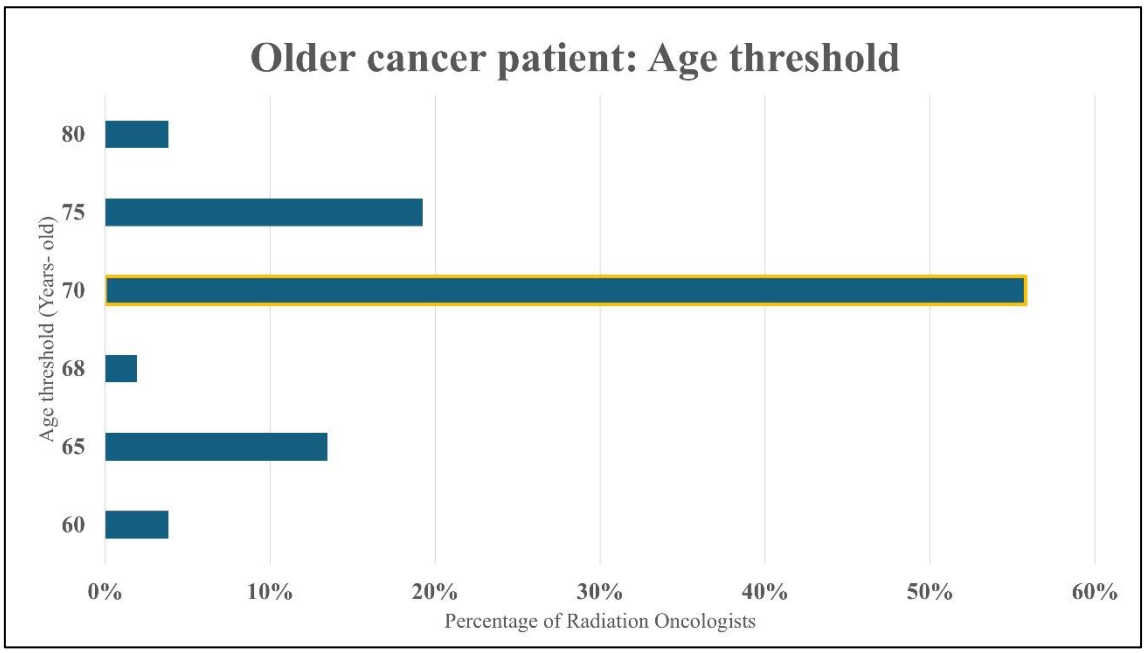


Figure 6.1 – Representation of the age thresholds that Radiation Oncologists considered for defining a cancer patient as older.

The clinical decision-making process was predominantly influenced by age, with 29 participants (55.8%) reporting that age was considered either most of the time or always. Concerning awareness of guidelines specific to older cancer patients, 26 respondents (50%) reported familiarity with National Comprehensive Cancer Network - NCCN Older Adult Oncology Guidelines, 13 (25%) with American Society of Clinical Oncology - ASCO, three (5.8%) with International Society of Geriatric Oncology - SIOG, 19 (36.5%) with European Organisation For Research And Treatment Of Cancer - EORTC, and 17 (32.7%) indicated awareness of none. Most respondents, comprising 38 individuals (73.1%), indicated a lack of awareness regarding the International Geriatric Radiotherapy Group. Regarding frailty screening, it was performed by 15 participants (28.8%), while four participants (7.7%) stated that frailty was assessed during CGA in another department. Of those implementing screening tools, nine (17.3%) utilized the G8 tool, and two respondents (3.8%) employed the Triage Risk Screening Tool.

In routine clinical practice, RO reported assessing various domains of older persons, encompassing walking (n=13, 25%), activities of daily living (n=34, 65.4%), instrumental activities of daily living (n=4, 7.7%), nutrition (n=7, 13.5%), cognition (n=23, 44.2%), depression (n=2, 3.8%), comorbidities (n=10, 19.2%), social aspects (n=27, 51.9%), polypharmacy (n=22, 42.3%), and falls (n=11, 21.2%).

A significant proportion, 46 respondents (88.5%), acknowledged an observed increase in the number of older cancer patients attending RO departments. Furthermore, 51 participants (98.1%) expressed the need for enhanced training in geriatric oncology. The preferred methods for training included case studies discussions (n=27, 51.9%), workshops (n=23, 44.2%), constitution of cancer type-specific interest groups (n=26, 50%), and easy access to international geriatric oncology guidelines (n=34, 65.4%).

There were no significant differences between the answers from consultants and residents for all the questions, as shown on Table 6.1 and Figure 6.2.

Table 6.1. Comparison of responses between residents and consultants in Radiation Oncology.

	Total		**Residents**		**Consultants**		
	(n=52)		**(n=13)**		**(n=39)**		
	n	%	n	%	n	%	p
Gender							
Female	31	59.6	10	76.9	21	53.8	0.142
Male	21	40.4	3	23.1	18	46.2	
Workplace							
University hospital	27	51.9	8	61.5	19	48.7	0.091
Tumour-specific expertise							
Genitourinary	15	28.8	0	0.0	15	38.5	**0.006**
Breast	15	28.8	0	0.0	15	38.5	**0.006**
Gastrointestinal	13	25.0	0	0.0	13	33.3	**0.013**
Head and Neck	13	25.0	0	0.0	13	33.3	**0.013**
Lung	10	19.2	0	0.0	10	25.6	**0.040**
Central nervous system	7	13.5	0	0.0	7	17.9	0.171
Haematology	9	17.3	0	0.0	9	23.1	**0.011**
Gynaecology	6	11.5	0	0.0	6	15.4	0.160
Skin/sarcomas	6	11.5	0	0.0	6	15.4	0.160
Geriatric training							
Pre-graduated	4	7.7	1	7.7	3	7.7	1.000
Pos-graduated	1	1.9	0	0.0	1	2.6	1.000
CGA available at institution	6	11.5	1	7.7	5	12.8	1.000
Decision-making process heavily influenced by age	29	55.8	9	69.2	29	74.4	0.341
Awareness about geriatric oncology-specific guidelines							
NCCN Older Adults Oncology	26	50.0	8	61.5	18	46.2	0.523
SIOG	3	5.8	0	0.0	3	7.7	0.564
EORTC	19	36.5	5	26.3	14	35.9	1.000
ASCO	13	25.0	5	38.5	8	20.5	0.269
None	17	32.7	4	30.8	13	33.3	1.000
Frailty screening tools used in RO practice							
Frailty screening performed	15	28.8	1	7.7	14	35.9	0.049
Frailty assessed during CGA in another department	4	7.7	0	0.0	4	10.3	0.304
G8	9	17.3	1	7.7	8	20.5	0.275
TRST	2	3.8	0	0.0	2	5.1	0.559
VES 13	0	0.0	0	0.0	0	0.0	NA
CGA domains evaluated in RO practice							
At least one domain evaluated	46	88.5	12	92.3	34	87.2	0.528
Complete CGA performed	3	5.8	0	0.0	3	7.7	0.414
Walking	13	25.0	4	30.8	9	23.1	0.415
ADL	34	65.4	9	69.2	25	64.1	0.507
IADL	4	7.7	1	7.7	3	7.7	0.696
Nutrition	7	13.5	2	15.4	5	12.8	0.568
Cognition	23	44.2	7	53.8	16	41.0	0.629

Depression	2	3.8	0	0.0	2	5.1	0.559
Comorbidities	10	19.2	1	7.7	9	23.1	0.214
Social	27	51.9	7	53.8	20	51.3	0.564
Polypharmacy	22	42.3	7	53.8	15	38.5	0.517
Falls	11	21.2	2	15.4	9	23.1	0.438

ADL – Activities of daily living; ASCO - American Society of Clinical Oncology; CGA - Comprehensive geriatric assessment, EORTC - European Organisation for Research and Treatment of Cancer; G8 - Geriatric 8; IADL – Instrumental activities of daily living; NA- Not applicable; RO - Radiation Oncology, TRST - Triage Risk Screening Tool; VES-13 - Vulnerable Elders-13 Survey, SIOG- International Society of Geriatric Oncology.

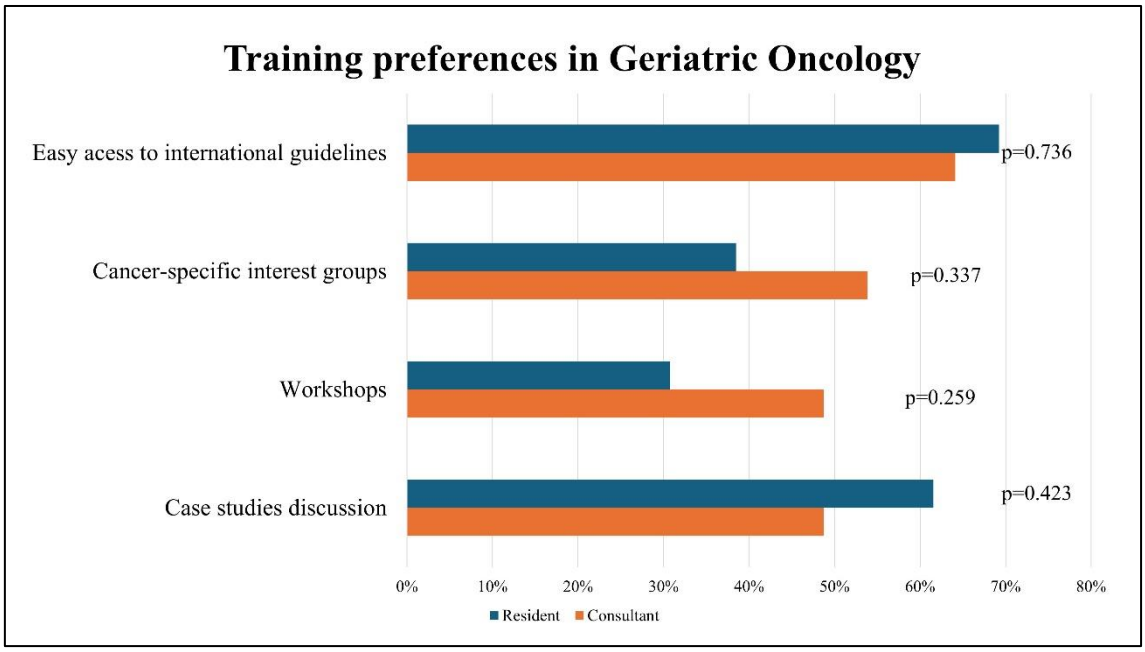


Figure 6.2 - Comparison between responses within residents and consultants in Radiation Oncology (RO), regarding their training needs and preferences.

Discussion

This analysis involved 52 respondents, including 13 residents (25%) and 39 consultants (75%) in RO, with diverse expertise covering various cancer subtypes. Most of the respondents reported a lack of awareness regarding guidelines for older cancer patients, and 98.1% expressed the need for enhanced training in geriatric oncology. The preferred training methods included case studies discussions, workshops, constitution of cancer type-specific interest groups, and easy access to international geriatric oncology guidelines.

Our findings indicate that a minority of respondents had received training in geriatrics. This aligns with the outcomes of a cross-sectional online survey distributed across 45 cancer centres in Australia, New Zealand, and Singapore, revealing that 91.8% of respondents had not undergone any formal or informal instruction related to geriatric oncology during their radiation oncology training (L. Morris et al., 2017). Our findings, in conjunction with literature, highlight that the lack of training in geriatrics is common among RO regardless of the country of practice.

Approximately half of the survey participants mentioned that age significantly impacts clinical decision-making. Unfortunately, this trend aligns with findings from a comprehensive scoping review, emphasizing the prevalent use of patient age, either explicitly or implicitly and consciously or unconsciously, as a determinant in guiding clinical decisions in cancer care (Tranvag et al., 2018). Additionally, there is evidence that healthcare professionals have negative biases toward older women with breast cancer resulting in less optimal care. Neal et al, performed a study that used the Implicit Association Test to assess healthcare professionals' biases toward older women, revealing a moderate negative implicit association with older women ($M = 0.52$, $p < 0.001$). These biases may influence treatment decisions, leading to assumptions that older patients are less capable of decision-making or prefer less aggressive treatments (Neal et al., 2022). The findings published in the literature along with the results from our survey, emphasize the need for objective assessments to counteract age-based assumptions and ensure personalized, evidence-based treatment for older cancer patients.

Regarding the utilization of frailty screening tools within the context of RT, approximately one-third of our study respondents reported their implementation.

Despite no specific data being available regarding the use of frailty screening tools within the scope of RT, an international survey addressing frailty assessment in cancer patients revealed a 37% utilization rate among European respondents. In this international survey, reasons cited for non-utilization of screening tools included lack of awareness, time constraints, and a perceived lack of associated benefits (Banna et al., 2022).

The relationship between frailty and RT, as well as its potential role as a predictor of radiotoxicity and other clinical outcomes, remains inadequately understood. A cohort study found that frailty or vulnerability, as assessed by the G-8, VES-13, or Fried phenotype, was linked to higher rates of radiotoxicity, with areas under the curve of 0.86, 0.79, and 0.61, respectively (Runzer-Colmenares et al., 2017). A different prospective study investigating the Edmonton Frail Scale as a predictor of radiotoxicity in older patients found no significant statistical correlation (Keenan et al., 2017). Data from head and neck cancer patients indicate that frailty, assessed using the CGA, Groningen Frailty Indicator, and G-8, as well as limitations in geriatric domains, were not linked to acute radiation-induced toxicity (Bras et al., 2021). In patients with early-stage non-squamous cell lung cancer undergoing stereotactic RT, the modified frailty index (mFI) was associated with a reduced 3-year overall survival compared to those considered fit (37.3% vs 74.7%; p=0.003). However, the higher mortality rate appeared to be primarily attributed to factors unrelated to lung cancer (Franco et al., 2018). Another study found that in this patient group, frailty, as assessed by the modified frailty index (mFI), was a significant predictor of decreased overall survival (HR = 1.98, 95% CI 1.02-3.85, p=0.04) (Raghavan et al., 2018). Data from a Greek radiation therapy department indicate that, among patients aged 75 or older receiving curative or palliative RT, a VES-13 score greater than 3 was linked to a 2.12-fold higher likelihood of an incomplete RT course, with this likelihood increasing to 3.34 times higher when the score exceeded 7 (Spyropoulou et al., 2014). In urological cancer patients undergoing initial surgery or radiotherapy, those classified as frail based on the CGA had a higher risk of cancer-related hospitalizations compared to their fit counterparts (OR = 6.79, 95% CI 1.42-32.51) (Monfardini et al., 2017). These findings underscore the critical importance of assessing frailty status in older adults proposed for RT, as it may facilitate the identification of individuals at increased risk for adverse outcomes. Furthermore, such assessments could enable

the development of personalized treatment strategies, in this manner optimizing the potential benefits of RT for each older patient.

In the context of interpreting the domains evaluated within RT, our findings indicate that social aspects are the most frequently assessed, with cognition following closely. Notably, while pertinent data specific to the geriatric assessment domains within radiation oncology are not presently available, recent insights derived from a survey conducted by the ASCO reveal that cognitive assessment prominently ranks among the top five domains evaluated in the geriatric assessment of older adults with cancer. In accordance with these results, the assessment of functional status and falls predominates among the frequently employed tools in geriatric assessment. Additionally, other tools were utilized, involving evaluations of weight loss, comorbidities, life expectancy, chemotherapy toxicity, mood, and noncancer mortality risk (Dale et al., 2021).

The observed increase in older cancer patients attending RT departments, acknowledged by the majority of respondents, aligns with published projections. Over the next two decades, Europe is predicted to witness a notable increase in the number of new cancer cases annually, reaching 4.5 million, with 65% and 50% of patients aged over 65 and 75, respectively. By 2050, the typical cancer patient in Europe is expected to be 70 years of age or older, reflecting the significant demographic change (Baumann et al., 2020).

Furthermore, most participants emphasized the critical need for further training in geriatric oncology. Comprehensive training is imperative for healthcare professionals, as it is crucial for them to recognize that chronological age inadequately predicts tolerance and outcomes in older adults with cancer, emphasizing the need for treatment decisions to reflect this understanding (Anita O'Donovan & Michelle Leech, 2020). Expanding on this imperative, Morris et al. contribute valuable insights by providing an extensive compilation of global educational courses and strategies tailored to meet the upcoming training needs (Lucinda Morris et al., 2017).

The authors would like to highlight that this study has several limitations. The number of respondents falls short of the minimum threshold of 139 required to achieve a 95% confidence level with a 5% margin of error. Another limitation of this study is the use of closed-ended questions, which limited participants' ability to elaborate on their responses. Including open-ended text boxes would have

provided valuable data. Nevertheless, this pilot study underscores the necessity for further training in geriatric oncology and the importance of having dedicated geriatricians working alongside RO.

Conclusion

Our study highlights the imperative for enhanced training in geriatric oncology among radiation oncology professionals, given the prevailing lack of awareness, limited geriatric training, and the need to recognize that chronological age poorly predicts tolerance and outcomes in older adults with cancer, emphasizing the necessity for treatment decisions to reflect this understanding.

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CHAPTER 7. PRELIMINARY EVALUATION OF THE VALIDATION PROCESS OF ONCO-MPI PROGNOSIS TOOL IN OLDER ADULTS WITH CANCER UNDERGOING RADIOTHERAPY IN PORTUGAL

Edna Darlene Rodrigues [1,2]; Catarina v .d. Elzen [3]; Alice Alves [3]; Maria José Moura [3]; Elisabete Soares [4]; Paulo Almeida [5] ; Escarlata López Ramírez [6]; Laetitia Teixeira [1,2]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal

[2] Center for Health Technology and Services Research-AgeingC / RISE – Health Research Network, Porto, Portugal

[3] Radiotherapy Department, Unidade Local de Saúde de São João, E.P.E, Porto, Portugal

[4] Radiotherapy Department, Instituto Português de Oncologia do Porto, Francisco Gentil, E.P.E, Porto, Portugal

[5] Internal Medicine Department, Unidade Local de Saúde de São João, Porto, Portugal

[6] Radiation Oncology Department, GenesisCare Andalucia, Malaga, Spain

Abstract

Introduction

Cancer management in older adults is complex, requiring tools like the Comprehensive Geriatric Assessment (CGA) to evaluate physical, cognitive, and psychosocial vulnerabilities. The Onco-Multidimensional Prognostic Index (Onco-MPI) uses various geriatric assessment domains to predict mortality risk in older cancer patients. It was This study aims to validate the Onco-MPI in the context of Radiotherapy (RT).

Methods

Data were collected from 227 older patients across two RT departments in Portugal. The inclusion criteria targeted individuals aged 70 or older who were diagnosed with cancer and undergoing RT treatment, whether for palliative or curative purposes. Variables included age, sex, BMI, ADL, IADL, ECOG performance status, MMSE, education level, caregiver information, comorbidities, medications, cancer stage, and treatment details. Statistical analyses, including Kaplan-Meier survival curves and ROC curves, were performed using IBM SPSS and MedCalc software.

Results

Among 227 patients, 88.5% received RT for curative purposes. Compared to the original cohort of 658, the validation group had a median age of 75 and no significant differences in age, BMI, ADL, ECOG, and CIRS-G scores, but had a lower median IADL score (5 vs. 8) and slightly fewer patients with MMSE <24 (11.5% vs. 18.09%). The validation cohort had fewer women (33.0% vs. 65.81%) and breast cancer cases (16.7% vs. 46.5%) but more prostate cancer cases (39.2% vs. 5.47%). The Onco-MPI tool demonstrated significant associations with 12-month survival, with an AUC of 0.785 for low-medium risk and 0.786 for medium-high risk groups, effectively stratifying 12-month survival rates (97% low-risk, 87% medium-risk, 59% high-risk).

Discussion

An association between Onco-MPI score and one-year survival was found. However, as these positive results are part of an ongoing validation process, they should be interpreted with caution as they are not definitive evidence of the predictive value of this prognosis tool.

Introduction

The decisions about cancer treatments for older adults are complex (Kravchenko et al., 2015). Also, age itself does not correlate with functional capacity, so in the absence of an individualized geriatric assessment (CGA), cancer treatments may be omitted in healthy older adults with cancer (Rogers et al., 2015). CGA aims to improve the understanding of functional capacity of each older adult, evaluate frailty and other impairments, but also, to implement prehabilitation interventions. Furthermore, CGA surpasses the guess of a very experienced physician based solely on age concerning functional status of an older adult with cancer (Tucci et al., 2009). Once completed, this evaluation allows healthcare providers to adapt the cancer treatment to the functional capacity and avoid the decision making based solely on age (Hurria, 2009). Efforts has been made to standardize CGA and create protocols of assessment that provide measurable outcomes. Piloto et al., developed the Multidimensional Prognostic Index (MPI), based on CGA of hospitalised older patients that allows to predict one-year mortality (Pilotto et al., 2008). The MPI can be a useful toll guiding clinical decisions and predicting 1-year mortality risk based on CGA domains. The relevance of MPI has been shown in several clinical contexts. The outcomes in patients with cancer, community acquired pneumonia and heart failure could be predicted based on MPI scores (Giantin et al., 2018; Pata et al., 2021; Pilotto et al., 2009; Pilotto et al., 2010). Also, based on predictive relevance of MPI, other authors have been developing and validating other MPI formats such as telephone-administered and self-administered versions (C. Custodero et al., 2021; Pilotto et al., 2019).

Considering MPI great potential to be a suitable tool for supporting decision-making in geriatric oncology, Brunello et al. developed the Oncology Multidimensional Prognostic Index (Onco-MPI). Similarly to MPI, Onco-MPI takes into consideration CGA domains to predict 1-year mortality risk in older adults with cancer. A total of 658 patients aged 70 years or over, with a confirmed diagnosis of cancer and who underwent CGA and attended the Geriatric Oncology Programme at the Istituto Oncologico Veneto in Padua, Italy, between September 2004 and June 2011, were included in the development and validation of Onco-MPI. Based on a multivariable Cox proportional hazard model of the CGA domains and cancer characteristics, the factors impacting 1-year mortality, and respective weights were defined. The patients included in the Onco-MPI development cohort were followed up every 3-6 months, with an average follow-up time of 2.5 years (Brunello et al., 2016).

Around half of all cancer cases may be recommended to performed Radiotherapy (RT) at some point of their cancer journey. RT is a local treatment that uses radiation to destroy cancer cells, aiming to target the tumour while avoiding the irradiation of surrounding healthy tissues. Considering the localized and precise nature of RT, this cancer treatment modality may be relevant for those patients that are considered ineligible to more invasive treatments or with contraindications for systemic treatment. For those patients, RT will not replace the benefits of other cancer modalities but will be able to contribute to QoL maintenance since it is able to control symptoms such as active haemorrhage and cancer related pain (Dohm et al., 2021).

However, Onco-MPI performance has not been extensively validated in the specific context of RT. The authors believe that the information provided by Onco-MPI may help physicians in their decision-making process regarding older cancer patients.

This study aimed to assess the reliability of Onco-MPI to predict 1-year mortality among older Portuguese cancer patients undergoing RT. In this paper, the authors present the interim results of this validation process.

Materials and Methods

Study Population and data collection

The inclusion criteria targeted individuals aged 70 or older who were diagnosed with cancer and undergoing RT treatment, whether for palliative or curative purposes. Patients were recruited using convenience sampling methods. This approach involved selecting participants based on their availability. Specifically, individuals were recruited between April 2022 and February 2023, from two RT departments, namely Unidade Local de São João (ULSJ) and Instituto Português de Oncologia do Porto (IPO-P), facilitating efficient data collection within the constraints of the study's resources and timeline. Ethical approval was obtained from the relevant hospital ethics committees (CES ULSJ 138-21, IPO-P CES 263/021). All patients provided informed consent prior to the in-person interviews, performed by the first author. This preliminary analysis includes findings from patients who have completed a 12-month follow-up period.

Onco-MPI

We collected variables to compute the Onco-MPI and additional variables to describe the context of data collection within RT departments.

Age, sex, body mass index (BMI), basic activities of daily living (ADL) (Katz et al., 1970), instrumental activities of daily living (IADL) (Lawton & Brody, 1969), Eastern Cooperative Oncology Group Performance Status (ECOG-PS))(Oken et al., 1982), Mini-Mental State Examination (MMSE) (Pfeiffer, 1975), education level and caregiver information were assessed during an in-person interview on one of the days the patient attended the department for RT. Considering the time gap between undergoing RT and diagnosis, and considering the prognostic nature of this tool, efforts were made to collect the status of patients either previously or at the time of diagnosis. For example, if a patient experienced weight loss during treatment, medical records were assessed to determine their normal weight before cancer treatment. Additionally, patients were directly asked if their performance status was better or worse before their cancer diagnosis. Number of severe comorbidities classified accordingly with Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (B. S. Linn et al., 1968), number of drugs, cancer stage (Amin et al., 2017), tumour location, RT intent, and previous/concomitant cancer treatments were extracted from electronic medical records. The time spent collecting data during interviews and from electronic medical records was recorded for each patient.

The information collected through in-person interviews took between 10 to 15 minutes, while the data extracted from electronic medical records required approximately 5 to 10 minutes. In total, the time dedicated to collecting all the necessary information to calculate the Onco-MPI was around 20 minutes.

Statistical analysis

The Onco-MPI was computed utilizing estimated domain weights, and its groups were determined following the method outlined by Brunello et al, presented in Table 7.1.

Table 7.1 – Onco-MPI domains and its weights, accordingly with the methods described by Brunello et al.

Variable	Reference Group/Value	Weight
Age (Continuous)	-	0.04730
Gender	Female (Reference)	0
	Male	0.01706
Body Mass Index (BMI) (Continuous)	-	-0.09782
Activities of Daily Living (ADL) (Continuous)	-	-0.07717
Instrumental Activities of Daily Living (IADL) (Continuous)	-	0.04983
ECOG Performance Status (Continuous)	-	0.70607
Number of Serious Comorbidities (CIRS) (Continuous)	-	-0.12960
Cancer Stage	Stage I (Reference)	0
	Stage II	1.11712
	Stage III	0.74957
	Stage IV	1.80828
Tumour Site	Other (Reference)	0
	Breast	-1.93081
	Colorectal	-1.03025
	Lung	0.36265
	Prostate	-1.57998
	Other Genitourinary Organs	0.19956
Mini Mental State Examination (MMSE) (Continuous)	-	-0.06270
Number of Medications (Continuous)	-	-0.01218
Caregiver	No Caregiver (Reference)	0
	Yes	0.21035

The Onco-MPI raw score is calculated by adding the products of the domain weights (Si) and their respective values (Di), according to the formula:

$$R = \sum (Si \times Di)$$

This raw score is then normalised using the formula:

$$\text{Normalised Onco-MPI} = \frac{R+2.371}{8.034}$$

The Onco-MPI score predicts one-year mortality in older cancer patients by categorizing them into three risk levels: low (0 - 0.46), moderate (0.47 - 0.63), and high (0.64 - 1.00) (Brunello et al., 2016).

A descriptive analysis of the validation cohort was conducted using IBM® SPSS® Statistics (version 27). This analysis included a comparison between the Brunello et al cohort (original) and the validation cohort (Brunello et al., 2016). Follow-up time was defined as the period from the interview until death from any cause or up to 12 months after the interview if the patient remained alive.

Kaplan-Meier survival curves were generated with IBM® SPSS® Statistics (version 27) to compare survival rates between the Brunello et al and validation cohorts. Overlapping survival curves were used to facilitate this comparison. Cox regression models were employed for univariate and multivariate analysis using IBM® SPSS® Statistics (version 27).

The area under the curve (AUC) from the receiver operating characteristic (ROC) curve was calculated to assess the diagnostic accuracy of the Onco-MPI, following the method described by DeLong et al., using MedCalc® software (version 23).

Results

Baseline characteristics of validation cohort

In our research, we examined a group of 227 patients from two RT departments at tertiary cancer centres in northern Portugal to evaluate the validation process of the Onco-MPI prognosis tool. Among them, 201 patients (88.5%) underwent RT with the aim of curing their cancer. Notably, 68 patients (30.0%) had previously undergone systemic treatment, while 110 patients (48.5%) were simultaneously receiving hormonal therapy. Additionally, 84 patients (37.0%) had a history of prior surgery. Most patients reported maintaining their functional status post-cancer diagnosis, with only 5.3% experiencing a decline and 7.9% reporting an improvement during cancer treatments.

The original cohort included 658 older cancer patients and revealed a median age of 77, with a majority female, having a range of functional and health metrics including comorbidities, performance status, and treatment details, with predominantly breast and colorectal cancer types. When comparing our validation group with the original cohort, as displayed on Table 7.2, no significant differences were found for age, BMI, ADL, ECOG, and CIRS-G percentages. The validation group had a median IADL score that was 3 points lower compared to the original group. Additionally, there was a 7% higher rate of patients scoring below 24 on the MMSE in the validation group. However, this difference in MMSE scores was reduced to 6% after accounting for variations in education level.

Table 7.2 - Comparison of demographic and clinical characteristics between the validation cohort (n=227) and the original cohort (n=658). This table displays median values and ranges for age, body mass index (BMI), and various health assessment measures, along with percentages for sex distribution, limitations in activities of daily living (ADL) and instrumental activities of daily living (IADL), cognitive impairment (MMSE), polypharmacy, caregiver presence, cancer treatment status, cancer location, and cancer stage.

		Validation cohort (n=227)	**Original cohort** (n= 658)
Age	median (min-max)	75 (70-92)	77 (70-96)
Sex	%		
females		33.0	65.81
males		67.0	34.19
BMI	median (min-max)	26.34 (17.28-38.57)	25.22 (15.5-47.5)
ADL	median (min-max)	6 (1-6)	6 (0-6)
ADL - 1 or more limitation	%	12.3	NA
IADL	median (min-max)	5 (0-8)	8 (0-8)
IADL - 1 or more limitation	%	41.0	NA
ECOG	median (min-max)	1 (0-3)	0 (0-4)
ECOG 0	%	39.2	NA
ECOG 1	%	46.7	NA
ECOG 2	%	12.3	NA
ECOG 3	%	1.8	NA
CIRS-G number of severe comorbidities	median (min-max)	1 (0-4)	0 (0-4)
0 CIRG-G severe comorbidities	%	48.0	NA
1 CIRG-G severe comorbidities	%	34.4	NA
2 CIRG-G severe comorbidities	%	15.0	NA
3 CIRG-G severe comorbidities	%	2.2	NA
4 CIRG-G severe comorbidities	%	0.4	NA
MMSE <24	%	11.5	18.09
Cognitive impartment -adjusted to education level	%	12.3	NA
Number of drugs	median (min-max)	5 (0-18)	3 (0-13)
Polypharmacy (≥5 drugs)	%	55.5	NA
Caregiver yes	%	10.1	70.67
Under cancer treatment	%	100	75.68
Cancer location			
Breast	%	16.7	46.5
Colorectal	%	1.8	21.28
Lung	%	11.9	6.38
Prostate	%	39.2	5.47
Other genitourinary	%	2.2	5.02
Other	%	28.2	15.35
Cancer stage			
I	%	16.7	36.39
II	%	32.2	21.88
III	%	32.6	18.39
IV	%	18.5	22.34

Approximately half of the participants in our validation cohort met the criteria for polypharmacy (defined as the use of 5 or more drugs) and had a higher median number of medications compared to the original cohort. Notably, the presence of caregivers was significantly lower in the validation cohort (10.1%) compared to the Brunello et al cohort (70.67%).

The validation cohort had fewer women (33.0%) and consequently fewer breast cancer cases (16.7% vs. 46.5%), with a shift towards more prostate cancer cases (39.2% vs. 5.47%) and fewer colorectal cancer cases (1.8% vs. 21.28%). There was also a difference in cancer stage distribution, with fewer stage I cases and more stage II and III cases in the validation cohort, while the proportion of stage IV cases remained similar.

Onco-MPI and 1-year survival

The 1 year-survival rates were 97% for the low-risk group, 87% for the medium-risk group, and 59% for the high-risk group. Correspondingly, 1-year mortality rates were 3% in the low-risk group, 13% in the medium-risk group, and 41% in the high-risk group, demonstrating the model's effectiveness in stratifying patients according to their 1-year survival probabilities, as illustrated on Figure 7.1.

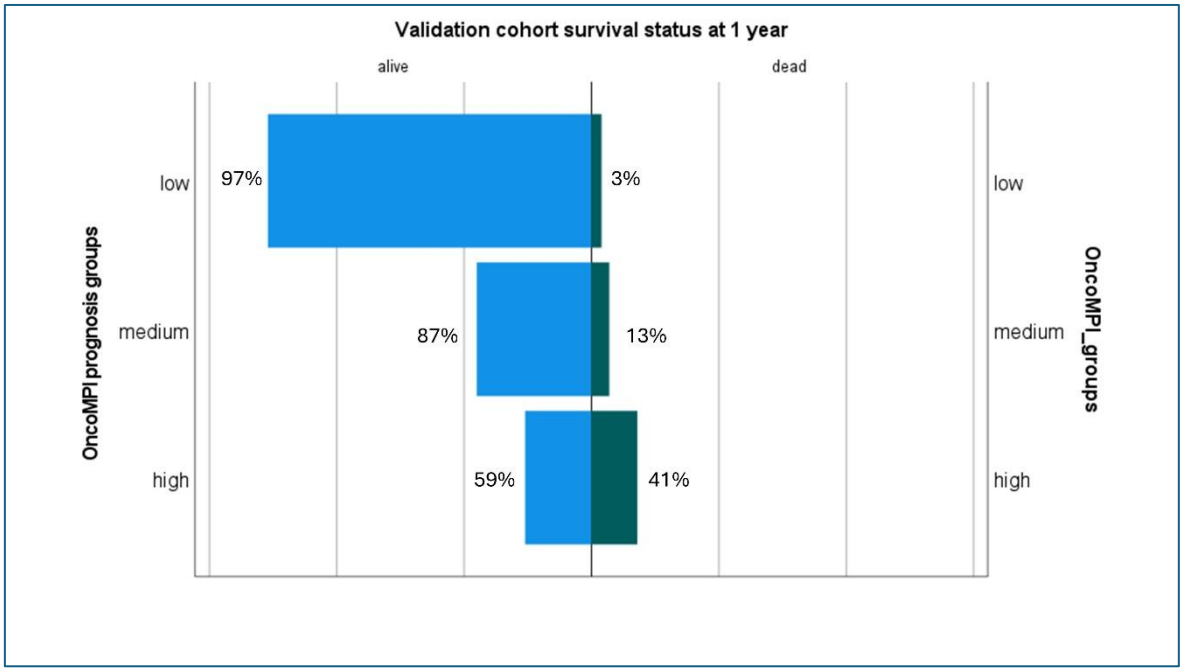


Figure 7.1. Illustrates the one-year survival status of patients in the validation cohort, categorized into low, medium, and high-risk groups based on the Onco-MPI prognostic model.

Our univariate analysis of 12-month survival rates in the validation cohort revealed significant associations between mortality and several factors including BMI, ADL, IADL, MMSE, cancer stage, ECOG, caregiver status, and tumour location (Table 7.3). Furthermore, survival curves comparison between validation and original cohorts showed higher survival rates for medium and high-risk Onco-MPI groups in the validation cohort.

Table 7.3 - Univariate and multivariate analysis - Hazard Ratios (HR) and Confidence Intervals (CI) for prognostic variables in the original and validation cohorts. This table presents the HR and 95% CI for various prognostic variables in both the original, accordingly with Brunello et al and validation cohorts (Brunello et al., 2016). Key factors analysed include age, sex, body mass index (BMI), functional status (ADL, IADL), comorbidities (CIRS), cognitive function (MMSE), number of drugs, performance status (ECOG), caregiver presence, tumour location, and cancer stage. Given the small number of colorectal cancer participants, these cases were classified as other for the purposes of this analysis.

		Univariate Analysis				**Multivariate Analysis**			
		Validation cohort		**Original cohort** (Brunello et al., 2016)		**Validation cohort**		**Original cohort** (Brunello et al., 2016)	
Variable	**Category**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age	Continuous	0.973 (0.893-1.060)	0.533	1.076 (1.039–1.114)	**<0.001**	0.948 (0.855-1.050)	0.335	1.040 (0.996–1.086)	0.075
Sex	Male versus female	0.619 (0.264-1.449)	0.269	2.084 (1.422–3.056)	**<0.001**	0.078 (0.006-0.985)	**0.049**	1.018 (0.647–1.600)	0.939
BMI	Continuous	0.857 (0.775-0.948)	**0.003**	0.870 (0.824–0.918)	**<0.001**	0.888 (0.786-1.004)	0.057	0.912 (0.859–0.968)	**0.002**
ADL	Continuous	0.542 (0.408-0.723)	**<0.001**	0.667 (0.582–0.764)	**<0.001**	0.496 (0.259-0.952)	**0.035**	0.920 (0.751–1.128)	0.423
IADL	Continuous	0.710 (0.563-0.895)	**0.004**	0.765 (0.709–0.825)	**<0.001**	1.724 (0.774-3.839)	0.182	1.008 (0.870–1.167)	0.92
No of severe comorbidities CIRS	Continuous	1.116 (0.731-1.704)	0.612	1.288 (0.985–1.685)	0.065	0.595 (0.338-1.047)	0.072	0.914 (0.749–1.114)	0.372
MMSE	<24 versus ≥24	3.435 (1.521-7.759)	**0.003**	1.913 (1.253–2.922)	**0.003**	2.558 (0.897-7.299)	0.079	0.971 (0.595–1.584)	0.906
ECOG	≥3 versus 0	7.165 (1.565-4.793)	**0.011**	6.184 (2.163–17.679)	**<0.001**	1.134 (0.448-2.869)	0.790	7.747 (1.744–34.411)	**0.007**
	2 versus 0	1.638 (0.560-4.793)	0.368	7.418 (4.223–13.031)	**<0.001**	0.781 (0.152-4.027)	0.752	3.827 (1.777–8.244)	**<0.001**
	1 versus 0	0.994 (0.429-2.300)	0.988	4.232 (2.658–6.738)	**<0.001**	2.476 (0.170-36.053)	0.507	3.122 (1.877–5.191)	**<0.001**
Number of drugs	Continuous	0.996 (0.899-1.104)	0.945	1.036 (0.960–1.117)	0.363	1.067 (0.917-1.241)	0.402	1.023 (0.923–1.133)	0.668
Caregiver	Yes versus no	3.227 (1.378-7.558)	**0.007**	1.603 (1.002–2.565)	**0.049**	0.428 (0.050-3.635)	0.428	1.193 (0.708–2.010)	0.508

Tumour location	Breast versus other	0.115 (0.015-0.871)	**0.036**	0.078 (0.038–0.157)	**<0.001**	0.241 (0.024-2.376)	0.241	0.164 (0.068–0.396)	**<0.001**
	Colorectal versus other	NA	NA	0.401 (0.234–0.685)	**<0.001**	NA	NA	0.379 (0.214–0.671)	**<0.001**
	Lung versus other	2.178 (0.989-4.799)	0.053	1.429 (0.815–2.506)	0.213	3.252 (1.308-8.082)	**0.011**	1.407 (0.767–2.579)	0.270
	Prostate versus other	0.049 (0.006-0.375)	**0.004**	0.335 (0.131–0.856)	**0.022**	0.041 (0.004-0.379)	**0.005**	0.209 (0.073–0.599)	**0.004**
	Other genitourinary versus other	2.035 (0.462-8.960)	0.348	1.372 (0.747–2.520)	0.308	2.912 (0.472-17.981)	0.250	1.260 (0.652–2.433)	0.492
Cancer stage	IV versus I	19.863 (2.641-149.405	**0.004**	17.089 (8.189–35.659)	**<0.001**	10.972 (1.219-98.753)	**0.033**	6.689 (2.950–15.166)	**<0.001**
	III versus I	3.713 (0.457-30.183)	0.220	4.555 (1.966–10.555)	**<0.001**	3.900 (0.427-35.602)	0.228	2.129 (0.854–5.306)	0.105
	II versus I	2.138 (0.239-19.129)	0.497	3.614 (1.546–8.443)	**0.003**	5.989 (0.541-66.356)	0.145	3.335 1.389–8.009)	**0.007**

Furthermore, survival curves comparison between validation and original cohorts showed higher survival rates for medium and high-risk Onco-MPI groups in the validation cohort, as illustrated in Figure 7.2.

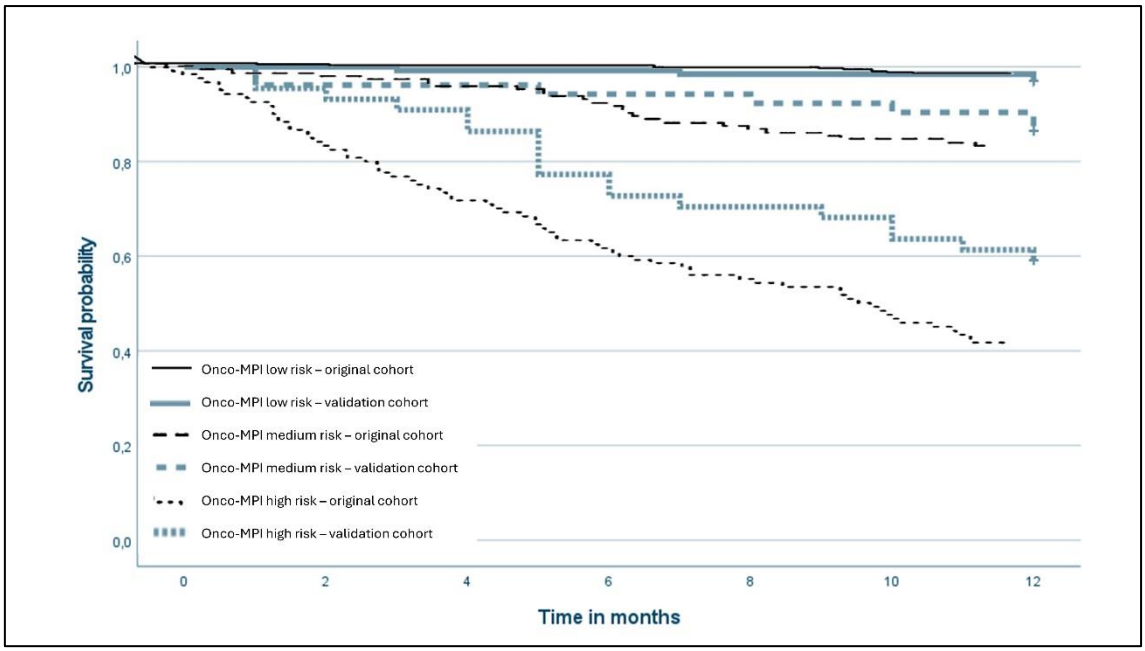


Figure 7.2 - Kaplan-Meier Survival Curves for Onco-MPI Prognosis Groups in Original and Validation Cohorts. This Kaplan-Meier plot compares the survival probabilities over 12 months for low, medium, and high-risk groups as classified by the Onco-MPI prognostic model in both the original and validation cohorts. The curves show consistently higher survival probabilities for the low-risk groups, with a sharp decline in survival for high-risk groups.

We evaluated the diagnostic precision of Onco-MPI using ROC curves, which showed an AUC of 0.785 ($p<0.001$) for distinguishing low and medium-risk groups (threshold 0.46) and 0.786 ($p<0.001$) for discriminating medium and high-risk groups (threshold 0.63). Sensitivities of 63.64% and 72.00%, and specificities of 73.84% and 63.38% were determined for the 0.46 and 0.63 thresholds, respectively, in the validation cohort.

Discussion

This study presents the preliminary evaluation of the Onco-MPI in a group of 227 older adults receiving RT at two cancer centres in Portugal. In comparison with the Brunello et al cohort, differences were found in demographics and clinical profiles for our validation cohort. A trend between Onco-MPI score and one-year survival was found. However, as these results are part of an ongoing validation process, they should be interpreted with caution as they are not definitive evidence of the predictive value of this prognosis tool.

One major difference between the original and our validation cohort is that we focused only patients receiving RT, while in the original cohort, only 75.68% of the patients received cancer treatment. Additionally, the original cohort was assessed under a Geriatric Oncology Program with a complete CGA, whereas our validation cohort was evaluated only by the geriatric domains listed in Onco-MPI. It is unclear whether these variations in patient selection and assessment may influence the Onco-MPI prognostic accuracy, so further evaluation is needed to understand its impact.

We found disparities in baseline patient characteristics between our cohort and the original model, specifically in primary tumour site distribution. This disparity likely reflects the differences between medical oncology and RT departments. The original cohort was assessed under a Geriatric Oncology Program, in close collaboration with medical oncology departments, which included a higher proportion of colorectal cancer patients. Specifically, for the colon cancer, RT is rarely recommended except for specific situations such metastasis ablation, being surgery and systemic treatment the preferred approach. In contrast, our cohort, with patient recruited in RT setting, showed a higher percentage of prostate cancer. RT has well-established role for this cancer, especially for older patients unsuitable for surgery (Barton et al., 2014). The performance of the Onco-MPI may be different due to these variations in patient population characteristics. Also, the application of this tool and the interpretation of its results should consider the RT-specific context.

In our preliminary cohort, older women with breast cancer represented only a small proportion. This lower percentage can be related with the emerging trend of omitting RT for older women with low-risk breast cancer. Despite RT being

often recommended for breast cancer, the number of older women with breast cancer undergoing RT has been declining in recent years according to American data, from around 80% in the early 2000s for those aged 70-80, to around 60% in recent years. This decline is motivated by the Cancer and Leukemia Group B (CALGB) 9343 study, which showed that adding radiation therapy to hormonal therapy after breast-conserving surgery in women aged 70 and older with early-stage, oestrogen receptor-positive breast cancer reduced locoregional recurrence but did not affect mastectomy rates, distant metastases, or overall survival (Hughes et al., 2013; Hughes et al., 2004).

It is important to compare community-dwelling cohorts with cancer-specific cohorts to understand whether the latter experience a higher burden of geriatric impairments. Community cohorts serve as a reference point for what might be expected in a "normal" ageing process, unaffected by the burden of cancer or its treatment. In terms of ADL impairment, our results showed that around 12% of our patients had one or more limitations in ADL. This rate aligns with previously published data on community-dwelling older adults in 17 European countries, which reported a rate of 14% (Jerez-Roig et al., 2018). In relation to polypharmacy, defined in our cohort is defined as the use of five or more medications, it was reported in 55.5% of our patients. These findings align with previous data from the AdHOC (Aged in Home Care) European project. This project reported a polypharmacy rate of 51%, defined as the use of six or more medications (Fialova & Onder, 2009).

This comparison between community cohorts with cancer-specific settings emphasizes that geriatrics impairments should not be over-attributed to cancer or its treatment.

Despite these differences between original and validation cohorts, our preliminary results present a satisfactory correlation between the Onco-MPI domains and one-year survival.

In our cohort, the AUC scores for Onco-MPI were 0.785 for distinguishing between low and medium-risk groups and 0.786 for discriminating between medium and high-risk groups. While statistically significant ($p<0.001$), these values fall just short of the 0.80 threshold typically considered indicative of very good discrimination. Compared to the general standards where an AUC above 0.90 is seen as excellent discrimination, the results for Onco-MPI indicate room

for improvement (Hanley & McNeil, 1982). These findings reflect the performance of Onco-MPI in this preliminary cohort, and further analysis is needed to confirm its predictive accuracy in a broader patient population.

Other authors, such as Shenoy et al., conducted a retrospective observational study to evaluate the performance of the Onco-MPI index in predicting mortality in older Indian patients with cancer. In comparison with our cohort, Shenoy et al included younger patient, with a median age of 68 years (range 60-90), a similar proportion of males (74.5%), lower median BMI (21.5 kg/m^2), higher percentage of patients with ECOG2/3 (41.4%), higher percentage of patients with MMSE<24 (20.7%), and a lower median number of drugs of 4 (range 0-17). Also, their cohort had a higher proportion of stage IV cancer (54.4%), lower cases of prostate cancer (7.5%), higher cases of lung cancer (40.1%), lower proportion of patients with CIRS-G severe comorbidities (29.8%). Regarding the comparison of the predictors of 1-year mortality, the multivariate analysis in their study agreed with our findings regarding the lower mortality risk for patients with higher BMI and prostate cancer. However, upon analysing the Kaplan Meier curves. their survival rates at 1 year were considerably lower across all Onco-MPI groups. This may be a consequence of their higher proportion of stage IV cancers and lung cancer patients (Shenoy et al., 2023).

Additionally, a study by Chiusole et al. on older patients (aged 70 and older) with advanced/metastatic soft tissue sarcoma found that the Onco-MPI is an effective predictor of survival. The Onco-MPI score was a strong predictor of one-year survival in both univariate and multivariate analyses. Patients in the high-risk group had significantly worse one-year survival compared to those in the intermediate-risk group. However, while the Onco-MPI score showed trends in survival outcomes in the univariate analysis, it did not remain significant in predicting overall survival when other factors were considered in the multivariate analysis (Chiusole et al., 2023).

The prognostic value of Comprehensive Geriatric Assessment (CGA) and Onco-MPI in 488 older patients with metastatic colorectal cancer (mCRC) in an outpatient setting was evaluated by Procaccio *et al*. Due to a lack of CGA-based guidelines for this patient group, treatment decisions were guided by oncologist expertise, patient preference, CGA results, and general guidelines. The CGA

classified 52% of patients as fit, 28% as vulnerable, and 20% as frail. Onco-MPI scores categorized 9% of patients as low-risk, 54% as intermediate-risk, and 37% as high-risk. Both CGA and Onco-MPI classifications significantly influenced treatment administration, with high-risk and frail patients receiving less chemotherapy ($p < 0.0001$). Chemotherapy improved overall survival (OS) across all risk groups. High-risk patients who received chemotherapy had a median OS of 15.9 months, compared to 11.2 months for those who did not. Low- and intermediate-risk patients were combined for analysis due to the small sample size of low-risk patients. For this combined group, median OS was 26.6 months with chemotherapy and 12.3 months without. Although high-risk patients primarily received monotherapy, their survival rates were comparable to the expected outcomes for older patients, suggesting effective use of CGA and Onco-MPI in treatment planning (Procaccio et al., 2022).

The data from Chiusole et al and Procaccio *et al* highlight that the stratification using Onco-MPI can help to identify patients at higher risk of mortality and assist into tailoring treatment decisions. Nonetheless there remains room for improvement in understanding the role of Onco-MPI in diverse clinical scenarios and determining the optimal approach to incorporating it into clinical decision-making.

As a preliminary evaluation, this study has several limitations. The smaller sample size (227 patients compared to 658 in the original cohort), affects the statistical power and may limit the interpretation of the results. Differences in baseline characteristics, such as having fewer women and more prostate cancer cases compared to the original cohort, may reduce the applicability of Onco-MPI tool to different patient groups. Furthermore, the absence of CGA framework may have affected the accuracy of risk stratification, as it relied solely on Onco-MPI domains, leaving other factors that might influence survival unmeasured. Finally, the study only focused at 12-month survival, so long-term outcomes were not assessed. These limitations highlight the role of expanding the validation cohort to provide additional information about the accuracy of Onco-MPI in predicting 1-year survival.

In conclusion, this study provides preliminary evidence supporting the utility of Onco-MPI in stratifying older adults undergoing RT into distinct risk groups based on survival outcomes. The authors highlight that these findings represent

an initial step in the validation process. If future expansions of the validation cohort corroborate the accuracy of this tool, it may allow for the for the adaptation of RT to individual patient characteristics rather than the avoidance of treatment. Future research should focus on refining the Onco-MPI to improve its predictive performance and better accommodate the diverse characteristics of various patient groups. Strengthening these aspects could enhance the Onco-MPI's role in clinical decision-making and personalized care in older cancer patients.

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CHAPTER 8. ASSESSING THE QUALITY OF LIFE DURING RADIOTHERAPY AND ONE YEAR AFTER IN PORTUGUESE OLDER CANCER PATIENTS

Edna Darlene Rodrigues [1,2]; Catarina v .d. Elzen [3]; Alice Alves [3]; Paulo Almeida [4] ; Escarlata López Ramírez [5]; Laetitia Teixeira [1,2]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal

[2] Center for Health Technology and Services Research-AgeingC / RISE – Health Research Network, Porto, Portugal

[3] Radiotherapy Department, Unidade Local de Saúde de São João, E.P.E, Porto, Portugal

[4] Internal Medicine Department, Unidade Local de Saúde de São João, Porto, Portugal

[5] Radiation Oncology Department, GenesisCare Andalucia, Malaga, Spain

Abstract

Purpose

The International Society of Geriatric Oncology (SIOG) states that Quality of Life (QoL) must be placed at the centre of the care of older adults with cancer. The aim of this study was to analyse changes in the QoL of older adults with cancer who were treated with radiotherapy (RT).

Methods

Patients aged 70 years and older who underwent RT were recruited from two Portuguese cancer centres. QoL was assessed using the EORTC QLQ-ELD14 tool. During RT, patients were interviewed in person within the first three weeks of RT. and follow-up interviews were conducted via telephone 1 year after the first evaluation. A change in QoL was considered clinically relevant if the difference between the two evaluation moments exceeded 10 points.

Results

QoL assessment during RT reveal that lower life purpose, mobility issues, and burden of illness were more frequently reported by women, or patients with ECOG PS 2/3, or those with higher dependence in activities of daily living (ADL), or patients with breast, lung, or other remaining cancers. Also, joint stiffness was higher among women, in overweighted and those with poorer ECOG status; no differences in future worries or family support were noted.

Regarding QoL outcomes at one year after, sub-group analyses showed that women experienced greater significant deterioration in joint stiffness, burden of illness, and concerns about others. Likewise, patients with instrumental ADL impairment experienced more mobility issues and worries about others.

Conclusion

Overall, QoL in older patients who underwent RT is inherently complex and influenced by multiple factors. Our findings, along with recent evidence, indicate that a tailored QoL assessment that considers individual patient profiles, treatment contexts, and frailty might be necessary for capturing the nuanced experiences of each patient.

Introduction

In the domain of geriatric oncology, we must ensure that decisions are concordant with the values and preferences of older adults with cancer, which in turn requires a careful assessment and clarification of their Quality of Life (QoL). QoL is a multifactorial concept that involves the domains of physical health, cognitive status, independence, and social relationships. Older people with cancer perceive these domains as crucially important to their general wellbeing and their satisfaction with life (Florian et al., 2018). Unfortunately, most clinical trials for patients with cancer rely on traditional clinical endpoints such as tumour control rate, overall survival, or disease-free survival (Yucel et al., 2014).

Furthermore, there is clear evidence that younger and older cancer patients might have different priorities for QoL and survival (Wedding et al., 2007). Rationally, assessing QoL in geriatric oncology is complex because of differences across the cancer trajectory (Matelot et al., 2021).

The International Society of Geriatric Oncology (SIOG) working group published that QoL must be a core component of all aspects of care for the older cancer patient and that treatment decisions should not be made solely based on age. Instead, these decisions should focus on individual needs and utilising QoL tools such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and ELD-14 in conjunction with comprehensive geriatric assessment. Regular QoL assessments must be performed with the input of a multidisciplinary team (Scotte et al., 2018).

The EORTC established 70 years old to be the cut-off age for ‘older patients’ and developed the EORTC QLQ-ELD14 questionnaire to ‘measure health-related QoL in older patients’ with cancer. The EORTC QLQ-ELD14 questionnaire, aims to “assess the ability of the older adults to cope with cancer, and the way the disease may affect them” (Wheelwright et al., 2013).

While radiotherapy (RT) can provide curative effects which will improve the QoL of older adults with cancer, the side effects of RT can impair QoL. Therefore, it is necessary to investigate the effect of RT on the QoL of this group of patients objectively. The aim of this study is to analyse changes in the QoL of older adults with cancer treated with RT.

Methods

Study Population and data collection

This study took place at two Portuguese cancer centres. Approval from the two hospital ethics committees has been granted (CES IPO-P 263/021, CES CHSJ 138-21). All patients had given informed consent in writing before the in-person interviews. Data collection started in April 2022 and ended in April 2024.

Timeline for QoL assessment

Patients were evaluated at two different times. The first evaluation occurred during RT, within the first three weeks of treatment, and the second evaluation took place one year after the first.

Sample

One-hundred and ninety-nine patients were recruited by convenience sampling. Patients who received RT during the recruitment period were invited to participate in the study. The inclusion criteria were age 70 or older, curative or palliative treatment. Exclusion criteria was presence of cognitive impairment.

Cognitive function assessment

All the recruited participants completed a brief cognitive function assessment by Folstein's Mini-Mental State Examination (MMSE) (Pfeiffer, 1975). The number of years of education was asked and MMSE cut-off for cognitive impairment was defined as follows; 15 or less, 22 or less, and 27 or less for those with no education, with 1 to 11 years, and more than 11 years in education, respectively. Only those without cognitive impairment were qualified for QoL assessment.

Procedure

In-person interviews were conducted with consenting patients by the same investigator in a private room. If a patient so desired, a friend or family member could be present during the interview. The questionnaire was administered in person on a day that the patient was scheduled to visit the RT department for treatment. Patient's survival status was checked the next year around the time of first QoL assessment. If the patient was still alive, a phone call was made for an explanation of the purpose of the contact and administration of the EORTC QLQ-ELD14 over the phone.

QoL assessment was part of an integrated geriatric assessment protocol. Age, sex, body mass index (BMI), basic activities of daily living (ADL) (Katz et al., 1970), instrumental activities of daily living (IADL) (Lawton & Brody, 1969), Eastern Cooperative Oncology Group performance status (ECOG-PS) (Oken et al., 1982), MMSE, education level, and information about caregivers were evaluated in-person. Number of severe comorbidities as defined by Cumulative Illness Rating Scale-Geriatric (CIRS-G) (B. S. Linn et al., 1968), number of drugs, cancer stage (Amin et al., 2017), tumour location, RT intent, and previous/concomitant cancer treatments were extracted from electronic medical records.

QoL assessment

QoL was measured with the EORTC QLQ-ELD14, developed by the EORTC Quality of Life Group to measure the QoL of older cancer patients. The EORTC QLQ-ELD14 module contains 14 items with four response levels, including age-specific scales related to each item such as mobility, joint stiffness, family support, worries about others and worries about the future, maintenance of purpose, and burden of illness. For questions evaluating symptoms, higher scores indicate worse mobility and more joint stiffness, higher worries about others or the future, and higher burden of illness. On the other hand, for questions focusing on functional domains, a lower score reflects lower family support and purpose (Wheelwright et al., 2013). This module was already validated to the Portuguese population by Cipriano et al (Cipriano et al., 2021).

The Figure 8.1 outlines the inclusion and exclusion of participants during QoL evaluation of older adults with cancer receiving RT.

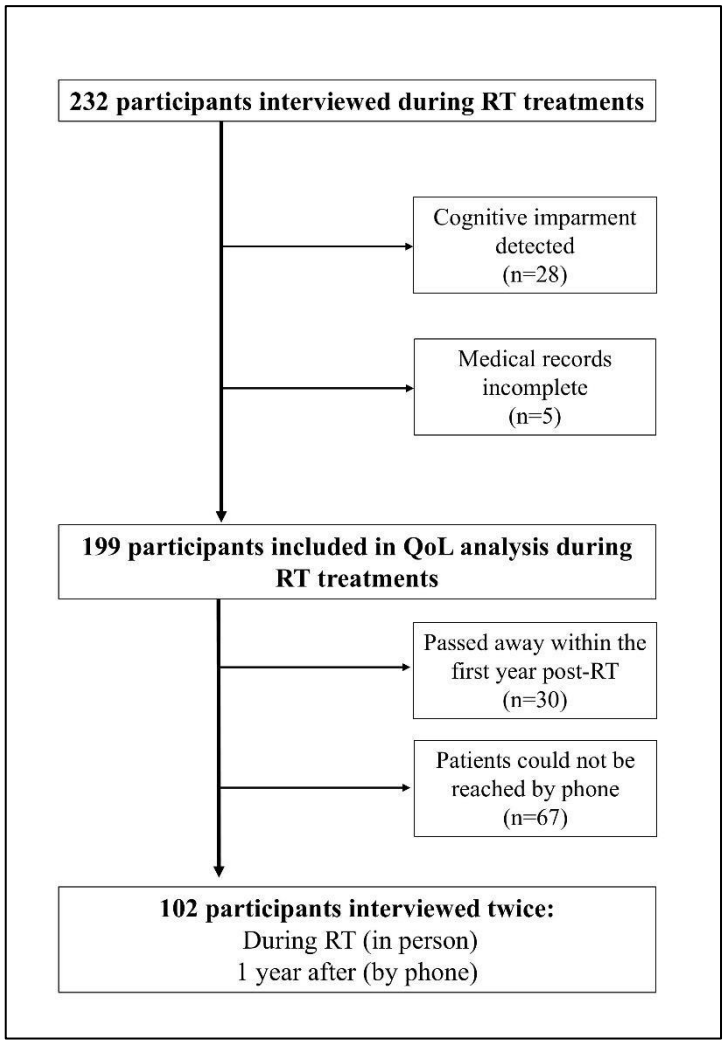


Figure 8.1 - Flowchart of participant inclusion and exclusion for the Quality of Life (QoL) assessment in older patients undergoing radiotherapy (RT). In total, 232 patients were interviewed during RT treatments, 28 participants were excluded because of cognitive impairment, and 5 due to missing medical records. So, in total, 199 participants were included for the evaluation of QoL during RT treatments; at the end of analysis, 30 passed away during the first year after, and 67 were lost for follow-up because the team could not reach them by phone. The final number of participants includes 102 who were interviewed twice: once during RT (in person), and one year after (by phone).

Statistical analysis

The QoL domain scores were converted into raw score, dichotomous variable, and linear transformation, according to the EORTC QLQ-ELD14 manual. The dichotomous variable was defined as “not at all” and “a little” vs. “quite a bit” and “very much”. Moderate to severe functional problems and symptoms were the ones scored as ‘quite a bit’ and ‘very much’) (Wheelwright et al., 2013).

QoL during RT

A descriptive analysis and search for an association between moderate to severe functional problems and symptoms during RT and sociodemographic/health variables was made for the 199 patients. Chi-square (χ^2) test and Fisher-test were used.

QoL comparison between during RT and 1 year after

For those 102 patients that were interviewed twice, a box plot analysis of the QoL linear transformation trends recorded between two different time points have been performed - during RT and one year after.

Paired sample t-test was used, for comparing the means of QoL linear transformation domains during RT and 1 year after.

To study the changes in the prevalence, moderate to severe functional problems and symptoms (scored as 'quite a bit' and 'very much') during RT compared with one-year post-RT, the prevalence of moderate to severe problem or symptom score was described using percentages and Wilcoxon-test for each problem or symptom were performed. A difference of ≥10 points on the linear transformation scale was considered as clinically significant (Osoba et al., 1998); the patients were stratified into two groups based on clinically significant difference in QoL between during RT and one year after as follow: those who had clinically significant deterioration in QoL and other patients. Their frequencies were compared between subgroups using Chi-square (χ^2) test: age groups, sex, school years, BMI, caregiver, ADL, IADL, two or more CIRS-G grade 3 or 4 comorbidities, polypharmacy (≥5 drugs), tumour locations, RT intent, previous or concomitant chemotherapy, previous surgery and concomitant hormonal therapy. All analyses were performed using IBM® SPSS® Statistics version 27 and p-values were considered statistically significant at less than 0.05.

Results

For QoL evaluation, 199 and 102 older adults were included during RT and 1-year after, respectively. Among patients interviewed only during RT, the majority were male (67.8%), with most aged between 70-84 years (46.7%), a higher proportion had prostate cancer (35.2%), and 60.8% were independent in IADL. In the group interviewed twice, a larger percentage were female (45.1%), most were similarly aged 70-84 years (46.1%), there was a greater representation of breast cancer patients (26.5%), and a higher proportion were independent in IADL (83.3%). Patients' characteristics are presented on Supplementary Table S8.1, along with the comparison of both groups. In general, both groups presented similar characteristics. The only difference presented was related to the percentage of females, that was higher for patients interviewed twice (32.2% vs 45.1%), and some variability in tumour's location was noticed, especially concerning breast cancer (17.1% vs 26.5%).

QoL during RT

Table S8.2 and S8.3 in the supplementary data summarize the distribution of patients in different categories regarding sex, age group, body mass index, ECOG performance status, caregiver, location of tumour in terms of maintaining purpose, family support, mobility, worries about others, worries about future, burden of illness and joint stiffness. Life purpose was reported lower for those with ECOG PS 2 (p=0.002),women (p=0.014), with ADL dependence (p=0.031), with IADL dependence (p=0.005), and breast, lung or other remaining cancers (p=0.002). Mobility problems were more frequent reported as moderate to severe in those older adults with IADL dependence (p<0.001). with ECOG PS 2-3 (p<0.001), that needed a caregiver (p=0.006). Worries about others were more frequently reported as moderate to severe in women (p=0.008). Burden of illness was reported moderate to severe for the following: women (p=0.007). ECOG PS 2-3 (p=0.004) caregiver needed (p=0.009), older persons with IADL dependence (p<0.001), lung or gynaecological cancer (p<0.001). Joint stiffness was reported as moderate to severe by women (p<0.001), overweight (p=0.002), ECOG PS 2-3 (p<0.001). No sub-group differences regarding future worries and family support were found.

QoL comparison between during RT and 1 year after

Figure 8.2 illustrates how the linear scores of QoL were distributed at two-time points; during RT and 1 year later. For the functional domains, the figure was quite

similar between the two timepoints for the family support. However, for the maintaining purpose, the range was wider and higher 1 year after in comparison with the baseline timepoint. For the symptoms/problems domains, only future worries kept a similar pattern at baseline and 1 year after. For the burden of illness and worries about others, a lower median was found 1 year after. On the other hand, for joint stiffness a pattern of decline in QoL appeared because the number of persons with lower score at baseline decreased 1 year after.

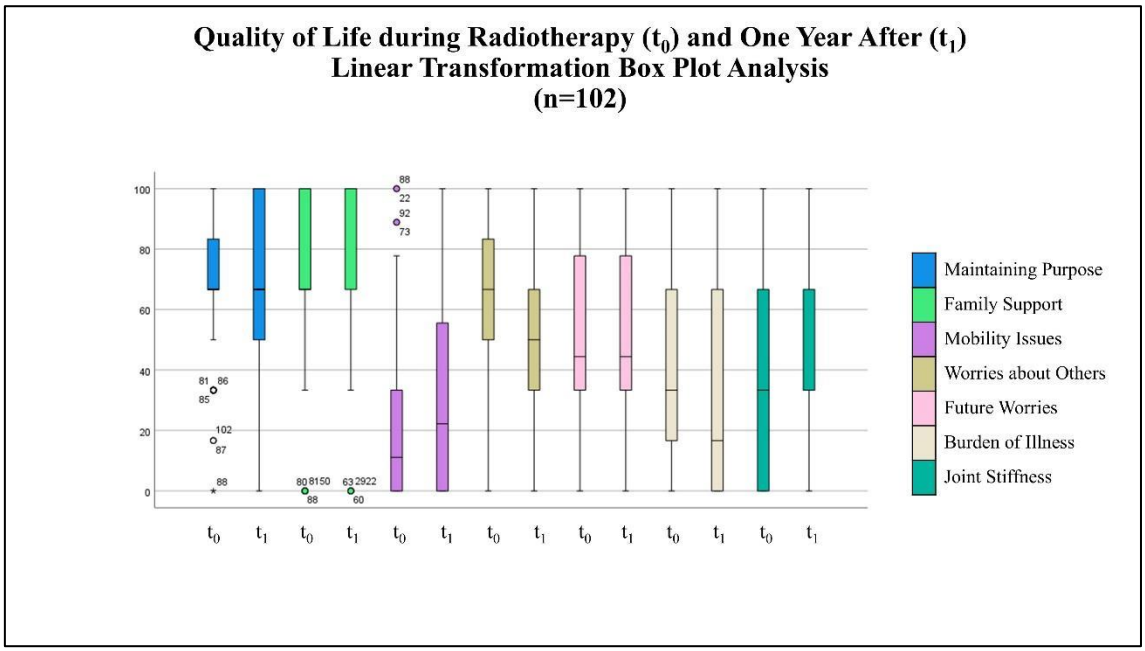


Figure 8.2 - Quality of Life During Radiotherapy and One Year After. The box plot illustrates how several quality-of-life factors have changed for patients who have been subjected to radiotherapy at a t0 (during radiotherapy) and at another time point t1 (one year after). The medians of most factors have changed slightly during the one-year treatment period. There were some improvements in mobility and reductions in worries about others. On the other hand, joint stiffness had increased.

A statistically difference was found between mean linear QoL scores during RT and one-year after for joint stiffness, with a higher mean score one year after ($p = 0.017$); for burden of illness, with a lower mean score one year after ($p = 0.014$); and for worries about others, with lower mean score one year after ($p = 0.003$). No differences were found for family support, purpose, future worries, or mobility.

Table 8.1 shows the differences in prevalence of moderate to severe functional problems and symptoms during RT and one-year post-treatment. Worries about others were significantly lower one year after ($p=0.002$). No statistically significant differences noted for the remaining QoL domains. However, there was a trend towards increased prevalence of i) reduced life purpose, ii) mobility problems, iii)

joint stiffness, iv) future worries. At the same time, there was a trend to decreased prevalence of i) perception of lower family support, and ii) greater burden of illness.

Table 8.1 - Prevalence of moderate to severe functional problems and symptoms during radiotherapy and one-year post-treatment. The table shows the changes in moderate to severe functional problems and symptoms during RT and one year after treatment in older adults with cancer undergoing RT. The number and percentage of patients having this problem or symptom during RT and one year after the end of RT, and a trendline indicating whether the problem increased (↑) or decreased (↓) after, along with the p-value, are presented.

	Moderate to severe problems or symptoms					
	During RT		1-year after			
	n	%	n	%	Trendline	p - value
Functional problems						
Lower life purpose	25	24.5%	31	30.4%	↑	0.343
Perception of reduced family support	21	20.6%	16	15.7%	↓	0.369
Symptom items						
Mobility difficulties	10	9.8%	17	16.7%	↑	0.144
High level of worries about others	61	59.8%	40	39.2%	↓	**0.002**
High level of Future Worries	38	37.3%	39	38.2%	↑	0.893
Greater Burden of Illness	33	32.4%	29	28.4%	↓	0.537
Joint Stiffness impacting QoL	31	30.4%	42	41.2%	↑	0.116

Table 8.2 - Significant deterioration in Quality of Life (QoL) Among Older Patients who performed Radiotherapy: Functional and Symptom Item Analysis. This table presents the results of a study investigating the deterioration in Quality of Life (QoL) among older patients who undergone radiotherapy, characterized by more than a 10% deterioration in linear transformation scores of EORTC QLQ-ELD14 module within the 1-year follow-up. The table compares functional problems and symptom items across different demographic and health-related variables using crosstabs and Chi-square (χ^2)

	Significative deterioration (difference of ≥10 points on the linear transformation scale)																				
	Functional problems						Symptom items														
	Maintaining Purpose			Family support			Mobility			Joint Stiffness			Worries about others			Future Worries			Burden of Illness		
	n	%	p	n	%	p	n	%	p	n	%	p	n	%	p	n	%	p	n	%	p
Age																					
70-74	20	40%	0.42	15	30%	0.189	13	26%	0.431	13	26%	0.557	27	54%	0.41	24	48%	0.596	28	56%	0.322
75-84	15	32%		11	23%		18	38%		13	28%		23	49%		22	47%		24	51%	
85+	3	60%		3	60%		2	40%		0	0%		1	20%		1	20%		1	20%	
Sex																					
female	15	33%	0.5	11	24%	0.486	20	43%	0.05	18	39%	**0.008**	34	74%	**<0.001**	22	48%	0.358	30	65%	**0.026**
male	23	41%		18	32%		13	23%		8	14%		17	30%		23	41%		23	41%	
School years																					
none	0	0%	0.541	0	0%	0.56	0	0%	0.101	0	0%	0.818	0	0%	0.786	0	0%	0.887	1	100%	0.422
1 to 11	34	40%		23	27%		31	36%		23	27%		42	49%		39	46%		42	49%	
≥12	4	25%		6	38%		2	13%		3	19%		9	56%		8	50%		10	63%	
BMI		0%																			
Underweight: <22	4	31%	0.688	2	15%	0.494	3	23%	0.258	3	23%	0.778	7	54%	**0.023**	8	62%	0.483	7	54%	0.179
Normal: 22-27	17	43%		13	33%		10	25%		9	23%		14	35%		17	43%		16	40%	
Overweight: >27	16	36%		13	29%		18	40%		13	29%		29	64%		22	49%		27	60%	
ECOG																					
Fully active	17	53%	0.106	14	44%	**0.021**	7	22%	**0.027**	4	13%	0.062	15	47%	0.918	12	38%	0.485	13	41%	0.312
Restricted in physically strenuous activity	17	29%		11	19%		18	31%		18	31%		29	50%		30	52%		32	55%	
Ambulatory and capable of all selfcare	4	36%		3	27%		7	64%		3	27%		6	55%		5	45%		7	64%	
Capable of only limited selfcare	0	0%		1	100%		1	100%		1	100%		1	100%		0	0%		1	100%	

tests. Statistical significance is indicated by p-values, with p<0.05 considered significant.

Caregiver needed																				
no	34	37%	1	25	27%	0.503	28	31%	0.328	24	26%	0.725	45	49%	1	45	49%	0.1	49	54%	0.437
yes	4	36%		4	36%		5	45%		2	18%		6	55%		2	18%		4	36%	

ADL																				
Total dependence	0	0%	0.898	0	0%	1	0	0%	0.784	0	0%	0.369	0	0%	0.673	0	0%	0.529	0	0%	0.898
Extensive assistance	0	0%		0	0%		0	0%		0	0%		0	0%		0	0%		0	0%	
Limited assistance	1	25%		1	33%		1	25%		2	50%		3	75%		1	25%		2	50%	
Needs minimal help	4	44%		2	22%		4	44%		3	33%		5	56%		3	33%		4	44%	
Independent	33	37%		26	29%		28	31%		21	24%		43	48%		43	48%		47	53%	
IADL		0%																		
Total dependence	0	0%	0.270	0	0%	1	0	0%	**0.042**	0	0%	0.649	0	0%	1	0	0%	0.027	0	0%	0.924
Extensive assistance	0	0%		0	0%		0	0%		0	0%		0	0%		0	0%		0	0%	
Limited assistance	2	29%		2	29%		4	57%		2	29%		4	57%		0	0%		3	43%	
Needs minimal help	6	60%		3	30%		6	60%		1	10%		5	50%		3	30%		5	50%	
Independent	30	35%		24	28%		23	27%		23	27%		42	49%		41	48%		45	0%	

CIRS moderate/severe ≥2																				
no	35	42%	0.085	25	30%	0.722	27	32%	1	20	24%	0.389	43	51%	0.795	36	43%	0.250	45	54%	0.657
yes	3	17%		4	22%		6	33%		6	33%		8	44%		11	61%		8	44%	
Polypharmacy																				
no	19	30%	0.066	15	23%	0.221	25	39%	0.097	18	28%	0.577	35	55%	0.306	32	50%	0.409	40	63%	**0.010**
yes	19	50%		14	37%		8	21%		8	21%		16	42%		15	39%		13	34%	

Cancer site																			
Breast	8	30%		8	30%		11	41%		11	41%		18	67%		13	48%		16	59%	
CNS	1	50%		1	50%		1	50%		1	50%		0	0%		1	50%		1	50%	
GI	2	50%		1	25%		0	0%		1	25%		2	50%		2	50%		2	50%	
GU	14	45%	0.72	10	32%	0.996	7	23%	0.349	5	16%	0.283	8	26%	0.003	11	35%	0.885	11	35%	0.663
GYN	4	44%		2	22%		4	44%		2	22%		8	89%		5	56%		5	56%	
Haem	2	33%		1	17%		2	33%		3	50%		2	33%		2	33%		3	50%	
HN	2	17%		3	25%		5	42%		2	17%		6	50%		6	50%		8	67%	
Lung	4	50%		2	25%		1	13%		1	13%		4	50%		5	63%		5	63%	
Skin/sof tissue	1	33%		1	33%		2	67%		0	0%		3	100%		2	67%		2	67%	
RT intent																					
curative	37	39%	0.252	27	29%	1	30	32%	0.711	22	23%	0.198	45	48%	0.269	43	46%	1	46	49%	0.061
palliative	1	13%		2	25%		3	38%		4	50%		6	75%		4	50%		7	88%	
Previous or concurrent QT																					
no	23	34%	0.529	19	28%	1	24	36%	0.416	17	25%	1	30	45%	0.211	33	49%	0.496	32	48%	0.334
yes	15	43%		10	29%		9	26%		9	26%		21	60%		14	40%		21	60%	
Concurrent HT																					
no	21	38%	1	14	25%	0.531	18	32%	1	13	23%	0.724	29	52%	0.842	27	48%	0.781	31	55%	0.577
yes	17	37%		15	33%		15	33%		13	28%		22	48%		20	43%		22	48%	
Previous Surgery																					
no	21	36%	0.842	13	22%	0.146	16	27%	0.267	11	19%	0.103	26	44%	0.229	27	46%	1	30	51%	0.95
yes	17	40%		13	30%		17	40%		15	35%		25	58%		20	47%		23	53%	

Details of sub-group analyses of clinically significant QoL deterioration (difference of ≥10 points on the linear transformation scale) are presented in Table 8.2. Several QoL domains presented a clinically significant deterioration for women. Women reported significantly more stiffness of joints than men ($p = 0.01$). There were more worries about others reported by women than by men ($p < 0.001$), as well as significantly higher burden of illness for women ($p = 0.03$). People with higher BMI-based categories had significantly more worries about others than people with lower BMI ($p = 0.02$).

Patients with better ECOG PS reported greater family support ($p = 0.02$) and experienced less mobility deterioration ($p = 0.03$) than those with poorer performance statuses. Patients with dependence in their IADL status reported higher mobility deterioration ($p = 0.04$) and worries about others ($p = 0.03$). No significant differences were found for other variables.

Discussion

A total of 199 older adults with cancer completed the QoL assessment during RT, and 102 patients were assessed one year after treatment. One year later, despite the absence of statistically significant differences regarding the prevalence of moderate to severe problems/symptoms, some trends emerged. There was a trend towards increased prevalence of i) reduced life purpose, ii) mobility problems, iii) joint stiffness, and iv) future worries. At the same time, there was a trend towards decreased prevalence of i) lower perception of family support, ii) high levels of worry about others, and iii) greater burden of illness. Focusing on the clinically significant QoL deterioration, our results show that women reported significantly more stiffness of joints, worries about others, and burden of illness than men. Also, patients with dependence in their IADL status reported higher mobility deterioration and worries about others.

For this study, we included a heterogenous group of older adults, with different diagnosis and treatments, with RT being the common treatment among them. The QoL outcomes showed diverse profiles of the patient's QoL over time, indicating that the extent of the QoL's impact can depend on the type of cancer and the different cancer treatment modalities.

Undoubtedly, the concept of QoL for older cancer patients is not a simple, Seghers et al studied this topic in people aged 70 and older, who had been diagnosed with cancer within the previous two years. Their findings revealed that QoL for older people with cancer is largely perceived in terms of physical functioning, health and social interactions, with social functioning being one of the main components of what makes life worth living (Seghers et al., 2022). Additionally, results from Matelot et al, report that determinants of QoL for older people with cancer not only reflect health-related issues, but also social relationships, autonomy, and financial security. This demonstrates how what constitutes QoL can vary considerably from one person to another (Matelot et al., 2021).

Our results regarding QoL during RT revealed that lower life purpose, mobility issues, and burden of illness were more frequently reported by females, or those who had ECOG PS 2/3, or higher dependence in ADL and IADL, or breast/lung/other remaining cancers. Also, joint stiffness was higher in women, higher BMI and in patients with poorer ECOG status.

A few studies have investigated changes in QoL during RT. One study investigated older women with breast cancer receiving RT, using EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. The study found statistically significant differences between the start and the end of RT in the following domains: breast symptoms, future perspective, sexual functioning, pain, fatigue, and physical health (Arraras et al., 2016). Another study evaluated QoL in adults aged 80 years and older with various cancer types (lung, gastrointestinal, breast, head and neck, and gynaecological cancers). The EORTC QLQ-C30 and EORTC QLQ-ELD14 questionnaires were used. No statistically significant changes of QoL were found between the start and completion of RT in all domains (Kaufmann et al., 2015).

Regarding QoL outcomes at 1 year after, we would like to highlight that sub-group analyses showed that women experienced greater significative deterioration in several QoL domains at 1 year follow-up, including joint stiffness, illness burden, and concerns about others. Also, patients with IADL impairment experienced more mobility issues and worries about others.

Published data on the QoL of older adults evaluated one year after are mixed. The EORTC QLQ-ELD14 was used by Aghdam et al to measure QoL in prostate cancer patients aged 70 and older with localised disease who had been treated with stereotactic body radiotherapy (SBRT). There did not appear to be any substantial changes in the QoL burden of disease or treatment over 12 months, but there were minor fluctuations, with burden peaking at one-month post-treatment and lowest at three months (Aghdam et al., 2019).

In a second study, the authors evaluated QoL in older adults aged 80 and older with a range of solid tumours, using the EORTC QLQ-ELD14. The results pointed to a clinically meaningful deterioration in family support, burden of illness and worry about the future from the beginning of RT to six months later (Kaufmann et al., 2015).

Furthermore, there is published data that compares QoL patterns between younger and older adults that underwent RT. Berg et al evaluated QoL of 311 head and neck cancer patients, most of whom (85%) received a RT, using the EORTC QLQ-C30, EORTC QLQ-H&N35, and EORTC QLQ-ELD14 questionnaires. Of these, 105 were aged 70 or older. In general, younger patients generally reported better physical function, while older patients showed better emotional function and less pain. Older patients also faced significant challenges related to mobility and joint

stiffness but had fewer issues with symptoms like nausea and appetite loss. However, the analysis of EORTC QLQ-ELD14 results revealed that older patients overall had worse mobility at baseline and at 12 months, reported more worries about others, and about their future at certain points in time. Older patients reported greater stiffness of joints, particularly after 12 months. Of particular interest, at 12 months, younger patients also did better than older ones on the questionnaire item 'maintaining purpose' (Berg et al., 2022).

Additionally, data pooled from 25 different EORTC randomised controlled trials were analysed using the EORTC QLQ-C30 mean scores, to assess how a cancer diagnosis impacted QoL. Baseline QoL data were available for 6,106 cancer patients. Using regression models, with age treated as a categorical variable, older adults (>70 years old) with cancer reported significantly worse QoL in physical and cognitive functioning, as well in constipation. In contrast, they reported significantly better QoL in social and role functioning, emotional functioning, and experienced fewer issues with insomnia and financial problems when compared with younger patients (Chantal et al., 2015).

The evaluation of QoL in older adults with cancer is further complicated by the ageing itself – with its increased prevalence of comorbidities, frailty and other geriatric syndromes – which further influences QoL (Matelot et al., 2021).

Therefore, the relation between frailty risk and QoL was explored by Kinoshita et al.. QoL was measured using the EORTC QLQ-ELD14 in 827 older adults aged 70 and above with cancer. They were also assessed using the G8 frailty screening tool, and an abnormal G8 score indicated potential problems such as frailty, malnutrition and other health issues. A significant association was observed between an abnormal G8 score and lower values of the three QoL domains: mobility, concerns about the future, and burden of illness. Moreover, QoL was significantly affected by an abnormal G8 score in relation to the joint stiffness. There was a significant effect of abnormal G8 score on the sense of maintaining purpose, but no relevant impact on the family support (Kinoshita et al., 2023).

Despite our findings, combined with recent evidence, highlight the importance of evaluating QoL of older adults who underwent RT, our study has several limitations.

One of our study limitations is the use of convenience sampling for our patient recruitment and data collection. As we recruited our cohort from a group of patients over the age of 70 undergoing RT, they do not represent a broader

population of older cancer patients who perhaps do not receive RT or who may be cognitively compromised and unable to participate in our study due to other factors. Furthermore, variability in the data collection is another limitation as we obtained data from in-person interviews during RT and follow-ups conducted by phone. In addition, due to the dropout rate of patients (30 dead and 67 lost to follow-up), this limits the interpretation of our findings.

Overall, QoL in older patients who underwent RT is inherently complex and influenced by multiple factors. Our findings, along with recent evidence, indicate that a tailored QoL assessment that considers individual patient profiles, treatment contexts, and frailty might be necessary for capturing the nuanced experiences of each patient.

The authors would like to highlight that healthcare professionals should carefully evaluate the potential QoL domains impacted one year after, such as those identified in our study—namely, reduced life purpose, mobility problems, joint stiffness, and future worries—to prevent or reduce them by implementing preventive measures or actively addressing them with targeted solutions or treatments.

Table S8.1. Comparison of Patient Characteristics at Initial and Follow-up Interviews. The table illustrates the distribution of patient characteristics in two interview different times: during radiotherapy (RT) and one year after. The information is presented through percentages (%) for categorical variables. The size of sample (n) is also given.

	Interviewed once (during RT) n=199 %	**Interviewed twice (during RT and 1-y after)** n=102 %	**P value**
Sex			
Female	32.2	45.1	0.001
Male	67.8	54.9	
Age groups			
70-74	50.3	49.0	0.351
75-84	46.7	46.1	
85+	3.0	4.9	
Body mass index (kg/m^2)			
Underweight: <22	9.7	13.3	0.558
Normal: 22-27	45.6	40.8	
Overweight: >27	44.6	45.9	
ECOG Performance status			
Fully active	40.2	31.4	0.088
Restricted in physically strenuous activity	47.7	56.9	
Ambulatory and capable of all selfcare	11.1	10.8	
Capable of only limited selfcare	1.0	1.0	
Caregiver			
Not needed	92.5	89.2	0.610
Caregiver needed	7.5	10.8	

Supplementary data

Activities of daily living			
Extensive assistance	0.5	0.0	0.451
Limited assistance	3.0	3.9	
Needs minimal help	7.5	8.8	
Independent	88.9	87.3	
Instrumental activities of daily living			
Total dependence	1.0	0.0	0.013
Extensive assistance	4.5	0.0	
Limited assistance	30.2	6.9	
Needs minimal help	3.5	9.8	
Independent	60.8	83.3	
RT treatment intent			
Curative	91.0	92.2	0.495
Palliative	9.0	7.8	
Tumour location			
Prostate	35.2	29.4	0.002
Breast	17.1	26.5	
Lung	11.1	7.8	
Gynaecologic	6.0	8.8	
Haematologic	4.0	5.9	
Other remaining locations	26.6	21.6	

Supplementary data

Table S8.2 – Quality of Life during Radiotherapy. Summarizes the distribution of patients in different categories regarding sex, age group, body mass index, ECOG performance status, caregiver, location of tumour in terms of maintaining purpose, family support, mobility and worry about others. Score 1/2 relates to not at all" and "a little" and score 3/4 to "quite a bit" and "very much".

		Maintaining Purpose					Family Support					Mobility					Worries about Others				
		Score 1/2		Score 3/4			Score 1/2		Score 3/4			Score 1/2		Score 3/4			Score 1/2		Score 3/4		
		n	%	n	%	p value	n	%	n	%	p value	n	%	n	%	p value	n	%	n	%	p value
Sex	female	20	46.5%	42	26.9%	**0.014**	12	34.3%	50	30.5%	0.660	55	29.6%	7	53.8%	0.116	21	22.1%	41	39.4%	**0.008**
	male	23	53.5%	114	73.1%		23	65.7%	114	69.5%		131	70.4%	6	46.2%		74	77.9%	63	60.6%	
Age groups	70-74	16	37.2%	84	53.8%		17	48.6%	83	50.6%		96	51.6%	4	30.8%		46	48.4%	54	51.9%	
	75-84	25	58.1%	69	44.2%	0.087	18	51.4%	76	46.3%	0.666	86	46.2%	8	61.5%	0.127	46	48.4%	48	46.2%	0.759
	85+	2	4.7%	3	1.9%		0	0.0%	5	3.0%		4	2.2%	1	7.7%		3	3.2%	2	1.9%	
Body mass index	Underweight: <22	5	11.6%	14	9.0%		2	5.7%	17	10.4%		18	9.7%	1	7.7%		9	9.5%	10	9.6%	
	Normal: 22-27	17	39.5%	74	47.4%	0.632	16	45.7%	75	45.7%	0.672	88	47.3%	3	23.1%	0.176	48	50.5%	43	41.3%	0.402
	Overweight: >27	21	48.8%	68	43.6%		17	48.6%	72	43.9%		80	43.0%	9	69.2%		38	40.0%	51	49.0%	
ECOG Performance status	Fully active	9	20.9%	72	46.2%		10	28.6%	71	43.3%		80	43.0%	1	7.7%		39	41.1%	42	40.4%	
	Restricted in physically strenuous activity	25	58.1%	71	45.5%		18	51.4%	78	47.6%		91	48.9%	5	38.5%		45	47.4%	51	49.0%	
	Ambulatory and capable of all selfcare	8	18.6%	13	8.3%	**0.002**	7	20.0%	14	8.5%	0.133	15	8.1%	6	46.2%	**<0.001**	11	11.6%	10	9.6%	0.946
	Capable of only limited selfcare	1	2.3%	0	0.0%		0	0.0%	1	0.6%		0	0.0%	1	7.7%		0	0.0%	1	1.0%	
Caregiver	Not needed	37	86.0%	149	95.5%	**0.026**	31	88.6%	155	94.5%	0.250	177	95.2%	9	69.2%	**0.006**	91	95.8%	95	91.3%	0.205
	Caregiver needed	6	14.0%	7	4.5%		4	11.4%	9	5.5%		9	4.8%	4	30.8%		4	4.2%	9	8.7%	

Supplementary data

Activities of daily living	Total dependence	0	0.0%	0	0.0%	**0.031**	0	0.0%	0	0.0%	0.121	0	0.0%	0	0.0%	0.083	0	0.0%	0	0.0%	0.126
	Severe dependence	1	2.3%	0	0.0%		1	2.9%	0	0.0%		1	0.5%	0	0.0%		0	0.0%	1	1.0%	
	Moderate dependence	2	4.7%	3	1.9%		2	5.7%	3	1.8%		3	1.6%	2	15.4%		1	1.1%	4	3.8%	
	Low dependence	6	14.0%	9	5.8%		2	5.7%	13	7.9%		15	8.1%	0	0.0%		4	4.2%	11	10.6%	
	Independence	34	79.1%	144	92.3%		30	85.7%	148	90.2%		167	89.8%	11	84.6%		90	94.7%	88	84.6%	
Instrumental activities of daily living	Total dependence	2	4.7%	1	0.6%	**0.005**	1	2.9%	2	1.2%	0.106	2	1.1%	1	7.7%	**<0.001**	1	1.1%	2	1.9%	0.099
	Severe dependence	4	9.3%	9	5.8%		5	14.3%	8	4.9%		9	4.8%	4	30.8%		6	6.3%	7	6.7%	
	Moderate dependence	19	44.2%	40	25.6%		11	31.4%	48	29.3%		54	29.0%	5	38.5%		21	22.1%	38	36.5%	
	Low dependence	18	41.9%	106	67.9%		18	51.4%	106	64.6%		121	65.1%	3	23.1%		67	70.5%	57	54.8%	
	Independence	0	0.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Tumour location	Prostate	7	16.3%	74	47.4%	**0.002**	11	31.4%	70	42.7%	0.719	79	42.5%	2	15.4%	0.191	49	51.6%	32	30.8%	0.072
	Breast	10	23.3%	25	16.0%		8	22.9%	27	16.5%		31	16.7%	4	30.8%		13	13.7%	22	21.2%	
	Lung	6	14.0%	15	9.6%		3	8.6%	18	11.0%		19	10.2%	2	15.4%		9	9.5%	12	11.5%	
	Gynaecologic	3	7.0%	8	5.1%		2	5.7%	9	5.5%		11	5.9%	0	0.0%		5	5.3%	6	5.8%	
	Haematologic	1	2.3%	7	4.5%		1	2.9%	7	4.3%		8	4.3%	0	0.0%		4	4.2%	4	3.8%	
	Others	16	37.2%	27	17.3%		10	28.6%	33	20.1%		38	20.4%	5	38.5%		15	15.8%	28	26.9%	

Supplementary data

Table S8.3 - Quality of Life during Radiotherapy. Summarizes the distribution of patients in different categories regarding sex, age group, body mass index, ECOG performance status, caregiver, location of tumour in terms of future worries, burden of illness and joint stiffness. Score 1/2 relates to “not at all” and “a little” and score 3/4 to “quite a bit” and “very much”.

		Future Worries					Burden of Illness					Joint Stiffness				
		Score 1/2		Score 3/4			Score 1/2		Score 3/4			Score 1/2		Score 3/4		
		n	%	n	%	p value	n	%	n	%	p value	n	%	n	%	p value
Sex	female	36	27.7%	26	37.7%	0.148	37	25.7%	25	45.5%	**0.007**	34	23.8%	28	50.0%	**<0.001**
	male	94	72.3%	43	62.3%		107	74.3%	30	54.5%		109	76.2%	28	50.0%	
Age groups	70-74	67	51.5%	33	47.8%		72	50.0%	28	50.9%		78	54.5%	22	39.3%	
	75-84	60	46.2%	34	49.3%	0.845	69	47.9%	25	45.5%	0.742	62	43.4%	32	57.1%	0.111
	85+	3	2.3%	2	2.9%		3	2.1%	2	3.6%		3	2.1%	2	3.6%	
Body mass index	Underweight: <22	13	10.0%	6	8.7%		13	9.0%	6	10.9%		16	11.2%	3	5.4%	
	Normal: 22-27	58	44.6%	33	47.8%	0.896	69	47.9%	22	40.0%	0.601	74	51.7%	17	30.4%	**0.002**
	Overweight: >27	59	45.4%	30	43.5%		62	43.1%	27	49.1%		53	37.1%	36	64.3%	
ECOG Performance status	Fully active	59	45.4%	22	31.9%		68	47.2%	13	23.6%		70	49.0%	11	19.6%	
	Restricted in physically strenuous activity	59	45.4%	37	53.6%	0.162	64	44.4%	32	58.2%	**0.004**	62	43.4%	34	60.7%	**<0.001**
	Ambulatory and capable of all selfcare	11	8.5%	10	14.5%		12	8.3%	9	16.4%		10	7.0%	11	19.6%	
	Capable of only limited selfcare	1	0.8%	0	0.0%		0	0.0%	1	1.8%		1	0.7%	0	0.0%	
Caregiver	Not needed	125	96.2%	61	88.4%	0.066	139	96.5%	47	85.5%	**0.009**	135	94.4%	51	91.1%	0.523
	Caregiver needed	5	3.8%	8	11.6%		5	3.5%	8	14.5%		8	5.6%	5	8.9%	
Activities of daily living	Total dependence	0	0.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%	0	0.0%	
	Severe dependence	0	0.0%	1	1.4%		1	0.7%	0	0.0%		1	0.7%	0	0.0%	
	Moderate dependence	2	1.5%	3	4.3%	0.249	2	1.4%	3	5.5%	0.313	2	1.4%	3	5.4%	0.428
	Low dependence	9	6.9%	6	8.7%		10	6.9%	5	9.1%		11	7.7%	4	7.1%	
	Independence	119	91.5%	59	85.5%		131	91.0%	47	85.5%		129	90.2%	49	87.5%	

Instrumental activities of daily living	Total dependence	0	0.0%	3	4.3%		2	1.4%	1	1.8%		2	1.4%	1	1.8%	
	Severe dependence	8	6.2%	5	7.2%		7	4.9%	6	10.9%		9	6.3%	4	7.1%	
	Moderate dependence	36	27.7%	23	33.3%	0.074	33	22.9%	26	47.3%	**<0.001**	33	23.1%	26	46.4%	**0.005**
	Low dependence	86	66.2%	38	55.1%		102	70.8%	22	40.0%		99	69.2%	25	44.6%	
	Independence	0	0.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Tumour location	Prostate	56	43.1%	25	36.2%		73	50.7%	8	14.5%		67	46.9%	14	25.0%	
	Breast	22	16.9%	13	18.8%		26	18.1%	9	16.4%		17	11.9%	18	32.1%	
	Lung	14	10.8%	7	10.1%	0.916	10	6.9%	11	20.0%	**<0.001**	18	12.6%	3	5.4%	**0.003**
	Gynaecologic	6	4.6%	5	7.2%		5	3.5%	6	10.9%		8	5.6%	3	5.4%	
	Haematologic	5	3.8%	3	4.3%		5	3.5%	3	5.5%		6	4.2%	2	3.6%	
	Others	27	20.8%	16	23.2%		25	17.4%	18	32.7%		27	18.9%	16	28.6%	

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PART III – DISCUSSION AND CONCLUSIONS



DISCUSSION

The main objective of this project was to improve knowledge in geriatric oncology and apply it within Radiation Oncology. The project involved the following steps: (i) exploring the importance of frailty assessment in the specific context of radiotherapy, (ii) evaluating the future needs for external RT, (iii) analysing the utilisation patterns of Radiotherapy Services by older adults, (iv) assessing the knowledge of radiation oncologists regarding geriatric oncology, (v) validating the Onco-MPI prognostic tool, and (vi) assessing the quality of life of older adults with cancer who have undergone RT. The results of this research opened the discussion related to RT treatments for older and frail older adults with cancer and highlight the importance of frailty assessment in RT. In addition, data regarding future RT needs and the pattern of utilisation of RT services by older adults in Portugal were updated.

The radiation oncologists' knowledge about geriatric oncology was assessed through a survey. Also, every opportunity was taken to increase awareness about older adults with cancer - informally during the data collection and collaboration with health professionals from RT departments, and formally during meetings to present the project and its results.

Furthermore, the implementation and validation of tools, such as the Onco-MPI and the EORTC ELD 14 for geriatric assessment and quality of life, facilitated their integration into future treatment protocols.

Frailty and Radiotherapy

It was hypothesised that cancer outcomes and quality of life may be improved by adapting RT treatments for frail patients; however, there is a lack of evidence exploring the relationship between frailty and cancer outcomes in patients who have undergone RT. Some evidence agrees that there is a complex interaction between frailty and RT.

Frailty is influenced by multiple factors such as senescence, inflammation, metabolic problems, multimorbidity, and polypharmacy. In older adults with cancer, the side effects of treatments such as anaemia, immunosuppression and pain can contribute to frailty. In addition, treatment-related factors, such as RT toxicity, frequent hospital visits and cancer-related symptoms can further aggravate frailty (Goede et al., 2021).

Even after reviewing the literature, many questions remain unanswered about the impact of RT on frail older patients. It is understood that that RT delivered in conventional fractionated doses affects redox metabolism by generating free radicals. In relation to this effect, it is important to considerer that Viña et al. suggested that frailty is linked to oxidative damage in tissues rather than to aging itself, a concept known as the theory of free radical fragility (Viña, 2019).

This raises the question of whether radiotherapy techniques should be adjusted for frail patients to minimise the production of free radicals. Advanced techniques such as Deep Inspiration Breath Hold (DIBH), hypofractionated treatments, and emerging technologies such as FLASH radiotherapy offer promising options to minimize exposure to healthy tissues and reduce oxidative stress.

Although older cancer patients often tolerate modern RT well, the impact of frailty on radiotoxicity and treatment outcomes remains unclear. For some studies, frailty measured by certain instruments was associated with increased radiotoxicity, but not by others (Bras et al., 2021; Keenan et al., 2017). Data from a Greek RT department revealed that older patients with high frailty scores were more likely to have incomplete treatments and that frailty in urological cancer patients was associated with more cancer-related hospitalisations. These results indicate the need for more research to understand the role of frailty in RT outcomes and to adapt treatment techniques to frail older adults with cancer (Spyropoulou et al., 2014).

Future needs for RT

Given the hypothesis that demand for external beam radiotherapy (RT) will increase significantly by 2040 due to an ageing population and rising cancer incidence rates, this study provides important insight into future healthcare needs. The results of this study regarding the future RT needs for 2040 shows that, in comparison to 2020, an 18% increase in the optimal number of RT courses is expected, translating to around 34,000 additional courses. Based on the recommendations for the number of RT machines required to meet the expected demand for RT courses, our results suggest that an additional 18 to 30 RT machines will be needed to cover future demand. Also, based on recommended staffing per RT machine, 28 to 46 radiation oncologists, 22 to 36 medical physicists, and 61 to 102 radiation therapists will need to be recruited.

Despite valuable of our findings, there are several limitations, including potential biases due to incomplete data in the GCO database and the fact that the recommended guidelines are from different sources. These limitations may impact the accuracy of the projections, emphasising the need for further research.

Nevertheless, there is an anticipated increase in RT demand, calling for urgent measures to adjust cancer-related policies and resource allocation strategies. The substantial increase in infrastructure and personnel required to cover RT future needs emphasises the need for policy reforms and significant investments (*Segunda Revisão Rede Nacional de Especialidade Hospitalar e de Referenciação de Radioterapia*, 2015).

Currently, a shortage of RT machines has already been stated by several national entities, so ensuring that future demand is met will require additional efforts to address the existing resource constraints. Preparing for the expected increase in demand for RT implies the involvement of both the public and private sectors to fill the existing gaps.

Staffing represents another critical challenge. To meet the rising demand for RT, there will need to be a proportional increase in trained healthcare professionals. Effective strategies must be implemented to recruit and train the required radiation oncologists, medical physicists, and radiation therapists. Furthermore, to prepare for the anticipated complexity of future RT treatments, plans should be developed to support and further train current staff already working in RT departments.

If policymakers and stakeholders make joint efforts to proactively address these future needs, the demand for RT can be managed, and patients can be assured that they will have access to RT as part of their cancer journey.

Use of radiotherapy by older adults

This research reinforces the hypothesis that RT is used differently by older adults compared to their younger counterparts, and that treatment patterns are different between these groups.

We analysed data from 24,819 cancer cases registered in the Portuguese National Cancer Registry, including 9,498 cases of patients aged 70 or over. Our results show that the use of external beam radiotherapy (RT) in Portugal is generally below the ESTRO-HERO recommendations, except for vulvar cancer patients aged 70 and

over. Approximately 3,381 patients aged 0-69 and 2,093 aged 70 or over - representing around 22 per cent of new cancer cases - potentially did not have access to RT. Moreover, actual use of RT in Portugal was lower than the optimal levels adjusted for comorbidities across all age groups and types of cancer.

Although our study benefited from the data integration and validation processes of the RON database, there was some limitations. Specific timing information on diagnosis and RT was not requested from the RON database, which may affect utilisation rates calculations. Furthermore, the use of RT may be overestimated due to the lack of distinction between external and internal/brachytherapy types of radiation when considering whether a patient underwent RT treatment. Also, a common reason for underutilization of RT in older populations is that patients with several comorbidities are often considered ineligible for RT. Due to the lack of information about comorbidities in the RON database, our findings are limited by this absence which means that the reasons of underutilization remain unexplored.

Despite the reasons for underutilisation of RT, it is a fact that our findings align with previous publications from ESTRO-HERO, which states that over a quarter of European cancer patients who theoretically have indication to undergo RT do not receive it. Focusing on RT utilisation in Portugal, the actual use of RT is around 50-60% of the optimal levels, similar to the utilisation rates of Estonia and Albania, while other European countries have higher utilisation rates (Lievens, Borras, et al., 2020).

These significant gaps persist despite ongoing awareness of disparities in cancer care for older patients. This awareness was addressed by the European Beating Cancer Plan, which advocates for improving access to RT and the creation of a European Cancer Scoreboard to monitor inequalities. It is expected that enhancing access to RT could potentially save up to 1 million lives in Europe by 2035 (Monfardini et al., 1993a; Organization, 2022).

The disparities in cancer care for older patients and the underutilisation of RT are linked to several factors. These include the concentration of RT equipment in urban areas, which limits access to older people living in Portuguese rural areas. The distance to the RT department can compromise convenience and create problems with transportation. Also, the decision to refuse RT may be influenced by patient's trust in the treating physician, and other treatment-related factors such as success rates, discomfort, and side effects(Puts et al., 2015).

From the perspective of the healthcare professional, understanding that chronological age is a poor indicator of treatment tolerance and outcomes can positively influence the decision to propose RT treatment for older adults with cancer. Undoubtedly, more training in geriatric oncology is needed to incorporate biological age and frailty into cancer treatment decisions and reduce the underutilization of RT. (Anita O'Donovan & Michelle Leech, 2020).

Professionals' knowledge of geriatric oncology

One of the aims of this study was to assess the level of knowledge in geriatric oncology among radiation oncology consultants and residents and to understand how this knowledge gap affects treatment decisions. It was hypothesized that this gap negatively impacts treatment decisions, with chronological age identified as a limiting factor, bringing into attention the preponderance of improving education in this field. Our survey findings, which included 52 participants - 13 radiation oncologist residents and 39 consultants - confirmed this hypothesis.

Despite alignment between our hypothesis and our findings, there are limitations in our study that need to be mentioned. The number of Portuguese radiation oncologists registered in 2021 was 172 (80%) consultants and 43 (20%) residents (Council, 2022). Based on these statistics, our sample size is a major limitation of our study, which was too small to meet the minimum threshold for a 95% confidence level. This limits the extrapolation of these findings to all Portuguese radiation oncologists. Nevertheless, this study is the first survey on the knowledge of geriatric oncology and highlights the need for more training and collaboration with geriatric professionals within the radiation oncology teams.

A key finding was that most respondents (88.5%) had observed an increase in the number of older cancer patients, but only a small percentage (28.8%) had carried out frailty screening. Similarly, our study found that only a minority of respondents used frailty screening tools, a finding comparable to a 37% utilisation rate reported in an international survey of European cancer patients (Banna et al., 2022). Reasons cited for the low utilisation of these tools included lack of awareness, time constraints and a perceived lack of benefit, which underlines the need to place greater emphasis on geriatric considerations in oncology training.

In addition, most respondents were unaware of specific guidelines for the treatment of older adults with cancer and a significant 98.1% expressed the need for better training in geriatric oncology.

These results suggest that age significantly influences clinical decision-making, a trend consistent with previous studies such as the comprehensive review by Tranvag et al. (2018), which highlighted that the patient's age is often used as a primary factor in treatment decisions, either explicitly or implicitly (Tranvag et al., 2018). Our study supports the hypothesis that there is a critical need to improve geriatric oncology education among radiation oncology professionals. The limited awareness and training in this area are concerning, especially given that chronological age is a poor predictor of a patient's ability to tolerate treatment and outcomes in older adults with cancer.

Furthermore, our results align with other studies, such as a cross-sectional online survey conducted in cancer centres in Australia, New Zealand and Singapore, where 91.8% of respondents reported no formal or informal training in geriatric oncology during their radiation oncology education (L. Morris et al., 2017).

In the future, more studies should be dedicated to creating and delivering a geriatric oncology training platform for radiation oncologists. This platform could share clinical case studies and access its impact by comparing treatment decisions strategies for older adults both before and after training. These programmes would be valuable to bridge the knowledge gap and improve the care of older cancer patients.

Validation of the Onco-MPI tool

One aims of this study was to validate the Onco-MPI tool as a predictor of one-year survival in older Portuguese cancer patients undergoing RT, with the hypothesis that it would prove to be valid and reliable. Our results confirm this hypothesis.

Among the 227 patients included in the validation cohort, 88.5% received RT with the aim of curing their cancer. The validation cohort had a median age of 75. Although there were some demographic and clinical differences from the original cohort of 658 patients, such as a lower median IADL score (5 vs. 8) and fewer patients with an MMSE score below 24 (11.5 per cent vs. 18.09 per cent), there were no significant differences regarding age, BMI, ADL, ECOG or CIRS-G scores.

Additionally, the original and validation cohorts were different regarding the distribution of cancer types, with fewer cases of breast cancer and more cases of prostate cancer in the validation cohort.

Although our study presents preliminary positive results, the authors acknowledge its limitations. The smaller sample size of 227 patients compared to the original cohort could impact the reliability of the results. The validation of the reliability of Onco-MPI may be affected by the differences in distribution of cancer types between the original and validation cohorts. Likewise, the validation of Onco-MPI prognostic role may also be affected by differences noted between the original and validation cohorts regarding the cognitive and functional assessments. From a broader perspective, the study focussed only on 12-month survival, without an evaluation of the long-term outcomes or consideration of all the potential factors affecting survival.

Despite these differences between the original and validation cohorts, the Onco-MPI tool showed a strong association with survival at 12 months, with an area under the curve (AUC) of 0.785 for low-medium risk groups and 0.786 for medium-high risk groups in the validation cohort. At 12 months, the survival rates were 97% for low-risk patients, 87% for medium-risk patients and 59% for high-risk patients, indicating that Onco-MPI effectively stratifies patients by mortality risk.

Our findings are in line with the existing literature which focuses on the predictive value of Onco-MPI for survival prediction in older adults with cancer. For example, Shenoy et al. conducted a retrospective observational study to assess the performance of the Onco-MPI index in predicting mortality in older Indian cancer patients. The authors found that the Onco-MPI correlates with survival, reporting a median survival of 18.9 months for low-risk patients, 11.2 months for medium-risk patients and 4.9 months for high-risk patients. Factors such as age, male gender, limitations in daily life, cognitive impairment, and severe comorbidities were associated with a higher risk of mortality, while cancer stage and specific tumour sites did not individually influence the risk of mortality (Shenoy et al., 2023). Similarly, Chiusole et al. validated the Onco-MPI's prognostic value for older adults with advanced soft tissue sarcoma, noting its strong performance in the univariate analysis, although its significance was reduced in the multivariate analysis (Chiusole et al., 2023). Procaccio et al. also confirmed the Onco-MPI's correlation with survival in metastatic colorectal cancer, reporting that patients classified as

high-risk according to the Onco-MPI had worse survival compared to those in the low- and intermediate-risk categories (Procaccio et al., 2022).

Future studies should aim to enhance predictive accuracy of the Onco-MPI tool and allow its application to diverse patient populations. Also, involving longer-term survival and other prognostic variables could help tool's performance. Overall, our study supports the hypothesis that the Onco-MPI tool may be a valuable instrument for predicting one-year survival in older cancer patients. Its ability to stratify patients into distinct one-year mortality risk categories may bring additional guidance to clinical decision-making and allow personalised treatment for older adults with cancer.

Quality of life of older adults undergoing radiotherapy

Regarding the quality of life, measured by the EORTC QLQ-ELD 14 survey of older adults undergoing radiotherapy we hypothesised that it declines while undergoing RT and one-year after.

Our results showed that QoL during RT regarding lower life purpose, mobility issues, and burden of illness were more frequently reported by women, or patients with ECOG PS 2/3, or those with higher dependence in activities of daily living (ADL), or patients with breast, lung, or other remaining cancers. Also, joint stiffness was higher among women, in overweighted and those with poorer ECOG status; no differences in future worries or family support were noted.

Regarding QoL outcomes at one year after, sub-group analyses showed that women experienced greater significant deterioration in joint stiffness, burden of illness, and concerns about others. Likewise, patients with instrumental ADL impairment experienced more mobility issues and worries about others.

Comparing our results with the hypothesis, we do not find QoL decline for all patients undergoing RT, but only for certain subgroups, especially women and patients with poorer functional status.

Similar results were found by previous author that focused on QoL of older adults with cancer regardless of the RT treatment. Thomé et al, analysed older adults with cancer aged above 75 or over, including 74 women and 76 men and found that QoL was poor for some subgroups. In their cohort, they found that women with cancer had lower QoL in comparison with male counterparts. The authors also

concluded that requiring assistance in daily activities, comorbidities, degree of complains and pain were factors associated to lower QoL indicators (Thomé & Hallberg, 2004). Comparable findings were reported by Decoster et al., on their analysis of 2972 patients aged 70 years and older with a solid tumour, in the context of a prospective, multicentre, observational cohort study performed in 22 hospitals in Belgium. The multivariate analysis of determinant prognostic socio-demographic, clinical and geriatric factors for baseline EORTC QLQ-C30 quality of life, allowed the authors to identify the following determinants correlating with poorer QoL: i) age; ii) ECOG-PS; iii) cancer stage; iv) IADL; v) pain and fatigue; vi) malnutrition and vii) comorbidities (Decoster et al., 2019).

Findings about QoL for older adults undergoing RT are scarce. Kaufmann et al., performed a prospective QoL evaluation of 50 older adults aged ≥80 years, with a malignant tumour who received RT. EORTC-QLQ-ELD14 was applied in three timepoints, at the start (t1) at the end (t2), and to 6 months after RT (t3). No statistically significative changes were noted between t1 and t2. Between t1 and t3, a decline was observed in the domain of future worries, burden of illness, and family support (Kaufmann et al., 2015). Data regarding the impact of RT in QoL was published by Yucel et al., but it is not specific for older population, once the cohort included patients with age between 16-86 years. The cohort included patients receiving RT to different cancer locations, with different cancer stage ranging 1 to 4. A total of 316 patients had their QoL assessed using EORTC QLQ-C30 at four timepoints: at the start (t1); at the end (t2); 1 month (t3) and to 6 months after RT (t4). Two QoL domain were significantly different between t1 and t2, namely, mean global health status score that was lower and mean nausea/vomiting and appetite scores that were higher. On the other hand, QoL improved at t4, with higher mean health status and functional scores and lower mean symptom scores (Yucel et al., 2014).

There is no vast data available to direct comparison between our findings of QoL assessment of older adults who underwent RT using EORTC ELD14 tool. But in general, a poorer baseline functional status correlates with a lower QoL levels. This finding highlights the importance of identifying this group of patients and provide them with a close monitoring of their symptoms during and after RT.

Our results are consistent with data previously published elsewhere, but we need to acknowledge our study limitations such as the use of convenience sampling, variability in the data collection method, and dropout rate. Our cohort was recruited

from a group of patients who are over of 70 years old who were being treated with RT. So, they are not part of a wider group of older cancer patients who might be ineligible to RT or who may be cognitively compromised and unable to participate in our study for any reason. Furthermore, data collection method varied for the two timepoints of QoL assessment, as data derived from in-person interviews for QoL during RT and one-year after QoL assessment was conducted by phone. In addition, due to the dropout rate of patients (30 dead and 67 lost to follow-up), this limits the interpretation of our findings.

Taking into consideration all the factors that can influence QoL in older patients who have undergone RT, this evaluation is inherently complex. Based on our findings and recent evidence, a personalized QoL assessment may be needed to capture the nuanced experiences of each patient. This assessment should consider individual patient profiles, treatment contexts, and levels of frailty. The authors would like to emphasise that healthcare professionals should be aware of the potential QoL domains likely to decline one year after RT, such as those identified in our study—namely, reduced life purpose, mobility problems, joint stiffness, and future worries. Efforts should be made to prevent or reduce these issues by implementing preventive measures or proactively addressing them with targeted interventions.

CONCLUSIONS

This project research was conducted on older adults with cancer aged over 70 years receiving RT. It covered several topics including the importance of integrating frailty assessment in treatment decisions and identifying knowledge gaps about geriatric oncology of radiation oncologists. It also focused on RT use and underutilisation of RT among older adults was found. Furthermore, a higher RT demand in the future was predicted, stressing the necessity for resource planning and policy changes. Moreover, preliminary results of this research suggest that the Onco-MPI may be a reliable predictor of one-year survival. Through QoL assessments of older adults who received RT, it was confirmed that, in general, RT is not linked to a QoL decline one year later, except in some subgroups.

Of course, that the results from this study will not translate instantly into clinical practice, research, and policies changes. But this study allowed to increase awareness about:

the importance of incorporating frailty assessment into RT protocols for older adults. Also, more efforts need to be taken to produce evidence linking frailty directly to RT outcomes and to understand the complexity of interactions between frailty and treatment outcomes. Additionally, research and clinical teams should work together to adapt advanced RT techniques to account for frailty to improve patient QoL by minimizing treatment-related side effects in frail older adults.

But denying the projected rise in demand for RT due to the aging population will impact negatively access to RT for older cancer patients. Coordinated efforts between policy makers, healthcare providers, and institutions are needed to proactive plan and address infrastructure gaps, such as increasing the number of RT machines and expanding the workforce.

Moreover, not recognizing the inequalities in access to RT in Portugal will continue to perpetuate its underutilisation among older adults. This underutilisation can be the result of several factors such as geographical access, comorbidities, and age-related preferences. So, to fight these disparities, targeted interventions and policies are needed. These should aim to ensure access to RT regardless of your post code and age, particularly in rural areas and among older populations with complex health needs.

The Portuguese landscape regarding geriatric oncology is unique, as Geriatrics is not a recognized as separate medical specialty, and it is expected that any doctor

who frequently treats older adults is prepared and trained to do so. The knowledge gap in geriatric oncology among radiation oncology professionals, affecting clinical decision-making, has become critical, especially given that by 2045 older adults aged 70 years or over are expected to account for about 60% of all new cancer cases in Europe. Thus, increasing training and awareness in geriatric oncology is essential for all healthcare professionals working with older adults with cancer.

Given the demands on productivity in healthcare systems and with the anticipated rise in the cancer cases, it is important to develop tools that add value to treatment decisions without extra time-consuming tasks. One such tools is the Onco-MPI tool. Our preliminary results demonstrate its promising prognostic value for predicting one-year survival in older cancer patients undergoing RT. Its ability to stratify patients into distinct risk categories could support personalized treatment approaches. It is important to mention that further research is needed to improve the tool's accuracy and expand its applicability to diverse populations and longer-term outcomes.

Although survival is one of the most reported outcomes in regarding the benefits of cancer treatment and guides treatment approval by regulatory entities, QoL is often considered as more important than survival by older adults with cancer. Then, it is a critical to prioritize QoL as one of the most important outcomes for older adults undergoing RT. While a decline in QoL one-year after RT was reported in specific subgroups of this study, such as women and those with poorer functional status, other groups of patients maintained their QoL. This highlights the importance of incorporating QoL assessment into routine clinical practice and identifying patients at risk of QoL decline.

The authors hope that the conclusions from this study contribute to a positive change in the care of older adults with cancer, especially those requiring RT. This project aimed to emphasise the importance of personalized care and the need to address the complexities of older adults with cancer. Also, the authors hope that these results can contribute to prepare the workforce to meet the future demand for RT. This project aim was to emphasise the importance of personalized care and the need to address the complexities of older adults with cancer.

The ultimate goal of this research was to make a small contribution to improve treatment outcomes and the well-being of older adults.

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PART IV – APPENDICES





Esta imagem revela a harmonia entre a radioterapia e a luta contra o cancro na população idosa. A radioterapia, com a sua precisão tecnológica, reflete o poder da ciência no combate às adversidades da vida. A cadeia de DNA, como um fio de luz, guarda a essência única de cada pessoa. E a árvore da vida, cujas folhas representam as memórias e o tronco simboliza a longevidade, é um reflexo do ciclo contínuo da existência. A radioterapia, como uma opção de tratamento, permite a continuidade do florescimento da vida, possibilitando a criação de novas memórias na caminhada da pessoa idosa.

This image reveals the harmony between radiotherapy and the fight against cancer in the older population. Radiotherapy, with its technological precision, reflects the power of science in overcoming life's adversities. The DNA strand, like a thread of light, holds the unique essence of each person. The tree of life, with its leaves representing memories and its trunk symbolising longevity, reflects the continuous cycle of existence. Radiotherapy, as a treatment option, allows the continuation of life's blossoming, enabling the creation of new memories in the journey of the older person.

Table 4.1 - Survey assessing perspectives in geriatric oncology targeting Radiation Oncologists, specialists/consultants and residents, actively involved in cancer patient care in Portugal.

Geriatrics Oncology within the scope of Radiotherapy
Knowledge related to knowledge in Geriatric Oncology

INFORMED, FREE AND INFORMED CONSENT TO PARTICIPATE IN RESEARCH PROJECTS
In accordance with the Declaration of Helsinki and the Oviedo Convention.
Please read the following information carefully. If you feel something is incorrect or unclear, please don't hesitate to ask for more information. If you agree with the proposal made to you, please accept participation in this study.

Study title
Geriatric assessment of older people proposed for radiotherapy

Framework
Within the scope of the Doctoral Program in Gerontology and Geriatrics, Institute of Biomedical Sciences Abel Salazar-ICBAS-UP and University of Aveiro, I am developing a study on knowledge related to geriatric oncology and its application in Radiotherapy. This PhD project will be developed under the guidance of Professor Laetitia da Costa Teixeira and Professor Escarlata López Ramírez.

Explanation of the study
Your participation consists of completing a brief questionnaire, lasting approximately 5-10 minutes. General data such as age, gender, professional experience and data regarding your knowledge of Geriatric Oncology will be collected. There are no right or wrong answers, our goal is to increase awareness about the difficulties experienced by professionals and possible measures to adopt in the future. It is important that you read carefully and answer all the questions. If you would like any clarification about this study, please contact researcher Edna Darlene Rodrigues Pinto by email up201610921@g.uporto.pt

Conditions and financing

This project is carried out within the scope of research grants for doctoral students, concluded between FCT and the R&D Unit Center for Research in Health Technologies and Services CINTESIS, UDP/4255/2020.
There is no payment of compensation to study participants. Participation in this research is voluntary, so you can deny it or decide to stop completing the questionnaire at any time, if you wish. You may also withdraw from participation in the study/research project at any time, without any prejudice or justification.
The present study received a favorable opinion from the ICBAS-UP Ethics Committee.

Confidentiality and anonymity
All data collected is anonymous and confidential and its use will be exclusive for the present study.

I declare that I have read and understood this document, as well as the verbal information provided to me by the person/s who signed above, which I consider sufficient. I was guaranteed the possibility of, at any time, refusing to participate in this study without any consequences, Therefore, I agree to participate in this study and allow the use of the data that voluntarily provide, trusting that they will only be used for this investigation and in the guarantees of confidentiality and anonymity given to me by the researcher.
□ I agree to participate

2. **Age**

   Your answer

3. **Sex**

   Masculine| Feminine

4. Do you practice your professional activity as a **specialist/consultant in Radioncology**?

   Yes| No - Resident

5. How **many years** have you been practicing clinically in Radiation Oncology?

   Your answer

6. Do you work as a **Radioncologist dedicated** to any cancer type? This dedication is defined as membership of a multidisciplinary oncology group, execution of specific treatment techniques for this cancer type and personal case series with significant representation of this same group.

   Bladder | Head and neck | Colorectal | Gynecology | Liver and Pancreas | Leukemia/Lymphomas | Breast | Multiple Myeloma | Skin | Prostate | Lung | Kidney | Central Nervous System | Sarcomas | Testicle | Thyroid | Upper gastrointestinal tract | Others

7. Did you have **pre-graduate training in Geriatrics**?

   Yes | No

8. Did you **have postgraduate training in Geriatrics**?

   Yes | No

9. In what **context** do you carry out your **professional activity**?

   Hospital institution-University | Hospital institution-Non-University | Both | Others

10. In the Center(s) where you carry out your professional activity, is there a **professional dedicated to geriatric oncology**?

    Yes | No

11. In the Center(s) where you carry out your professional activity, are you able to **request a geriatric assessment** as an aid to therapeutic decisions?

    Yes | No

12. What is the **age limit** at which a person is defined as **older**?

    Your answer

13. Is **age a determining factor** in the clinical decision-making process?

    Ever | Most of the time | Sometimes | Rarely | Never

14. In this **decision-making process** regarding an older person, is an **assessment carried out**?

    Formal assessment using validated tools for the elderly population | Informal assessment based on my clinical experience | No specific assessment is carried out | Others

15. Indicate **specific international recommendations for the older population** you come into contact within your clinical practice:

    American Society of Clinical Oncology (ASCO) | National Comprehensive Cancer Network (NCCN) Older Adult Oncology Guidelines | International Society of Geriatric Oncology (SIOG) | European Organization for Research and Treatment of Cancer (EORTC) | None of the options | Others

16. Are you aware of the existence of the **International Geriatric Radiotherapy Group**?

    Yes | No

17. In your routine assessment of older patients, do you apply any **frailty assessment tools**?

    Yes | No | I do not assess frailty because elderly people undergo a "Global Geriatric Assessment" by another healthcare professional.

18. If you are assessing frailty, what **tool do you use**?

    Geriatric 8 (G8) | Triage Risk Screening Tool (TRST) | Vulnerable Elders-13 Survey (VES-13) | I do not evaluate fragility | I do not assess frailty because elderly people undergo a "Global Geriatric Assessment" by another healthcare professional. | Others

19. Of the following **domains of the older person's life**, which are **routinely questioned/evaluated** in their clinical activity:

    Gait: e.g. Time up and go or Holden's Functional Gait Classification | Activities of daily living: e.g. Katz | Instrumental activities of daily living scale: e.g. Lawton&Brody | Nutritional Status: e.g. Mini nutritional assessment (MNA) | Cognitive Function: e.g. Mini-Cog or Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MOCA)) | Depression: e.g. Yesavage Geriatric Depression Scale | Comorbidity assessment scales: e.g. Charison Index, ACE 27; Cumulative Iliness Rating Scale for Geriatrics (CIRS-G) | Social situation | Polypharmacy | Falls | I do not evaluate because older people undergo a "Global Geriatric Assessment" by another healthcare professional. | None of the options | Others

20. Based on your personal experience, have you noticed an **increase in older people** using **Radiotherapy** services?

    Yes | No

21. Based on your personal experience, do you feel the **need to deepen your knowledge** related to the particularities of the **geriatric population**?

    Yes | No

22. Based on your personal experience, would you like to **improve your knowledge** of evaluating and managing therapeutic options in **older people**?

    Yes | No

23. **How** would you like to **improve your knowledge**:

Discussion of clinical cases | Workshops | Creation of working groups by pathology | Dissemination of international recommendations | Others

Table 4.2 - Portuguese and English versions of the EORTC-ELD14, a module developed by the European Organisation of Research and Treatment of Cancer Quality of Life Group to evaluate QoL in older cancer patients.

EORTC QLQ-ELD14 – Portuguese version

Por vezes, os/as pacientes afirmam sentir os seguintes sintomas ou problemas. Por favor, indique até que ponto sentiu estes sintomas ou problemas durante a última semana. Responda fazendo um círculo à volta do número que melhor se aplica a si.

Durante a última semana: 1=Não 2=Um pouco 3=Bastante 4=Muito

31. Sentiu dificuldades a subir degraus ou escadas? 1 2 3 4
32. Sentiu problemas nas articulações (p. ex., rigidez, dor)? 1 2 3 4
33. Sentiu-se inseguro quando estava de pé? 1 2 3 4
34. Precisou de ajuda em tarefas domésticas, tais como fazer a limpeza ou compras? 1 2 3 4
35. Sentiu-se capaz de falar sobre a sua doença com a sua família? 1 2 3 4
36. Preocupou-se com o modo como a sua família está a lidar com a sua doença e o tratamento? 1 2 3 4
37. Preocupou-se com o futuro das pessoas que são importantes para si? 1 2 3 4
38. Preocupou-se com o seu estado de saúde no futuro? 1 2 3 4
39. Sentiu incerteza em relação ao futuro? 1 2 3 4
40. Preocupou-se com o que poderá acontecer no final da sua vida? 1 2 3 4
41. Na última semana teve uma atitude positiva em relação à vida? 1 2 3 4
42. Sentiu-se motivado(a) para continuar a realizar os seus passatempos e atividades normais? 1 2 3 4
43. Em que medida a sua doença tem sido um fardo para si? 1 2 3 4
44. Em que medida o tratamento tem sido um fardo para si? 1 2 3 4

EORTC QLQ-ELD14 – English Version

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week: 1= Not at all 2= A Little 3= Quite a Bit 4= Very Much

31. Have you had difficulty with steps or stairs? 1 2 3 4
32. Have you had trouble with your joints (e.g. stiffness, pain)? 1 2 3 4
33. Did you feel unsteady on your feet? 1 2 3 4

34. Did you need help with household chores such as cleaning or shopping? 1 2 3 4
35. Have you felt able to talk to your family about your illness? 1 2 3 4
36. Have you worried about your family coping with your illness and treatment? 1 2 3 4
37. Have you worried about the future of people who are important to you? 1 2 3 4
38. Were you worried about your future health? 1 2 3 4
39. Did you feel uncertain about the future? 1 2 3 4
40. Have you worried about what might happen towards the end of your life? 1 2 3 4
41. Have you had a positive outlook on life in the last week? 1 2 3 4
42. Have you felt motivated to continue with your normal hobbies and activities? 1 2 3 4
43. How much has your illness been a burden to you? 1 2 3 4
44. How much has your treatment been a burden to you? 1 2 3 4