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Quality of Life and Side Effects Management in Cancer Treatment (Volume II)

Edited by
António Araújo

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Guest Editor

António Araújo

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Guest Editor
António Araújo
Department of Medical
Oncology
ICBAS, University of Porto
Porto
Portugal

Editorial Office
MDPI AG
Grosspeteranlage 5
4052 Basel, Switzerland

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About the Editor

António Araújo

António Araújo is Full Professor at the School of Medicine and Biomedical Sciences (ICBAS) and at the Faculty of Dental Medicine, University of Porto, and currently serves as Head of the Department of Medical Oncology at ULS Santo António. He is also the Director of the Integrated Master's Degree in Medicine at ICBAS. Professor Araújo has long been active in national cancer policy and oversight, serving since 2013 as a member of the Portuguese National Council for Oncology and since 2019 as a member of the Scientific Committee of the Portuguese National Cancer Registry. Internationally, he has contributed to educational and ethical deliberations through his work with the International Association for the Study of Lung Cancer (IASLC), including membership on its Education and Ethics Committees. His clinical and academic focus lies in thoracic oncology, immunotherapy, patient-centered outcomes, and the interface between cancer and quality of life. He has published extensively, contributing to over 140 scientific papers and book chapters. Professor Araújo is a full member of ESMO, ASCO, IASLC, and multiple national societies in oncology and pulmonology. For his service to the city of Porto and his role in the fight against COVID-19, he has been honored with several distinctions, including the Municipal Medal of Merit (Gold Grade), the Ricardo Jorge Distinction of Merit, the Professional Merit Award of the Rotary Club Porto-Foz, and the Merit Medal of the Portuguese Medical Association. In 2025, he was appointed Honorary Member of the Portuguese Office of the National Test of Access to Medical Specialties. His current work focuses on improving long-term outcomes and survivorship for cancer patients through integrative, translational, and multidisciplinary approaches.

Preface

This Special Issue reprint of *Cancers*, curated by the Guest Editor António Araújo, brings together a collection of original research articles and reviews dedicated to understanding and improving the quality of life of individuals living with cancer. The scope of this reprint extends across a wide spectrum of topics including long-term survivorship, symptom burden, psychosocial adaptation, the impact of emerging treatments such as immunotherapy, and patient-reported outcomes. The central aim is to shed light on how cancer and its treatments affect not only survival but also physical, emotional, social, and functional well-being.

The motivation for assembling this Special Issue arose from the growing recognition that traditional clinical outcomes are not sufficient to capture the full experience of people living with cancer. As therapeutic advances extend life expectancy, the challenge of maintaining or restoring quality of life becomes increasingly relevant for patients, caregivers, and healthcare systems. This reprint addresses this challenge through a multidisciplinary lens, involving contributions from oncologists, psychologists, palliative care specialists, and researchers from diverse fields.

The intended audience includes clinicians, oncology researchers, healthcare policymakers, and all professionals interested in patient-centered care. We also hope this reprint will resonate with those involved in the design of supportive interventions, quality metrics, and survivorship programs.

We express our sincere gratitude to all contributing authors for their valuable work, and to the reviewers and editorial team of *Cancers* for their critical insights and support in bringing this Special Issue to completion. This reprint is the result of their collaborative effort and shared commitment to advancing a holistic vision of cancer care.

António Araújo
Guest Editor

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Article

Factors Associated with Poor Quality of Life in Breast Cancer Survivors: A 3-Year Follow-Up Study

Soo-Hyun Kim * and Ha-Yeon Jo

Department of Nursing, Inha University, Incheon 22212, Republic of Korea; dddus92@inha.edu
* Correspondence: soohyun@inha.ac.kr; Tel.: +82-32-860-8213

Simple Summary: Although quality of life (QOL) improves over time for most breast cancer survivors (BCSs), specific subgroup of BCSs may show persistently low or deteriorated QOL even after their treatment ends. Early identification of high-risk groups for QOL deterioration is crucial for quality cancer care. This study was conducted to identify subgroups of QOL change among 101 Korean BCSs, and to examine factors associated with subgroups that show poor QOL. During a 3-year observation, 22.6% of the participants showed consistently low or deteriorated QOL. Persistent symptoms of insomnia, fatigue, anxiety, depression, and comorbidity were found to be significant risk factors of poor QOL in BCS. These findings are helpful to identify high-risk groups for QOL deterioration among BCSs.

Abstract: The purpose of this study was to identify subgroups of quality of life (QOL) changes in breast cancer survivors (BCSs), and to determine factors associated with subgroups of consistently low or deteriorated QOL. We enrolled 101 women recently diagnosed with breast cancer in South Korea and asked them to complete a questionnaire at baseline (within 1 month of diagnosis), 1 year later (Year 1), 2 years later (Year 2), and 3 years later (Year 3). We assessed QOL using the global QOL subscale from the EORTC QLQ-C30. We defined low QOL as a global QOL score 10 points below the mean score of the general population. Based on low QOL as defined in this study, we identified subgroups of QOL changes over 3 years. We identified four subgroups of QOL changes: improved (47.4%), stable (30%), continuously low (8.8%), and deteriorated (13.8%), and considered the last two categories (22.6%) poor QOL. Logistic regression analyses demonstrated that significant determinants of poor QOL were insomnia at Year 1, fatigue and anxiety at Year 2, and fatigue, depression, and comorbidity at Year 3. In conclusion, persistent symptoms of insomnia, fatigue, anxiety, depression, and comorbidity are potential risk factors for poor QOL in BCSs.

Keywords: breast cancer; depression; fatigue; insomnia; quality of life

1. Introduction

Breast cancer is the most common female cancer in South Korea, as it is worldwide [1]. Due to advances in early detection and treatment, the relative 5-year survival rate for breast cancer survivors (BCSs) in high-income countries exceeds 90% [2], resulting in a constantly growing number of long-term survivors. As the number of BCSs has increased, quality of life (QOL) issues have become a vital consideration for care in this population.

Previous studies reveal that a substantial portion of BCSs suffer from long-term or late effects of cancer treatment, including pain, fatigue, insomnia, and lymphedema [3,4], ultimately decreasing their QOL [4]. In several large population-based studies, QOL in post-treatment BCSs was significantly lower than that in the general population [5–7]. Longitudinal studies on QOL among BCSs indicate that overall, QOL tends to deteriorate during the first year post diagnosis and improve in the long term [8–14].

The QOL of many BCSs recovers to that of the general population between 1 and 3 years post diagnosis [11,15]; however, specific groups continue to have a low or deteriorated QOL [16–18]. Di Meglio et al. [18] characterized long-term QOL trajectories in a

large sample (n = 4131) of BCSs. During 4 years of follow-up, 10% of participants (n = 413) showed a deteriorated QOL, and 6.6% (n = 272) showed a consistently low QOL. Similarly, Goyal et al. [17] reported that 14.2% (93/653) of a BCS cohort showed a consistently low QOL 18 months after a breast cancer diagnosis. In a study of Korean BCSs (n = 126) [16], 58.9% had a consistently low QOL from pre-chemotherapy to 6 and 12 months after chemotherapy's completion. Such subgroups that show consistently low or deteriorated QOL should be a prioritized target for survivorship care. Thus, identification of characteristics associated with this subgroup (hereafter defined as the "poor QOL group") is crucial.

Previous studies revealed that younger age, low economic status, excess body weight, comorbidity, endocrine therapy, current smoking, insufficient physical activity, and depression have been associated with long-term poor QOL [16–18]. Psychological factors, including low social support, passive coping, and less optimism have been associated [17]. Few studies, however, have examined the association of long-term BCSs' symptoms with poor QOL.

We have reported our longitudinal observations of coping style and QOL—and their association from diagnosis to 3 years post-diagnosis—among 101 BCSs [19]. Using those cohort data, we conducted a second analysis to better understand QOL changes and their correlates. The purpose of the current study was to identify subgroups of QOL changes in BCSs over 3 years after diagnosis, and to determine factors associated with this poor QOL group, including sociodemographic, clinical, lifestyle, and symptom variables.

2. Materials and Methods

2.1. Study Design and Participants

This is a secondary analysis of a longitudinal study [19] that examined the association between coping style at diagnosis and subsequent QOL for 3 years among BCSs. Included were women aged ≥19 years who had received a first-time diagnosis of breast cancer within 1 month, had a plan for cancer treatment, and were able to read and write Korean. Women were excluded if they had other cancer(s), had cognitive impairment, or were already undergoing cancer treatment. We screened 165 women and enrolled 101. The retention rate was 82.2% (n = 83) at 1 year after enrolment ('Year 1'), 85.1% (n = 86) at 2 years after enrolment ('Year 2'), and 79.2% (n = 80) at 3 years after enrolment ('Year 3'). A detailed participant flow is presented in Figure 1.

2.2. Data Collection

Between 2010 and 2011, after approval from the Institutional Review Board of Inha University Hospital in South Korea, participants were recruited within 1 month of breast cancer diagnosis. Physicians screened subjects for their interest in participating in this study, which a research nurse explained in face-to-face interviews. Women who agreed to participate were provided with an informed consent form followed by a questionnaire. Data collection was conducted 1, 2, and 3 years after enrolment. Follow-up questionnaires were mailed to participants to complete and return to the research team. Clinical information was obtained through electronic medical records after completion of primary treatment. Participants were followed until 2015.

2.3. Measures

We measured physical symptoms and financial impact using the symptom subscales and items from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), including fatigue (3 items), nausea/vomiting (2 items), pain (2 items), dyspnea (1 item), insomnia (1 item), appetite loss (1 item), constipation (1 item), diarrhea (1 item), and financial difficulties (1 item). The scoring principle and imputation of missing values follow the EORTC scoring manual [20]. Scores ranges from 0 to 100, with higher scores representing more severe symptoms. The Korean version of the EORTC QLQ-C30 has been validated [21]. In this study, the Cronbach's alpha of

the three subscales ranged from 0.62 to 0.72. In order to analyze symptom variables as binary variables, we dichotomized them using the thresholds for clinical importance (TCIs) developed by Giesinger et al. [22]. The TCIs for the symptom variables were fatigue (39), nausea/vomiting (8), pain (25), dyspnea (17), insomnia (50), appetite loss (50), constipation (50), diarrhea (17), and financial difficulties (17). These TCIs were used in a previous BCS study [18].

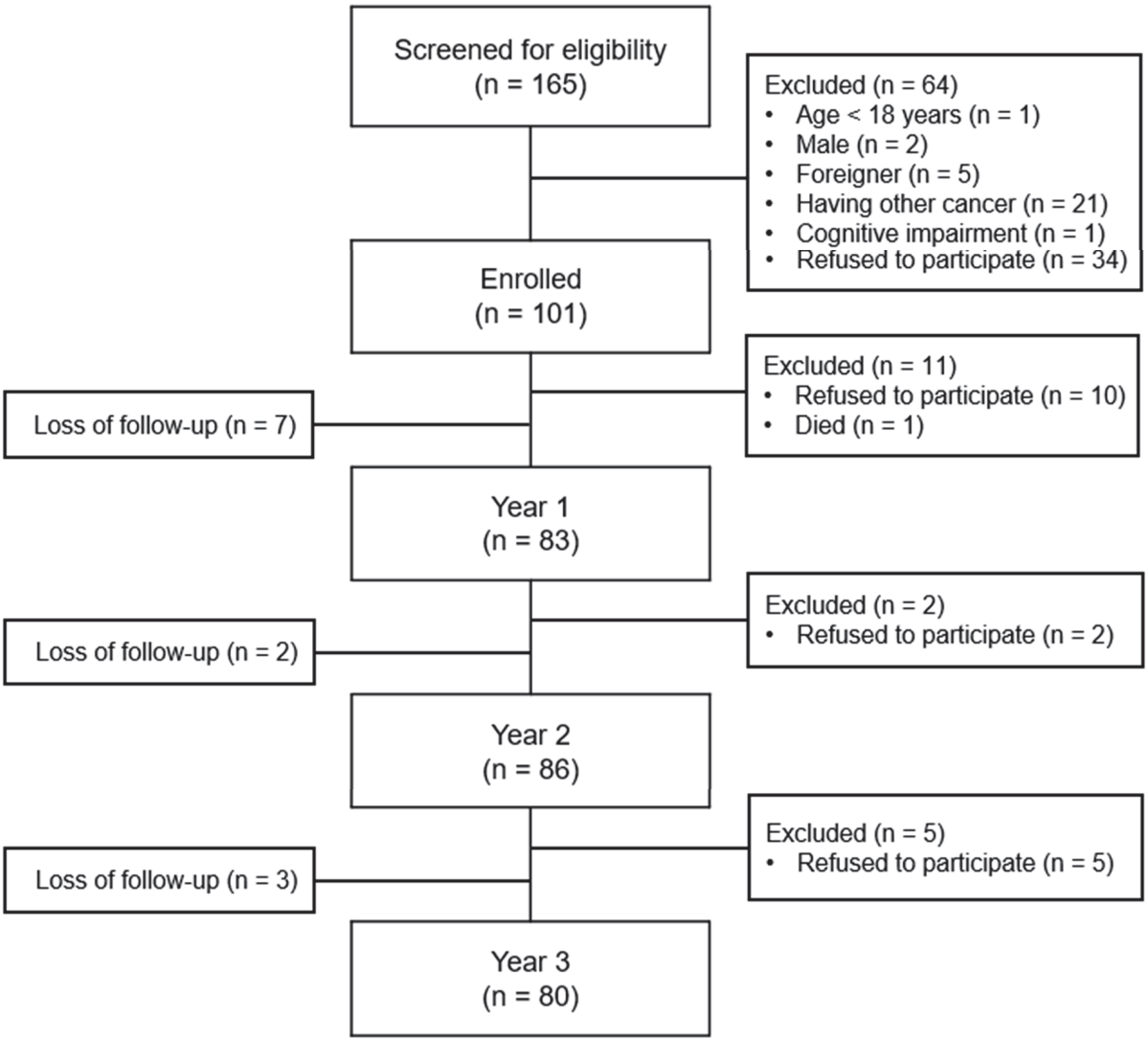

Figure 1. Flow of the study participants.

We measured QOL using the global QOL subscale (2 items) from the Korean version of EORTC QLQ-C30 [21]. The scoring principle and imputation of missing values follow the EORTC scoring manual [20]. The score ranges from 0 to 100, with a higher score representing a better QOL. In this study, the Cronbach alpha of the global QOL subscale was 0.85. To analyze the QOL as a binary variable, we dichotomized it using normative reference data. We based our binary QOL variable on whether the global QOL score had fallen more than the minimal clinically important difference (MCID) below the Korean female general population mean of 67.7 [23]. The MCID of the EORTC QLQ-C30 used was 10 points, in keeping with previous studies [24,25] and resulting in a score of 57.7 for the study cut-off. Thus, a low QOL was defined as a global QOL score of <57.7.

We measured psychological symptoms using the Korean version of the Hospital Anxiety and Depression Scale (HADS) [26]. The HADS consists of two subscales with anxiety (7 items) and depression (7 items), each on a 4-point Likert scale (0–3). The score

is obtained by summing the scores within each subscale, which ranged from 0 to 21. A higher score denotes more severe symptoms. In this study, the Cronbach's alpha was 0.86 for the anxiety subscale and 0.80 for the depression subscale. In order to analyze symptom variables as binary variables, we used a cut-off score of ≥8 for each subscale, as in a previously validated study [27].

Sociodemographic variables that we collected included age, marital status, educational level, religion, employment status, monthly income, menopausal status, and comorbidity. Clinical variables included cancer stage at diagnosis, type of surgery, and type of treatments (chemotherapy, radiation therapy, and anti-hormone therapy). Lifestyle variables included regular exercise (yes/no), tobacco use behavior (current, former, never smoking), and alcohol consumption behavior (yes/no).

2.4. Statistical Analysis

In this longitudinal study, we analysed data from at least three time points (i.e., baseline, Year 1 and/or Year 2, and Year 3), resulting in a dataset of 80 participants. We analyzed data with SPSS 26.0 software (SPSS Inc., Chicago, IL, USA), using standard descriptive measures.

We identified 4 subgroups of QOL changes. For the "improved" group, baseline QOL scores were <57.7 but increased to ≥57.7 at Year 3, regardless of Year 1 or Year 2 scores. For the "stable" group, baseline QOL scores were ≥57.7 and maintained until Year 3. For the "continuously low" group, baseline QOL scores were <57.7 and maintained until Year 3. For the "deteriorated" group, baseline QOL scores were ≥57.7 but decreased to <57.7 at Year 3, regardless of Year 1 or Year 2 scores. In this study, we clustered the "consistently low" and "deteriorated" QOL groups as the "poor" QOL group.

We performed univariate logistic regression analyses at three time points (Year 1, Year 2, and Year 3), calculating odds ratio (OR) and corresponding 95% confidence intervals (CIs) to identify potential correlates of poor QOL. Variables with a p-value < 0.05 in the univariate analyses at each time point were included in the corresponding multivariable logistic regression model. For assessing multicollinearity, we analysed the correlation coefficients among potential predictors with magnitudes of 0.80 or higher. We obtained best-fitting multivariable logistic regression models using a forward stepwise elimination procedure. We reported the adjusted OR and 95% CIs for the final models. The significance level was set at $p < 0.05$, and all significance tests were two-sided.

3. Results

3.1. Characteristics of the Participants

Table 1 presents the Year 3 sociodemographic and clinical characteristics of the participants. The mean age of the participants was 54.1 years (SD = 8.9), with most (43.7%) in their 50 s. All women received surgery; 73.8% underwent breast-conserving surgery. The majority received chemotherapy (73.8%) or radiation therapy (71.3%).

Table 1. General characteristics of the study participants (n = 80).

Characteristics	Category	*n* (%)
Age (years)	<40	3 (3.8)
	40–49	22 (27.5)
	50–59	35 (43.7)
	≥60	20 (25.0)
Marital status	Married	65 (81.3)
	Single	3 (3.7)
	Divorced/widowed	12 (15.0)

Table 1. *Cont.*

Characteristics	Category	*n* (%)
Education (*n* = 79)	Elementary school	9 (11.3)
	Middle school	17 (21.3)
	High school	42 (52.5)
	College or university	11 (13.8)
Religion	No	32 (40.0)
	Yes	48 (60.0)
Employment status	No	46 (58.2)
	Yes	33 (41.8)
Monthly income (*n* = 78)	<$2000	28 (35.9)
	≥$2000	50 (64.1)
Menopause (*n* = 77)	No	12 (15.6)
	Yes	65 (84.4)
Comorbidity [1]	No	50 (62.5)
	Yes	30 (37.5)
	Hypertension	13 (16.3)
	Diabetes	3 (3.8)
	Cardiovascular	4 (5.0)
	Musculoskeletal	5 (6.3)
	Thyroid disease	2 (2.5)
	Liver disease	2 (2.5)
	Pulmonary disease	1 (1.3)
	Others	4 (5.0)
Cancer stage at diagnosis	0	7 (8.7)
	1	29 (36.3)
	2	36 (45.0)
	3	8 (10.0)
Type of surgery	Mastectomy	21 (26.3)
	Breast-conserving surgery	59 (73.8)
Chemotherapy	No	22 (27.5)
	Yes	58 (72.5)
Radiation therapy	No	23 (28.7)
	Yes	57 (71.3)
Anti-hormone therapy	No	18 (22.5)
	Yes	62 (77.5)

[1] Multiple responses were possible.

3.2. Lifestyle and Symptoms Characteristics over Time

Table 2 displays lifestyle and symptom characteristics for 3 years after diagnosis. More than 60% maintained regular exercise across three time points, and the number who smoked decreased remarkably. Alcohol consumption behavior, on the other hand, worsened over time, with the number of drinkers increasing.

EORTC QLQ-C30 symptom results showed that fatigue, nausea/vomiting, pain, dyspnea, and insomnia were the most common symptoms across the three time points (ranging from 17.5% to 35.0%). The prevalence of these symptoms did not decrease; even the prevalence of fatigue, nausea/vomiting, and pain at Year 3 was the same or slightly greater than at Year 1. Financial difficulties were highly reported at all three time points but decreased gradually over time. The prevalence of anxiety ranged from 23.8% to 32.5%, and that of depression ranged from 23.8% to 28.7%. Two psychological morbidities improved slightly at Year 3 compared with Year 1 (Table 2).

Table 2. Lifestyle and symptoms characteristics over time (n = 80).

Variables	Year 1	Year 2	Year 3
		n **(%)**	
Lifestyle			
Regular exercise	50 (62.5)	51 (63.7)	51 (63.7)
Tobacco use	8 (10.0)	3 (3.8)	1 (1.3)
Alcohol consumption	11 (13.8)	13 (16.3)	16 (20.0)
Symptoms			
EORTC QLQ-C30			
Fatigue	17 (21.3)	23 (28.7)	18 (22.5)
Nausea/vomiting	20 (25.0)	16 (20.0)	20 (25.0)
Pain	26 (32.5)	24 (30.0)	26 (32.5)
Dyspnea	26 (32.5)	28 (35.0)	24 (30.0)
Insomnia	18 (22.5)	16 (20.0)	14 (17.5)
Appetite loss	3 (3.8)	5 (6.3)	4 (5.0)
Constipation	5 (6.3)	8 (10.0)	2 (2.5)
Diarrhea	16 (20.0)	15 (18.8)	16 (20.0)
Financial difficulties	40 (50.0)	38 (47.5)	33 (41.3)
HADS			
Anxiety	26 (32.5)	19 (23.8)	22 (27.5)
Depression	23 (28.7)	22 (27.5)	19 (23.8)

3.3. QOL Change Subgroups

Table 3 shows the frequency of low-QOL cases over time and their patterns. At baseline, 56.4% had a low QOL, but the frequency gradually decreased to 33.7% at Year 1, 23.3% at Year 2, and 22.5% at Year 3. Among the QOL change subgroups, 47.4% showed an improved QOL, 30% were stable, 8.8% showed a continuously low QOL, and the QOL of 13.8% deteriorated. Thus, 22.6% of cases showed a poor QOL.

Table 3. Quality of life (QOL) change patterns.

	n **(%)**
Cases with low QOL	
Baseline (n = 101)	57 (56.4)
Year 1 (n = 83)	28 (33.7)
Year 2 (n = 86)	20 (23.3)
Year 3 (n = 80)	18 (22.6)
QOL change subgroups	
Improved	38 (47.4)
Stable	24 (30.0)
Continuously low	7 (8.8)
Deteriorated	11 (13.8)

3.4. Univariate Logistic Regression Analyses for Poor QOL

Among sociodemographic and clinical factors, only comorbidity was significantly associated with poor QOL. Type of surgery showed borderline significance (p = 0.052), while no lifestyle factors showed any association. Among symptom variables, dyspnea, insomnia, and anxiety at Year 1; fatigue, pain, insomnia, anxiety, and depression at Year 2; and all symptoms except for diarrhea at Year 3 were significantly associated with poor QOL (Table 4). Due to their low frequency, smoking and constipation were not available for analysis at Year 3.

Table 4. Univariate logistic regression analyses for poor QOL.

Variables		OR	95% CI	*p*
Sociodemographic				
Age ≥ 50 years		1.263	0.418–3.815	0.679
No spouse		0.968	0.272–3.446	0.960
Education < high school		1.584	0.524–4.790	0.415
No religion		1.062	0.362–3.111	0.913
Not employed		1.152	0.399–3.327	0.794
Monthly income < $2000		2.065	0.713–5.986	0.182
Menopausal		3.896	0.467–32.374	0.209
Having comorbidity		4.889	1.590–15.028	0.006
Clinical				
Stage 2–3 (ref. stage 0–1)		1.875	0.625–5.629	0.262
MRM (ref. BCS)		3.015	0.991–9.175	0.052
Receiving chemotherapy		2.209	0.572–8.540	0.251
Receiving radiation therapy		0.547	0.181–1.651	0.284
Receiving anti-hormone therapy		1.021	0.289–3.601	0.974
Lifestyle				
Year 1	Exercises regularly	1.015	0.037–3.356	0.980
	Smokes	1.167	0.214–6.348	0.858
	Drinks	0.313	0.037–2.653	0.287
Year 2	Exercises regularly	1.128	0.372–3.425	0.831
	Smokes	7.600	0.645–89.574	0.107
	Drinks	0.557	0.111–2.782	0.476
Year 3	Exercises regularly	0.871	0.280–2.709	0.811
	Drinks	0.677	0.169–2.705	0.581
Symptoms				
Year 1	Fatigue	1.603	0.479–5.367	0.444
	Nausea/vomiting	2.399	0.777–7.409	0.128
	Pain	2.647	0.900–7.790	0.077
	Dyspnea	3.594	1.208–10.688	0.021
	Insomnia	5.889	1.840–18.845	0.003
	Appetite loss	1.765	0.151–20.658	0.651
	Diarrhea	1.783	0.526–6.040	0.353
	Financial difficulties	1.000	0.350–2.586	>0.999
	Anxiety	3.594	1.208–10.688	0.021
	Depression	2.507	0.837–7.504	0.100
Year 2	Fatigue	13.520	3.938–46.423	<0.001
	Nausea/vomiting	2.600	0.790–8.555	0.116
	Pain	5.923	1.918–18.295	0.002
	Dyspnea	2.263	0.776–6.599	0.135
	Insomnia	3.747	1.149–12.221	0.028
	Appetite loss	6.000	0.919–39.185	0.061
	Diarrhea	2.000	0.582–6.867	0.271
	Financial difficulties	2.037	0.697–5.953	0.193
	Anxiety	7.361	2.290–23.664	0.001
	Depression	7.286	2.307–23.010	0.001
Year 3	Fatigue	8.281	2.518–27.231	0.001
	Nausea/vomiting	4.636	1.497–14.361	0.008
	Pain	4.924	1.620–14.996	0.005
	Dyspnea	5.923	1.918–18.275	0.002
	Insomnia	7.467	2.130–26.172	0.002
	Appetite loss	12.200	1.184–125.717	0.036
	Diarrhea	1.190	0.332–4.271	0.789
	Financial difficulties	2.120	0.732–6.136	0.166
	Anxiety	3.769	1.245–11.414	0.019
	Depression	7.361	2.290–23.664	0.001

QOL, quality of life, CI = confidence interval, OR = odds ratio, MRM = modified radical mastectomy, BCS = breast-conserving surgery.

3.5. Multivariable Logistic Regression Analyses for Poor QOL

Multivariable logistic regression analyses for poor QOL were conducted at three time points. Before conducting the analyses, multicollinearity was checked using a correlation matrix between potential predictors. No multicollinearity problem was found. The correlation coefficients between potential predictors for the Year 1 model ranged from −0.223 to 0.329, those for the Year 2 model ranged from −0.270 to 0.511, and those for the Year 3 model ranged from 0.225 to 0.498.

In the model for Year 1, only insomnia was significantly associated with poor QOL; in the model for Year 2, fatigue and anxiety were significantly associated with poor QOL; and in the model for Year 3, comorbidity, fatigue, and depression were significantly associated with poor QOL (Table 5).

Table 5. Multivariable logistic regression analyses for poor QOL.

Time Points	Variable	aOR	95% CI	*p*
Year 1	Insomnia	5.889	1.840–18.845	0.003
Year 2	Fatigue	22.783	4.493–115.515	<0.001
	Anxiety	13.985	2.627–74.461	0.002
Year 3	Comorbidity	5.056	1.275–20.051	0.021
	Fatigue	9.070	2.167–37.954	0.003
	Depression	6.540	1.641–26.069	0.008

QOL = quality of life, aOR = adjusted odds ratio, CI = confidence interval. Variables entered into the Year 1 model were type of surgery, dyspnea, insomnia, and anxiety; variables entered into the Year 2 model were type of surgery, fatigue, pain, insomnia, anxiety, and depression; and variables entered into the Year 3 model were type of surgery, comorbidity, fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, anxiety, and depression.

4. Discussion

Although QOL improves over time for most BCSs, some women may have consistently low or deteriorated QOL (defined as poor QOL in this study). We identified subgroups of QOL changes using longitudinal cohort data and sought to examine characteristics that relate to the poor QOL group. We believe that our results provide important evidence for the development of a care program for those survivors who are at risk of a poor QOL during their follow-up period.

The four subgroups of QOL changes that we identified among BCSs were characterized by improved (47.4%), stable (30.0%), consistently low (8.8%), and deteriorated (13.8%) QOL. Interestingly, in Di Meglio et al.'s study [18] of 4131 BCSs, the patterns of QOL changes were quite similar to ours, although their sample was larger: excellent (51.7%), very good (31.7%), deteriorated (10.0%), and continuously low (6.6%). Goyal et al. [17] identified six subgroups of QOL changes among 653 BCSs: consistently high (36.0%), recovery to high (10.3%), consistently medium (26.5%), recovery to medium (13.0%), consistently low (10.3%), and consistently very low (4.0%). Considering our results along with previous studies, approximately 15–20% of BCSs may be at risk of poor QOL after cancer treatment. These women constitute a prioritized target for a survivorship care programs.

On the other hand, we found a marked difference in the proportion of survivors in the consistently low group (8.8% vs. 58.9%) compared with Park et al.'s study of 126 BCSs [16]. This discrepancy might result from the difference in treatment characteristics of the participants; all Park et al.'s [16] subjects had received chemotherapy [16], while ours had not. In addition, they tracked QOL after chemotherapy and at 6 and 12 months after its completion, while we followed-up QOL at 1, 2, and 3 years after diagnosis. This means that Park et al.'s [16] sample would have been more significantly affected by treatment than ours, which might have caused the higher proportion of those individuals in the consistently low QOL group.

Early identification of high-risk groups for poor QOL is crucial for prevention of QOL deterioration. From this clinical perspective, our findings provide important results by exploring potential risk factors for poor QOL at each time point. Among Year 1 variables, we found insomnia to significantly increase risk of poor QOL, which was consistent with

Lee et al. [8], who also found that increased insomnia among BCS was significantly associated with deteriorated QOL 1 year after diagnosis. Insomnia is one of the five most burdensome long-term issues in BCS [28]. In the current study, the prevalence of insomnia was highest at Year 1 (22.5%), and persisted. Insomnia is a major side effect of anti-hormone therapy (e.g., tamoxifen). Many BCSs initiate this therapy during the first year, and this might cause insomnia. Natural menopause may also be a cause. In South Korea, the most common age for breast cancer diagnosis is 40–50 years, so menopause might be the cause of insomnia in many. Our results suggest that screening for insomnia and appropriate interventions should be required, particularly in the first year of treatment. Evidence-based guidelines from the National Comprehensive Cancer Network (NCCN) [29] recommend cognitive behavioral treatments (e.g., relaxation therapy, stimulus control, sleep restriction) for insomnia in cancer survivors. Such approaches are preferred over pharmacologic interventions as a first choice [29].

Among Year 2 variables, we found fatigue and anxiety to significantly increase poor QOL risk. Fatigue is one of the most distressing symptoms among all cancer survivors, and approximately a third of BCSs report chronic fatigue [30]. In this study, the prevalence of fatigue was highest at Year 2 (28.7%) and decreased to 22.5% at Year 3, which was slightly higher than at Year 1 (21.3%). Our results support the finding that fatigue persists even after cancer treatment ends. Consistent with our findings, Lee et al. [8] reported that persistent fatigue among BCSs was a significant predictor of deteriorated QOL. Currently, fatigue management is well established, and therapies, including physical activity, psychoeducational intervention, mindfulness-based stress reduction (MBSR), and cognitive behavioral therapy [29], need to be applied more actively in clinical practice.

Many cancer survivors do not have psychiatric clinical diagnoses, but still have psychological symptoms such as anxiety and depression, which can have a negative impact on QOL. Anxiety or depression affects up to 29% of cancer survivors, and the symptoms do not necessarily resolve with time [29]. At Year 1 in our study, 32.5% of BCSs had anxiety, and 28.7% had depression. This prevalence did not resolve at Year 3. Anxiety was found to be a risk factor for poor QOL at Year 2, as was depression at Year 3. Those findings were in line with previous longitudinal studies [10,16,17]. In a 14-month longitudinal study on QOL among 83 BCSs, Hsiao et al. [10] found that increased anxiety and depression predicted worse QOL. Appropriate interventions include a strong recommendation of regular physical activity [29]. In fact, evidence suggests that exercise may be as effective as antidepressants in the treatment of depression [31]. Other alternative treatments include yoga, tai chi, and MBSR [29]. Mindfulness is possibly the best-studied alternative treatment for psychological distress in cancer survivors. For example, in a randomized controlled trial among 322 BCSs, Lengacher et al. [32] found that a 6-week MBSR program significantly reduced anxiety and fear of recurrence.

Among Year 3 variables, comorbidity, fatigue, and depression significantly increased risk of poor QOL. Comorbidity is an important issue among cancer survivors because cancer and/or its treatment increases the risk of comorbidities such as cardiovascular disease, diabetes mellitus, and osteoporosis [33]. Several cross-sectional studies of BCSs have revealed comorbidity severity to be associated with a decrease in QOL [9,34,35]. In Schoormans et al.'s study of BCSs [35], the negative impact of comorbidity on QOL increased with time after diagnosis. Specifically, cardiovascular disease and depression were the strongest associates. Among longitudinal studies, Di Meglio et al. [18] also found severity of comorbidity to be significantly associated with deteriorated QOL. Longitudinal studies about the impact on QOL of specific types of comorbidities, however, are still lacking. Further research is required.

Unexpectedly, we could not find anything significant regarding lifestyle factors. Di Meglio et al. [18] found that insufficient physical activity and tobacco smoking were significantly associated with deteriorated QOL, suggesting the importance of a healthy lifestyle. The small sample size in our study may have diminished its power to detect

significant results. Moreover, the number of smoking women was too small for analysis. Due to these methodological flaws, definite conclusions cannot be drawn.

Our finding of no significant sociodemographic-, disease- or treatment-related factors was unexpected. Prior longitudinal studies demonstrated that sociodemographic factors such as age [14,16,18,34], education [8,17], economic status [16,18], and employment status [8] were significant correlates of continuously low or deteriorated QOL. In addition, clinical factors such as chemotherapy [8,17], type of surgery [10], and endocrine therapy [18] were found to have a significant correlation with QOL. From a clinical perspective, those findings yield a better understanding of where particular attention could be given to specific groups, such as survivors who are younger and/or belong to a low social class. This study's non-significant findings may be attributed to the small sample size. Hence, further research with larger sample sizes is needed.

4.1. Implications

Our finding of the poor QOL of post-treatment BCSs is evident from symptom problems. Since persistent insomnia, fatigue, anxiety, and depression were found to increase the risk of poor QOL, their periodic screening and effective interventions should be incorporated into clinical practice. Since comorbidity may also increase poor QOL risk, referrals should be made during the survivorship period. Our results may be valuable for guiding the development of a survivorship care program for post-treatment BCSs.

4.2. Limitations

This study had several limitations. First, the study sample was enrolled from a single institution in South Korea, which limits its generalizability. Second, our sample size was relatively small, so it may have not detected low-frequency subgroups of QOL changes, thus increasing the likelihood of a Type II error. Future studies from other institutions and larger sample sizes are required. Third, given its secondary analysis nature, this study did not include other psychological factors (e.g., coping, social support, self-efficacy) likely to affect QOL change. Fourth, the EORTC QLQ-C30 used in this study is not a breast cancer-specific measurement, which may limit our ability to identify the QOL of breast cancer survivors. Lastly, our data are somewhat outdated. Thus, caution is needed in the interpretation of the study results.

5. Conclusions

This study identified subgroups of QOL changes in BCSs for 3 years after diagnosis. Most BCSs maintained or recovered their QOL over time, but 22.6% showed continuously low or deteriorated QOL. Persistent symptoms, such as insomnia, fatigue, anxiety, and depression, as well as comorbidity, were found to be potential risk factors for continuously low or deteriorated QOL. The findings offer clinically important insight for the development of interventions to preserve QOL in post-treatment BCSs, including periodic symptom assessment and management, as well as timely referral for comorbidity management.

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Article

Work Ability in Patients with Chronic Myeloid Leukemia: A Danish Nationwide Cohort Study

Eva Futtrup Maksten [1,*], Jonas Faartoft Jensen [1], Gitte Thomsen [1], Ditte Rechter Zenas [1], Maren Poulsgaard Jørgensen [1,2], Lene Udby [3], Kirsten Fonager [2,4] and Marianne Tang Severinsen [1,2]

1 Department of Haematology, Clinical Cancer Research Center, Aalborg University Hospital, 9000 Aalborg, Denmark; j.faartoft@rn.dk (J.F.J.); gith@rn.dk (G.T.); maren.joergensen@rn.dk (M.P.J.); m.severinsen@rn.dk (M.T.S.)
2 Department of Clinical Medicine, Aalborg University, 9000 Aalborg, Denmark; k.fonager@rn.dk
3 Department of Haematology, Zealand University Hospital, 4000 Roskilde, Denmark; lud@regionsjaelland.dk
4 Department of Social Medicine, Aalborg University Hospital, 9000 Aalborg, Denmark
* Correspondence: efm@rn.dk

Simple Summary: Patients with chronic myeloid leukemia (CML) often live as long as their peers due to treatment. However, the treatment has side effects that can interfere with work ability. The aim of this study was to determine work ability among patients of working age diagnosed with CML. This was established using the Danish registers. Patients with CML were compared with their peers without CML of same age and sex. A total of 489 patients with CML and 2445 peers were included. The peers were more likely to hold a job up to 10 years after the time of diagnosis. Moreover, patients with CML needed permanent disability compensation due to loss of work ability more often. The findings are important as work ability has a high impact on the quality of life for many persons, including patients with cancer.

Abstract: Background/Objectives: Patients with chronic myeloid leukemia (CML) have a long life expectancy due to modern treatment. However, treatment may have adverse effects that hamper work ability. **Methods**: Patients aged 25–60 years diagnosed in 2002–2020 were included in this nationwide matched cohort study examining work ability from diagnosis (index date), including the need for permanent disability compensation (flexible job or disability pension). Each patient was matched 1:5 on sex, birth year, and level of comorbidity with citizens from the general Danish population without CML. The risks of requiring flexible job and disability pension were calculated by cause-specific hazard ratios (HRs) using Cox proportional hazards regression, and the Aalen–Johansen estimator was used to determine cumulative risks. **Results**: A total of 489 patients with CML and 2445 matched comparators were included. The median age was 46 years, and males comprised 59.5% of the cohort. Matched comparators were more likely to work at index date and 1, 3, 5, and 10 years after the index date ($p < 0.001$). The HRs of requiring both flexible job (HR 8.7 (95% confidence interval (CI): 6.1;12.2, $p < 0.001$)) and disability pension (HR 3.7 (95% CI: 2.8;4.9, $p < 0.001$)) were higher among patients diagnosed with CML compared to matched comparators. The cumulative risk of requiring flexible job and disability pension also increased in patients with CML compared to matched comparators ($p < 0.001$). **Conclusions**: Patients with CML have a reduced work ability compared to the general population. More research is needed to determine the cause of their loss of ability to work.

Keywords: chronic myeloid leukemia; work disability; cancer treatment adverse events; quality of life in cancer patients

1. Introduction

Chronic myeloid leukemia (CML) is a chronic Philadelphia-positive myeloid neoplasia which saw a dramatic change in survival after the introduction of the first Tyrosine Kinase Inhibitor (TKI) in 2001. The follow-ups of participants in clinical trials show a 10-year survival now exceeding 80% [1,2]. After a few months of treatment, most patients attain a normalization of bone marrow function, and all signs of the cancer vanish within the bone marrow. Patients are therefore often expected to live a normal life in every context.

However, the treatment often comes with adverse effects. Musculoskeletal pain, fatigue, nausea, diarrhea, and headache are common long-term adverse effects of TKI treatment. Both CML itself at the time of diagnosis and the later adverse effects may affect the patients' ability to work. Ability to work is highly relevant in patients with CML, as it is a significant factor for quality of life [3]. An earlier study has shown that patients with CML are among the patients with hematological cancer that have the highest rate of return to work after diagnosis, but information on their work ability after the initial return to work is unknown [4]. Moreover, compared to other patients with hematological cancer, the proportion of patients with CML who have a permanently reduced work ability, which induces the granting of work disability compensation, is high [5,6]. Two recent French studies have shown that 65% of patients with CML are in need of work modifications, and more than 40% have at least one period of sick leave within the first two years after treatment initiation [7,8]. But there is a lack of studies on long-term work ability in patients with CML within the TKI era. Earlier studies have only included short-term follow-ups [7,8] or included patients diagnosed within the pre-TKI era [4–6].

As the Danish welfare system allows for compensation in case of reduced work ability, it is a unique setting for evaluating work function after the diagnosis of CML. The aim of the present study was to assess long-term work ability among patients diagnosed with CML in the TKI era and to assess the need for permanent work disability compensation compared to matched comparators without CML from the Danish population.

2. Materials and Methods

2.1. Study Population

Patients aged 25 to 60 years with a first-time diagnosis of CML between 1 January 2002 and 31 December 2020 were included in this study. Patients were identified through the Danish National Pathology Registry and the Danish National Chronic Myeloid Neoplasia Registry using the Danish pathology codes (the Danish version of the Systematized Nomenclature of Medicine (SNOMED) codes M98633 and M98753 [9,10]). The date of diagnosis was defined as the index date.

Patients granted any pension (disability, early retirement, or retirement) or flexible job (granted to persons with permanent partly reduced work ability) before the diagnosis of CML were excluded. Furthermore, patients not living in Denmark at the time of the diagnosis were excluded.

A cohort of matched comparators without CML was identified with individuals drawn from the Danish Civil Registration System (CRS) [11,12]. Each patient was matched randomly without replacement with five comparators using sex, birth year, and level of comorbidity as matching variables. The level of comorbidity was calculated 180 days before the date of diagnosis (or a corresponding date for matched comparators) using a modified Charlson comorbidity index (CCI) excluding leukemia [13–15]. The CCI was calculated

based on information from the Danish National Patient Register and supplemented with information from the National Prescription Registry (diabetes treated by general practitioners) and the Danish Psychiatric Central Research Register (dementia diagnosed by psychiatrists) [16–20]. All matched comparators were living in Denmark at the index date (the corresponding patient's date of diagnosis) and were not previously diagnosed with CML or granted flexible job or any pension (disability, early retirement, retirement) before the index date.

2.2. Outcomes and Confounders

The Danish welfare system ensures economic support when a citizen is either temporarily or permanently unable to work. In case of temporary sick leave, the citizen is paid their normal salary by the employer, which after four weeks is partly reimbursed by the state. In the case of unemployment, the sickness benefit is paid directly to the citizen by the state. If the work ability is permanently reduced, the citizen can either be granted flexible job or disability pension. Flexible job is granted if work ability is partly lost. In this case, work hours and obligations are scheduled according to the citizen's work ability with salary compensation for the discrepancy between the actual worked hours and a normal full-time work from the state. If the work ability is completely lost, the citizen can be granted disability pension with full compensation from the state. Data on social payments including sick leave and pensions are available and updated weekly in the DREAM registry (Danish acronym for "The evaluation of the extent of the marginalisation based on registries") [21]. All payment codes in DREAM were categorized into working, unemployed, sick leave, flexible job, disability pension, early retirement pension, retirement pension, or unclassified (Supplemental Table S1). For the sub-analysis looking at work ability state proportions over time from the index date, early retirement and retirement pension were combined into one to avoid personally identifiable data due to small groups. Patients and matched comparators were excluded from this sub-analysis at the time of censoring or death.

The first date of the first week with a social payment for disability pension, early retirement pension, retirement pension, or flexible job was used as the date of the respective type of social payment. The employment status before the index date was calculated as the predominant status from week thirty-five to week twenty-seven before the index date. The twenty-six-week skip was inserted to ensure that symptoms of undiagnosed CML did not influence the evaluation of work ability before diagnosis.

Cohabiting status and the highest educational level were categorized according to the status the year before index date. The educational level was grouped in four based on the ISCED11 level (ISCED 0–2, 3, 5–6, and 7–8) retrieved from the Danish Education Registries [22,23].

Equalized income (corresponding to the total disposable income for the household adjusted to the size of the household by the OECD-modified equivalence scale) was obtained the year before the index date from The Income Statistics Register [24,25]. The equalized income was grouped into four based on the patients' and matched comparators' age and their year of inclusion. The method is described in detail elsewhere [26].

2.3. Statistical Analysis

Baseline characteristics for both CML patients and matched comparators were presented as frequencies and percentages for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Overall survival was computed using the Kaplan–Meier estimator and differences between patients with CML and matched

comparators were tested using a log-rank test. Median follow-up was calculated using the reverse Kaplan–Meier estimator.

In the primary analysis, the distribution of individuals in relation to work ability status was examined at each week following the index date. Fischer's exact test was used to test whether the proportion of working, sick leave, flexible job, and disability pension differed between patients with CML and matched comparators at 1, 3, 5, and 10 years after the index date. In this analysis, participants were removed from the risk set when censored (31 December 2021 or emigration) or at the time of death.

In the secondary analysis, participants were followed from the index date until the work ability event (date of either disability pension or flexible job), competing event (eventual future CML diagnosis for matched comparators, death, early retirement pension, or date of entitlement to retirement pension), or censoring (31 December 2021 or emigration), whichever occurred first. Age at entitlement to retirement pension depends on birth year and is listed in Supplemental Table S2. The cumulative risks of disability pension and flexible job were calculated using the Aalen–Johansen estimator, and differences between patients and matched comparators were tested using Gray's test [27,28]. For the cumulative risk of requiring flexible job, disability pension was also treated as a competing event. Also, crude cause-specific hazard ratios (HRs) of disability pension and flexible job were calculated using Cox proportional hazards regression. Visual inspection of the Schoenfeld residuals was used to confirm the assumption of proportional hazards.

An exploratory analysis investigating the factors associated with the risk of flexible job and disability pension among patients with CML at 5 years after diagnosis was performed by the calculation of risk differences (RDs) in subgroups of patients with CML using a pseudo-observation approach. Both crude RDs and RDs adjusted for sex and age (25–36, 37–48, and 49–60 years) were presented.

All analyses were performed in SAS version 9.4 (SAS Institute Inc, Gary, NC, USA) and R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients and Matched Comparators

This study included 489 patients with CML and 2445 matched comparators with a median age of 46 years. The male sex was dominant (59.5%). Patients with CML were more prone to receive sick leave compensation six months before diagnosis than matched comparators (6.1% vs. 3.4%, Table 1). Patients with CML and matched comparators were followed for a median of 8.7 years (95% confidence interval [CI]: 7.9;9.6 years) and 9.3 years (95% CI: 9.0;9.6, Supplemental Table S3), respectively. Overall survival differed between patients and matched comparators ($p < 0.0001$, Supplemental Figure S1).

3.2. Work Ability

The work ability after the index date for patients and matched comparators is shown in Figure 1. At index date, only 50.1% of the patients were working, as opposed to 86.3% of the matched comparators ($p < 0.001$). The proportion of patients in work also differed from matched comparators at 1, 3, 5, and 10 years after the index date ($p < 0.001$). Furthermore, the proportion of sick leave differed between patients and matched comparators at index date and 1, 3, and 5 years after the index date, with a higher proportion of patients needing sick leave compared to matched comparators ($p < 0.001$–0.024). Finally, the proportion of flexible jobs and disability pensions differed at 1, 3, 5, and 10 years after the index date, with a higher need for permanent disability compensation among patients ($p < 0.001$, Table 2).

Table 1. Baseline characteristics for patients with CML and matched comparators. Abbreviations: CML, chronic myeloid leukemia; CCI, Charlson comorbidity index; ISCED, International Standard Classification of Education.

	Patients with CML (*n* = 489)	Matched Comparators (*n* = 2445)
Age, median (IQR)	46 (39–54)	46 (38–54)
Age group, *n* (%)		
25–36 years	101 (20.7%)	503 (20.6%)
37–48 years	181 (37.0%)	902 (36.9%)
49–60 years	207 (42.3%)	1040 (42.5%)
Sex, *n* (%)		
Male	291 (59.5%)	1455 (59.5%)
Female	198 (40.5%)	990 (40.5%)
CCI prior to diagnosis, *n* (%)		
0	406 (83.0%)	2030 (83.0%)
1	50 (10.2%)	250 (10.2%)
≥2	33 (6.7%)	165 (6.7%)
Cohabiting status, *n* (%)		
Living alone	118 (24.1%)	677 (27.7%)
Living with partner	366 (74.8%)	1744 (71.3%)
Unknown	5 (1.0%)	24 (1.0%)
Education level (ISCED), *n* (%)		
ISCED 0–2	98 (20.0%)	436 (17.8%)
ISCED 3	232 (47.4%)	1126 (46.1%)
ISCED 5–6	97 (19.8%)	595 (24.3%)
ISCED 7–8	48 (9.8%)	225 (9.2%)
Unknown	14 (2.9%)	63 (2.6%)
Equalized income, quartiles, *n* (%)		
Lowest	83 (17.0%)	493 (20.2%)
Second lowest	136 (27.8%)	577 (23.6%)
Second highest	127 (26.0%)	683 (27.9%)
Highest	138 (28.2%)	668 (27.3%)
Unknown	5 (1.0%)	24 (1.0%)
Employment status [1], *n* (%)		
Working	410 (83.8%)	2149 (87.9%)
Unemployed	42 (8.6%)	197 (8.1%)
Sick leave	30 (6.1%)	83 (3.4%)
Unclassified	7 (1.4%)	16 (0.7%)
Long-term sickness [2], *n* (%)		
Yes	59 (12.1%)	198 (8.1%)
No	430 (87.9%)	2247 (91.9%)
Year of diagnosis, *n* (%)		
2002–2007	139 (28.4%)	-
2008–2013	156 (31.9%)	-
2014–2020	194 (39.7%)	-

[1] Employment status is calculated over nine weeks from week thirty-five to week twenty-seven before index date. [2] Four or more consecutive weeks within week twenty-seven to seventy-eight before diagnosis or similar date for comparators.

3.3. Risk of Flexible Job and Disability Pension

Patients diagnosed with CML had a higher hazard rate of being granted both flexible job and disability pension compared to matched comparators, with HR 8.7 (95% CI: 6.1;12.2, $p < 0.001$) and HR 3.7 (95% CI: 2.8;4.9, $p < 0.001$), respectively. The same was evident for the cumulative risk of flexible job and disability pension ($p < 0.001$, Figure 2A,B). The 5-year cumulative risk of flexible job was 13.5% (95% CI: 10.3;16.7) for patients and 1.3% (95% CI:

0.8;1.8) for matched comparators. The 5-year cumulative risk of disability pension was 13.8% (95% CI: 10.5;17.0) for patients and 3.4% (95% CI: 2.6;4.1) for matched comparators.

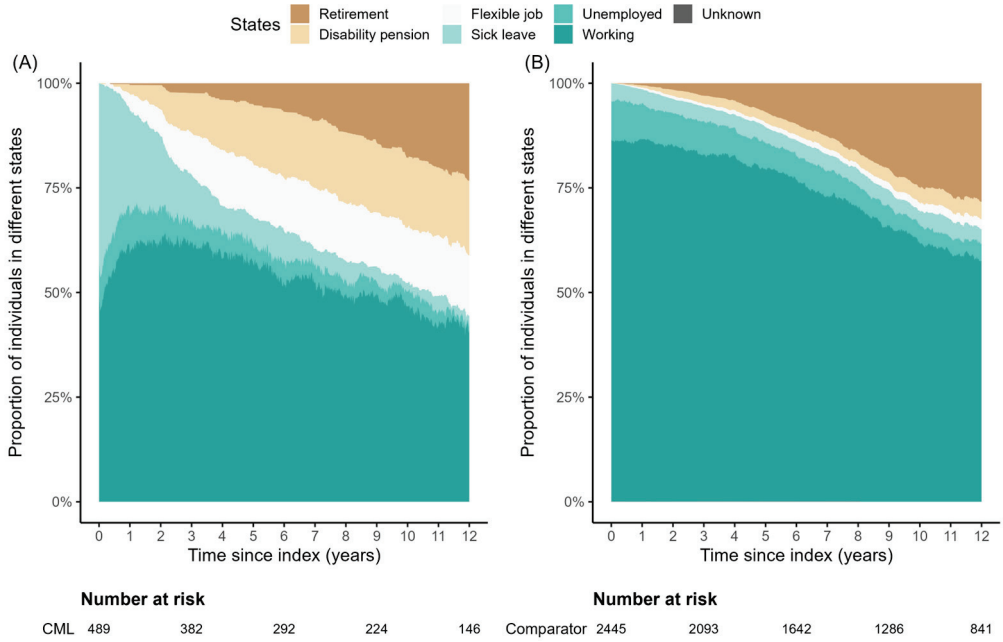

Figure 1. Work ability after index date (corresponding to date of diagnosis) for (**A**) patients with CML and (**B**) matched comparators. Retirement includes both retirement pension and early retirement pension. Number at risk included patients and matched comparators that were alive and not censored due to end of study or emigration. Abbreviations: CML, chronic myeloid leukemia.

Table 2. Proportion of patients with CML and matched comparators working or receiving sick leave, flexible job compensation, or disability pension. Abbreviations: CML, chronic myeloid leukemia.

Time Since Index (Years)	Working State	Patients with CML (%)	Matched Comparators (%)	*p*-Value
0	Working	50.1	86.2	<0.001
	Sick leave [1]	42.3	4.3	<0.001
	Flexible job	0	0	-
	Disability pension	0	0	-
1	Working	59.2	86.5	<0.001
	Sick leave [1]	25.5	3.3	<0.001
	Flexible job	3.9	0.4	<0.001
	Disability pension	2.2	0.5	0.002
3	Working	61.8	83.0	<0.001
	Sick leave [1]	11.3	3.3	<0.001
	Flexible job	9.9	0.7	<0.001
	Disability pension	9.4	1.9	<0.001
5	Working	56.8	79.3	<0.001
	Sick leave [1]	6.8	3.8	0.024
	Flexible job	12.7	1.0	<0.001
	Disability pension	14.3	2.6	<0.001

Table 2. *Cont.*

Time Since Index (Years)	Working State	Patients with CML (%)	Matched Comparators (%)	*p*-Value
10	Working	46.7	61.8	<0.001
	Sick leave [1]	2.0	3.4	0.505
	Flexible job	13.2	1.9	<0.001
	Disability pension	16.8	3.7	<0.001

[1] Sick leave only includes temporary sick leave payments.

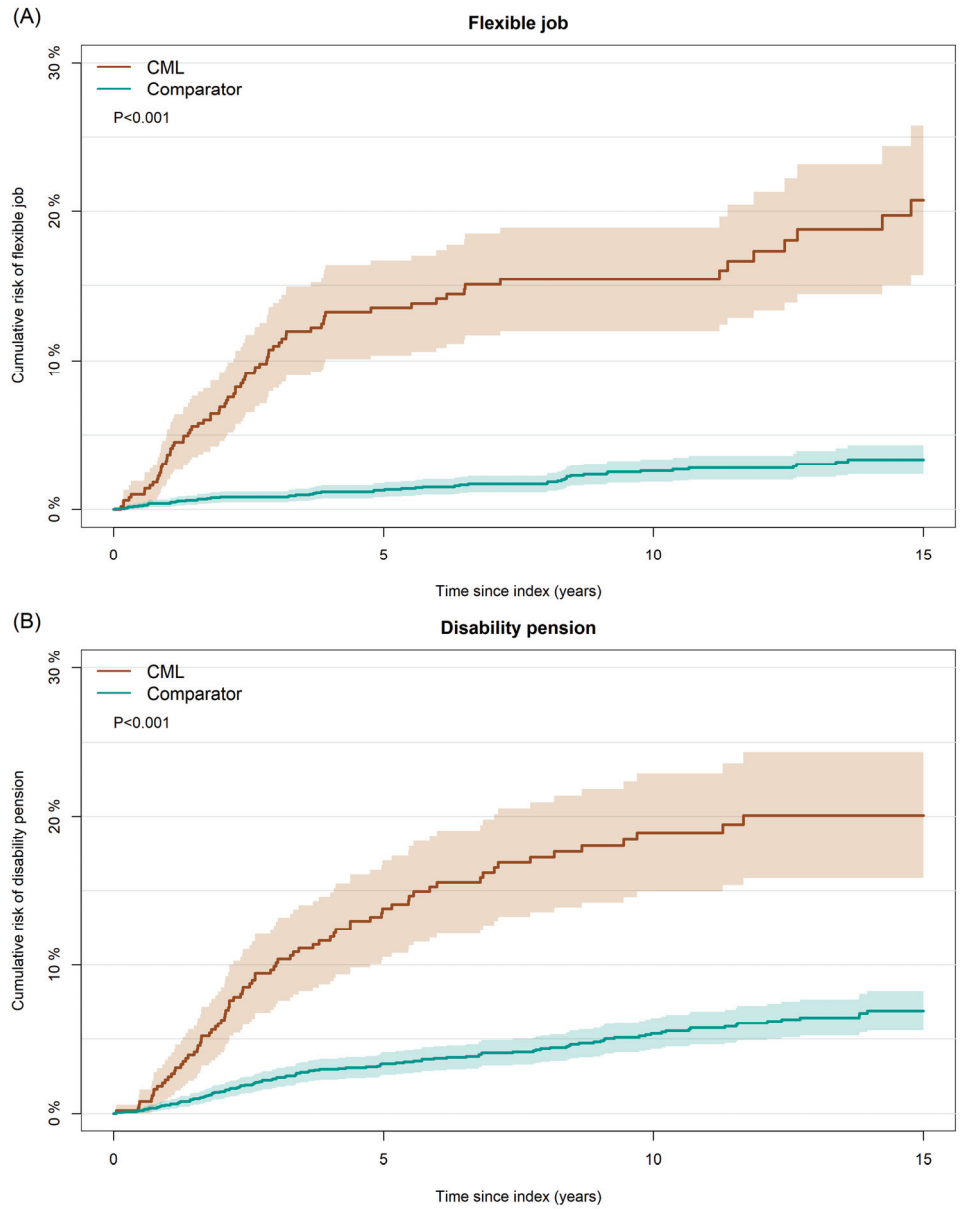

Figure 2. Cumulative risk of (**A**) flexible job and (**B**) disability pension among patients with CML and matched comparators. Abbreviations: CML, chronic myeloid leukemia.

Five years after diagnosis, the exploratory analysis identified the female sex and long-term sick leave before the index date as significant risk factors for flexible job. The risk of disability pension five years after diagnosis was significantly associated with the female

sex, higher age, living alone, lower income, and long-term sick leave before the index date. Contrary, the achievement of the second highest educational level was associated with a decreased risk of disability pension (Table 3).

Table 3. Risk of disability pension and flexible job and crude and adjusted risk difference between subgroups at five years after index date. Abbreviations: RD, risk difference; ISCED, International Standard Classification of Education; CCI, Charlson comorbidity index.

	Flexible Job			Disability Pension		
	Risk (%)	**RD (Crude)**	**RD (Adjusted) [1]**	**Risk (%)**	**RD (Crude)**	**RD (Adjusted) [1]**
Sex						
Male	7.8 (4.6;11.1)	0		9.7 (6.1;13.4)	0	
Female	21.9 (15.8;27.9)	14.0 (7.2;20.9) *		19.7 (13.9;25.5)	10.0 (3.1;16.9) *	
Age at diagnosis						
25–36 years	13.9 (6.9;21.0)	0		4.4 (0.2;8.7)	0	
37–48 years	13.3 (8.2;18.4)	−0.7 (−9.6;8.2)		12.9 (7.8;17.9)	8.6 (1.7;15.4) *	
49–60 years	13.6 (8.6;18.6)	−0.4 (−9.0;8.3)		19.5 (13.6;25.4)	14.9 (7.8;22.1) *	
Year of diagnosis						
2002–2007	16.8 (10.5;23.0)	0	0	17.5 (11.2;23.9)	0	0
2008–2013	13.5 (8.1;18.8)	−3.0 (−11.9;5.8)	−3.1 (−11.7;5.5)	12.8 (7.6;18.1)	−5.3 (−14.4;3.8)	−5.9 (−14.8;3.0)
2014–2020	11.6 (6.2;17.1)	−5.2 (−13.1;2.7)	−5.4 (−13.2;2.4)	12.5 (6.6;18.5)	−5.8 (−14.1;2.5)	−6.4 (−14.7;1.9)
Cohabiting status						
Living alone	8.8 (3.3;14.2)	0	0	18.2 (10.7;25.6)	0	0
Living with partner	14.9 (11.1;18.7)	6.1 (−0.5;12.7)	5.8 (−1.1;12.8)	12.6 (9.0;16.1)	−5.5 (−13.7;2.7)	−8.3 (−16.4;−0.2) *
Education level						
ISCED 0–2	17.0 (9.4;24.6)	0	0	21.3 (12.7;29.8)	0	0
ISCED 3	13.3 (8.8;17.9)	−3.8 (−12.9;5.3)	−3.1 (−11.9;5.7)	12.7 (8.2;17.2)	−8.8 (−18.7;1.2)	−8.1 (−17.9;1.7)
ISCED 5–6	12.9 (5.7;20.1)	−4.3 (−15.0;6.3)	−5.3 (−15.4;4.9)	10.5 (4.0;17.0)	−10.9 (−21.9;0.1)	−12.1 (−22.8;−1.5) *
ISCED 7–8	7.2 (0.0;15.1)	−9.9 (−21.1;1.4)	−9.7 (−20.7;1.3)	11.1 (1.9;20.4)	−10.3 (−23.2;2.7)	−8.8 (−21.5;3.9)
Equalized income						
Lowest	15.3 (7.3;23.3)	0	0	24.6 (14.9;34.3)	0	0
Second lowest	18.4 (11.5;25.2)	3.0 (−7.8;13.8)	3.2 (−7.6;14.0)	18.6 (11.7;25.5)	−6.6 (−18.9;5.8)	−12.3 (−24.0;−0.7) *
Second highest	12.4 (6.5;18.3)	−3.0 (−13.2;7.2)	−3.1 (−13.4;7.2)	10.4 (4.8;16.1)	−14.7 (−26.4;−3.1) *	−18.6 (−29.3;−8.0) *
Highest	8.1 (3.2;12.9)	−7.3 (−16.9;2.3)	−6.6 (−16.5;3.3)	5.5 (1.5;9.6)	−19.6 (−30.6;−8.6) *	−22.1 (−32.4;−11.9) *
Long-term sickness [2]						
No sick leave	11.5 (8.3;14.6)	0	0	11.7 (8.5;15.0)	0	0
Sick leave	28.5 (16.6;40.3)	16.9 (4.5;29.4) *	15.4 (2.9;27.9) *	28.6 (16.6;40.6)	17.1 (4.6;29.5) *	15.0 (2.7;27.4) *
CCI prior to diagnosis						
0	13.5 (10.0;17.0)	0	0	12.1 (8.7;15.4)	0	0
1	15.8 (5.0;26.6)	2.2 (−8.8;13.1)	2.5 (−8.9;13.9)	22.7 (10.2;35.2)	10.4 (−2.1;23.0)	9.2 (−2.9;21.3)
≥2	10.1 (0.0;21.1)	−3.1 (−14.5;8.3)	−3.4 (−15.4;8.7)	24.2 (6.7;41.8)	10.1 (−5.9;26.1)	7.2 (−8.4;22.7)

[1] RD (adjusted) was adjusted for sex and age (25–36, 37–48, and 49–60 years). [2] Four or more consecutive weeks within week twenty-seven to seventy-eight before diagnosis. * significant.

4. Discussion

This nationwide cohort study investigated work ability in patients diagnosed with CML compared to the Danish general population. This study revealed that patients with

CML have increased rates of both temporary and permanent reduced work ability, with cause-specific HRs of 8.7 and 3.7 for flexible job and disability pension, respectively.

Furthermore, a statistically significantly higher percentage of patients with CML needed sick leave at the time of diagnosis compared to their matched comparators. Likewise, this study revealed a tendency towards a higher percentage of patients receiving sick leave compensation six months before diagnosis. Even though some patients are asymptomatic at the time of diagnosis, other patients experience symptoms like fatigue, fever, night sweat, pain in the bones and spleen, and weight loss. Among those, especially fatigue and pain can have an impact on work ability. The results of the present study indicate that the symptoms could have an influence on everyday life before a diagnosis is established. Reduced capacity to work at the time of diagnosis was also described in a study by Svingel et al. [29]. The study examined labor market affiliation among patients with Philadelphia-negative myeloproliferative neoplasms (MPNs) and found patients with MPN to be less likely to work (patients with essential thrombocythemia, polycythemia vera, and unclassifiable MPN) and more likely to receive sick leave compensation (patients with all subtypes) compared to sex- and age-matched comparators.

The proportion of patients with CML that were able to work increased within the first year after diagnosis, probably reflecting a reduction in symptoms after treatment initiation. Since the early 2000s, the standard treatment for CML has been TKIs. TKIs are orally administrated drugs, which is much more compatible with an active work life than traditional chemotherapy [3]. However, studies have found that only 56.9% of patients are strictly adherent to the treatment, and more than half of patients experience adverse reactions, including, e.g., fatigue, musculoskeletal pain, nausea, vomiting, and diarrhea [30,31]. This could contribute to the reduced work ability among patients with CML in the present study. The proportion of patients in need of sick leave compensation was increased up to 5 years after diagnosis. This could reflect the fact that finding the right treatment takes time due to, e.g., resistance mechanisms and adverse effects [32]. Some patients may need sick leave compensation during this process. This is supported by a study by Conte et al., which showed that the proportion of patients in need of sick leave increased after the initiation of TKI treatment [8].

Short-term sick leave (comprising 14–30 days within the study period) is, according to the Danish legislation, paid by the employer and therefore not registered in the DREAM register unless a special agreement has been entered. This agreement can be entered by employees with chronic diseases, and it gives the employer full compensation from the state from the first day of an employee's absence. This absence is registered as sick leave in the DREAM register. This could also be an explanation for the higher sick leave among patients with CML compared to the matched comparators, as patients with CML are more likely to have entered this agreement. However, the proportions of sick leave after ten years were not significantly different between patients with CML and the matched comparators, which argues against this being the only explanation for the increased rates of sick leave.

The risk of permanent loss of work ability (flexible job and disability pension) was increased among patients with CML compared to matched comparators. In previous studies, this was also observed among patients with other hematological diseases, like lymphoma, multiple myeloma, and acute leukemia, but not among patients with MPNs [5,6,26,29,33]. However, the median age in the study by Svingel et al. was equal to or exceeded the age of retirement pension, hindering the granting of flexible job or disability pension [29]. The increased risk of flexible job corresponds to an increased need for individual adjusted work functions, e.g., reduced work time and modified work functions. This is similar to a study by De Barros et al., who found that within the first year after a diagnosis of CML, two out

of three patients needed work modifications, with reduced working hours being the most required [7].

Within the present study, the cumulative risk of requiring flexible job increased up to four years after diagnosis, and then after a stable period, the need increased again approximately eleven years after diagnosis. However, the risk of disability pension stabilized approximately ten years after diagnosis. In 2013, the Danish legislation on disability pension was modified to increase work maintenance, which led to fewer patients with cancer being granted disability pension [34]. For patients diagnosed early in our study period, this could have led to more patients being granted flexible job instead of disability pension.

There was a trend towards a larger proportion of matched comparators being retired >5 years after index date. Retirement included early retirement, a special retirement scheme that is possible for citizens that have paid into the scheme and who have not been granted either flexible job or disability pension. It is a possibility that matched comparators were more prone to retire using this scheme than patients with CML. Likewise, as the cumulative incidence of both flexible job and disability pension is significantly increased among patients with CML, the possibility of using the early retirement scheme is consequently reduced.

The loss of work ability is multifactorial and may be affected by both physical and physiological disorders. Being diagnosed with a chronic cancer disease may affect many aspects of life. A study by Øvlisen et al. found that patients with chronic indolent lymphoma disease were more likely to receive long-term antidepressants than patients with aggressive lymphoma [35]. This indicates that living with a chronic disease can result in other complications that may also affect the ability to work.

Within the exploratory analysis, the 5-year risks of requiring flexible job and disability pension were both associated with the female sex and a higher need for sick leave within the year before diagnosis. For disability pension alone, a higher age, living alone, and lower income also increased the risk. These factors are well-known risk factors for disability pension [36]. We found no certain correlation between the risk of a reduced work capacity and educational level, which is another known risk factor. This could be caused by the low number of patients, especially in the highest education level.

This study has several strengths, including the use of high-quality registries with almost complete data capture. As patients with CML were identified in both the Danish National Pathology Registry and the Danish National Chronic Myeloid Neoplasia Registry, the latter being mandatory for all hematological departments in Denmark to report to, a high completeness of identification of patients with CML must be anticipated. Furthermore, we were able to combine information across registries and hence assure almost complete follow-up.

The drawbacks include a lack of information on why patients and matched comparators were unable to work. Patients with CML can lose work ability for many other reasons. Within the present study, patients with CML were more likely to have long-term sick leave before diagnosis. This is a known risk factor for work disability and could have increased the risk of disability within the group of patients. Furthermore, we did not match patients and comparators on level of education, a known predictor for loss of work ability. However, the levels were reasonably distributed, even though there was a trend towards a lower level of education among patients with CML. On the other hand, the equalized income for CML patients tended to be higher. These two are often correlated, and the little differences must again be related to the small subgroups. Finally, the registries used within this study did not include information on the quality of life. As work ability is highly correlated to quality of life, this information would have been relevant to include if available.

5. Conclusions

Compared to the general population, patients with CML have a reduced work ability, demonstrated by a significantly higher risk of sick leave, flexible jobs, and disability pensions following a disease diagnosis. Flexible jobs and disability pensions are granted to patients with permanent loss of work ability, meaning that patients with CML, even though often well treated for their CML, could have a reduced quality of life due to the loss of work ability. Further studies are needed to address what causes the loss of work ability.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers17091585/s1, Figure S1: Overall survival for patients with CML and matched comparators; Table S1: Grouping of social payments and work according to DREAM codes; Table S2: Age at entitlement to retirement pension according to year of birth; Table S3: Follow-up time categorized by endpoint.

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Institutional Review Board Statement: Ethical review and approval were waived for this study as register-based research in Denmark only requires approval from the owners of the registers and a registration in the regional research registry. The relevant approvals were obtained, and this study was registered in the research registry of the North Denmark Region (F2023-185).

Informed Consent Statement: Patient consent was waived as this is not mandatory for register-based research according to Danish legislation.

Data Availability Statement: This study was performed on a secured remote research platform hosted at Statistics Denmark without the possibility to share data beside figures and tables outside the platform. Hence, no data sharing is possible.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CML	chronic myeloid leukemia
TKI	Tyrosine Kinase Inhibitor
IQR	Interquartile Range
CRS	The Danish Civil Registration System
CCI	Charlson comorbidity index
RD	Risk difference
MPN	Philadelphia-negative myeloproliferative neoplasm

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Article

The Sarcoma Assessment Measure (SAM): Preliminary Psychometric Validation of a Novel Patient-Reported Outcome Measure

Lee Hulbert-Williams [1,*], Nicholas J. Hulbert-Williams [1], Ana Martins [2], Lesley Storey [3], Jennie Bradley [4], Hatty O'Sullivan [4], Lorna A. Fern [2], Maria Lawal [2], Rachael Windsor [5], Craig Gerrand [6], Jeremy S. Whelan [2], Lindsey Bennister [7], Mary Wells [8,9] and Rachel M. Taylor [10,11]

1 Department of Psychology, Edge Hill University, Ormskirk L39 4QP, UK
2 Cancer Clinical Trials Unit, University College London Hospitals NHS Foundation Trust, London NW1 2PG, UK
3 Department of Psychology, Anglia Ruskin University, Chelmsford CM1 1SQ, UK
4 Iqvia Ltd., Reading RG1 3JH, UK
5 Paediatric Directorate, University College London Hospitals NHS Foundation Trust, London NW1 2PG, UK
6 Sarcoma Unit, The Royal National Orthopaedic Hospital NHS Trust, Stanmore HA7 4LP, UK
7 St Luke's Hospice, Sheffield S2 1GQ, UK
8 Nursing Directorate, Imperial College Healthcare NHS Trust, London W2 1NY, UK
9 Department of Surgery and Cancer, Imperial College London, London SW7 5NH, UK
10 Centre for Nurse, Midwife and Allied Health Profession Led Research (CNMAR), University College London Hospitals NHS Foundation Trust, London NW1 2PG, UK; rtaylor13@nhs.net
11 Department of Targeted Intervention, University College London, London NW1 2PG, UK
* Correspondence: lee.hulbert-williams@edgehill.ac.uk

Simple Summary: The Sarcoma Assessment Measure (SAM) is a special questionnaire for patients with sarcomas, a type of cancer. It was created with input from both patients and healthcare professionals and is meant to be used by professionals to better understand how sarcoma affects a patient's life. We tested the SAM on 762 patients who had different types of sarcomas and ranged in age from 13 to 82. We found that the SAM could be a useful tool for both researchers and healthcare professionals to assess how sarcoma symptoms impact a patient's life. However, more testing with a larger and more diverse group of patients is needed to be sure it is a good outcome measure in drug trials.

Abstract: The Sarcoma Assessment Measure (SAM) was developed as a sarcoma-specific patient-reported outcome measure to be used in clinical practice. We have reported in detail how SAM has been developed in collaboration with patients and healthcare professionals. The aim of this paper is to report the preliminary validation of SAM. The 22-item SAM was administered alongside a validated quality of life questionnaire and measure of activities of daily living. Linear modelling was used to build a measure, which had predictive validity in comparison to more established outcome measures. Of the 762 patients who participated in the study, 44.1% identified as male, and participant age ranged from 13 to 82 years. Clinically, participants presented with a range of soft tissue (82.2%) and bone (21.8%) sarcomas. Our preliminary analysis indicates that SAM accounts for 35% of the global quality of life scale and 18% of the Toronto Extremity Salvage Scale (TESS); so psychometrically, it overlaps with quality of life and activities of daily living, but also measures distinct concerns. This demonstrates that this measure picks up issues that are important to patients with sarcoma that are not reflected in other measures. We have established the preliminary validity of SAM and believe it has utility as a patient-reported outcome measure both as a research tool and for assessing the impact of symptoms and dysfunction related to sarcoma as part of clinical care. Further validation using a larger and more clinically diverse sample is now needed.

Keywords: soft tissue sarcoma; bone tumours; gastrointestinal stromal tumours; quality of life; patient-reported outcome

1. Introduction

Sarcoma is a heterogeneous group of cancers of the connective tissue, which are inclusive of over 100 subtypes presenting as soft tissue, bone tumours, and gastrointestinal stromal tumours (GIST). Tumours can therefore be present in any part of the body, with the majority presenting in the upper and lower extremities. The treatment burden for sarcoma is high, often requiring extensive surgery, high-dose chemotherapy, and radiotherapy. Sarcomas are also associated with a high risk of developing metastases, recurrence, and poorer survival in comparison to the common cancers [1–3]. Further heterogeneity exists among patients with sarcoma because they can present from birth to old adulthood, and some subtypes are a common cancer in younger people [4].

The high risk of developing metastases and recurrence has resulted in treatment pathways in many countries, including the United Kingdom (UK), to comprise annual follow-up often accompanied with a scan. Repeated hospital attendances have a significant impact on patients' emotional well-being [5], as these require patients to revisit the experiences they had at diagnosis [6]. For this and other reasons, fears of sarcoma recurrence are common [7]. Clinical consultations are driven by these emotions, so patients either focus on what their treatment options are if the scans are positive or experience relief if they are clear. This relief overwhelms everything, so patients often forget anything additional they want to discuss with their clinician [8,9]. One way to overcome this is using outcome measures within clinical practice to help direct meaningful communication between clinicians and patients. However, to be meaningful, the outcome measure needs to reflect issues that are important to the patient and are representative of the disease.

Documenting the patient-reported experience of healthcare and outcomes is now considered a central component in providing and evaluating quality cancer care in the UK [10]. Aligned to the importance of patient-reported outcomes (PRO) has been the increase in instruments to measure them. This has progressed from generic measures that can be used across all disease states, such as the Short-Form-36 (SF36) [11], to condition-specific versions, for example, the European Organisation for Research and Treatment in Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [12]. Adoption of patient-reported outcome measures (PROM) into clinical practice can improve health-related processes, outcomes, and satisfaction with care; however, significant barriers to adoption and implementation are often reported, including length and perceived burden on the clinical teams [13], fear of bringing up topics of conversation that clinicians are not trained or equipped to follow through on [14], or that more generalisable measures may not be perceived as being patient-centred enough to be clinically useful [15].

The importance of using condition- or disease-specific measures also follows the observation that generic measures are often not responsive to small changes in clinical condition and functioning, and they may overlook clinically relevant aspects related to the specific condition [16]. Interpretation of results from generic measures may also be challenging in discerning assessment of overall health in relation to the patient's specific condition. Conversely, disease-specific measures may not be comprehensive enough to allow comparison to other conditions, where the normative data from generic measures enable interpretation to be more meaningful [16–18]. Administering PROMs alongside condition-specific measures is, therefore, recommended to capture the burden of disease whilst also facilitating comparisons to other populations.

Relating specifically to the age distribution of those diagnosed with sarcoma, very few validated PROMs span all age ranges and accommodate variance relating to developmental stages. Validation in specific target populations is critical; however, it is important to ensure that PROMs can be appropriately used in clinical practice and are applicable for assessing population-specific challenges over longer periods of follow-up and surveillance.

While many generic and generic-cancer PROMs often provide an additional cancer-type module (see EORTC: https://qol.eortc.org/ (accessed on 14 January 24); FACIT: https://www.facit.org/ (accessed on 14 January 24); PROMIS: https://www.promishealth.org/ (accessed on 14 January 24)), there are currently no PROMs specific for sarcoma. Measures currently available for sarcoma include the BtDux, which is specifically for teenagers and young adults with bone tumours [19]; the Soft Tissue Sarcoma questionnaire, which specifically focuses on symptoms associated with six soft tissue subtypes [20]; the Toronto Extremity Sarcoma Scale (TESS), which measures the impact of upper and lower limb sarcoma on activities of daily living [21]; and the Gounder/DTRF Desmoid Symptom/Impact Scale (GODDESS), which has been developed for patients with desmoid tumours or aggressive fibromatosis [22].

Due to the heterogeneity of sarcoma, there have been arguments that one outcome measure could not adequately reflect the impact of all subtypes [23]. There is also a clinical perception that patient-reported outcome, especially quality of life, is influenced by sarcoma-related features, such as tumour site and subtype or type of treatment. However, evidence to date does not support differences according to type of surgery [24] or tumour location [25]. Poorer quality of life may be seen according to age; however, in adolescents and young adults reported as having poorer quality of life than older adults and the elderly [26], generic consequences of cancer treatment per se, especially pain and fatigue, have been noted to have a greater association with poorer quality of life [27,28]. The lack of specificity of existing PROMs have led to repeated calls for measures to be developed specifically for patients with sarcoma [24–26,29].

To address this existing gap in available PROMs for sarcoma, we aimed to develop and validate an outcome measure that better reflects the patient experience of living with a sarcoma diagnosis across the lifespan. The PROM was based on the following definition of health-related quality of life: "... subjective, multidimensional, and dynamic. It is unique to each individual and includes aspects of physical, psychological and social function. It is dependent upon not only the stage of development but also the illness trajectory. This involves the achievement of goals and aspirations and the constraints imposed through ill health and treatment" [30].

The study used the broad methodology employed for developing quality of life measures in cancer [31]; significantly, content selection decisions were driven by patient experience rather than researcher or clinician bias to remain true to the "subjective" aspect of the above definition. Previous reports on the development of our novel Sarcoma Assessment Measure (SAM) are presented in detail elsewhere [8,9,32], and the methods of development are presented in Figure 1 [24,32].

The SAM was developed to be a measure that could guide clinical consultations and therefore focused on the issues that were more important and impacting on patients' outcome. This phase of the study aimed to validate the SAM in a larger sample in order to derive an appropriate scoring method and assess suitability for use of the SAM in clinical care.

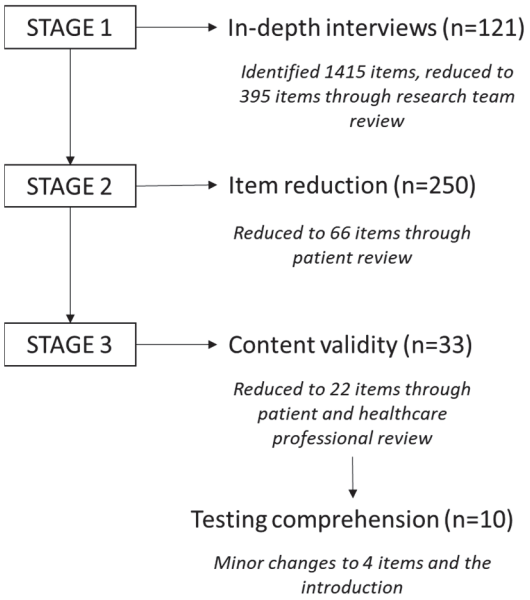

Figure 1. Summary of the development of the Sarcoma Assessment Measure (SAM) [32].

2. Materials and Methods

2.1. Study Design

This was a prospective cross-sectional survey, recruiting patients from across the United Kingdom (UK). The study was approved by the London–Riverside Research Ethics Committee (ref: 18/LO/0023) and survey administration was coordinated by Quality Health (IQVIA Ltd., Reading, UK).

2.2. Sample and Setting

Patients were eligible to participate if they had a diagnosis of sarcoma, were aged 13 or older, and were able to communicate verbally or in written English. In line with general recommendations for PROM development (e.g., Brysbaert [33]) our aim was to recruit a minimum of 220 participants (10 participants per item in SAM). However, due to the heterogeneous nature of sarcoma, a larger sample was sought in order that variance according to clinical factors could be explored [9].

Patients were recruited through three mechanisms. First, we recruited directly through participating hospitals. For young people aged 13–15 years, the study was explained to the parent/guardian, and if they were happy for their child to participate, it was explained to the young person, who then received the questionnaire if they too expressed interest. Second, we recruited through the National Cancer Patient Experience Survey (NCPES), which was coordinated by Quality Health, the original contracted hosts of the NCPES. When patients returned this survey, they had the opportunity to leave contact details to be invited to participate in future research. Patients participating in the 2014–2017 NCPES with a diagnosis of sarcoma who provided future research consent were approached for this study. Finally, we re-invited those who had participated in the development phases of the study [32]. Details of these participants were transferred securely to Quality Health. Regardless of identification method, all patients were given or sent information, and the return of the questionnaire was implicit of consent. SAM was approved by the London–Riverside Research Ethics Committee (reference 18/LO/0023), the Health Research Authority, and the Research and Development department in each participating hospital.

2.3. Data Collection

Data to test the psychometric properties of the SAM were collected using established, validated questionnaires. These were administered as a single questionnaire pack in paper format sent postally by Quality Health or given directly to patients in participating hospitals.

Patients were instructed to complete the questionnaires without help and leave anything blank that was unclear. These were returned in a pre-paid envelope. No reminders were sent to patients recruited through participating hospitals. Patients sent questionnaires by Quality Health were sent two reminders after 2 and 4 weeks, and the data collection process was entirely managed by Quality Health.

The version of the SAM used in this study (version 1.0) contained 22 items, each scored on a 5-point Likert-type scale ranging from "strongly agree" to "strongly disagree", with the option of responding as "not applicable" (see tables in results section for included items). The purpose of this study was to establish whether any items were redundant and to establish a method of scoring the SAM.

Alongside our novel SAM, we included two additional questionnaires with established reliability and validity in cancer patients. These were selected due to the frequency with which they have previously been used in other studies involving patients with sarcoma [24]. First, we included the EORTC QLQ-C30 [12], a 30-item measure of quality of life, incorporating 9 multiple-item scales: 5 functional scales (physical, role, emotional, social, and cognitive); 3 symptom scales (fatigue, pain, and nausea and vomiting) and a global health and quality of life scale. Five single items assess the physical symptoms of dyspnoea, insomnia, appetite, diarrhoea, and constipation, and 1 item evaluated the financial impact of the disease. The first 28 items on the questionnaire are rated on a response scale from 1 ("not at all") to 4 ("very much"), and compose the functioning, symptom, and financial difficulties scales. Items 29 and 30, which assess global health/QOL, use a response scale ranging from 1 ("very poor") to 7 ("excellent"). Scores on the EORTC QLQ-C30 are transformed to a 0–100-point scale. Higher mean scores for the functional scales and global health status/QOL scale represent better functioning and overall QOL. While the QLQ-C30 is demonstrably reliable and valid for patients over 18 years, it has also been used in younger adolescents [34]. Higher mean values for the multi-item symptom scales and higher scores for single items represent more frequent and/or more intense symptoms and a higher financial impact.

Second, we included the TESS. There are two versions of the TESS to reflect upper and lower extremity limitations in daily life, such as restrictions in body movement, mobility, self-care, and performance of daily tasks and routine [21]. These are commonly used in clinical practice in patients with extremity sarcoma. Items reflect activities of daily living that could be impacted by upper/lower limb disability rather than treatment side-effects. With permission from the author (personal correspondence), the upper and lower extremity versions were combined so it could be administered as a single measure. It included 17 unique upper and 16 lower extremity items, and 13 that were common across both (total of 46 items). Patients can answer questions concerning activities they do not perform in daily life with "not applicable." The degree of physical disability is rated from 0 (not possible) to 5 (without any problem). Higher total scores indicate fewer functional limitations. The two final items, which related to overall perceptions of activity and disability, were left as stand-alone items.

2.4. Analysis

Neither traditional factor analytic approaches using the classical test theory (CTT) nor the alternative item response theory (IRT) approaches were suitable for this kind of checklist measure. Both CTT and IRT approaches assume that within a potential new measure, items will group together because they are each assessing a different aspect of a coherent underlying psychological construct; for example, the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith [35]) is suitable for these analyses because a sub-set of items collectively assess anxiety as a construct, and the remainder assess depression. Here, we had developed a list of items that could be best described as a problem checklist: not all participants were expected to identify with the relevance of all items (e.g., not everyone will be using a prosthesis or taking painkillers). Though the items on the checklist might all be caused by sarcoma, there is substantial variation in the

presentation of sarcoma such that the measure would not meet the strict assumption of causation by a latent variable which underlies CTT and IRT (see Loehlin and Beaujean [36] for a discussion).

An alternative approach might have been to ask respondents to weight each item on the perception of importance, as has been done with psychometric scales such as the Social Readjustment Rating Scale [37]. However, Cox et al. [38] warn against such approaches, as subjective weighting techniques can be erratic and lead to implausible conclusions. As Cox et al. (p. 34) conclude: "Given the general lack of a pre-eminent weighting scheme, a prudent course includes checks on the robustness of conclusions to alternative, but still arbitrary, choices of weighting schemes".

Consequently, to test whether a scoring scheme might be desirable in principle, we adopted a pragmatic approach to calculating a total score. First, we undertook a separate regression analysis for each item of the SAM to calculate how much each one predicted global QOL as measured by the EORTC QLQ-C30 (our measure of convergent validity). To minimise respondent burden, it is generally desirable to remove items which contribute poorly to convergent validity, and so we removed the three items which predicted 0% of the variance in global QOL (rounded to two decimal places). We then compared two approaches of calculating an overall score: first, a simple mean score from all items; and second, a weighted mean with weights determined by their regression coefficient of prediction of global quality of life. We used an odd-even data split, creating Subsamples A and B, to avoid over-fitting the data: the first sample (odd numbered respondents) was used to create scoring weights using the regression analysis, and the second sample (even numbered respondents) was used to calculate total scores on which to test comparative efficacy of the two approaches. Given the level of "not applicable" responses, we adopted a generous cut-off for pro-rating in calculating total scores: where 10 or more items had been completed, a mean score was generated from the questions they did answer. Higher scores represent better functioning.

3. Results

Valid questionnaires were received from a total of 762 participants (Table 1). The majority of patients had soft tissue sarcoma (72%) and were off treatment (77%). Despite our best efforts to recruit a younger sample, the mean age was 63 years (SD = 17).

Table 1. Characteristics of participants.

Characteristic		Number	%
Gender	Male	349	46
	Female	407	54
	Unknown	6	
Marital status	Married/civil partnership/long-term relationship	479	64
	Widowed	88	12
	Single	71	9.5
	Cohabiting	59	7.9
	Divorced	50	6.7
	Unknown	15	
Sexuality	Heterosexual/Straight	669	96
	Prefer not to say	13	1.9
	Gay or Lesbian	9	1.3
	Bisexual	6	0.9
	Unknown	65	
Gender identity	Cisgender	685	99.7
	Transgender	2	0.3
	Unknown	75	
Age	13–39	84	11
	40–64	231	31
	65+	434	58
	Unknown	14	

Table 1. *Cont.*

Characteristic		Number	%
Ethnicity	White	714	95
	Asian/Asian British	17	2.3
	Black/African/Caribbean/Black British	11	1.5
	Mixed	5	0.7
	Other	2	0.3
	Unknown	13	
Employment status	Employed	213	28
	Retired	380	52
	In education/training	15	2
	Other	129	17
	Unknown	27	
Type of sarcoma	Soft tissue	549	72
	Bone	166	22
	GIST	78	10
	Multiple	46	6
Site of tumour	Lower limb	209	27
	Abdominal organ	143	19
	Head and neck	133	17
	Pelvis	76	10
	Upper limb	74	9.7
	Chest	57	7.5
	Spine	25	3.3
	Other	186	24
Amputation	No	614	84
	Not applicable (did not have surgery)	63	8.6
	Yes	54	7.4
	Unknown	31	
Treatment	Surgery alone	274	37
	Surgery and radiotherapy	177	24
	Chemotherapy and surgery	121	17
	Surgery, radiotherapy and chemotherapy	65	8.9
	Chemotherapy alone	39	5.3
	Radiotherapy and chemotherapy	20	2.7
	Radiotherapy alone	16	2.2
	No treatment	12	1.6
	None of these combinations [1]	9	1.2
	Unknown	29	
Current status	On treatment	169	23
	Being followed up only	551	77
	Unknown	42	

GIST: gastrointestinal stromal tumour. [1] A treatment combination not specified above.

The mean score on the TESS was 180 (SD = 52; N = 614). Of the total sample, 68 (9.1%) rated their participation in activities of daily living as being "extremely difficult" or "impossible" to do, and 34 (4.5%) stated that they were either "severely disabled" or "completely disabled". For this paper, we used only the QLQ-C30 global quality of life score; within this sample, we recorded a mean score of 70.3 (SD = 20.6).

3.1. Acceptability of the SAM

Table 2 summarises the number of respondents and the median and inter-quartile range (IQR) of the scores for each item. Sixteen questions were responded to by more than 75% participants. The six questions with a lower response related to items targeted at specific groups: amputations (questions 5 and 6), extremity surgery (question 4), younger patients (questions 8 and 19), and those experiencing pain (question 7).

3.2. Scoring the SAM

Table 3 summarises results from the regression coefficient models in which we used each item of the SAM to predict global QOL. Based on these data, three items predicted <2% of the variance (number 2, 11, and 15), so these were removed from further analysis.

Table 2. Acceptability of the items in the SAM, including the number of missing/not applicable responses.

Item	N	IQR			Missing or N/A
		Median	Lower	Upper	
1. I do whatever I can to keep healthy	753	4	4	5	9
2. I am more conscious of what I eat since I was diagnosed with sarcoma	728	4	3	4	34
3. I can do everything without help	735	4	2	5	27
4. My arm/leg is not as strong as it was before diagnosis	482	4	3	5	280
5. My prosthesis is heavy and uncomfortable	109	3	2	4	653
6. My prosthesis fits well enough to do the things I want to	104	4	2.75	4	658
7. My painkillers don't take all the pain away	264	4	3	4	498
8. I worry about whether I will be able to have a family	118	3	1	4	644
9. I worry that my sarcoma may return	666	4	3	5	96
10. I feel anxious before my scan/appointment	697	4	3	4	65
11. Since my diagnosis I appreciate everyday things more	735	4	4	5	27
12. I have not accepted how sarcoma has changed my body	658	2	2	3	104
13. I try to keep a sense of humour	740	5	4	5	22
14. I focus on what I can do rather than what I can't do	696	4	4	5	66
15. I try and cope emotionally on my own	707	4	4	5	55
16. I put fears about my sarcoma to the back of my mind	727	4	3	4	35
17. I have friends/family I talk to about things I worry about	728	4	4	5	34
18. I am self-conscious of my physical appearance	604	3	2	4	158
19. I have been able to go back to work/university/school	327	4	2	5	435
20. My friends/family treat me normally	719	5	4	5	43
21. I find the costs of travelling to and from the hospital difficult to meet	573	2	2	3	189
22. My treatment for sarcoma has affected my intimacy with others	610	3	2	4	152

Table 3. Regression models predicting global quality of life from each SAM item (using Subsample A).

Item	Beta	Std Error	*t*	*p*	Adj. R^2
1. I do whatever I can to keep healthy	7.06	1.51	4.69	<0.001	0.05
2. I am more conscious of what I eat since I was diagnosed with sarcoma	0.04	1.04	0.04	0.969	0
3. I can do everything without help	7.99	0.68	11.8	<0.001	0.28
4. My arm/leg is not as strong as it was before diagnosis	−2.88	1.02	−2.82	0.005	0.03
5. My prosthesis is heavy and uncomfortable	−7.99	2.05	−3.9	<0.001	0.25
6. My prosthesis fits well enough to do the things I want to	7.66	2.54	3.02	0.004	0.17
7. My painkillers don't take all the pain away	−4.6	1.54	−2.98	0.003	0.06
8. I worry about whether I will be able to have a family	−3.34	1.76	−1.89	0.063	0.04
9. I worry that my sarcoma may return	−4.7	1.13	−4.15	<0.001	0.05
10. I feel anxious before my scan/appointment	−2.27	0.94	−2.41	0.017	0.01
11. Since my diagnosis I appreciate everyday things more	0.01	1.25	0.01	0.992	0
12. I have not accepted how sarcoma has changed my body	−5.92	0.93	−6.36	<0.001	0.11
13. I try to keep a sense of humour	7.13	1.74	4.09	<0.001	0.04
14. I focus on what I can do rather than what I can't do	5.6	1.47	3.82	<0.001	0.04
15. I try and cope emotionally on my own	1.39	1.11	1.25	0.212	0
16. I put fears about my sarcoma to the back of my mind	4.17	1.03	4.05	<0.001	0.04
17. I have friends/family I talk to about things I worry about	4.2	1.18	3.56	<0.001	0.03
18. I am self-conscious of my physical appearance	−4.87	0.87	−5.62	<0.001	0.09
19. I have been able to go back to work/university/school	6.49	1.04	6.23	<0.001	0.2
20. My friends/family treat me normally	8.78	1.38	6.38	<0.001	0.1
21. I find the costs of travelling to and from the hospital difficult to meet	−3.24	0.98	−3.31	0.001	0.03
22. My treatment for sarcoma has affected my intimacy with others	−5.59	0.88	−6.34	<0.001	0.12

Pearson's r correlation tests were then used to compare correlations between the weighted and unweighted mean scores with both global quality of life and TESS total scores (see Table 4). The SAM weighted mean score explained 1.7% more variance in total TESS scores and approximately 1.2% extra variance in global QOL than the simple unweighted mean. The SAM therefore explained 34.8% of the variance in global QOL and 18.5% of TESS.

Table 4. Correlation coefficients of both scored versions of the SAM against construct validity measures (using Subsample B).

Parameter 1	Parameter 2	r	CI	t	*p*	Method	N
C30 global QOL	SAM total prorated	0.58	[0.51, 0.65]	13.14	<0.001	Pearson	338
C30 global QOL	SAM total weight prorated	0.59	[0.51, 0.65]	13.24	<0.001	Pearson	338
TESS total	SAM total prorated	0.41	[0.31, 0.51]	7.58	<0.001	Pearson	279
TESS total	SAM total weight prorated	0.43	[0.33, 0.52]	7.93	<0.001	Pearson	279

TESS: Toronto Extremity Salvage Score; QOL: quality of life.

4. Discussion

The purpose of this study was to develop an outcome measure that could be used to guide clinical consultations. We also wanted to be able to derive a scoring formula to enable patients and/or clinicians to monitor changes over time. Health models suggest clinical care only contributes to 20% of clinical outcome [39], and therefore, we wanted to base the content of the measure on the aspects of living with a sarcoma diagnosis that were most important to patients. While some authors equate "experience" to "experience of healthcare" [23]—the biomedical model of assessing outcome—we aimed to take a more holistic person-centred approach. Patients are more than their illness, and after a sarcoma diagnosis, we strive to support patients to reintegrate to their pre-diagnosis lives or to find their "new normal" [8,9]. Having an outcome measure that goes beyond symptoms is therefore important. Whilst symptom-based items were included in SAM, (e.g., pain), the measure assessed the personal impact of that symptom, for example, whether it was manageable using pain-relieving medications.

The conceptual basis for the SAM was a model of quality of life [30], so it included items related to the three domains of health (physical, emotional, and social functioning) [40]. However, it was interesting to note in the development phase of SAM, there was a preponderance of items rated highly important and impactful by patients within the emotional well-being domain [32]. This concurs with previous literature demonstrating a prevalence of anxiety and depression in patients with sarcoma in a fifth to a third of patients [41,42]. We have also identified fear of recurrence as having a significant impact on patients' lives [5], which was higher than reports in other types of cancer [7]. Given the seemingly higher weighting patients place on the emotional impact of sarcoma, and the relatively superficial exploration of this in the literature, this is an area that warrants more detailed investigation.

Based on our regression analyses, we excluded three of the twenty-two items from further analysis (2. I am more conscious of what I eat since I was diagnosed with sarcoma; 11. Since my diagnosis I appreciate everyday things more; 15. I try and cope emotionally on my own). Given our sample size, we are confident that these items do not contribute to our knowledge of the impact of sarcoma for most participants and so can be excluded from future iterations of the SAM.

Our results show that a weighted mean score on the SAM explained slightly more variance in TESS total scores than a simple mean, suggesting that not all questions are equally important in predicting outcomes. It is likely that for maximised predictive validity, future users of the SAM may want to apply a weighting in calculating total scores. Whilst we provide the regression weights from our sample, researchers and clinicians will need to decide whether our sample is sufficiently similar to their own participants and clients in deciding whether to use these weights or to re-weight the items based on fresh data. It is

also worth noting that the increased validity lent to SAM by using a more complex scoring approach is apparently minimal, so users may prefer to calculate a more parsimonious unweighted total score.

During the development of SAM, there appeared to be increased awareness across the sarcoma community of patient-reported outcomes and an interest in using SAM, not just for clinical practice, but also as an endpoint in clinical trials and biomarker studies, e.g., ICONiC (Improving Outcome Through Collaboration in Osteosarcoma). The lack of sensitivity and/or specificity of existing generic cancer PROMs [24] has highlighted the challenge of including these in research in sarcoma if there is the potential no difference will be detected over time. Consequently, there have been several subtype-specific PROMs developed for leiomyosarcoma, synovial sarcoma, liposarcoma, or undifferentiated [20] and desmoid tumours or aggressive fibromatosis [22]. These are undoubtably valuable during the treatment phase of the patient journey, but we found a significant flooring effect with the EORTC QLQ-C30 symptom scales; given most of our participants were off treatment, this suggests that these were not symptoms experienced by this broader population of cancer survivors. As patients with sarcoma were not included in the development of the original EORTC measure and given that it was developed over 30 years ago when treatment for sarcoma was quite different, this is not surprising. It also raises the question whether a PROM developed from a biomedical perspective or focused more on the physical aspects of health will be suitable as an outcome in complex intervention trials, for example, those testing psychological and behavioural interventions.

We are confident that SAM has clinical relevance, especially as clinicians and patients were involved in every stage of the development and testing. However, we are cautious about the use of the current version as a sole outcome measure in biomedical studies, as this is beyond the reason for its development. We are currently making changes to the wording and structure of SAM, for example, adding filter questions for those items targeted at specific populations, e.g., amputees, childbearing age. We are now revalidating SAM-2 with these additional changes to be a PROM that can be used in research.

Limitations

The current study had several limitations. First, although we aimed to capture a broad range of participants through multiple recruitment methods, we had under-representation of patients with GIST. The number of adolescents and young adults participating was also small (11%), so whilst the SAM as presented here might reflect the sarcoma-related experience overall, it may miss the nuances of developing sarcoma at this earlier life stage, which is recognised as being a challenging time to be diagnosed with cancer [43–45]. Further validation in these groups may therefore be required. Second, we struggled with the amount of missing data in this dataset because of the response options provided to participants. It is obvious from the list of items that not all items in SAM will be applicable to all sarcoma patients. For example, not all will be taking painkillers (item 7) or living with a prosthesis (items 5 and 6). Closer analysis of these items shows that although a substantial number of participants responded, "not applicable", a large proportion also missed these items out entirely. We can assume here that some participants were leaving the question blank because it was irrelevant to them. A consequence of this is that we cannot be certain that data in SAM were missing not at random, which complicates how we can interpret and deal with missing data [46]. It will be necessary in developing the next version of SAM to alter item response options. One way to do this might be to replace statements of agreement with statements of scale of the problem (i.e., instead of strongly disagree to strongly agree, we could use definitely not a problem for me to definitely a problem for me). Alternatively, it might be possible to present the "not applicable" option in a way that makes the explicit meaning clearer; for example, for item 5 ("my prosthesis is heavy and uncomfortable") the "not applicable" option could be clarified as "I don't wear a prosthesis", or for Item 7 it could be clarified as "I don't take painkillers". Finally, while we recruited a large number of participants, we had no mechanism to track the number of patients who were approached,

and therefore we do not know the response rate. This would be helpful as an indicator of importance to patients but would also provide an estimate for future studies using SAM. Despite these limitations, this study recruited a substantial number of people who had been diagnosed with a range of sarcoma types, from across the UK, and represents the first PROM for patients with all types of sarcomas. Moreover, we were able to demonstrate the broad applicability and acceptability of a PROM designed to capture the holistic experience of those living both with and beyond treatment for sarcoma.

5. Conclusions

Our study aimed to validate a PROM for patients aged 13 onward with sarcoma. We are confident that SAM provides a comprehensive patient-reported outcome of multiple domains of the impact of sarcoma and its treatment, and that it is possible to generate a meaningful score of the total impact for individual patients. Given correlations with both global quality of life and total TESS scores, the SAM has high clinical relevance and could be a useful adjunct to clinical consultation discussions. Importantly, we have demonstrated that SAM picks up issues that are important to patients with sarcoma that are not reflected in other measures. With some minor alterations to response options, our data indicate that SAM is likely a useful outcome measure for treatment trials and patient experience research in this population.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available on request from the authors.

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cancers

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Article

Immunotherapy in Elderly Patients—Single-Center Experience

Maria João Ramos [1,*], Ana Sofia Mendes [1], Raquel Romão [1], Joana Febra [1] and António Araújo [1,2]

[1] Medical Oncology Department, Centro Hospitalar Universitário de Santo António, 4099-001 Porto, Portugal; u12649@chporto.min-saude.pt (A.S.M.); antonio.araujo@chporto.min-saude.pt (A.A.)
[2] Oncology Research Unit, UMIB—Unit for Multidisciplinary Research in Biomedicine, ICBAS—School of Medicine and Biomedical Sciences, Universidade do Porto, 4050-346 Porto, Portugal
* Correspondence: mjoao.rglr@gmail.com; Tel.: +351-22-207-7500

Simple Summary: The rising global aging population poses a notable challenge in cancer management due to increased cancer incidence with age. The use of immune checkpoint inhibitors (ICI) in the treatment of different solid tumors presented as a less toxic alternative compared to chemotherapy treatment for elderly patients. However, the age-related remodeling process of the immune system, termed immunosenescence, is hypothesized to impact the efficacy of ICI in the geriatric oncology population. This study provides additional evidence to support the safety and efficacy of ICI in the treatment of elderly cancer patients by using a retrospective, single-center cohort design to analyze survival outcomes and the response rate of 220 patients. Overall, the study challenges the notion of age as a sole determinant for treatment decisions, highlighting the importance of comprehensive geriatric assessments for personalized cancer care in the elderly and the need for further research in this area.

Abstract: Cancer management faces a substantial challenge posed by the aging demographic. Aging is marked by accumulated DNA damage, and this phenomenon is implicated in the process of tumorigenesis. The concept of immunosenescence, postulated to manifest in elderly individuals, is defined by an age-related decline in T cells and a simultaneous elevation in proinflammatory status, leading to a diminished efficacy in response to immunotherapy. Notably, despite the rising prevalence of cancer in the elderly population, their underrepresentation in clinical trials persists. This underscores the unmet need to evaluate the safety and efficacy of cancer treatment in the elderly. This retrospective, single-center cohort study aimed to assess and evaluate the effectiveness and safety of immunotherapy in patients compared to younger individuals with metastatic solid tumors receiving ICI. A total of 220 patients were included, mostly males, with a median age of 64. The proportion of patients $\geq$ 65 years old was 56.5%. The use of ICI showed no significant differences concerning overall survival (OS) and progression-free survival (PFS) among age groups across different cancer types (melanoma, non-small-cell lung cancer (NSCLC), renal, and bladder cancer; p = 0.388). Concerning the response to treatment in renal cancer patients, a significant difference was observed (p = 0.041), suggesting a potential negative impact of age on the treatment response. In patients that presented immune-related adverse events (irAEs), oral corticosteroid therapy was marginally associated (p = 0.059) with the elderly population. When evaluating the NSCLC population alone (n = 131, 59.5%), our study revealed a strong association between the development of irAEs, patients' PFS and OS, and the duration of ICI treatment, but not directly correlated with age. The NSCLC elderly population presented a marginally greater number of irAEs, although without statistical significance (p = 0.86). ICI maintained efficacy and safety in elderly patients, challenging the notion that age alone should determine treatment decisions. The findings emphasize the necessity of a comprehensive geriatric assessment rather than relying solely on chronological age for personalized cancer treatment in the elderly population. Further prospective studies are needed to better understand immune responses in older adults and derive predictive biomarkers for cancer treatment.

Keywords: elderly cancer patients; immune checkpoint inhibitors; geriatric oncology; survival; prognosis

1. Introduction

The World Health Organization (WHO) delineates individuals as elderly if they are 60 years or older in developing countries and 65 years or older in developed countries [1]. The global demographic landscape is on the brink of a significant transformation, with the anticipated tripling of the population aged 80 years or older by 2050, soaring from 143 million in 2019 to a projected 426 million [2]. This surge is predominantly fueled by the dual forces of population aging and growth [3]. The escalating burden of cancer incidence and mortality mirrors the profound impact of aging, population expansion, and shifts in the prevalence and distribution of key cancer risk factors, many of which are intertwined with socioeconomic development [3–5].

Aging, characterized as a time-dependent decline in the functionality of living organisms, is intricately linked with cancer progression [4,6,7]. Despite research positing aging as a potential tumor-suppressor mechanism, the abnormal behavior of most senescent cells poses significant threats, potentially culminating in tumor development [6]. Accumulated DNA damage, a pivotal driver of senescence, and the events associated with cellular senescence have been implicated in the process of tumorigenesis. Notably, systematic senescence, where the scale gradually increases and affects the entire system, is a prerequisite for the manifestation of senescent phenotypes and age-related diseases, such as malignant tumors [7–9].

Proposed by Walford in 1964, immunosenescence is characterized by diminished adaptive immunity, reduced infection resistance, and an increased autoimmune risk [10]. This natural process of immune system aging results in a decline in immune function, thereby influencing various aspects of immune functional networks and increasing the risk of cancer [11–13]. The hallmarks of immunosenescence are age-related declines in coping capacity and concurrent increases in proinflammatory status, a phenomenon termed "inflammaging" by Claudio Franceschi in 2000 [14]. The concept of "inflammaging" signifies a systemic state of chronic low-grade inflammation characterized by heightened blood inflammatory markers, serving as a central pillar of the aging process. Factors such as genetics, exercise, nutrition, prior exposure to microorganisms, gender, and human cytomegalovirus infection exert considerable influence on this inflammatory status [14–17]. Thymic involution stands out as an important change, affecting both innate and adaptive immune systems, with certain immune cell types exhibiting varying degrees of susceptibility [18,19].

The tumor response of innate and adaptive immune systems differs between young and elderly individuals, yet the clinical impact and underlying mechanisms remain largely elusive. For instance, T cells, the primary effectors of acquired immunity, undergo substantial aging-related defects that contribute to immune system damage, increased disease susceptibility, and the occurrence of malignant tumors in the elderly [16,20]. Aging emerges as a paramount risk factor for most cancers, with projections indicating that, by 2050, approximately 6.9 million new cancer cases will be diagnosed in individuals aged 80 years or older worldwide, constituting 21.5% of global cases across all age groups [2].

Despite the significant increase in elderly individuals with cancer, their representation in clinical trials remains inadequate, comprising less than 10% of cancer patients over 75 years old [21–23].

More recently, the development of immune checkpoint inhibitors (ICI) has revolutionized treatment for a larger group of patients with locally advanced/metastatic disease [24]. Two different ICI have been the most investigated: the PD-1/PD-L1 inhibitors and the CTLA-4 inhibitors. ICI are generally considered as safe agents. Notably, when compared with chemotherapy or other systemic treatments, ICI are associated with a low rate of high-grade adverse events (AEs) and, generally, a more tolerable profile, as detected by

quality-of-life assessment [24]. For these reasons, the introduction of ICI in the front-line palliative treatment of diverse tumor types led to reconsidering the treatment paradigm in elderly patients.

Lung cancer is predominantly a disease of the elderly. According to the 2023 annual report of the American Cancer Society, about 80% of newly diagnosed NSCLC patients were 65 years of age or older, reflecting the advanced median age of diagnosis (71 years) [25].

Consequently, most of the available evidence about elderly patients concerns NSCLC, and meta-analyses have been conducted to assess the safety and efficacy of ICI in these patients. Overall, in the pretreated setting, comparable efficacy was observed in older and younger adults treated with ICI monotherapy using a cut-off of 65 years. However, in a meta-analysis of 12 randomized clinical trials (RCT), OS benefit with mono-immunotherapy was not observed when considering a cut-off of 75 years [26].

Despite this, studies and clinical trials evaluating the effects of host age on ICI outcomes are limited, and the impact of the elderly microenvironment on immunotherapy responses is often overlooked [27–29].

Consequently, a comprehensive understanding of ICI tolerance and effects in the elderly remains elusive [29–31]. The age-related remodeling process of the immune system, termed immunosenescence, is hypothesized to impact the efficacy and toxicity of ICI in the geriatric oncology population [31–33].

This study aimed to assess the effectiveness and safety of immunotherapy in elderly patients (defined by the WHO definition as $\geq$65 years old) compared to younger individuals (<65 years old) with solid tumors in a palliative care setting.

2. Materials and Methods

2.1. Patient Population

This was a retrospective, single-center cohort study of patients aged 18 years or older, with histologically or cytologically confirmed metastatic solid tumors (melanoma, renal cancer, NSCLC, and bladder cancer) who received at least one dose of ICI (pembrolizumab, nivolumab, ipilimumab, avelumab, and atezolizumab) as a single therapy, administered intravenously, at Centro Hospitalar Universitário de Santo António from July 2012 to January 2022. Patients with prior ICI therapy and patients with incomplete data were excluded.

2.2. Data Collection

Demographic data, such as patients' age, Eastern Cooperative Oncology Group (ECOG) performance status, diagnosis date, date of widespread disease confirmation, histology type, number of metastasis locations, metastasis location, prior therapeutic regimens, number of doses of ICI, immune-related adverse events (irAEs) graded according to Common Terminology Classification Adverse Events (CTCAE) version 5.0, tumor response based on Response Evaluation Criteria in Solid Tumors version 1.1, progression date, and death date or last follow-up visit, were all retrieved from the patients' digital health records.

2.3. Statistical Analysis

Descriptive statistics were presented as means and standard deviations for normally distributed variables and medians and quartiles otherwise. For categorical variables, frequencies and percentages were presented. Statistical tests included chi-square tests or Fisher's exact tests for assessing associations between categorical variables. The use of chi-square or Fisher's exact tests was based on the Cochran rules. Mann–Whitney tests were used to compare continuous variables after checking normality with the Kolmogorov–Smirnov test and histograms.

The objective response rate (ORR) was defined as the percentage of patients who have a confirmed complete response (CR) or partial response (PR) to the treatment. The overall survival (OS) was defined as the time from the initial administration of ICI therapy until death. The progression-free survival (PFS) was defined as the time from the initial administration of ICI therapy until the documentation of tumor progression or death, whichever occurred first. At the end of the follow-up period, patients who were still alive or had not shown progression of their tumor were considered censored in the analysis.

Survival curves were generated by using the Kaplan–Meier product limit method, and differences in OS and PFS were analyzed by stratifying by age (<65 years old/≥65 years old) using the log-rank and Wilcoxon–Peto tests. Univariate and multivariate Cox regression were used to identify factors with potential prognostic significance.

Data were analyzed with SPSS, version 27.0 (IBM Corp., Armonk, NY, USA, 29.0), and $p < 0.05$ was considered significant [34].

3. Results

3.1. Patients' Characteristics

A total of 220 patients were studied, mostly males aged from 32 to 85 years old, with a mean age of 64.5 (SD = 10.0). The proportion of patients ≥ 65 years old was 56.5% (n = 122). Table 1 shows the baseline characteristics for the two groups of age.

Regarding gender distribution, a significant difference was observed between age groups. In the younger age group (<65 years old), 34.0% of the patients were females, whereas in the older age group (≥65 years old), this percentage was 21.3% ($p = 0.036$).

When examining the presence of pleural metastasis, another significant difference emerged. In the younger age group, 5.3% of patients had pleural metastasis, whereas in the older age group, a higher percentage, 17.2%, had pleural metastasis ($p = 0.008$). This finding suggests that the likelihood of developing pleural metastasis may be influenced by age. The occurrence of bone metastasis in these patients was significantly associated with age ($p = 0.030$). In the younger group, 27.7% had bone metastasis, while in the older group, 15.6% had this condition. This trend suggests a potential age-related difference in the prevalence of bone metastasis.

In addition to these significant findings discussed above, some non-significant results contributed to improving the comprehension of the study. Smoking history fell short of statistical significance ($p = 0.091$).

The proportion of patients with a history of smoking in the younger group (77.7%) was higher than that in the older group (67.2%). In patients that presented irAEs, oral corticosteroid therapy was marginally associated ($p = 0.059$) with patients ≥ 65 years of age (34.0%), when compared with patients < 65 years of age (16.7%).

The distribution of patients across ECOG scores (0, 1, and 2) was balanced in both age groups.

Concerning cancer type and histology, the analysis did not identify significant age-related differences in the distribution of cancer types ($p = 0.388$) or histology. Whether patients had melanoma, non-small-cell lung cancer (NSCLC), renal cancer, or bladder cancer did not show substantial variations between the two age groups.

Several other clinical factors, including the number of metastasis locations, the specific sites of metastasis (such as lung, lymph nodes, brain, adrenal gland, hepatic, pleural, bone, peritoneal, skin, pancreatic, and renal), the number of ICI, the specific type of ICI treatment (e.g., ipilimumab, pembrolizumab, nivolumab, atezolizumab, and avelumab), the presence of irAEs, their severity, and treatment (supportive care and/or the use of oral or IV corticosteroids), did not demonstrate statistically significant differences between the two age groups.

Table 1. Patients' baseline characteristics.

Variable	<65 Years Old	≥65 Years Old	*p*-Value
Gender			
Female	32 (34.0%)	26 (21.3%)	**0.036 (a)**
Male	62 (66.0%)	96 (78.7%)	
Smoking history			
No	21 (22.3%)	40 (32.8%)	0.091 (a)
Yes	73 (77.7%)	82 (67.2%)	
ECOG			
0	33 (35.1%)	32 (26.2%)	
1	57 (60.6%)	81 (66.4%)	0.283 (a)
2	4 (4.3%)	9 (7.4%)	
Cancer type			
Melanoma	16 (17.0%)	13 (10.7%)	
NSCLC	58 (61.7%)	73 (59.8%)	0.388 (a)
Renal Cancer	10 (10.6%)	18 (14.8%)	
Bladder Cancer	10 (10.6%)	18 (14.8%)	
Number of metastasis locations			
1	56 (59.6%)	75 (61.5%)	
2	26 (27.7%)	39 (32.0%)	0.277 (a)
≥3	12 (12.8%)	8 (6.6%)	
Metastasis location			
Lung			
No	50 (53.2%)	71 (58.2%)	0.462 (a)
Yes	44 (46.8%)	51 (41.8%)	
Lymph node			
No	60 (63.8%)	70 (57.4%)	0.337 (a)
Yes	34 (36.2%)	52 (42.6%)	
Brain			
No	85 (90.4%)	113 (92.6%)	0.562 (a)
Yes	9 (9.6%)	9 (7.4%)	
Adrenal gland			
No	86 (91.5%)	115 (94.3%)	0.427 (a)
Yes	8 (8.5%)	7 (5.7%)	
Hepatic			
No	82 (87.2%)	111 (91.0%)	0.376 (a)
Yes	12 (12.8%)	11 (9.0%)	
Pleural			
No	89 (94.7%)	101 (82.8%)	**0.008 (a)**
Yes	5 (5.3%)	21 (17.2%)	
Bone			
No	68 (72.3%)	103 (84.4%)	**0.030 (a)**
Yes	26 (27.7%)	19 (15.6%)	
Peritoneal			
No	93 (98.9%)	119 (97.5%)	0.634 (b)
Yes	1 (1.1%)	3 (2.5%)	
Skin			
No	92 (97.9%)	122 (100.0%)	0.188 (b)
Yes	2 (2.1%)	0 (0.0%)	
Pancreatic			
No	93 (98.9%)	121 (99.2%)	>0.990 (b)
Yes	1 (1.1%)	1 (0.8%)	
Renal			
No	94 (100.0%)	121 (99.2%)	>0.990 (b)
Yes	0 (0.0%)	1 (0.8%)	
Number of ICI lines			
1	51 (54.3%)	56 (45.9%)	
2	41 (43.6%)	61 (50.0%)	0.443 (a)
≥3	2 (2.1%)	5 (4.1%)	
ICI			
Ipilimumab			
No	87 (92.6%)	120 (98.4%)	**0.043 (b)**
Yes	7 (7.4%)	2 (1.6%)	
Pembrolizumab			
No	48 (51.1%)	50 (41.0%)	0.140 (a)
Yes	46 (48.9%)	72 (59.0%)	

Table 1. *Cont.*

Variable	<65 Years Old	≥65 Years Old	*p*-Value
Nivolumab			
No	62 (66.0%)	82 (67.2%)	0.846 (a)
Yes	32 (34.0%)	40 (32.8%)	
Atezolizumab			
No	87 (92.6%)	115 (94.3%)	0.613 (a)
Yes	7 (7.4%)	7 (5.7%)	
Avelumab			
No	92 (97.9%)	121 (99.2%)	0.581 (b)
Yes	2 (2.1%)	1 (0.8%)	
Toxicity			
No	52 (55.3%)	72 (59.0%)	0.586 (a)
Yes	42 (44.7%)	50 (41.0%)	
Toxicities (n = 42)			
Toxicity ≥ G3			
No	34 (81.0%)	39 (78.0%)	0.728 (a)
Yes	8 (19.0%)	11 (22.0%)	
Supportive care			
No	9 (21.4%)	15 (30.0%)	0.351 (a)
Yes	33 (78.6%)	35 (70.0%)	
Oral corticosteroid			
No	35 (83.3%)	33 (66.0%)	0.059 (a)
Yes	7 (16.7%)	17 (34.0%)	
IV corticosteroids			
No	37 (88.1%)	42 (84.0%)	0.574 (a)
Yes	5 (11.9%)	8 (16.0%)	

Results are presented as n (%); *p*-values were computed with (a) chi-square tests or (b) Fisher's exact tests when the Cochran rules were not met.

3.2. Treatment Response and Efficacy

The overall median duration of ICI treatment was 6.0 months (Q1 = 2.0, Q3 = 16.0), overall median follow-up time was 14.5 months (Q1 = 5.0, Q3 = 28.0), and overall median progression-free survival was 6.0 months (Q1 = 2.0, Q3 = 18.0). No differences were found between age groups, with $p = 0.237$, $p = 0.748$, and $p = 0.450$, respectively.

A significant result was found for renal cancer ($p = 0.041$). Of the patients below 65 years old, 6 (26.1%) had no response. Seventeen patients aged 65 years or older (73.9%) had no response. No other significant associations were found in other cancer types. The overall association of age groups with ORR, assessed with the chi-square test, was also not significant ($p = 0.890$). Table 2 presents age comparisons stratified by cancer type.

Table 2. Comparison of treatment responses among age groups stratified by cancer type.

Cancer Type	Age Groups	ORR = No Response	ORR = Response	*p*-Value
Melanoma	<65 years old (n = 16)	14 (56.0%)	2 (50.0%)	>0.990
	≥65 years old (n = 13)	11 (44.0%)	2 (50.0%)	(b)
NSCLC	<65 years old (n = 58)	41 (46.1%)	17 (40.5%)	0.548 (a)
	≥65 years old (n = 73)	48 (53.9%)	25 (59.5%)	
Renal Cancer	<65 years old (n = 10)	6 (26.1%)	4 (80.0%)	**0.041 (b)**
	≥65 years old (n = 18)	17 (73.9%)	1 (20.0%)	
Bladder Cancer	<65 years old (n = 10)	6 (33.3%)	4 (40.0%)	>0.990
	≥65 years old (n = 18)	12 (66.7%)	6 (60.0%)	(b)

Results are presented as n (%); *p*-values were computed with (a) chi-square tests or (b) Fisher's exact tests when the Cochran rules were not met.

Figures 1 and 2 show Kaplan–Meier survival curves for PFS and OS compared by age groups (<65/≥65), stratified by cancer type. No significant differences were found between age groups, regardless of the cancer type.

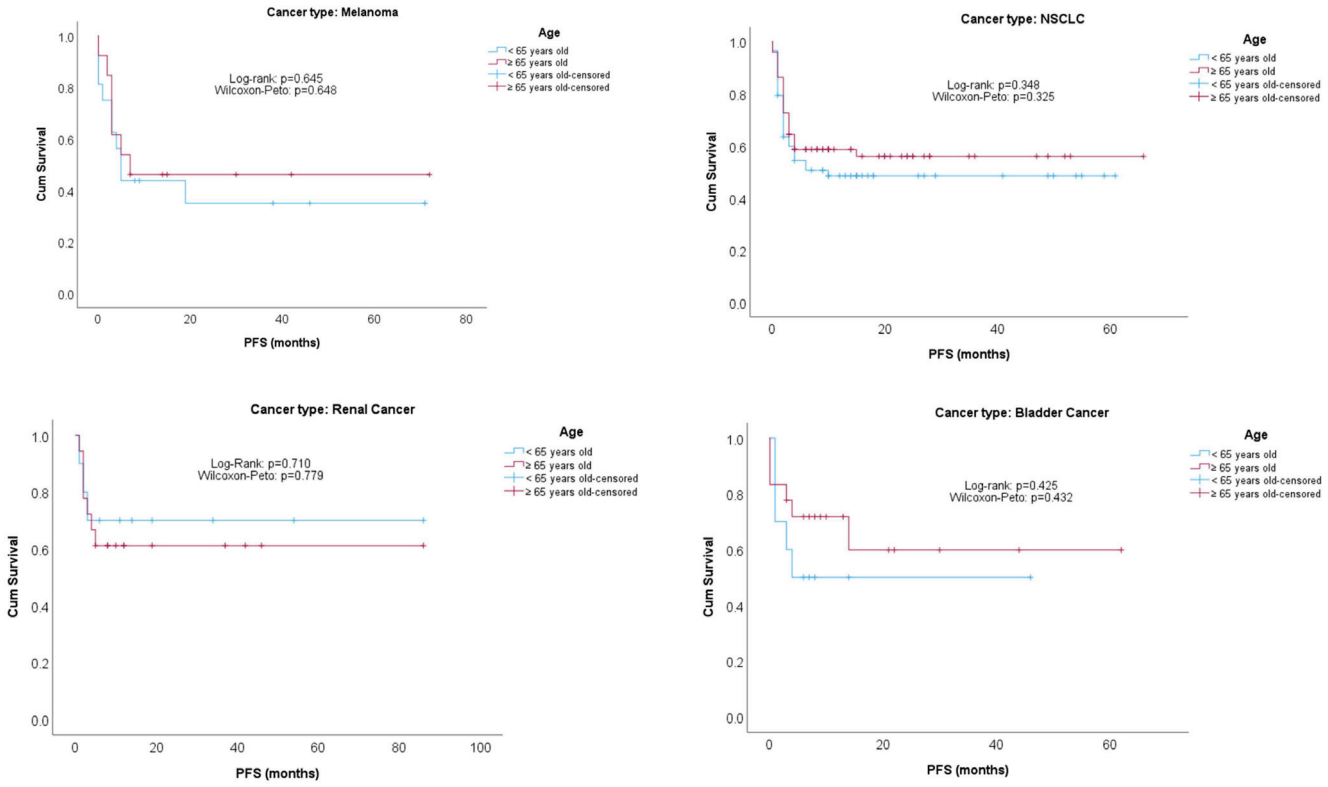

Figure 1. PFS comparisons by age groups, stratified by cancer type.

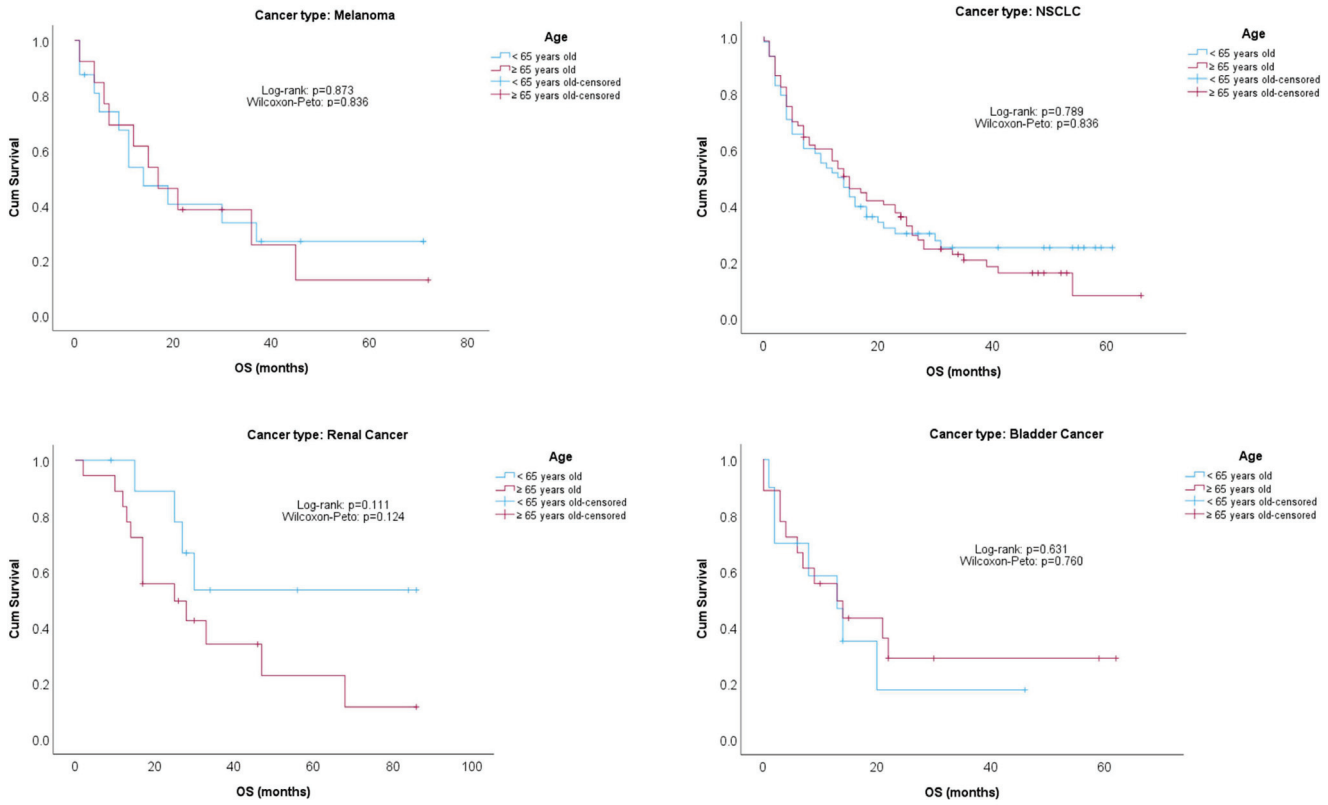

Figure 2. OS comparisons by age groups, stratified by cancer type.

Table 3 presents the duration of ICI treatment stratified by cancer type. The duration of ICI treatment was not associated with age groups for each cancer type. The overall age comparison of the duration of ICI treatment, assessed with the Mann–Whitney test, was also not significant ($p = 0.237$).

Table 3. Duration of ICI treatment, stratified by cancer type.

Cancer Type	Age Groups	Median (Q_1–Q_3)	*p*-Value
Melanoma	<65 years old (n = 16)	7.0 (2.0–22.0)	0.983
	≥65 years old (n = 13)	7.0 (4.0–11.0)	
NSCLC	<65 years old (n = 58)	4.0 (1.0–15.0)	0.277
	≥65 years old (n = 73)	4.0 (2.0–16.0)	
Renal Cancer	<65 years old (n = 10)	12.5 (4.0–28.0)	0.759
	≥65 years old (n = 18)	10.0 (4.0–19.0)	
Bladder Cancer	<65 years old (n = 10)	4.0 (1.0–8.0)	0.286
	≥65 years old (n = 18)	8.5 (3.0–21.0)	

Results are presented as median (Q_1–Q_3); *p*-values were computed with Mann–Whitney tests.

For our predominantly NSCLC patient population, a separate analysis was conducted. Tables 4 and 5 showcase the outcomes of multivariate regressions assessing PFS and OS specifically for NSCLC patients. These analyses were adjusted for various factors, including age groups (<65/≥65), ECOG performance status, smoking history, toxicity, treatment duration, histology (non-squamous vs. squamous), and the number of metastasis locations. Concerning PFS (as demonstrated in Table 4), the presence of irAEs emerged as a significant factor affecting PFS (HR = 0.50, 95% CI: 0.28–0.89, $p = 0.018$), and patients experiencing these adverse events seemed to be less likely to progress in their disease.

Regarding OS, Table 5 shows that patients that experienced irAEs were more likely to live longer than those who did not (HR = 0.61 (95% CI: 0.40–0.95, $p = 0.027$)). The duration of ICI treatment (months) was associated with OS (HR = 0.87 (95% CI: 0.84–0.90, $p < 0.001$)), indicating that longer ICI treatment increases the length of survival time.

In contrast, other factors, such as age, gender, ECOG performance status, smoking history, histological subtype, and the number of metastasis locations, did not yield statistically significant associations with PFS or OS, emphasizing toxicity and ICI treatment duration as important determinants of survival in this context.

Table 4. Multivariate Cox regression for PFS in NSCLC.

	B (SE)	HR	95% CI for HR	*p*-Value
Gender (male)	0.16 (0.40)	1.17	0.54–2.56	0.691
Age ≥ 65	−0.41 (0.31)	0.66	0.36–1.22	0.184
ECOG = 0				
ECOG = 1	−0.62 (0.41)	0.54	0.24–1.20	0.132
ECOG = 2	−0.06 (0.67)	0.95	0.25–3.52	0.934
Smoking history (yes)	−0.23 (0.55)	0.79	0.27–2.34	0.675
Toxicity (yes)	−0.70 (0.30)	0.50	0.28–0.89	0.018
Duration of ICI treatment (months)	−0.46 (0.08)	0.63	0.54–.74	<0.001
Histology = Adenocarcinoma	−0.08 (0.39)	0.93	0.43–2.00	0.848
Histology = Other	0.00 (0.72)	1.00	0.24–4.15	0.995
Number of metastasis locations = 1				
Number of metastasis locations = 2	0.10 (0.32)	1.11	0.60–2.06	0.744
Number of metastasis locations ≥ 3	0.24 (0.45)	1.28	0.53–3.07	0.585

Table 5. Multivariate Cox regression for OS in NSCLC.

	B (SE)	HR	95% CI for HR	*p*-Value
Gender (male)	−0.27 (0.29)	0.76	0.43–1.35	0.352
Age ≥ 65	0.30 (0.23)	1.35	0.85–2.12	0.201
ECOG = 0				
ECOG = 1	0.36 (0.33)	1.44	0.75–2.74	0.274
ECOG = 2	0.95 (0.55)	2.58	0.87–7.64	0.087
Smoking history (yes)	0.46 (0.40)	1.58	0.72–3.48	0.252
Toxicity (yes)	−0.49 (0.22)	0.61	0.40–0.95	0.027
Duration of ICI treatment (months)	−0.14 (0.02)	0.87	0.84–0.90	<0.001
Histology = Adenocarcinoma	−0.04 (0.27)	0.96	0.56–1.64	0.885
Histology = Other	−0.72 (0.58)	0.49	0.16–1.51	0.212
Number of metastasis locations = 1				
Number of metastasis locations = 2	0.30 (0.24)	1.35	0.85–2.15	0.209
Number of metastasis locations ≥ 3	0.86 (0.36)	2.36	1.17–4.77	0.016

3.3. Immune-Related Adverse Reactions

Overall, the elderly population presented a greater number of irAEs, although without statistical significance ($p = 0.86$). Arthralgia had the highest prevalence in patients aged below 65 years old and pruritus and rash had the highest prevalence among patients aged ≥ 65 years old. Table 6 presents a comparative analysis of toxicity between different age groups.

Table 6. Immune-related adverse events stratified by age groups.

	<65 Years Old	≥65 Years Old
Hypothyroidism	7 (7.4%)	6 (4.9%)
Pruritus	9 (9.6%)	11 (9.0%)
Rash	6 (6.4%)	11 (9.0%)
Myalgia	7 (7.4%)	4 (3.3%)
Arthralgia	10 (10.6%)	7 (5.7%)
Pneumonitis	3 (3.2%)	4 (3.3%)
Colitis	1 (1.1%)	6 (4.9%)
Bullous pemphigus	0 (0.0%)	1 (0.8%)
Vasculitis	0 (0.0%)	1 (0.8%)
Herpes Zoster	0 (0.0%)	1 (0.8%)
Hepatitis	3 (3.2%)	4 (3.3%)
Nephritis	1 (1.1%)	3 (2.5%)
Hyperthyroidism	4 (4.3%)	0 (0.0%)
Diarrhea	1 (1.1%)	1 (0.8%)
Inflammatory myopathy	1 (1.1%)	0 (0.0%)
Proteinuria	0 (0.0%)	1 (0.8%)
Vitiligo	1 (1.1%)	0 (0.0%)
Cholangitis	1 (1.1%)	1 (0.8%)
Pancytopenia	1 (1.1%)	0 (0.0%)
Fever	1 (1.1%)	2 (1.6%)
Astenia	0 (0.0%)	2 (1.6%)

4. Discussion

The rising global aging population poses a notable challenge in cancer management due to increased cancer incidence with age. The introduction of ICI as part of the management of several advanced solid tumors has considerably improved patients' outcomes. ICI are indeed of paramount importance in the treatment of patients with advanced NSCLC, melanoma, bladder, and renal cancer, as well as other cancer types, and for that reason, efforts are needed to evaluate the impact of aging on the effectiveness of ICI and optimize their use also in the older population [35].

To our knowledge, this study is the first to evaluate the efficacy and safety of ICI in elderly patients beyond NSCLC but also in melanoma, bladder, and renal cancers, and tumors with high prevalence in the older population.

In our study, the use of ICI showed no significant differences concerning OS and PFS among age groups across various cancer types. These findings align with a retrospective study of 410 adult patients with different tumor types (lung, melanoma, and genitourinary), where age did not significantly impact OS or PFS outcomes among those treated with a single-agent ICI. Similarly, irAEs showed no statistically significant disparity between older ($\geq$65 years) and younger patients [31,36]. Notably, a significant difference was observed in the response to treatment among renal cancer patients ($p = 0.041$), suggesting a potential negative impact of age on the treatment response. However, this finding contrasts with existing evidence that indicates no distinct outcomes based on age and could probably be explained by the limited number of patients analyzed [31]. When assessing patients who presented with irAEs, the management of elderly patients showed a marginal association ($p = 0.059$) with oral corticosteroid therapy (34.0%), as opposed to the younger group (16.7%). This could be explained by the fact that elderly individuals often have more comorbidities, necessitating a more cautious approach to toxicity management.

When focusing solely on NSCLC, our study revealed a strong association between the development of irAEs, patients' PFS and OS, and the duration of ICI treatment, but not directly correlated with age. While several studies have reported the tolerability and efficacy of ICI in NSCLC patients aged $\geq$ 65, uncertainties persist regarding patients over 75. The scarcity of older patients participating in ICI-related trials, coupled with the increasing prevalence of individuals aged 70 years or older, emphasizes the urgent need for treatment personalization [31]. This calls for a shift toward implementing geriatric assessments rather than solely relying on chronological age for treatment decisions and inclusion criteria in clinical trials.

These observations underscore the need for further investigation to comprehensively understand immune response mechanisms in elderly patients and to identify predictive biomarkers for older adults with cancer [37,38]. Nevertheless, this study has limitations, including its retrospective nature, leading to potential information bias, wide population heterogeneity, and that many patients were primarily treated with anti-PD1 drugs, limiting generalizability to other ICI agents, such as anti-PD-L1 or anti-CTLA-4 agents. Interpretation of the weighted average outcomes should consider these limitations accordingly.

5. Conclusions

The transformative impact of immune checkpoint inhibitors on the treatment paradigms for advanced melanoma, NSCLC, bladder, and renal cancer is indisputable.

Age did not affect the efficacy and toxicity of treatment with immunotherapy, suggesting that anticancer immunity remains uncompromised in elderly patients.

The limitations of relying solely on chronological age as a determinant for treatment decisions in the elderly become apparent when considering the heterogeneous nature of this population. Beyond chronological age, our study highlighted the diverse range of molecular and immune alterations present in elderly patients, underscoring the necessity for a more individualized approach to treatment decisions. Recognizing the unmet need to incorporate comprehensive geriatric assessments into daily practice, further prospective studies with a focus on geriatric assessment are warranted to optimize therapeutic strategies in this prevalent and heterogeneous population.

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Informed Consent Statement: Patient consent was waived due to the retrospective and non-interventional nature of the study.

Data Availability Statement: The datasets generated and/or analyzed during the current study are not publicly available. However, they are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare that they have no conflict of interest.

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Article

Reasonability of Frequent Laboratory Analyses during Therapy with Nivolumab and Nivolumab+Ipilimumab in Patients with Advanced or Metastatic Renal Cell Carcinoma during the Phase 2 Clinical Trial TITAN-RCC

Klara Franke [1,2], Susan Foller [1,2], Michele Estephania Rosero Moreno [1,2], Nalyan Ali [1,2], Lutz Leistritz [2,3], Katharina Leucht [1,2,†] and Marc-Oliver Grimm [1,2,*,†]

[1] Department of Urology, Jena University Hospital, Friedrich-Schiller University, 07747 Jena, Germany; klara.franke@uni-jena.de (K.F.); susan.foller@med.uni-jena.de (S.F.); michele.roseromoreno@med.uni-jena.de (M.E.R.M.); nalyan.ali@med.uni-jena.de (N.A.); katharina.leucht@med.uni-jena.de (K.L.)
[2] Comprehensive Cancer Center Central Germany (CCCG), 07743 Jena, Germany; lutz.leistritz@med.uni-jena.de
[3] Institute of Medical Statistics, Informatics and Data Science, Jena University Hospital, Friedrich-Schiller University, 07747 Jena, Germany
* Correspondence: marc-oliver.grimm@med.uni-jena.de; Tel.: +49-3641-9329901
† These authors contributed equally to this work.

Simple Summary: In this work, we evaluated the need for frequent laboratory assessments in patients with metastatic renal cell carcinoma treated with nivolumab and nivolumab+ipilimumab during the TITAN-RCC clinical trial. We analysed how often reached criteria for dose delay or permanent discontinuation of therapy would have been missed if the frequency of laboratory testing had been reduced, in order to avoid over-sampling patients and to optimise clinical workflow and staffing. Our study showed that if the frequency of laboratory tests had been reduced, reached dose delay criteria would hardly have been missed. This would have affected up to 1% (2/207) of patients. An exception was dose delay due to the elevation of lipase blood levels which would have been missed in up to 7% (15/207) of patients. However, these patients presented with symptoms and would have been identified based thereupon. Discontinuation criteria would have only been overlooked for lipase (2% [4/207] of patients) and amylase (0.5% [1/207] of patients). Again, these patients would have been identified, since only symptomatic patients would have needed to discontinue treatment due to amylase or lipase laboratory values. In conclusion, in asymptomatic patients in our setting, laboratory analyses do not seem to be necessary before every treatment application.

Abstract: In clinical trials, laboratory values are assessed with high frequency. This can be stressful for patients, resource intensive, and difficult to implement, for example in office-based settings. In the prospective, multicentre phase 2 TITAN-RCC trial (NCT02917772), we investigated how many relevant changes in laboratory values would have been missed if laboratory values had been assessed less frequently. Patients with metastatic renal cell carcinoma (n = 207) received a response-based approach with nivolumab and nivolumab+ipilimumab boosts for non-response. We simulated that laboratory values were obtained before every second dose instead of every dose of the study drug(s). We assessed elevated leukocyte counts, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, amylase, lipase, and thyroid-stimulating hormone. Dose delay and discontinuation criteria were defined according to the study protocol. With the reduced frequency of laboratory analyses, dose delay criteria were rarely missed: in a maximum of <0.1% (3/4382) of assessments (1% [2/207] of patients) during nivolumab monotherapy and in a maximum of 0.2% (1/465) of assessments (1% [1/132] of patients) during nivolumab+ipilimumab boosts. An exception was lipase-related dose delay which would have been missed in 0.6% (25/4204) of assessments (7% [15/207] of patients) during nivolumab monotherapy and in 0.8% (4/480) of assessments (3% [4/134] of patients) during nivolumab+ipilimumab boosts, but would have required

the presence of symptoms. Discontinuation criteria would have only been missed for amylase (<0.1% [1/3965] of assessments [0.5% (1/207) of patients] during nivolumab monotherapy, none during nivolumab+ipilimumab boosts) and lipase (0.1% [5/4204] of assessments [2% (4/207) of patients] during nivolumab monotherapy; 0.2% [1/480] of assessments [0.7% (1/134) of patients] during nivolumab+ipilimumab boosts). However, only symptomatic patients would have had to discontinue treatment due to amylase or lipase laboratory values. In conclusion, a reduced frequency of laboratory testing appears to be acceptable in asymptomatic patients with metastatic renal cell carcinoma treated with nivolumab or nivolumab+ipilimumab.

Keywords: immune-related adverse events; side effects; immune-checkpoint inhibitors; renal cell carcinoma; immune therapy; lab values

1. Introduction

Immune checkpoint inhibitors (ICI), either as mono- or combination therapies, have been established as therapeutic options for various cancer types [1], including metastatic renal cell carcinoma (mRCC) [2–8]. A commonly used combination approved for first-line treatment of patients with intermediate or poor risk mRCC combines the anti-PD-1 ICI nivolumab and the anti-CTLA-4 ICI ipilimumab [3].

In the TITAN-RCC study, patients with mRCC received a response-based approach with nivolumab and nivolumab+ipilimumab boosts for non-response [9]. ICI therapy is commonly associated with immune-related adverse events, mainly concerning skin, liver, colon, lungs, and the endocrine system [10–12]. In the protocol of TITAN-RCC, certain criteria were defined that would require a delayed dose application or even permanent discontinuation of study medication, many of those being based on laboratory values. This is in accordance with the up-to-date investigator brochure or, in the case of already approved medication, the official summary of product characteristics (SmPC) published by the European Medicines Agency (EMA) [13]. The study protocol includes the assessment of several laboratory values prior to each dose of the study drug(s), which may be used for decisions about continuation, dose delay, or discontinuation. Especially at sites participating in clinical trials, this is a standard procedure and may be implemented relatively easily due to available structures and capacities in the laboratories involved. In everyday clinical practice, however, approved therapies are also administered by resident physicians. When blood sampling is carried out in office-based settings, it usually takes longer for the results of laboratory value analyses to be available. Additionally, the procedures tie up time and personnel. For this reason, we have investigated whether, retrospectively, the high frequency of laboratory value analyses applied in TITAN-RCC would have actually been necessary with regard to detection of laboratory value alterations, determination of adverse events, and consequences for continuation of therapy.

2. Materials and Methods

2.1. Study Design and Participants

TITAN-RCC was a multicentre, single-arm, phase 2 trial that recruited patients at 28 sites across Europe (Austria, Belgium, Czech Republic, France, Germany, Italy, Spain, and the UK). The study design, and its inclusion and exclusion criteria have been reported previously [9]. In brief, eligible patients were adults (aged $\geq$18 years) with histologically confirmed advanced or metastatic renal cell carcinoma (RCC) with a clear cell component and intermediate or poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [14]. Patients were either formerly untreated (first-line) or pre-treated with one previous systemic therapy (anti-angiogenic or temsirolimus; second-line). Measurable disease per Response Evaluation Criteria in Solid Tumours [15], a Karnofsky Performance Status score $\geq$ 70, and a tumour sample for analysis of PD-L1 expression were mandatory.

The trial was approved by all relevant national competent authorities and independent ethics committees, and conducted in compliance with the Declaration of Helsinki [16], Good Clinical Practice, and local regulatory requirements. All patients provided written informed consent before enrolment in the study. TITAN-RCC is registered with ClinicalTrials.gov, NCT02917772.

2.2. Procedures

The study procedures have been described in detail before [9]. The study scheme is displayed in Figure 1. All patients started treatment with induction nivolumab monotherapy (240 mg, intravenous) once every 2 weeks for 16 weeks. On early progressive disease (week 8) or non-response during tumour assessment (CT or MRI) at week 16, patients received either two or four doses of intravenous nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) boosts (once every 3 weeks), whilst responders continued with intravenous nivolumab (240 mg, once every 2 weeks). In case of progressive disease during the treatment, the responders could also receive two to four boost doses of nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) boosts. After two or four boost cycles with resulting complete response, partial response, or stable disease, the patients received intravenous nivolumab (240 mg, once every 2 weeks). Patients who had a progressive disease after four boost cycles were defined as immune therapy resistant. Tailored treatment was administered until immunotherapy resistance, unacceptable toxicity, or withdrawal of consent. After discontinuation, patients completed two follow-up visits 4 weeks after the last dose and 12 weeks thereafter and were subsequently monitored for survival every 3 months.

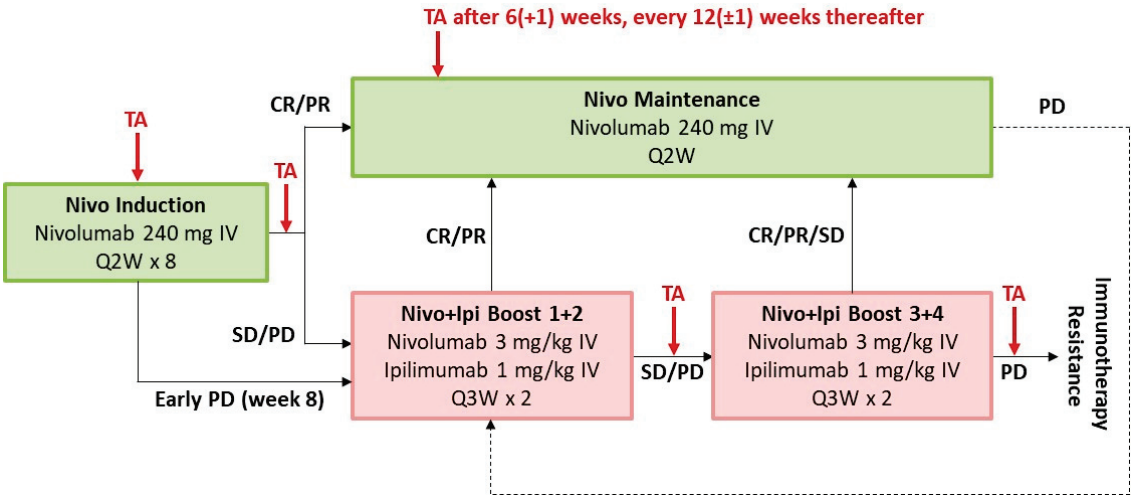

Figure 1. Study design. All response information is taken from time point response data. Nivo, nivolumab; Ipi, ipilimumab; IV, intravenous; Q2W/Q3W/Q4W, once every 2/3/4 weeks; SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response; TA, tumour assessment.

2.3. Laboratory Assessments

In TITAN-RCC, the following laboratory values were assessed at screening (within 14 days prior to registration), within 72 h prior to every dose of nivolumab induction monotherapy, nivolumab maintenance monotherapy, and nivolumab+ipilimumab combination therapy, as well as at both follow-up visits: differential blood count, erythrocytes, thrombocytes, haemoglobin, haematocrit, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, bilirubin, serum urea, creatinine, calcium, albumin, magnesium, sodium, potassium, chloride, lactate dehydrogenase (LDH), glucose, amylase, lipase, thyroid-stimulating hormone (TSH), free triiodothyronine, and free thyroxine. For this work, we focussed on the laboratory parameters associated with common adverse events that can be diagnosed using laboratory parameters: leucocytes (activation of the immune system in general); ALAT, ASAT, bilirubin (immune-related hepatitis); creatinine (immune-related nephritis and renal dysfunction); amylase, lipase (pancreatic dysfunction), and TSH (hypothyroidism).

2.4. Outcomes

In our exploratory analyses, we assessed how often and at what time dose delay and discontinuation criteria were reached across the selected laboratory values. These criteria were defined and applied according to the protocol of TITAN-RCC based on CTCAE v4.0 [17]. As a control, we applied the respective criteria according to the current version of the SmPC for nivolumab published by the EMA (last updated 4 April 2024) [13], being also valid for the combination of nivolumab+ipilimumab and based on CTCAE v4.0. All applied criteria are summarised in Table 1. If the presence or absence of symptoms was included for a respective criterion, these were looked up in the patients' records.

Table 1. Dose delay and discontinuation criteria according to the TITAN-RCC protocol or to the SmPC of nivolumab.

Lab Value	Dose Delay Criteria		Discontinuation Criteria	
	Protocol of TITAN-RCC	**Current SmPC**	**Protocol of TITAN-RCC**	**Current SmPC**
Leukocytes (leukocytosis)	**grade 3** (>100,000/mm^3)	**grade 3** (>100,000/mm^3), **first occurrence**	**grade 4** (clinical manifestations of leukostasis; urgent intervention indicated)	**grade 4** (clinical manifestations of leukostasis; urgent intervention indicated) or **recurrent grade 3** (>100,000/mm^3) [1,2]
ASAT or ALAT	**baseline normal:** **grade 2 or 3** (>3.0 × ULN) [3] **baseline abnormal:** **grade 3** (>5.0 × ULN) [3]	**grade 2** (>3.0–5.0 × ULN)	≥8 × ULN or AST/ALT ≥ 3 × ULN *and* bilirubin ≥2 × ULN	**grade 3 or 4** (>5.0 × ULN)
Bilirubin	**baseline normal:** **grade 2 or 3** (>1.5 × ULN) [3] **baseline abnormal:** **grade 3** (>3.0 × ULN) [3]	**grade 2** (>1.5–3.0 × ULN)	≥5 × ULN or AST/ALT ≥ 3 × ULN *and* bilirubin ≥2 × ULN	**grade 3 or 4** (>3.0 × ULN)
Creatinine	**grade 3** (>3.0xbaseline or >3.0–6.0 × ULN)	**grade 2** (>1.5–3.0xbaseline or >1.5–3.0 × ULN) or **grade 3** (>3.0xbaseline or >3.0–6.0 × ULN)	**grade 4** (>6.0 × ULN)	**grade 4** (>6.0 × ULN)
Amylase or Lipase	**grade 3** (>2.0–5.0 × ULN) (**symptomatic** [4])	**grade 3** (>2.0–5.0 × ULN), **first occurrence**	**grade 4** (>5.0 × ULN) (**symptomatic** [4])	**grade 4** (>5.0 x ULN) or **recurrent grade 3** (>2.0–5.0 × ULN) [1,2]
TSH (hypothyroidism)	**grade 3** (severe symptoms; limiting self care ADL; hospitalisation indicated)	**grade 2** (symptomatic; thyroid replacement indicated [5]; limiting instrumental ADL) or **grade 3** (severe symptoms; limiting self care ADL; hospitalisation indicated)	**grade 4** (life-threatening consequences; urgent intervention indicated)	**grade 4** (life-threatening consequences; urgent intervention indicated)

ADL, activities of daily life; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CTCAE, Common Terminology Criteria of Adverse Events; SmPC, summary of product characteristics/product information; TSH, thyroid-stimulating hormone; ULN, upper limit of normal; LLN, lower limit of normal. [1] Per SmPC for nivolumab discontinuation is also recommended for persistent grade 2 or 3 despite treatment modification (dose delay). This is not the subject of our analyses, since we assessed monitoring of laboratory values on treatment. [2] Per SmPC for nivolumab discontinuation is also recommended for the inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day. This criterion has not been applied since it is not dependent on laboratory analyses and therewith not the subject of our analyses. [3] Until discontinuation criterion is met. [4] Defined per protocol of TITAN-RCC, independent of CTCAE v4.0. [5] Only first occurrence of an indication for thyroid replacement was counted for usually long-term or permanent substitution.

To determine the necessity of frequent assessments of the selected laboratory values, we simulated that blood analyses had been performed with reduced frequency. The simulated frequencies were defined for each of the different phases of the therapy: nivolumab induction monotherapy, nivolumab+ipilimumab boost, and nivolumab maintenance monotherapy. We simulated that laboratory values had been determined at the first and second visit of each of the three treatment phases, and at every second visit thereafter (Table 2, variant A). As a control, we furthermore simulated that laboratory values had been determined at the first visit of each of the three treatment phases, and at every second visit thereafter (variant B). Data reported in the main paper refer to variant A, as this is considered to be more relevant in practice (control of laboratory values after the first administration of medication). The data we obtained with variant B are shown in the supplement. For nivolumab+ipilimumab boost phases this meant that laboratory values would have been taken before the first, second, and fourth of four doses, and, as a control, before the first and third of four doses. We assumed that during follow-up visits no laboratory values were assessed.

Table 2. Simulated assessment of laboratory values.

	Simulated Assessment of Laboratory Values	
	Variant A	**Variant B (Control; Supplementary Materials)**
Nivolumab induction monotherapy	First and second visit, every second visit thereafter	First visit, every second visit thereafter
Nivolumab+ipilimumab boost phase	First, second, and fourth visit	First and third visit
Nivolumab maintenance monotherapy [(1)]	First and second visit, every second visit thereafter	First visit, every second visit thereafter
Follow-up	No assessment	No assessment

[(1)] Either after nivolumab induction or after nivolumab+ipilimumab boosts.

We recorded relevant events that occurred during the visits that were simulated as being without laboratory testing. These relevant events were considered as overlooked. Relevant events were as follows: (i) elevation of laboratory values by at least one CTCAE grade, regardless of consequences for the continuation of therapy, (ii) reaching of dose delay criteria (according to the TITAN-RCC protocol or to the SmPC of nivolumab), and (iii) reaching of discontinuation criteria (according to the TITAN-RCC protocol or to the SmPC of nivolumab).

2.5. Statistical Analysis

Statistical calculations were performed with SPSS statistical software (version 28.0.0.0).

Demographics and baseline characteristics were summarised using descriptive statistics. Descriptive statistics were also applied to determine how often relevant events were overlooked across all of the selected laboratory values. Dose delay and discontinuation criteria that would have been overlooked in our setting were evaluated separately for nivolumab monotherapy (induction or maintenance) and for nivolumab+ipilimumab boosts. The differences between variants A and B on a per-patient level were assessed using McNemar's test. Time-to-event distributions were estimated using Kaplan–Meier methodology. A log rank test was used for comparison of different simulations.

3. Results

3.1. Baseline Characteristics

The study baseline characteristics have been reported in detail before [9]. Between 28 October 2016 and 30 November 2018, 207 patients were enrolled, with 109 patients being first-line and 98 second-line. Of the patients, 147 (71%) were male and 60 (29%) were female. A total of 147 patients (71%) had intermediate risk according to IMDC and

51 (25%) had poor risk. Upon source data review, nine patients (4%) were identified who had favourable IMDC risk. IMDC risk factors which form the basis for determination of the risk groups are detailed in Table 3. In the overall population, median follow-up was 27.6 months (interquartile range [IQR] 10.5–34.8).

Table 3. Baseline characteristics.

	Total (n = 207)
Median age, years (range, IQR)	65 (20–87, 57–71)
Line of therapy	
First-line	109 (53)
Second-line	98 (47)
Sex, n (%)	
Male	147 (71)
Female	60 (29)
IMDC risk factors, n (%)	
Karnofsky Performance Status < 80%	34 (16)
Initial diagnosis $\leq$ 12 months	135 (65)
Haemoglobin < LLN	110 (53)
Platelet count > ULN	39 (19)
Neutrophil count > ULN	26 (13)
Calcium (corrected) > ULN	27 (13)
IMDC risk group, n (%)	
Favourable	9 (4)
Intermediate	147 (71)
Poor	51 (25)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; LLN, lower limit of normal; ULN, upper limit of normal.

3.2. Rate and Time of Reaching of Dose Delay and Discontinuation Criteria

During the course of the study, 46/207 patients (23.2%) met at least one dose delay criterion as defined according to the protocol of TITAN-RCC across all pre-selected laboratory values. When defining dose delay criteria per SmPC of nivolumab, this applied to 70/207 patients (34%). The distribution over time significantly differed depending on the definition applied (log rank $p = 0.004$, Figure 2A). For both, however, dose delay criteria were mainly reached during the first 12 months of therapy.

With regard to these laboratory values, discontinuation criteria were met in 12/207 patients (6%) (per protocol) and 18/207 patients (9%) (per SmPC), respectively. The distribution over time is displayed in Figure 2B (log rank $p = 0.232$).

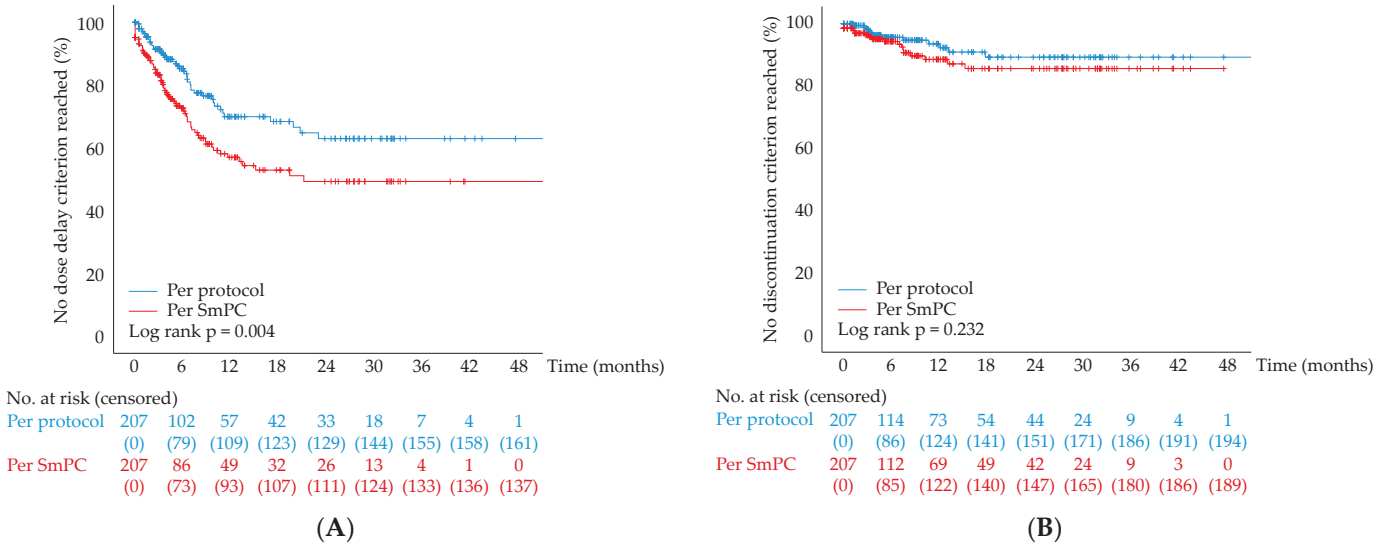

Figure 2. Reached dose delay and discontinuation criteria. (**A**) Patients without dose delay criterion reached as defined by the protocol of TITAN-RCC vs. as defined by the SmPC of nivolumab; (**B**) patients without discontinuation criterion reached as defined by the protocol of TITAN-RCC vs. as defined by the SmPC of nivolumab. All analyses are based on CTCAE v4.0. CTCAE, Common Terminology Criteria for Adverse Events; SmPC, summary of product characteristics/product information; NAR, number at risk.

3.3. Simulation of Reduced Frequency of Assessment of Laboratory Parameters

3.3.1. Elevation of Laboratory Values by at Least One CTCAE Grade, Regardless of Consequences for the Continuation of Therapy

The laboratory values assessed within this article have been analysed between 4606 and 5487 times in 207 patients over the course of TITAN-RCC.

Increased levels of laboratory parameters by at least one CTCAE grade (based on CTCAE v4.0), irrespective of consequences for treatment continuation, would have been missed in from 18/207 patients (9%, bilirubin) to 80/207 patients (39%, creatinine). This corresponds to a total number of missed laboratory value elevations ranging from 25/5404 analyses (0.5%, bilirubin) to 192/5475 analyses (4%, creatinine) (Table 4). Applying the control simulation (variant B) did not produce significantly different results for any of the laboratory values (Supplementary Table S1). On a per-patient level, a median of 22% (IQR 17–22) of patients would have been affected.

Table 4. Missed elevation of CTCAE grade by at least one grade.

	Missed Elevation per Patient, n/N (%)	Missed Elevation per Assessment, n/N (%)
Leukocytes	32/207 (15)	47/5487 (0.9)
ALAT	42/207 (20)	73/5396 (1)
ASAT	44/207 (21)	54/5252 (1)
Bilirubin	20/207 (10)	25/5404 (0.5)
Creatinine	83/207 (40)	192/5475 (4)
Amylase	52/207 (25)	120/4606 (3)
Lipase	66/207 (32)	152/4860 (3)
TSH	51/207 (25)	100/5297 (2)

Data were obtained with variant A. For variant B and *p* values for the per-patient level see Supplementary Table S1. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; TSH, thyroid-stimulating hormone.

3.3.2. Reaching of Dose Delay or Discontinuation Criteria

During nivolumab monotherapy phases of TITAN-RCC, the assessed laboratory values have been analysed between 3965 and 4522 times. During the nivolumab+ipilimumab boost phase, they were evaluated between 465 and 518 times.

Criteria Defined According to the TITAN-RCC Protocol

For leukocytes, ALAT, ASAT, bilirubin, creatinine, and TSH, reached dose delay criteria were most frequently missed during nivolumab monotherapy for ASAT (2/4327 [<0.1%] lab value assessments) and during nivolumab+ipilimumab boost phases for bilirubin (1/510 [0.2%] assessments). For details see Table 5. Regarding amylase, reached dose delay criteria would have been missed in 2/3965 (<0.1%) assessments during nivolumab monotherapy. This would have affected 2/207 (1%) symptomatic patients. During nivolumab+ipilimumab boost phases, for amylase in 1/465 (0.2%) assessments a reached dose delay criterion would have been missed. The affected patient was symptomatic. As for lipase, reached dose delay criteria would have been missed in 25/4204 (0.6%) assessments (15/207 [7%] symptomatic patients affected) during nivolumab monotherapy. During the boost phases, reached dose delay criteria would have been missed in 4/480 (0.8%) assessments. A total of 4/134 (3%) patients would have been affected. All were symptomatic.

Table 5. Missed dose delay and discontinuation criteria per assessment and per patient, criteria defined according to the TITAN-RCC protocol.

	Per Patient, n/N (%)		**Per Assessment, n/N (%)**	
	Dose Delay	**Discontinuation**	**Dose Delay**	**Discontinuation**
Nivolumab monotherapy (induction and maintenance)				
Leukocytes	1/207 (0.5)	0/207 (0)	1/4522 (<0.1)	0/4522 (0)
ALAT	1/207 (0.5)	0/207 (0)	1/4447 (<0.1)	0/4447 (0)
ASAT	1/207 (0.5)	0/207 (0)	2/4327 (<0.1)	0/4327 (0)
Bilirubin	1/207 (0.5)	0/207 (0)	1/4458 (<0.1)	0/4458 (0)
Creatinine	0/207 (0)	0/207 (0)	0/4511 (0)	0/4511 (0)
Amylase	2/207 (1)	1/207 (0.5)	2/3965 (<0.1)	1/3965 (<0.1)
Lipase	15/207 (7)	4/207 (2)	25/4204 (0.6)	5/4204 (0.1)
TSH	2/207 (1)	0/207 (0)	3/4382 (<0.1)	0/4382 (0)
Nivolumab+ipilimumab boost				
Leukocytes	0/138 (0)	0/138 (0)	0/518 (0)	0/518 (0)
ALAT	0/138 (0)	0/138 (0)	0/510 (0)	0/510 (0)
ASAT	0/137 (0)	0/137 (0)	0/502 (0)	0/502 (0)
Bilirubin	1/137 (0.7)	0/137 (0)	1/510 (0.2)	0/510 (0)
Creatinine	0/138 (0)	0/138 (0)	0/518 (0)	0/518 (0)
Amylase	1/132 (0.8)	0/132 (0)	1/465 (0.2)	0/465 (0)
Lipase	4/134 (3)	1/134 (0.7)	4/480 (0.8)	1/480 (0.2)
TSH	0/138 (0)	0/138 (0)	0/509 (0)	0/509 (0)

Data were obtained with variant A. For variant B and *p* values for the per-patient level see Supplementary Table S2. *Yellow*: dose delay or discontinuation criteria would have been missed at least once on a per-assessment or per-patient level. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; TSH, thyroid-stimulating hormone.

For leukocytes, bilirubin, creatinine, and TSH no discontinuation criteria were met at any laboratory assessment, neither during nivolumab monotherapy (induction or maintenance) nor during nivolumab+ipilimumab boost phases. Accordingly, no reaching of a respective discontinuation criterion would have been missed. ALAT- and ASAT-emergent discontinuation would have been required once over the course of the trial during nivolumab+ipilimumab boost. However, reaching of these discontinuation criteria would not have been missed. These data are mirrored on the per-patient level (Table 5). For amylase, in 1/3965 (<0.1%) assessments during nivolumab monotherapy a reached discontinuation criterion would have been missed. However, symptoms were required

for the discontinuation criterion to be met. Criteria for lipase-derived discontinuation would have been missed in 5/4204 (0.1%) assessments during nivolumab monotherapy, and in 1/480 (0.2%) during nivolumab+ipilimumab boost phases. This affected 4/207 (2%) patients during nivolumab monotherapy and 1/134 (0.7%) patient during boost. Of note, these patients were symptomatic, a prerequisite for a lipase-emergent discontinuation criterion to be met.

Data derived from the control simulation (variant B) were comparable and not statistically different (Supplementary Table S2).

Criteria Defined According to the SmPC of Nivolumab

For leukocytes, ALAT, ASAT, bilirubin, amylase, and TSH, numbers of overlooked dose delay and discontinuation criteria marginally differed from those described before, when defining the respective criteria according to the TITAN-RCC protocol. For details see Table 6.

Table 6. Missed dose delay and discontinuation criteria per assessment and per patient, criteria defined according to the SmPC of nivolumab.

	Per Patient, n/N (%)		Per Assessment, n/N (%)	
	Dose Delay	**Discontinuation**	**Dose Delay**	**Discontinuation**
Nivolumab monotherapy (induction and maintenance)				
Leukocytes	1/207 (0.5)	0/207 (0)	1/4522 (<0.1)	0/4522 (0)
ALAT	1/207 (0.5)	0/207 (0)	1/4447 (<0.1)	0/4447 (0)
ASAT	3/207 (1.4)	0/207 (0)	6/4327 (0.1)	0/4327 (0)
Bilirubin	1/207 (0.5)	0/207 (0)	4/4458 (<0.1)	0/4458 (0)
Creatinine	19/207 (9)	0/207 (0)	134/4511 (3)	0/4511 (0)
Amylase	0/207 (0)	1/207 (0.5)	0/3965 (0)	1/3965 (<0.1)
Lipase	7/207 (3)	7/207 (3)	7/4204 (0.1)	14/4204 (0.3)
TSH	10/207 (0.5)	0/207 (0)	10/4382 (0.2)	0/4382 (0)
Nivolumab+ipilimumab boost				
Leukocytes	0/138 (0)	0/138 (0)	0/518 (0)	0/518 (0)
ALAT	0/138 (0)	0/138 (0)	0/510 (0)	0/510 (0)
ASAT	0/137 (0)	0/137 (0)	0/502 (0)	0/502 (0)
Bilirubin	0/137 (0)	0/137 (0)	0/510 (0)	0/510 (0)
Creatinine	6/138 (4)	0/138 (0)	9/518 (2)	0/518 (0)
Amylase	0/132 (0)	0/132 (0)	0/465 (0)	0/465 (0)
Lipase	2/134 (1)	2/134 (1)	2/480 (0.4)	2/480 (0.4)
TSH	1/138 (0)	0/138 (0)	1/509 (0.2)	0/509 (0)

Data were obtained with variant A. For variant B and *p* values for the per-patient level see Supplementary Table S3. *Orange:* lower incidence as compared to Table 5 (criteria defined according to the TITAN-RCC protocol); *green:* higher incidence as compared to Table 5. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; TSH, thyroid-stimulating hormone.

For creatinine, clearly more reached dose delay criteria would have been overlooked than when applying the criteria according to the TITAN-RCC protocol: 134/4511 times (3%, 19 patients affected) during nivolumab monotherapy, and 9/518 times (2%, six patients affected) during nivolumab+ipilimumab boost phases. No reached discontinuation criteria would have been overlooked.

Regarding lipase, considerably fewer dose delay criteria would have been overlooked than when applying the criteria defined according to the TITAN-RCC protocol: 7/4204 times (0.1%) during nivolumab monotherapy, and 2/480 times (0.4%) during nivolumab+ipilimumab boost phases. The criteria could only be met once per patient, since they were defined as *first* occurrence of CTCAE grade 3. A total of 3/7 (43%) patients affected during nivolumab monotherapy were asymptomatic. Missed dose delay criteria during the boost phases only occurred to symptomatic patients. In contrast, more patients

reaching discontinuation criteria would have been overlooked during nivolumab monotherapy (14/4204 [0.3%] times, 7/207 [3%] patients affected) and nivolumab+ipilimumab boost (2/480 [0.4%] times, 2/134 [1%] patients affected). A total of 3/7 (43%) patients affected during nivolumab monotherapy showed neither symptoms nor had they previously shown increased lipase levels.

Data derived from the control simulation (variant B) were comparable and not statistically different (Supplementary Table S3).

4. Discussion

In this work, we simulated a reduced frequency of laboratory testing as compared to the one actually implemented over the course of the phase 2 TITAN-RCC clinical trial in patients with intermediate or poor risk mRCC [9]. We assessed whether this would have been sufficient to detect laboratory changes, to identify adverse events, and to draw conclusions for treatment continuation.

In TITAN-RCC, the majority of patients already had laboratory values outside the normal range at baseline, before starting treatment with checkpoint inhibitors. This directly related to the study's inclusion criteria. In line with the approved indication for nivolumab+ipilimumab in mRCC, the study population was limited to patients with intermediate and poor risk according to IMDC, which in turn is decisively influenced by haemoglobin, platelets/thrombocytes, neutrophils, and (corrected) calcium. Therefore, laboratory values outside the normal range were also to be expected during this study.

The choice of laboratory parameters analysed here was based on the common immuno therapy-related adverse events that can be diagnosed using laboratory values. These included immune-related hepatitis (ALAT, ASAT, bilirubin), immune-related nephritis and renal dysfunction (creatinine), pancreatic dysfunction (amylase, lipase), and hypothyroidism (TSH) [10–12,18,19].

When the frequency of laboratory testing was reduced, the number of missed CTCAE-grade elevations and the number of patients affected differed between the laboratory values analysed. However, the simulation of variants A or B (Supplementary Tables S1–S3) gave comparable, statistically non-significant results per laboratory value. For a median of 22% of the patients, an elevation of at least one CTCAE grade would have been missed. On a per-assessment level, rates of missed elevations were clearly lower, ranging from 0.5% (bilirubin) to 4% (lipase). It should be noted that an increase in CTCAE grade per se would not necessarily have indicated the need to discontinue or delay drug administration, e.g., an increase from CTCAE grade 0 to 1 or grade 1 to 2. Therefore, the analysis of missed criteria for dose delay and discontinuation was decisive.

Dose delay and discontinuation criteria were defined in the TITAN-RCC study protocol. They mainly depended on CTCAE grading (v4.0), taking into account a relative increase above the upper limit of normal and (for liver values and creatinine) baseline data. Dose delay and discontinuation criteria for amylase and lipase during TITAN-RCC required the presence of symptoms. However, ICIs represent relatively new therapeutics. In Europe, nivolumab was approved in 2016 [8,20] for second-line treatment of mRCC, and nivolumab+ipilimumab in 2019 for first-line treatment [3,21]. The first protocol version of TITAN-RCC was developed in 2016. Over time, experience with nivolumab and nivolumab+ipilimumab has increased and real-world data have improved knowledge on side effects and their management [22–25]. For this reason, the SmPCs have been and continue to be regularly updated. As a consequence, the criteria defined for TITAN-RCC do not necessarily apply to current clinical routines, so we additionally evaluated our data using the recommendations of the latest version of the SmPC for nivolumab as a control. It should be noted that the SmPC also explicitly refers to CTCAE v4.0, although version 5.0 [26] would be the most up to date. The criteria defined in the SmPC are not specific to a particular tumour type but apply to all tumour entities for which nivolumab is approved. Results significantly differed depending on the respective definition of dose delay and discontinuation criteria. This may be mainly due to different definitions of criteria for

creatinine, lipase, and TSH. Using the SmPC, for creatinine and TSH a dose delay criterion was met from CTCAE grade 2 (instead of grade 3 using the TITAN-RCC protocol), resulting in more patients being affected. For creatinine, however, it is not clear to what extent elevated blood levels are associated with the underlying renal disease or with possible immune-related side effects, such as colitis leading to exsiccosis resulting in (pre-)renal impairment. Unlike other tumour types, patients with renal tumours often live with a solitary kidney and have limited kidney function. The requirement for a general dose delay from CTCAE grade 2 may be too strict for renal disease, and for mRCC the disease-specific criteria of the TITAN-RCC protocol may be more appropriate than the cross-entity criteria defined in the SmPC.

Another major difference between the definitions of dose delay and discontinuation criteria concerned lipase and amylase. The criteria defined in the SmPC (based on CTCAE v4.0) were more restrictive. First, in contrast to the protocol, only the *first occurrence* of CTCAE grade 3 resulted in dose delay, whereas *recurrent* CTCAE grade 3 required permanent discontinuation of therapy. Second, the recommendations for dose delay or discontinuation were independent of the presence of symptoms [13]. However, it should be recognised that the current version of CTCAE, v5.0 [26], includes symptoms in the grading assessment for amylase and lipase. For the few amylase-related events that occurred, the differences in the definition of the criteria between the TITAN-RCC protocol and the SmPC had little effect. In contrast, the results for lipase shifted towards fewer met (and missed) dose delay criteria and towards more met (and missed) discontinuation criteria when using the SmPC instead of the protocol criteria. We believe that the symptom-based management of elevated laboratory values according to the TITAN-RCC protocol is more appropriate in our setting. However, the SmPC of nivolumab may be most commonly consulted in practice when managing dose delay and discontinuation criteria. This could be seen as critical, as symptoms are not taken into account when deciding on amylase- or lipase-dependent (dis)continuation of therapy.

Events requiring dose delay or discontinuation occurred mostly during the first 12 months of therapy. After this period, it became increasingly unlikely that these would be missed when choosing the simulated lower frequency of laboratory assessments. Over the entire duration of the study, missed dose delay and discontinuation criteria were not very common in the simulated settings. During the nivolumab+ipilimumab boost phases, the rates of affected patients were lower than during nivolumab monotherapy. We believe that this is due to the lower total number of nivolumab+ipilimumab administrations compared to nivolumab monotherapy and the corresponding laboratory assessments.

Irrespective of the definition and variant used, discontinuation criteria were only missed for lipase, amylase, and (once, during control simulation, see supplement) for ALAT. However, if the criteria according to the protocol of TITAN-RCC were used, amylase- and lipase-based discontinuation required the presence of symptoms (e.g., nausea, abdominal pain, and fatigue) that would not have been missed.

In general, with a reduced frequency of laboratory assessments, dose delay criteria would have been missed more often than discontinuation criteria, regardless of the applied definitions and variants. For each laboratory parameter assessed, a dose delay criterion would have been missed at least once in our simulated scenarios. Most missed relevant events occurred only once per patient and laboratory value, with the exception of lipase and creatinine, for which in some patients dose delay or discontinuation criteria would have been missed repeatedly. If one decides to reduce the frequency of laboratory testing, it could be considered to re-increase the frequency for lipase and creatinine if the dose delay criteria were met at least once.

To date, in routine clinical practice, nivolumab+ipilimumab is approved for patients with intermediate or poor risk mRCC, starting with dual checkpoint inhibition with nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) once every 3 weeks for four doses and followed by nivolumab monotherapy 240 mg once every 2 weeks or 480 mg once every 4 weeks. The phase 3 CheckMate-214 trial was pivotal for the combination therapy

and introduced the dosing regimen of 240 mg of nivolumab every 2 weeks during the monotherapy phase [3,27]. The option of using a higher dose of nivolumab at a reduced frequency came up later. Accordingly, the TITAN-RCC protocol demanded a dose of 240 mg of nivolumab every 2 weeks during induction and maintenance monotherapy. Due to the COVID-19 pandemic and the fact that it had been approved by then, the frequency was reduced in some cases to 480 mg every 4 weeks. This was not taken into account in our analysis. We strictly adhered to the specified simulation(s) and considered every second laboratory assessment as non-existent, regardless of whether there were 2 or 4 weeks between nivolumab administrations. In clinical routine, close monitoring is often undertaken, in particular at the beginning of a therapy, as most side effects occur early in the course of treatment [28]. We found no evidence that more frequent laboratory assessments were needed, either at the beginning or during the course of treatment. Also, interim assessments in patients receiving nivolumab every 4 weeks at a dose of 480 mg do not appear to be necessary in asymptomatic patients, and our chosen frequency of laboratory assessments in combination with the patients' clinic seemed to be sufficient.

5. Conclusions

In conclusion, this analysis suggests that laboratory assessments prior to each dose of nivolumab or nivolumab+ipilimumab are not mandatory in clinical practice in patients with mRCC. Reducing the frequency of testing did not substantially increase the risk of missing events relevant to treatment decisions, particularly when using the disease-specific dose delay and discontinuation criteria defined in the TITAN-RCC protocol. Applying these, in asymptomatic patients our analysis suggests that the chosen frequency of laboratory testing can be considered sufficient, offering potential time and resource savings in clinical settings. Careful consideration should be given to which laboratory values need to be determined, also in relation to the presence or absence of symptoms. Nevertheless, a re-increase of frequencies could be considered if dose delay criteria were met at least once, especially for lipase and creatinine.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16122287/s1, Table S1. Missed elevation of CTCAE-grade by at least one grade; Table S2. Missed dose delay and discontinuation criteria per assessment and per patient, criteria defined according to the TITAN-RCC protocol (data obtained with variant B); Table S3. Missed dose delay and discontinuation criteria per assessment and per patient, criteria defined according to the SmPC of nivolumab (data obtained with variant B).

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cancers

Article

The Descriptive and Disproportionality Assessment of EudraVigilance Database Reports on Capecitabine Induced Cardiotoxicity

Razvan Constantin Vonica [1], Anca Butuca [1,*], Andreea Loredana Vonica-Tincu [1,*], Claudiu Morgovan [1], Manuela Pumnea [1], Remus Calin Cipaian [2,3], Razvan Ovidiu Curca [4], Florina Batar [1], Vlad Vornicu [5], Adelaida Solomon [2,3], Adina Frum [1], Carmen Maximiliana Dobrea [1], Dan Damian Axente [6] and Felicia Gabriela Gligor [1]

[1] Preclinical Department, Faculty of Medicine, "Lucian Blaga" University of Sibiu, 550169 Sibiu, Romania; razvanconstantin.vonica@ulbsibiu.ro (R.C.V.); claudiu.morgovan@ulbsibiu.ro (C.M.); manuelapumnea@yahoo.com (M.P.); florina.batar@ulbsibiu.ro (F.B.); adina.frum@ulbsibiu.ro (A.F.); carmen.dobrea@ulbsibiu.ro (C.M.D.); felicia.gligor@ulbsibiu.ro (F.G.G.)
[2] Clinical Department, Faculty of Medicine, "Lucian Blaga" University of Sibiu, 550169 Sibiu, Romania; calin.cipaian@ulbs.ro (R.C.C.); solomonadelaida@gmail.com (A.S.)
[3] County Clinical Emergency Hospital of Sibiu, 2-4 Corneliu Coposu Str., 550245 Sibiu, Romania
[4] Department of Oncology, "Elysee Hospital", 510040 Alba Iulia, Romania; razvancurca@gmail.com
[5] Department IX Surgery, Discipline of Oncology, Faculty of Medicine, Victor Babes University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania; vornicuvlad91@gmail.com
[6] Fifth Surgical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania; damian.axente@umfcluj.ro
* Correspondence: anca.butuca@ulbsibiu.ro (A.B.); loredana.vonica@ulbsibiu.ro (A.L.V.-T.)

Simple Summary: Capecitabine (CAP), belonging to the fluoropyrimidines class, is one of the most common drugs used in the treatment of colon cancer. In this study we cover the real-world impact of adverse effects, with focus on cardiotoxicity. The frequency of reports of cardiac toxicity in the EudraVigilance database was studied. Following the analysis, we observed that CAP and 5-FU can cause heart diseases, such as acute myocardial infarction, angina pectoris, heart failure, etc. From a physio-pathological point of view, coronary vasospasm, endothelial dysfunction and oxidative stress are the main factors in the production of cardiotoxicity induced by fluoropyrimidines.

Abstract: Capecitabine (CAP) is one of the most commonly prescribed fluoropyrimidines in oncology, especially in the treatment of colon cancer. Cardiac toxicity is a severe and potentially lethal adverse drug reaction (ADR) against fluoropyrimidines. Cardiac ADRs, such as myocardial infarction (MI), heart failure (HF), arrhythmias, and a number of cardiomyopathies, are reported for these molecules. To have a better understanding of the risk–benefit ratio of colon cancer therapy, a pharmacovigilance study of real-world evidence of the cardiac toxicity of antineoplastic agents is required. Aim: This post-marketing research on CAP aims to assess the risk of cardiac toxicity. Five other antitumor drugs used in colorectal cancer, i.e., 5-fluorouracil (5-FU), irinotecan (IRI), oxaliplatin (OX), bevacizumab (BEV) and panitumumab (PAN), were also studied to create a relative profile of observed cardiotoxicity. Methods: A retrospective study based on reports submitted in the EudraVigilance (EV) database until 28 July 2024 was conducted. Using the aggregated data from EV, a descriptive analysis and disproportionality analysis of cardiac ADRs induced by fluoropyrimidines were performed. To evaluate the disproportionality of the signals, Reporting Odds Ratio (ROR) and 95% confidence interval (95% CI) were calculated by comparison with other drugs used in colorectal cancer: 5-FU, IRI, OX, BEV, and PAN. Results: "Cardiac disorders" represent 3.4% of the total reports for CAP. The value is comparable to 5-FU, but higher than for other drugs. t was observed that there are no significant differences in the occurrence of cardiac ADRs in patients exposed to CAP and 5-FU treatments, and in particular MI and HF. Compared to 5-FU, which could produce cardiac arrythmias with a higher probability than all other drugs, CAP has a higher probability of reporting this ADR only in comparison with IRI (ROR: 1.2971; 95% CI: 1.0196-1.6502). Conclusions: CAP induces adverse cardiovascular

reactions, especially MI, HF, and cardiomyopathies. Arrhythmias have been shown to be side effects more frequent associated with 5-FU than with CAP. The results emphasize the need for a rigorous cardiovascular monitoring of patients following treatment with CAP or 5-FU and especially for those with pre-existing cardiac pathology.

Keywords: colon cancer; cardiotoxicity; fluoropyrimidines; capecitabine; adverse drug reactions; pharmacovigilance; EudraVigilance

1. Introduction

Colon cancer is situated in the first half of the top 10 most common cancer forms. Among the newly diagnosed cancers, the frequency of colon cancer is 12%, according to the International Agency for Cancer Research. 40,000 cases are diagnosed in the United Kingdom each year [1]. It is known that the etiology is multifactorial, including (i) environmental factors, such as high intake of red meat, high consumption of fats and processed meat, low consumption of fruits and vegetables and fibers, (ii) pathological conditions: obesity, inflammatory bowel diseases, diabetes, etc. [2], (iii) genetic factors: familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (NHPCC), etc. [3]. The information found in the Global Cancer Observatory (GLOBOCAN) demonstrates a significant increase in cancer cases, with 19.98 million new cases registered in 2022 and 9.74 million patients who died of this disease [4]. The prevalence of survivors after diagnosis at 5 years with colorectal cancer was 50.6 million [1].

Colorectal cancer can be prevented through large-scale screening programs. This approach has had a good impact, triggering a decrease in the illness in countries with developed medical systems [5]. Historically, until the mid-1990s, colon cancer patients were treated with 5-Fluorouracil (5-FU) [6]. Along with the progress of medical technology, the pharmacotherapy for colon cancer has become more and more complex and effective, as there are drugs available from a variety of classes, which include (i) cytotoxic agents (oxaliplatin—OX and irinotecan—IRI) [7]; (ii) oral fluoropyrimidines, which bring benefits to the patients' quality of life due to the fact that the treatment can be administered at home (capecitabine—CAP); (iii) biological agents (bevacizumab—BEV, panitumumab—PAN, pembrolizumab, nivolumab) etc. [8]. More recently, anti-angiogenic agents, such as Ziv (aflibercept and regorafenib) were approved and introduced [9].

The most frequently used drugs in the treatment of colon cancer are fluoropyrimidines, such as 5-FU and CAP. These drugs have proven their effectiveness if they are also used in combination with other drugs, such as (i) FUFOL (5-FU + Leucovorin (LV)), (ii) CAPOX (CAP+ OX), (iii) FOLFOX (5-FU + OX + LV), (iv) FOLFIRI (5-FU + IRI + LV) or (v) FOLFOXIRI (5-FU + OX + IRI + LV) [1].

Following the use of fluoropyrimidines on a large scale, a series of side effects have been observed, among which the most severe is cardiac toxicity [10,11]. Coronary vasospasm is the most frequent and severe cardiac toxicity that can occur after treatment with 5-FU or CAP [12]. This manifestation can cause different degrees of cardiac ischemia, accompanied by angina pectoris, myocardial infarction or even sudden death [10]. Angina pectoris can be typical or atypical and represents the most frequent manifestation of cardiac toxicity post-administration of CAP [13,14].

In general, the cardiotoxicity of exposure to fluoropyrimidines occurs during the first administration cycle [15–17]. The first symptoms appear most frequently 12 h after starting the infusion with 5-FU, or in the first 2–3 days after taking, but cardiotoxicity can appear at any time, even 1–2 days after the infusion or longer [18]. Astrup et al. studied 106 patients to whom 5-FU was administered by infusion in the short-term in the FOLFOX regimen, and nine of the studied patients had angina pectoris during the treatment [19]. Acute symptoms can start with angina pectoris, cardiac arrhythmias, and hypertension. From the

point of view of chronic cardiotoxicity, this can become permanent and cumulative, being represented by heart failure [20].

Drug studies based on pharmacovigilance bring important benefits in clinical practice with the aim of personalizing and minimizing possible adverse reactions. In this way, health professionals will promptly recognize and treat possible adverse events by applying prophylactic, diagnostic or therapeutic measures to patients exposure to these types of injuries. Cardiac toxicity monitoring is essential in making early intervention more efficient, with the aim of reducing the mortality of patients treated with fluoropyrimidines [21]. The development of new clinical guidelines and monitoring protocols are supported by pharmacovigilance studies, which contribute to improving the quality and lifespan of patients [22].

To expand the knowledge of cardiotoxicity risk factors during fluoropyrimidine treatment, this research aimed to assess spontaneously reported cardiac adverse reactions following the use of CAP by investigating the EudraVigilance (EV) database. The safety profile of CAP comprises the identification and evaluation of adverse effects [23].

2. Materials and Methods

2.1. Study Design

A descriptive and disproportionality analysis of spontaneous ADRs reported for CAP were performed. For comparison, other antitumor drugs used in colorectal cancer were chosen. The analysis included all reports registered on the portal adrreports.eu, starting with the first report for each drug: CAP (28 January 2003), 5-FU (4 February 2003), IRI (11 February 2003), OX (26 August 2003), BEV (16 April 2004), and PAN (20 November 2006), until 28 July 2024 [24]. Data included in the Individual Case Safety Reports (ICSRs) were extracted between 1 and 3 August 2024. Health Professionals (HP) or Non-HP can fill ICSRs for patients originating from the European Economic Area (EEA) or Non-EEA [25].

2.2. Material

According to EMA regulations, different preferred terms (PTs), including 27 System Organ Classes (SOCs), can be used for reporting the ADRs in ICSRs. The Medical Dictionary for Regulatory Activities (MedDRA) is a hierarchic structure of different categories of terms classified as "medical and health-related". Thus, PTs represent a medical terminology used for the coding of the ADRs. They are preferred when presenting the unique adverse effects or clinical conditions reported in databases. On the other hand, SOC is the highest level of hierarchy and includes terms grouped according to the organ system affected [26].

Cardiotoxicity of CAP includes arrhythmias, heart failure (HF), cardiomyopathy, and myocardial infarction (MI). Thus, to evaluate cardiotoxicity, some PTs related to different medical conditions have been selected (Table 1).

Data were extracted from ICSRs containing at least one PT from Table 1, used for reporting cardiotoxicity.

Table 1. PTs used for evaluation of cardiotoxicity.

Medical Condition	PT
Arrythmias	Arrhythmia
	Arrhythmia supraventricular
	Atrial fibrillation
	Atrial flutter
	Atrial tachycardia
	Atrioventricular block
	Bradycardia
	Supraventricular tachycardia

Table 1. *Cont.*

Medical Condition	PT
Heart failure	Cardiac arrest
	Cardiac Tamponade
	Cardiac ventricular disorder
	Cardiogenic shock
	Coronary artery disease
	Left ventricular dysfunction
	Right ventricular dysfunction
Cardiomyopathy	Cardiac Hypertrophy
	Cardiomyopathy
	Cardiotoxicity
	Ischaemic cardiomyopathy
Myocardial infarction	Acute coronary syndrome
	Acute myocardial infarction
	Angina pectoris
	Angina unstable
	Arterio-spasm coronary
	Kounis syndrome
	Prinzmetal angina

2.3. Data Analysis

2.3.1. Descriptive Analysis

General characteristics included in ICSRs (patients' age, sex, geographical origin, reporter) were analyzed [27]. Subsequently, a comparative analysis of reports related to CAP use with other antitumoral drugs for colorectal cancers (5-FU, BEV, IRI, OX, and PAN) was performed. Thus, (i) the ratio of ADRs reported for each ICSR, (ii) the structure of ADRs by seriousness, (iii) the distribution of ADRs by SOCs, and (iv) the distribution of ADRs by outcome were compared. An ADR is classified as serious when it is life-threatening, and/or it determines significant incapacity, and/or causes congenital anomalies [28]. Some outcomes indicate a progression of patient status (R—recovered, RS—resolved, RG—recovering, RSG—resolving), while others reflect an unfavorable progression (NR—not recovered, NRS—not resolved, or recovered/resolved with sequelae) [24]. Finally, ADRs related to the main cardiac PTs used for reporting CAP cardiotoxicity in EV were analyzed.

2.3.2. Disproportionality Analysis

To evaluate disproportionate reporting, the Reporting Odds Ratio (ROR) and 95% confidence interval (95% CI) could be calculated by comparison with other drugs used in common therapeutic areas and in similar clinical contexts, based on the EMA recommendation. Thus, a signal of disproportionate reporting is defined if the lower bound of the 95% confidence interval (CI) is greater than 1 and the number of ICSRs is greater than or equal to 5 [29]. The calculation was conducted with MedCalc Software Ltd (MedCalc Software Ltd, Ostend, Belgium). on https://www.medcalc.org/calc/odds_ratio.php (accessed on 10 August 2024) (Version 20.123) [30]. The ROR was estimated for the cardiotoxicity reported for different medical conditions with PTs, included in Table 1. For the analysis, other antitumor drugs were used as comparators (5-FU, BEV, IRI, OX, PAN) [31]. Moreover, because 5-FU is the active metabolite of CAP, the disproportionality analysis was performed for both drugs, to observe the possible differences between them. Initially, a signal assessment was conducted for reports under the SOC "Cardiac disorders" for CAP and

5-FU, using other antitumor drugs as comparators. Subsequently, disproportionality was evaluated for each cardiotoxic condition (myocardial infarction, arrhythmias, heart failure, and cardiomyopathy) associated with CAP and 5-FU, respectively. Reporting is considered disproportionate if the case count is ≥5 and the lower limit of the 95% confidence interval exceeds 1.0 [31]. All reports with CAP, 5-FU, BEV, IRI, OX, and PAN mentioned as suspect, interacting or concomitant were included in these analyses.

2.4. Ethics

No personal information was contained in the ICSRs and these analyses do not refer to any identifiable person. Therefore, this study did not require ethics board approval [32].

3. Results

3.1. Descriptive Analysis

According to data submitted in EV until 28 July 2024, 37,983 cases were reported for CAP, similar to 5-FU (n = 36,683), but inferior to BEV (n = 57,757) and to OX (n = 56,460). Compared to other drugs used for reference, CAP had a higher number of reports (IRI—n = 17,728 and PAN—n = 6950). No significant differences regarding the proportions of each age category were registered between CAP and the other drugs. Thus, most reports were registered for CAP in the 18–64 years (44.8%) and 65–85 years (33.3%) groups (Table 2), similar to the other drugs. An interesting situation could be observed for CAP regarding the sex of patients. In the CAP group, the majority of ICSRs were submitted for females (56.8%), in comparison to 5-FU (43.2%), IRI (38.9%), OX (42.7%), and PAN (31.4%). The majority of ICSRs were reported from non-EU countries for CAP and for all other drugs used as references. HP was the most frequent category of reporters submitting ICSRs in EV for CAP and for the other antitumor drugs of interest.

Table 2. Characteristics of records associated with capecitabine in EudraVigilance. EEA—European Economic Area; NS—not specified.

Characteristics	*N*	%
	Age category	
NS	7837	20.6%
0–1 Month	12	0.0%
2 Months–2 Years	20	0.1%
3–11 Years	8	0.0%
12–17 Years	19	0.1%
18–64 Years	17,015	44.8%
65–85 Years	12,654	33.3%
More than 85 Years	418	1.1%
	Sex	
Female	21,557	56.8%
Male	14,706	38.7%
NS	1.72	4.5%
	Origin	
EEA	12,405	32.7%
NON-EEA	25,578	67.3%
NS	0	0

Table 2. *Cont.*

Characteristics	*N*	%
Reporter category		
Reporter		
HP	33,602	88.5%
Non-HP	4333	11.4%
NS	48	0.1%

The ratio between total ADRs and total ICSR submitted in EV was compared in Figure 1. For CAP (1.97), the ratio is higher than all other comparators, except for PAN (2.09).

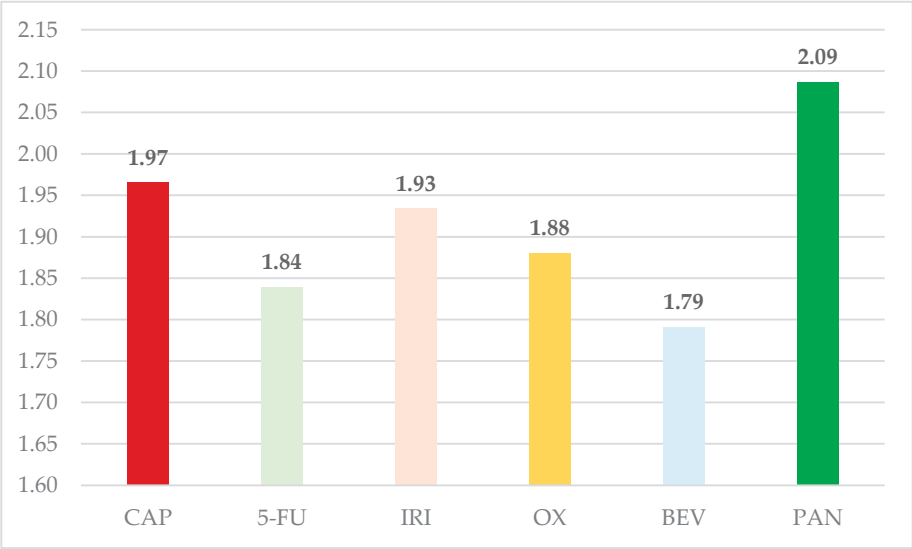


Figure 1. The comparative ratio of ADRs reported for each ICSR. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab.

According to data submitted in EV, 93.4% of ADRs reported for CAP were serious: higher than PAN (83.6%), OX (86.7%), 5-FU (86.8%), and IRI (87.1%) (Figure 2).

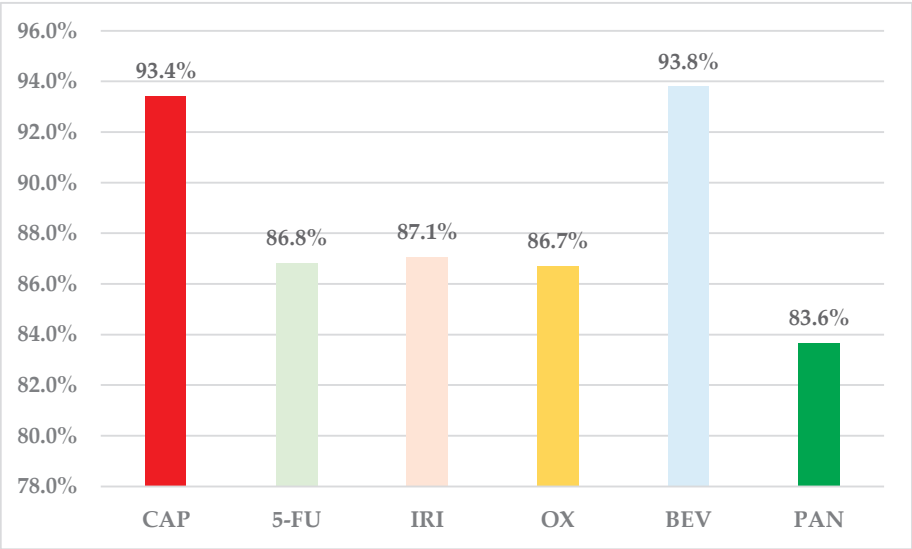


Figure 2. Structure of ADRs by seriousness. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab.

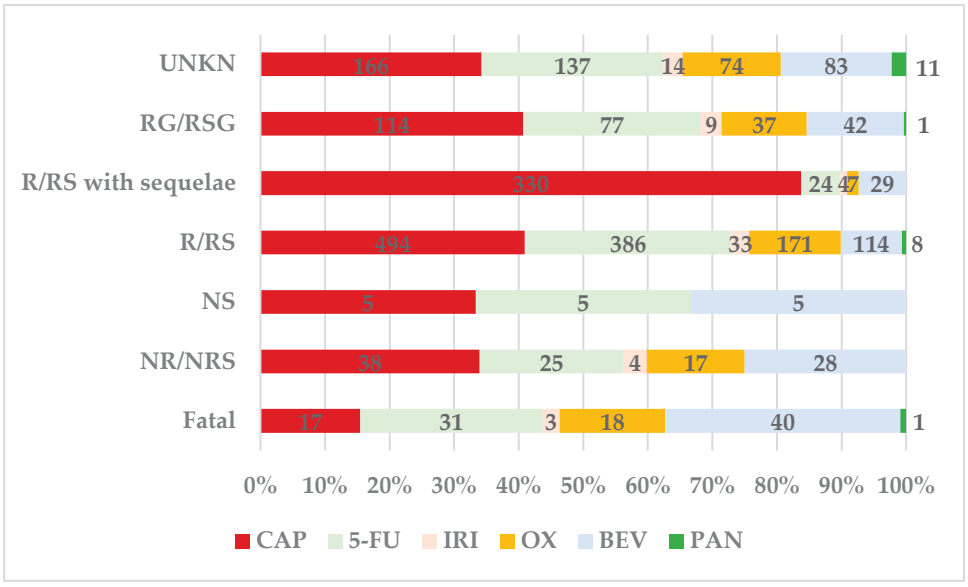
Regarding the distribution of ADRs in SOC, higher proportions were observed for CAP in "Cardiac disorder" (3.4%) and "Gastrointestinal disorder" (15.0%) SOCs. A lower proportion was noticed for CAP regarding ADRs from "Infections and infestation" (3.8%) and "Nervous system disorder" (6.1%) SOCs (Table 3).

Table 3. Distribution of ADRs by SOCs. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab.

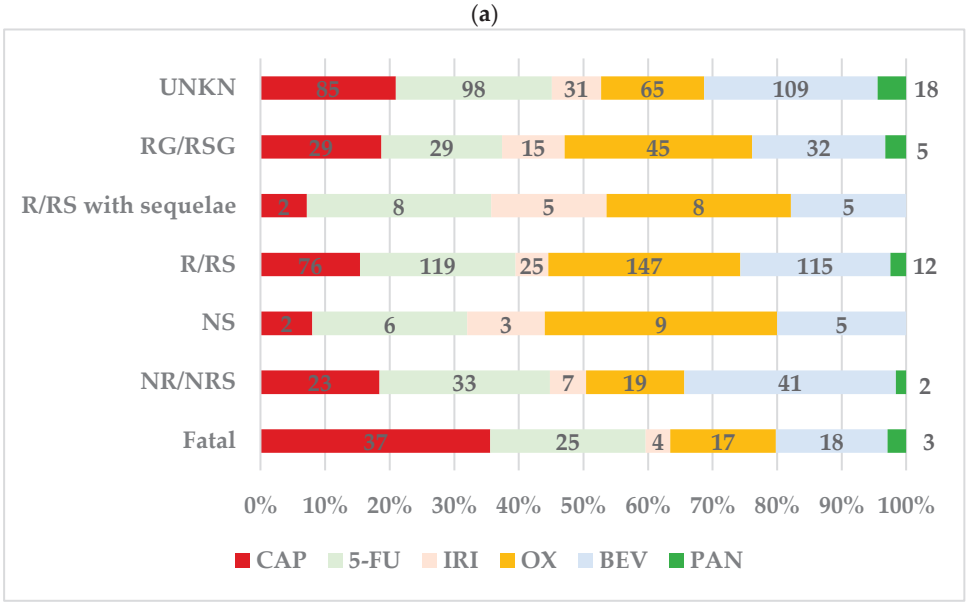
SOC	CAP	5-FU	IRI	OX	BEV	PAN
Blood and lymphatic system disorders	11.7%	16.5%	16.2%	13.0%	7.5%	5.3%
Cardiac disorders	3.4%	3.4%	1.5%	2.1%	2.7%	1.3%
Congenital, familial and genetic disorders	0.3%	0.2%	0.2%	0.1%	0.1%	0.2%
Ear and labyrinth disorders	0.3%	0.3%	0.2%	0.2%	0.2%	0.1%
Endocrine disorders	0.2%	0.3%	0.1%	0.1%	0.5%	0.1%
Eye disorders	0.9%	0.9%	0.7%	1.0%	3.1%	1.8%
Gastrointestinal disorders	15.0%	13.7%	17.9%	11.5%	12.7%	8.9%
General disorders and administration site conditions	13.7%	12.7%	12.1%	11.3%	12.5%	11.9%
Hepatobiliary disorders	2.5%	2.0%	1.7%	2.1%	2.2%	1.6%
Immune system disorders	0.6%	0.9%	1.1%	5.5%	0.9%	1.1%
Infections and infestations	3.8%	4.5%	4.4%	2.2%	5.5%	7.9%
Injury, poisoning and procedural complications	3.6%	3.3%	3.5%	2.6%	5.8%	3.8%
Investigations	7.4%	7.0%	7.1%	8.0%	6.0%	4.1%
Metabolism and nutrition disorders	3.9%	3.7%	4.2%	2.5%	2.2%	5.7%
Musculoskeletal and connective tissue disorders	2.2%	1.4%	1.4%	1.8%	2.5%	1.1%
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5.3%	4.4%	4.5%	2.0%	4.9%	7.1%
Nervous system disorders	6.1%	7.1%	6.6%	10.6%	7.4%	5.3%
Pregnancy, puerperium and perinatal conditions	0.0%	0.2%	0.0%	0.0%	0.0%	0.0%
Product issues	0.1%	0.2%	0.1%	0.1%	0.3%	0.0%
Psychiatric disorders	1.1%	0.9%	0.7%	0.7%	0.8%	0.5%
Renal and urinary disorders	1.9%	2.1%	2.0%	1.5%	4.0%	1.5%
Reproductive system and breast disorders	0.4%	0.3%	0.3%	0.2%	0.6%	0.3%
Respiratory, thoracic and mediastinal disorders	3.6%	4.9%	4.9%	8.1%	6.7%	5.9%
Skin and subcutaneous tissue disorders	9.0%	5.7%	5.2%	7.8%	3.4%	21.7%
Social circumstances	0.1%	0.1%	0.0%	0.1%	0.1%	0.1%
Surgical and medical procedures	0.3%	0.3%	0.2%	0.1%	0.3%	0.7%
Vascular disorders	2.5%	3.0%	3.1%	4.6%	6.9%	1.9%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

70.4% of the total ADRs related to myocardial infarction reported after CAP use (n = 608) had a favourable outcome (R/RS or RG/RSG), a higher proportion than for the other drugs. Among the drugs of interest, the lowest percentage of ADRs leading to death was reported for CAP (n = 17, 2.0%) (Figure 3a). For arrhythmias produced by CAP, the highest proportion of ADRs with fatal outcomes (n = 37; 14.6%) compared to the other drugs was registered. A favourable outcome was reported for 41.3% of total ADRs (n = 105) related to arrhythmia produced by CAP (Figure 3b). The proportion of ADRs related to heart failure with fatal outcomes reported for CAP (n = 93, 28.2%) was similar to that for

5-FU (n = 90, 28.8%) and BEV (n = 65, 27.8%). The proportion of ADRs with favourable outcomes (n = 142, 43.0%) was also similar to 5-FU (n = 143, 45.7%) and OX (n = 110, 47.2%) and higher than the others (Figure 3c). Of the total ADRs related to myopathy reported for CAP, 6.6% (n = 16) had fatal outcomes, similar to 5-FU (n = 20, 6.3%) and OX (n = 6, 5.8%). The ratio of cases with favourable outcomes reported for CAP (n = 116, 48.1%) was lower than for 5-FU (n = 181, 56.9%), OX (n = 56, 54.4%), and PAN (n = 4, 57.1%) (Figure 3d).

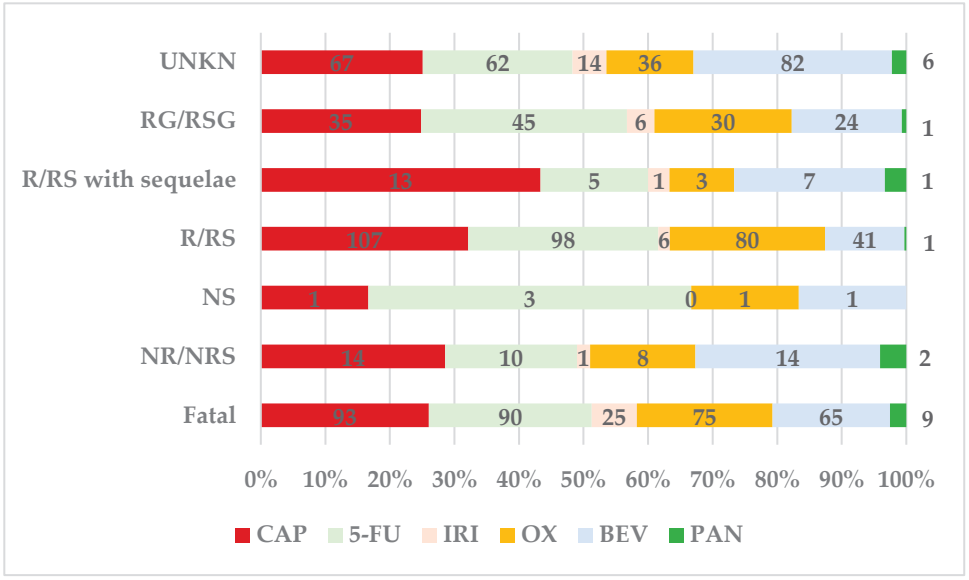


(**a**)

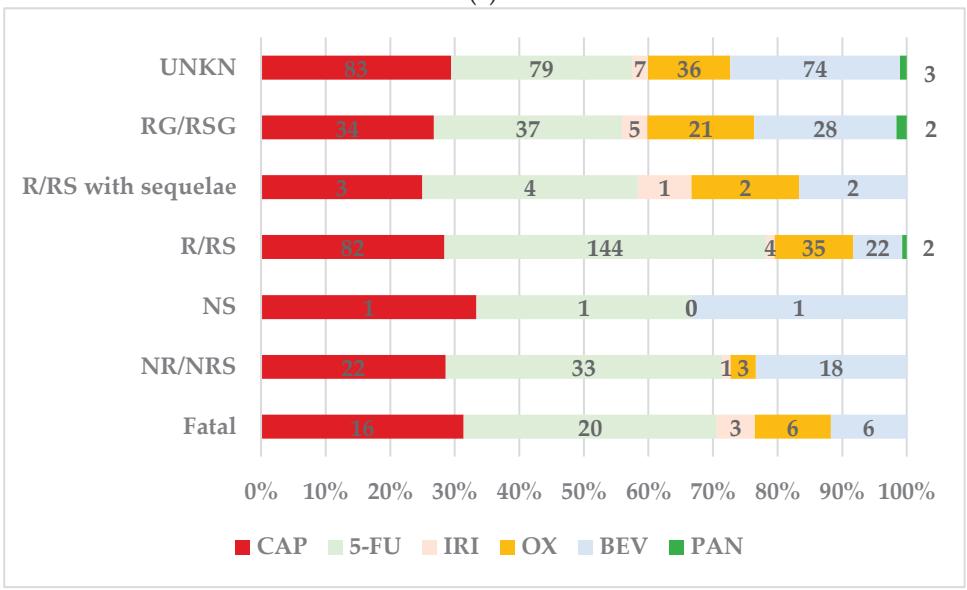


(**b**)

Figure 3. *Cont.*



(**c**)



(**d**)

Figure 3. Distribution of ADRs by outcome. ADRs related to (**a**)—myocardial infarction; (**b**)—arrhythmias; (**c**)—heart failure; (**d**)—cardiomyopathy. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab; R—recovered; RS—resolved; NR—not recovered; NRS—not resolved; RG—recovering; RSG—resolving; UNKN—unknown.

Figure 4 presents the distribution of the main cardiac PTs reported for CAP use. More than half of the total ADRs identified for the analysed medical conditions (n = 1689) are related to myocardial infarction (n = 864). ADRs for the other three medical conditions are approximately the same: cardiomyopathy—n = 241; heart failure—n = 330; arrhythmias—n = 254. According to this data, the distribution of the more frequent PTs used for each medical condition is as follows:

(i) MI: "Angina pectoris" (n = 271), "Arterio-spasm coronary" (n = 258), "Acute myocardial infarction" (n = 156), and "Acute coronary syndrome" (n = 105)
(ii) HF: "Cardiac arrest" (n = 185)
(iii) Cardiomyopathy: "Cardiotoxicity" (n = 173)
(iv) Arrhythmias: "Atrial fibrillation" (n = 128).

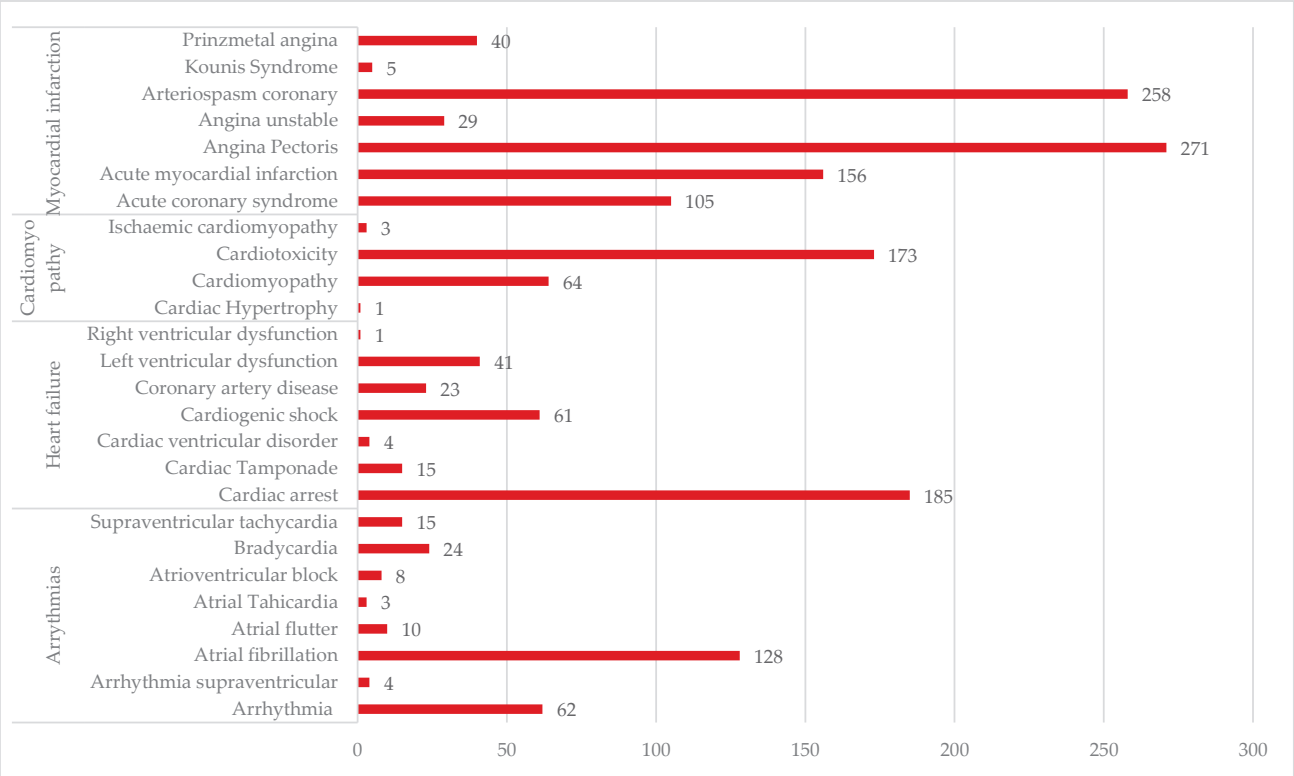
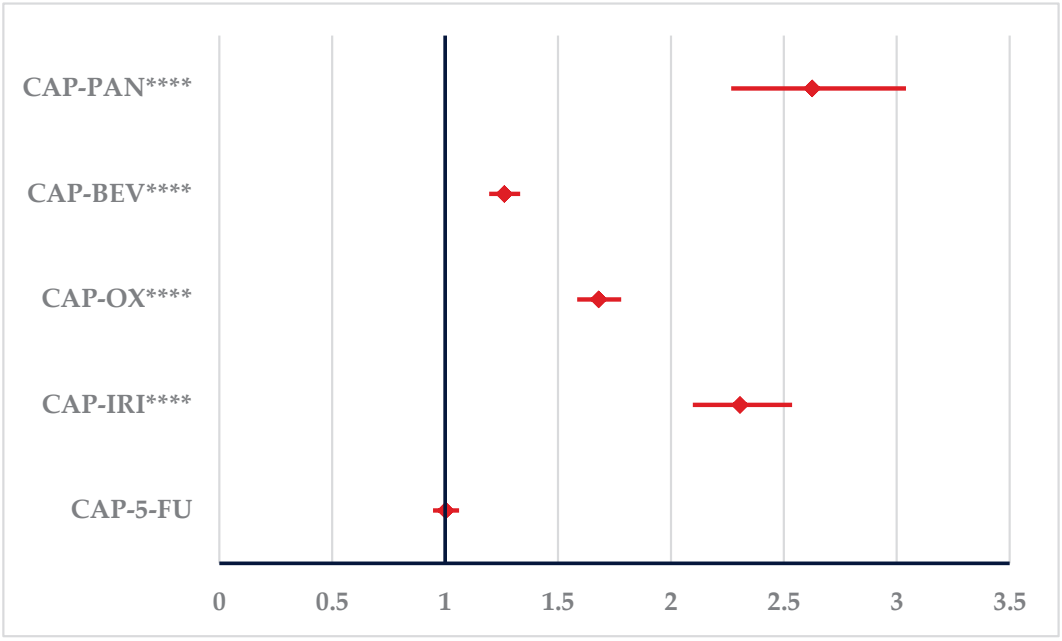


Figure 4. ADRs related to main cardiac PTs used for reporting in EV.

3.2. Disproportionality Analysis

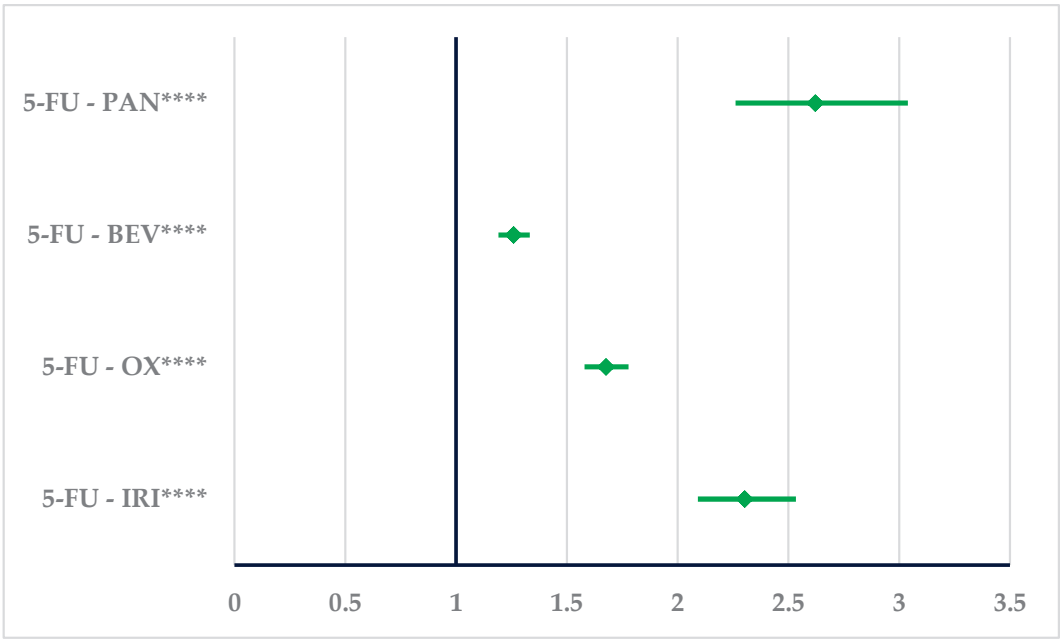
3.2.1. Analysis of Signals Reported in SOC "Cardiac Disorders"

Figure 5 represents the disproportionality analysis of signals reported in SOC "Cardiac disorders". Similar to 5-FU, CAP presents disproportionate signals compared to OX, IRI, BEV and PAN. On the other hand, a disproportionate signal could not be compared to 5-FU.



(**a**)

Figure 5. *Cont.*



(**b**)

Figure 5. Disproportionality analysis of ADRs produced by CAP and 5-FU and reported in "Cardiac disorders" SOC. (**a**)—capecitabine; (**b**)—5-fluorouracil. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab. **** $p \leq 0.0001$.

3.2.2. Analysis of Signals Related to Different Cardiac Diseases Reported After Capecitabine Use

According to Figure 6, CAP and 5-FU have a higher probability of reporting PTs related to myocardial infarction than IRI (ROR: 5.9799, 95% CI: 4.6623–7.6698), OX (ROR: 3.825 0, 95% CI: 3.3653–4.3474), BEV (ROR: 3.5402, 95% CI: 3.1220–4.0143), and PAN (ROR: 8.0770, 95% CI: 5.2372–12.4567). CAP also has a higher probability of reporting than 5-FU (ROR: 1.1418; 95% CI: 1.0323–1.2629).

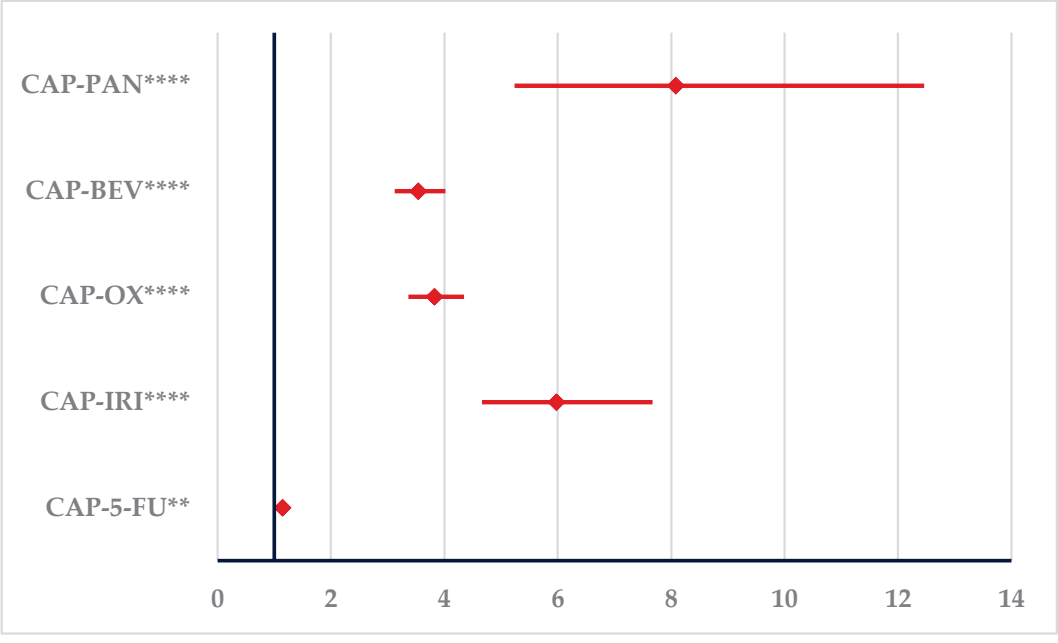


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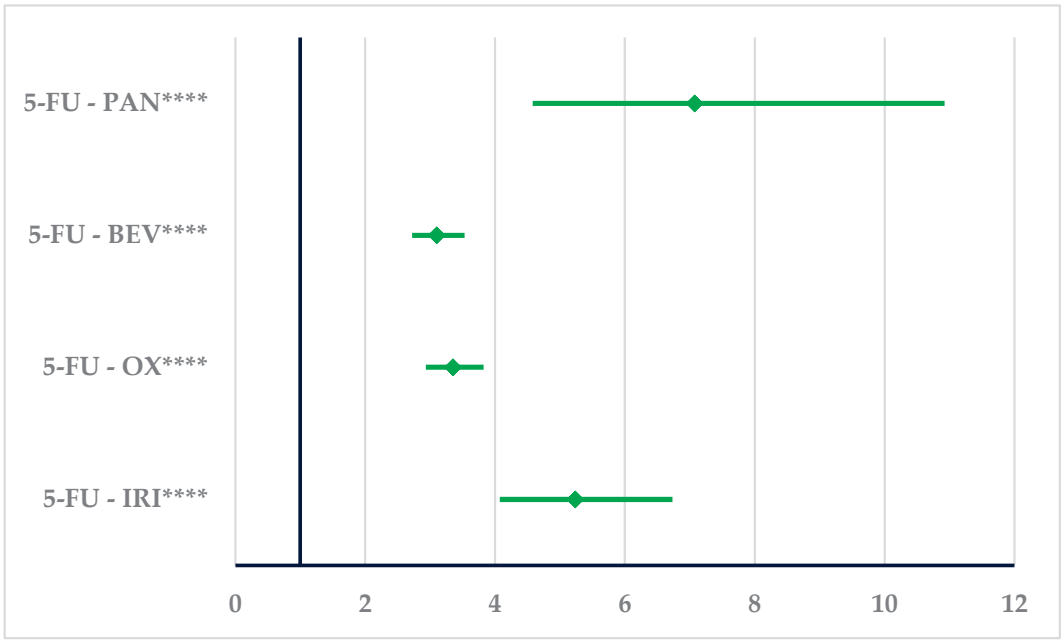
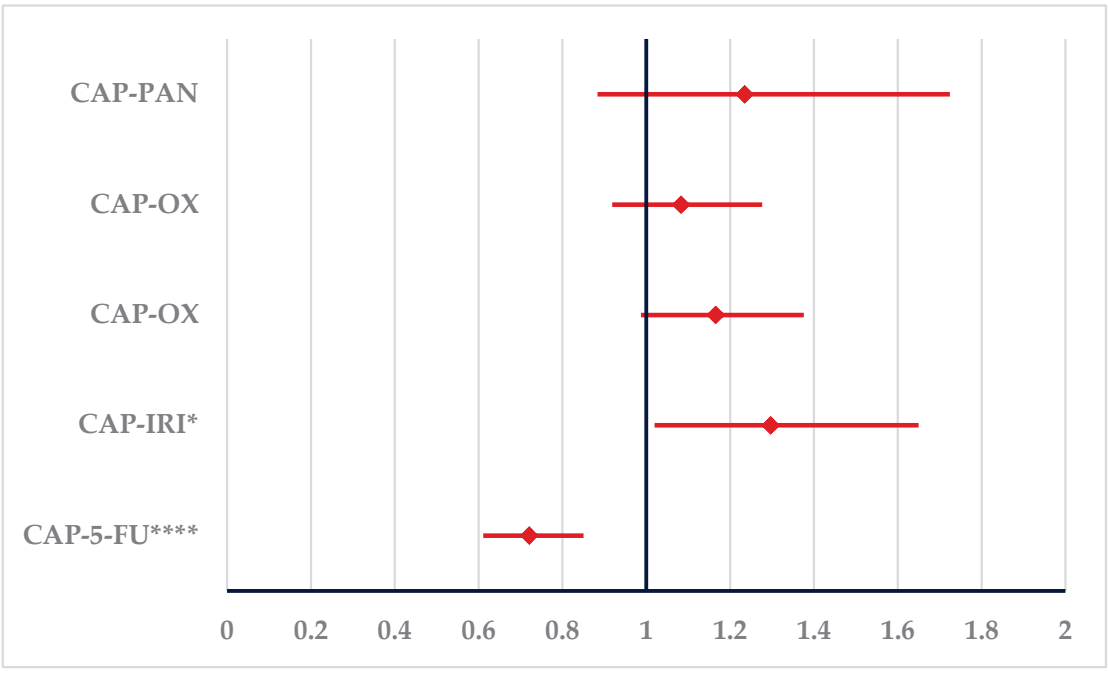
Figure 6. *Cont.*



(**b**)

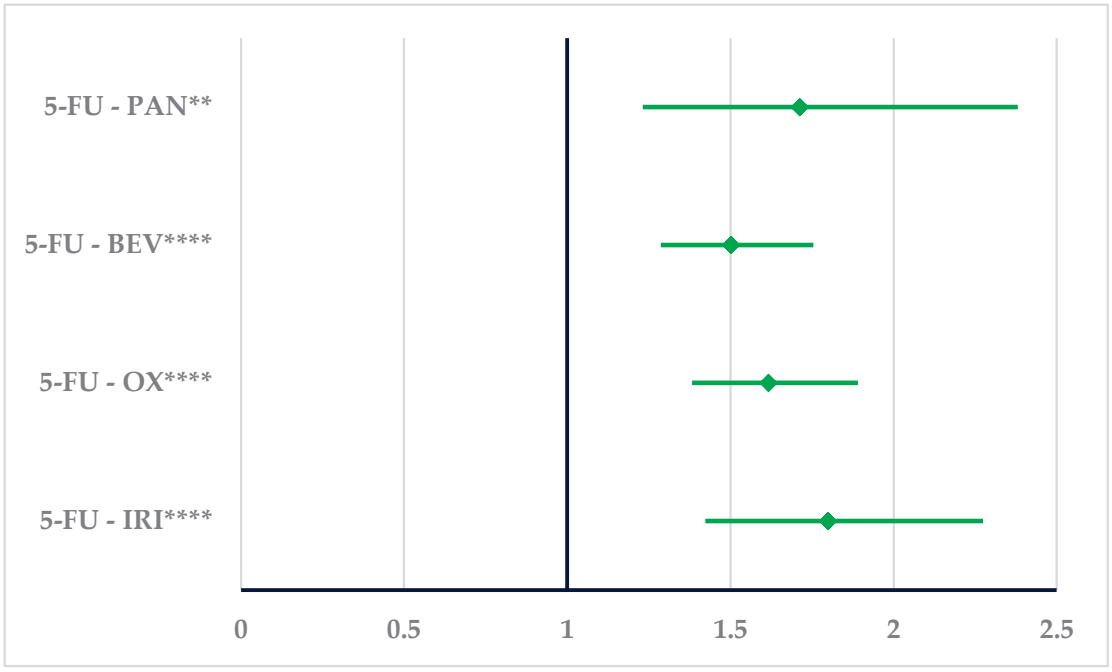
Figure 6. The signals for ADRs related to myocardial infarction produced by capecitabine and 5-fluorouracil. (**a**)—capecitabine (**b**)—5-fluorouracil. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab. ** $p \leq 0.01$; **** $p \leq 0.0001$.

Arrhythmias produced by 5-FU could be reported with a higher probability than all other drugs. On the other hand, CAP has a higher probability of reporting arrhythmias only in comparison with IRI (ROR: 1.2971; 95% CI: 1.0196–1.6502). For CAP, a lower probability of reporting arrhythmias could also be observed than for 5-FU (ROR: 0.7211, 95% CI: 0.6112–0.8507) (Figure 7).



(**a**)

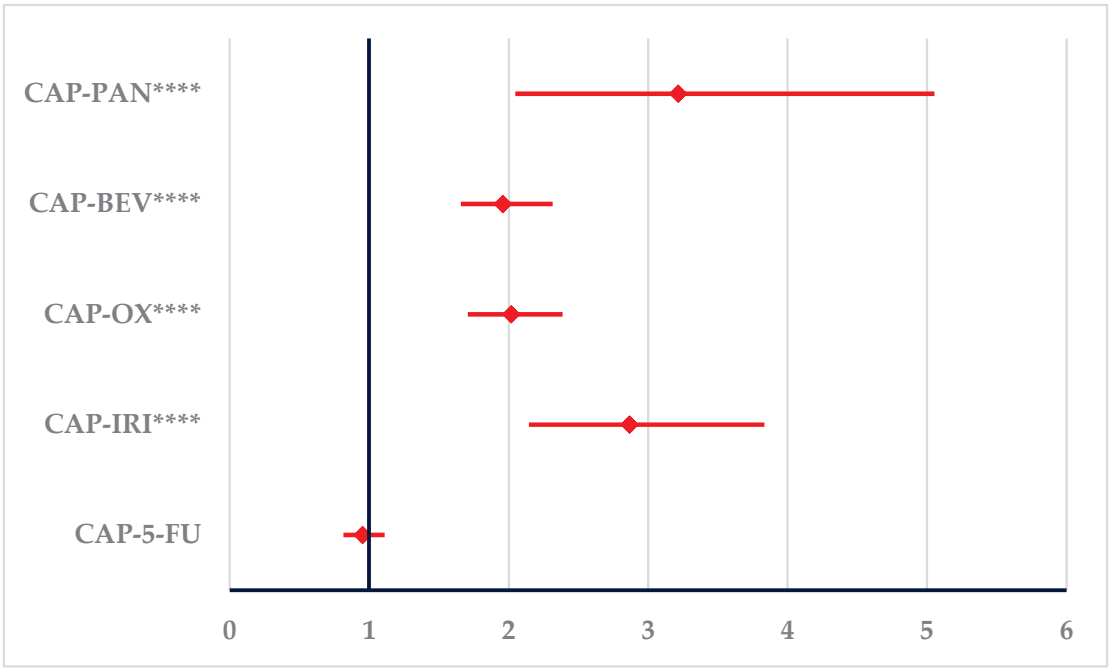
Figure 7. *Cont.*



(**b**)

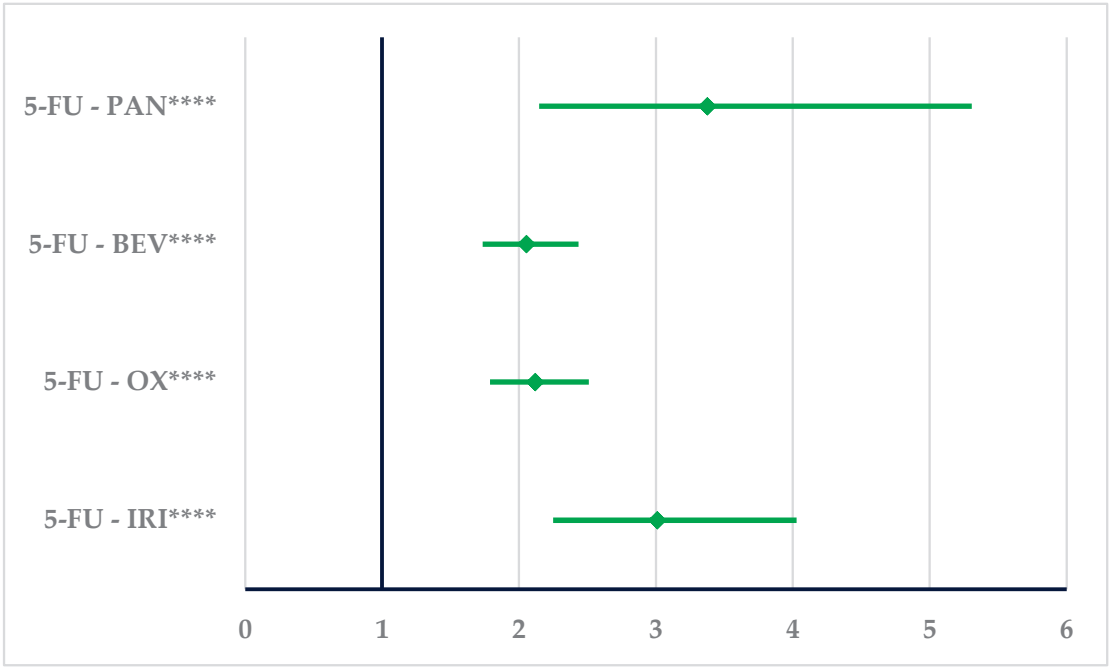
Figure 7. The signals in ADRs related to arrhythmias produced by capecitabine and 5-fluorouracil. (**a**)—capecitabine (**b**)—5-fluorouracil. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab. * $p < 0.05$; ** $p \leq 0.01$; **** $p \leq 0.0001$.

PTs related to heart failure (Figure 8) or cardiomyopathy (Figure 9) were reported with a higher probability for CAP and 5-FU than all other drugs. CAP presents a higher probability of reporting cardiomyopathy than 5-FU, but no differences between CAP and 5-FU could be observed for PTs related to heart failure.



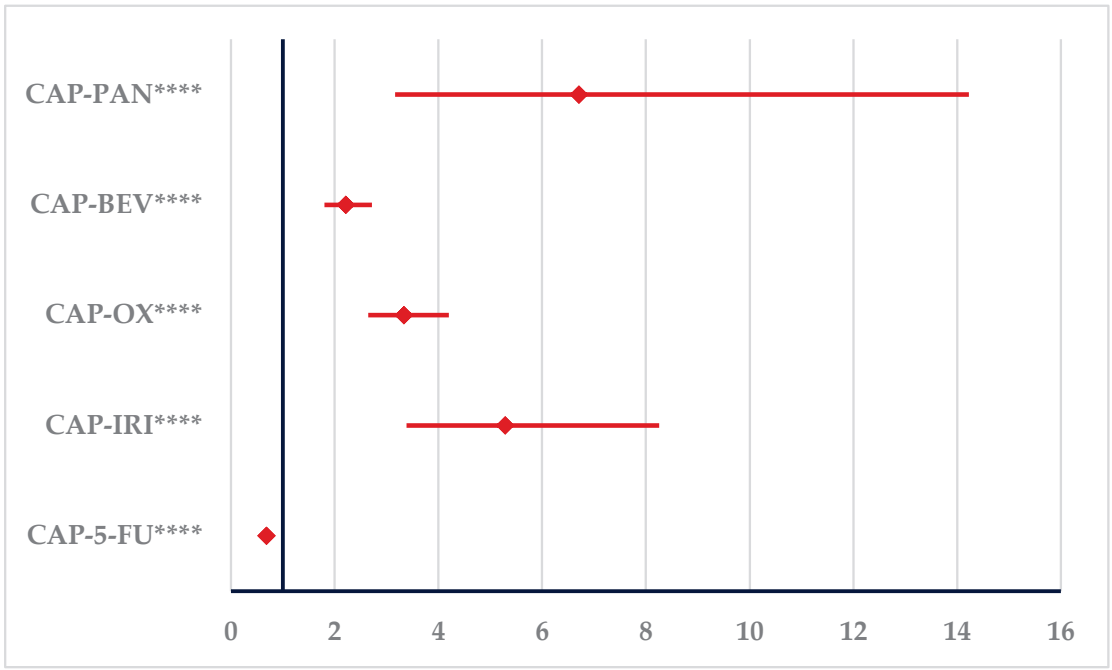
(**a**)

Figure 8. *Cont.*



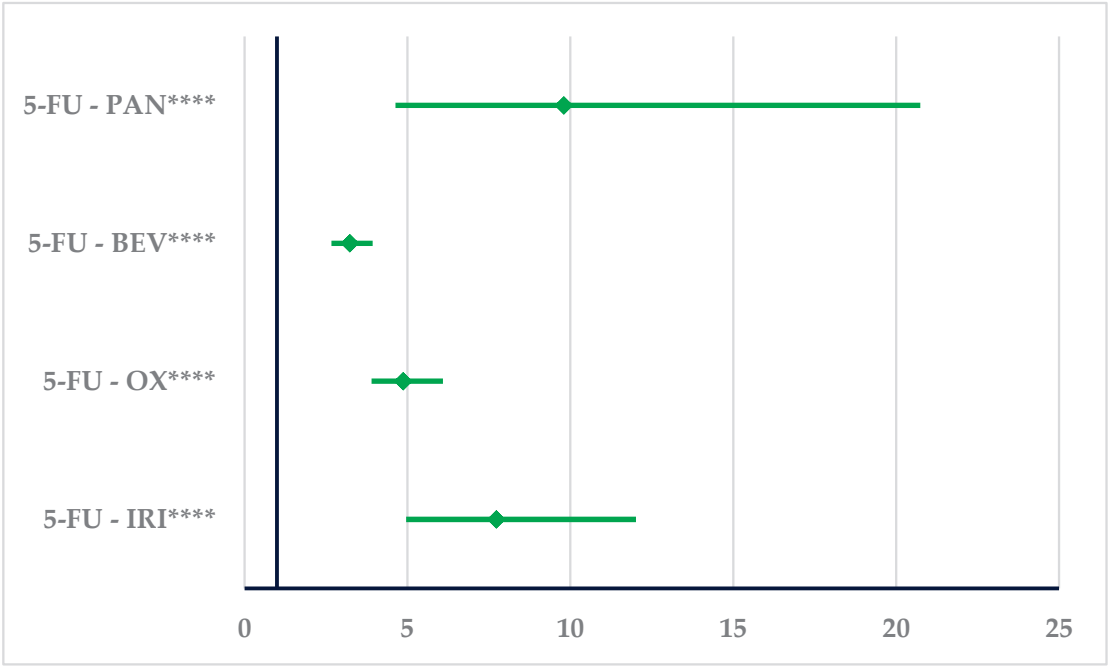
(**b**)

Figure 8. The signals in ADRs related to heart failure produced by capecitabine and 5-fluorouracil. (**a**)—capecitabine (**b**)—5-fluorouracil. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab. **** $p \leq 0.0001$.



(**a**)

Figure 9. *Cont.*



(**b**)

Figure 9. The signals in ADRs related to cardiomyopathy produced by capecitabine and 5-fluorouracil. (**a**)—capecitabine (**b**)—5-fluorouracil. 5-FU—5-fluorouracil; BEV—bevacizumab; CAP—capecitabine; IRI—irinotecan; OX—oxaliplatin; PAN—panitumumab. **** $p \leq 0.0001$.

4. Discussion

Our study highlights the distribution of cases reported in the EV database for CAP in comparison with other cytostatics for targeted therapies, such as 5-FU, OX, IRI, BEV, and PAN, respectively. The data analysed show a similar number of reported cases for CAP, as well as for 5-FU, but fewer reports are observed compared to OX and BEV. CAP has more reports than IRI and PAN.

More reports were identified in EV for OX and BEV than for CAP. There is a difference in reporting, possibly triggered by the diverse mechanisms of action and the different safety profiles of the drugs. OX is a platinum agent, having as its main side effect severe peripheral neurotoxicity, which can be cumulative, a reason why both patients and doctors report these adverse reactions more frequently [33]. BEV inhibits the vascular endothelial growth factor (VEGF), generating ADRs, such as arterial hypertension, thromboembolic events and gastrointestinal perforations, and negatively influencing the quality of life of patients [34,35].

In our study, more reports were registered for CAP compared to IRI and PAN, probably because of the frequent ADRs, but also because of the profiles of the well-known adverse reactions. CAP can present unpredictable and varied adverse reactions, especially cardiac and gastrointestinal toxicities, which are reported in large numbers on the EV platform [36]. PAN is a monoclonal antibody that acts against the epidermal growth factor receptor (EGFR) [37], which presents, especially, dermatological adverse reactions, such as less severe and frequent skin rashes, compared to cytostatic treatments. Its use is limited to stage IV disease, which may explain the small number of cases reported in EV [38,39].

It is important to mention that the distribution of cases reported in EV may vary depending on the differences in the clinical use of these drugs. Both CAP and 5-FU are used as a large proportion of treatments against colon cancer, while OX and BEV are treatments that are considered useful, especially in combination with other chemotherapeutics, which explains the important number of reports [37]. In advanced stages, PAN, BEV, and IRI are mainly used, thus reducing the probability of reporting frequent ADRs [40].

According to the data analysis, the highest number of reported ADRs occurs in patients aged 18–64 years with proportion of 44.8%, and 65–85 years at 33.3%, probably because there is a more frequent use of oncological treatments in this age group [41]. In the case of patients between the ages of 18 and 64, the detection and treatment of cancers are relatively fast, and therapies are more aggressive due to the patients' better health and their ability to tolerate intensive chemotherapy. Among patients in the 65–85 age group, the use of oncological treatments is higher due to the incidence of neoplasia that increases with age [42,43]. It is a well-known fact that the tolerance of elderly patients to oncological treatments is reduced due to associated pathologies on the one hand and to the decrease in the physiological metabolism of drugs on the other [44–46].

Further, it was observed that the adverse effects induced by CAP are more frequent in women than in men, in contrast to the toxicity profiles observed for 5-FU, IRI, OX, and PAN [47,48]. A study by Milano et al. demonstrates that the hepatic clearance for 5-FU is lower in women than in men, with increased accumulation and exposure of the drug in the body [49]. In comparison to men, for women the ratio of adipose tissue to muscular tissue is higher, and the body fluid volume is lower, which demonstrates the impairment of the distribution volume of the drug [50,51]. From the point of view of the enzymes that metabolize CAP, such as dihydropyrimidine dehydrogenase (DPD), it has been observed that a partial deficiency may appear in women, which increases the digestive toxicity of this drug [52]. The study by Schünemann et al. demonstrates that women report ADRs more frequently than men, who tend to neglect certain symptoms [41].

According to EV data, the largest share of ADR reporters is represented by medical professionals. This is explained by the necessity that oncological treatments are to be administered in hospitals, or under very careful monitoring by specialized personnel if the patients follow a drug treatment at home. Thus, the medical staff are directly involved in reporting ADRs. Moreover, in some countries, there are very good procedures established, which require that the medical personnel report adverse effects [22,53,54].

The study highlights more frequent ADR reporting outside the European Economic Area (EEA) compared to EEA regions. This can be explained by factors related to drug consumption, reporting protocols, as well as the large volume of patients treated in regions outside the EEA [55,56]. The therapeutic protocols are similar globally, yet their application varies between the EEA and non-EEA regions, and certain drugs can be used extensively, thus increasing the incidence of adverse reactions [57].

According to the EV database, serious ADRs were reported in 93.4% of total ADRs for CAP, and this proportion is visibly higher compared to PAN (83.6%), OX (86.7%), 5-FU (86.8%) and IRI (87.1%). Only BEV outranks CAP in this regard. Hoff et al., demonstrated that patients who were administered oral pharmaceutical forms containing CAP had a higher incidence of ADRs compared to patients treated with intravenous 5-FU [58].

Polak et al. highlighted the fact that cardiac ischemia is associated with exposure to fluoropyrimidines, and the pathophysiological mechanism is demonstrated by the reduction of coronary blood flow due to vasospasm [59]. Gamelin et al. (2004) demonstrated the connection between the administration of fluoropyrimidines and the increased risk of cardiac arrhythmias, requiring careful monitoring of patients during treatment [60].

According to the present study, MI was more frequent in patients who followed treatment with CAP, compared to the drugs analysed in the studies. The data suggest that fatal MI induced by treatment with CAP was significantly less frequent, a fact that is considered to be effective in the management of this pathology, reducing mortality [61]. In the study conducted by Johannes et al., patients were included in the treatment based on CAP. Of the total patients, 5.9% presented cardiotoxicity related to CAP. The combined treatment of CAP with OX and BEV also led to the highest risk of cardiotoxicity [62].

HF is one of the most severe side effects following treatment with CAP. The data suggest that more than a quarter of the ADRs had a fatal outcome, a worrying result that marks the severity of HF associated with CAP [63]. The proportion of adverse events with a favourable outcome in patients treated with 5-FU and OX is higher compared to other treatments, which indicates that HF management is properly managed [44].

Another study highlights a case of CAP—induced cardiogenic shock. Thus, Andrew's study presents the case of a patient diagnosed with appendicular mucinos adenocarcinoma, who developed cardiogenic shock 5 days after the start of capecitabine administration, being successfully treated by supportive care with dopamine, milrinone, noradrenaline and levosimendan [64].

The reported myopathies associated with treatment with CAP may be determined by cellular toxicity, impairment of cellular metabolism and the production of toxic metabolites. These events are rare and transitory [58].

Maharsy et al. indicate that MI caused/induced by fluoropyrimidines is associated with coronary vasospasm, the main triggering mechanism of acute myocardial ischemia [44].

Polka et al. demonstrated in 2022 that 4–10% of patients develop cardiotoxicity during treatment with fluoropyrimidines. In cases like this, the rate of MI is higher in comparison to cardiac pathologies [65].

Angina pectoris (n = 271), coronary arterio-spasm (n = 258) and cardiac arrest (n = 185), are the most frequent ADRs reported, these being important markers of cardiotoxicity associated with fluoropyrimidine-based chemotherapy. Moreover, they can have unpredictable developments regarding patients' safety [23]. A prospective study that followed cardiotoxicity during exposure to 5-FU by Holter monitoring reported that 14% of subjects showed ischemic changes on Holter, 5.6% acute coronary syndromes and 1.8% asymptomatic arrhythmias; in addition, 75% of the ischemic changes were asymptomatic [66].

Kounis syndrome was reported in five cases in the EV database. Kazuhiko Kido at al. describe the case of a patient who developed Kounis syndrome approximately 5 months after the start of CAP treatment. The diagnosis was based on high levels of histamine, interleukin (IL)—6 and IL—10 [67].

The analysis of disproportionality marks the increased probability of reporting cardiac disorders for CAP and 5-FU, a common characteristic of fluoropyrimidines [68]. They have been well documented in specialized literature and it has been shown that these drugs can induce myocardial ischemia, angina pectoris, myocardial infarction, heart failure, arrhythmias and cardiomyopathies, whose causal mechanism is coronary vasospasm, myocardial ischemia, oxidative stress, etc. [39,69]. Our results are consistent with the results published by Xin Chen et al. highlighting that 80% of cancer survivors face chronic pathologies associated with oncological treatments during their lifetime. Specifically, cardiovascular diseases occupy the second place in terms of morbidity and mortality after exposure of patients to oncological treatments, such as: fluoropyrimidines, anthracyclines, kinase inhibitors, proteasome inhibitors, etc. [70].

Pre-clinical studies have identified the active (5-FU) and inactive metabolites of CAP, confirming its activity on xenograft and animal models, and the therapeutic dose was established [71,72].

Pre-marketing studies have some limitations regarding the short-term study duration and the limited number of patients included, even though these studies are rigorously conducted. Generally, patients are selected based on different characteristics, but their group is not fully representative of the entire population. In this context, continuously performed post-marketing evaluations based on real-world data add to the pre-clinical and clinical evidence and improve safety assessment by detecting some rare or long-term ADRs [73–75].

In this context, it is essential to monitor the cardiac function during fluoropyrimidine treatment. An example in this regard can be found in the article published by McAndrew et al., in which two cases of cardiogenic shock are reported shortly after the administration of CAP. The cases in point highlight the importance of rapid and accurate diagnosis, immediate discontinuation of CAP and multidisciplinary collaboration with specialists of cardio-oncology, these being essential measures in saving the patients [76]. Also, patients with cardiovascular risk factors or pre-existing cardiovascular pathologies must be evaluated and monitored by ECG and cardiac ultrasound to prevent fatal events [39,77]. In support of patients, cardio-oncology has been rapidly developed in recent years, being indispensable in the personalized and multidisciplinary treatment of patients undergoing potentially cardiotoxic treatments [78].

Finding effective antineoplastic molecules with moderate side effects is a general desire of the scientific community. New strategies used in colorectal cancer include monoclonal antibodies (e.g., trastuzumab) and kinase inhibitors (e.g., tucatinib). In 2023, the FDA approved the combination of trastuzumab and tucatinib for HER2-positive, chemotherapy-refractory, RAS wild-type unresectable, or metastatic colorectal cancer [75].

The *Tucatinib Plus Trastuzumab in Patients With HER2+ Colorectal Cancer* clinical study (NCT03043313) shows a lower incidence of cardiotoxicity for tucatinib and trastuzumab. A single case of unstable angina in 86 patients (1.16%) included in Cohort A (Tucatinib + Trastuzumab) and one case of heart failure in 28 patients (3.57%) included in Cohort C (Tucatinib Monotherapy) were reported [79]. However, trastuzumab presents cardiotoxicity by reducing the left ventricular ejection fraction [80]. Our study could be useful in investigating the cardiotoxicity of trastuzumab in combination with tucatinib and CAP in colorectal cancer.

Limitations of the Study

Data collected from large pharmacovigilance databases that record spontaneous reports has intrinsic limitations. First of all, the lack of some types of information essential in such studies (e.g., the number of patients administered a certain drug), does not allow an exact calculation of the incidence rate or a real estimate of the risk associated with the use of a drug. The monitoring of the safety profile is carried out by the permanent amassing of ADRs, so that underreporting, for various reasons, is another limitation that can affect the validity and accuracy of the results. The detection and management of safety signals, the evaluation of updated periodic safety reports, and the evaluation of post-authorization safety studies are essential in this process, and underreporting remains a problem for which solutions are being sought. Another limitation refers to the accuracy of the information obtained from the reports, which may be incomplete, inaccurate and lack essential details, or may be subject to errors as a result of data entry, because reporting can be carried out both by healthcare professionals and by patients or consumers. On the other hand, aggregated data accessed for the present study did not allow the construction of a predictive relationship between variables and the probability of an adverse reaction. Thus, an advanced statistical method for evaluating the signals could not be applied. Moreover, the lack of information from the reports regarding the patients' medical history, pre-existing risk factors for cardiovascular diseases, the concomitant use of other drugs, and the criteria and methodology used to diagnose adverse reactions is also a limitation.

5. Conclusions

Cardiac toxicity associated with CAP treatment is a subject of high interest in the field of oncology. The analysis of the EudraVigilance database has shown that treatment with fluoropyrimidines induces adverse cardiovascular reactions, especially myocardial infarction, heart failure and cardiomyopathies. Arrhythmias have been shown to be more frequent side effects associated with 5-FU when compared with CAP.

Cardiac monitoring remains the essential assessment for patients treated with these drugs, especially in the case of patients with cardiovascular comorbidities. To manage cardiotoxicity, especially when presenting acute chest pain, a detailed patient history is essential, covering risk factors and specific information on drug administration (dose, administration route, and date of the last treatment cycle). Key investigations include ECG to detect ischemic changes or arrhythmias, along with cardiac ultrasound, troponin levels, BNP measurement, and, if necessary, coronary angiography for comprehensive diagnosis. Adjustment of treatment dosages or its interruption may be necessary to prevent a major adverse effect.

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editing, R.C.V., M.P., A.S. and A.L.V.-T.; visualization, R.C.V., A.B., A.L.V.-T., C.M., V.V., A.L.V.-T., M.P., A.F., C.M.D., D.D.A., R.C.C. and F.G.G.; supervision, A.B., A.L.V.-T., C.M. and F.G.G.; project administration, R.C.C. and F.G.G.; funding acquisition, R.C.C. and V.V. All authors have read and agreed to the published version of the manuscript.

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Article

Smell and Taste Alterations in Patients Receiving Curative or Palliative Chemotherapy—The CONKO 021—ChemTox Trial

Tobias Bleumer [1], Janine Abel [1], Wolfgang Böhmerle [2], Sebastian Schröder [1], Soo Ann Yap [1], Nigel Dross Engelbert Schaeper [1], Thomas Hummel [3], Sebastian Stintzing [1], Lars Uwe Stephan [1,4,†] and Uwe Pelzer [1,*,†]

[1] Department of Hematology, Oncology and Tumor Immunology, Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, 10117 Berlin, Germany; tobias.bleumer@charite.de (T.B.); janine.abel@charite.de (J.A.); sebastian.schroeder@charite.de (S.S.); soo-ann.yap@charite.de (S.A.Y.); nigel.schaeper@charite.de (N.D.E.S.); sebastian.stintzing@charite.de (S.S.); lars-uwe.stephan@charite.de (L.U.S.)

[2] Department of Neurology and Experimental Neurology, Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, 10117 Berlin, Germany; wolfgang.boehmerle@charite.de

[3] Smell & Taste Clinic, Department of Otorhinolaryngology, Technische Universität Dresden, 01307 Dresden, Germany

[4] Department of Internal Medicine, Bundeswehrkrankenhaus Berlin, 10115 Berlin, Germany

* Correspondence: uwe.pelzer@charite.de

† These authors contributed equally to this work.

Simple Summary: Taste and smell alterations (TSAs) are a distressing yet underdiagnosed side effect in cancer patients undergoing chemotherapy. However, long-term investigations using both questionnaires and chemosensory tests are scarce. We examined the prevalence of quantitative and qualitative TSAs, as well as their connection with clinical characteristics such as age, sex, anorexia, and neuropathy. We also compared patients receiving perpetual or temporary chemotherapy. All patients were examined up to five times within 12 to 24 months, commencing before the beginning of chemotherapy. We found TSAs in approximately 4 out of 5 patients during chemotherapy. The highest prevalence was documented among patients above 60 years of age as well as among those reporting anorexia or presenting signs of neuropathy. Post-therapy, taste and smell function recovered; however, scores did not reach baseline levels within 6 to 12 months. Future investigations will assess potential interventions to prevent or reduce TSAs.

Abstract: Previous data regarding chemotherapy-induced olfactory and gustatory dysfunction (CIOGD) are heterogeneous due to inconsistent study designs and small numbers of patients. To provide consistent, reliable data, we conducted a cohort study using standardized testing. Patients diagnosed with lymphoma, leukemia, or gastrointestinal malignancies were examined up to five times (T1 to T5), beginning prior to chemotherapy. We examined patients receiving temporary treatment up to 12 months post-therapy. Clinical assessment included extensive questionnaires, psychophysical tests of olfactory and gustatory function, and measurement of peripheral neuropathy. Statistical analysis included non-parametric tests to evaluate the longitudinal development of CIOGD. Our data (n = 108) showed a significant decline in olfactory and gustatory testing during chemotherapy (p-values < 0.001). CIOGD appeared stronger among patients above 60 years, while sex did not matter significantly. However, we identified distinct associations between CIOGD and reported anorexia as well as with higher neuropathy scores. Self-assessment appeared less sensitive to chemosensory dysfunction than psychophysical testing. Post-therapy, olfactory and gustatory function regenerated, though baseline levels were not attained within 6 to 12 months. In conclusion, our data highlight the wide prevalence and slow recovery of CIOGD. Understanding CIOGD as a potential neurotoxic effect may disclose new therapeutic prospects.

Keywords: chemotherapy; taste and smell alterations; dysosmia; dysgeusia; chemosensory function; neuropathy; CIPN; anorexia

1. Introduction

Global incidence of cancer is currently estimated at 20 million diagnoses per year [1]. Since the development and further advancement of chemotherapy in the 20th century, definite regimens have been used to treat a great variety of hematological and oncological diseases [2]. Hence, the number of patients relying on and receiving chemotherapeutics is expected to reach 15 million per year by 2040 [3]. One of the first curable malignancies using chemotherapy was Hodgkin's lymphoma [4]. To this day, its standard treatment relies on chemotherapeutic substances and achieves long-term remission in over 90% of patients [5,6]. This is just one example among many types of cancer with dramatically increased survival rates and improved prognosis over the past 50 years [7]. Having this in mind, the long-term consequences of chemotherapy grow increasingly relevant.

Chemotherapeutic agents target cells with high proliferation rates. Due to their inability to differentiate between malignant and physiological cells, patients frequently report or display various side effects. Nausea, alopecia, and fatigue having been among the most common for decades [8]. While chemotherapy regimens are updated and remission rates increase, long-term side effects like fatigue, negative prospects for the future, and taste and smell alterations become increasingly relevant [9–11]. Previous studies on the etiology of chemotherapy-induced olfactory and gustatory dysfunction (CIOGD) describe multiple determinants [12]. High proliferation rates of olfactory receptor neurons and gustatory sensory cells are the underlying pathophysiological factors [13]. Also, functional impairment through hyposalivation or xerostomia can add to chemosensory disorders [14]. Lack of concentration or memory disturbances can further modulate the correct sensation of smell and taste [15].

Consequently, CIOGD represents a frequently reported side effect in cancer patients. Current data range from 5% to 100%, with one systematic review suggesting a prevalence of 5 to 60% for dysosmia and 45 to 84% for dysgeusia [16,17]. However, results vary due to inconsistent study designs and often small numbers of patients [18,19]. Thus, longitudinal trials using standardized questionnaires and testing are needed to identify and help patients suffering from CIOGD [20]. Indisputably, CIOGD may reduce the quality of life and general condition of patients [21]. This is due to potential disturbances of food intake, suppressed appetite, and weight loss [13,22–24]. Also, CIOGD is associated with fatigue, nausea, and decreased food enjoyment [25–27]. Patients experiencing CIOGD even suffer social consequences as they share meals less often and show symptoms of depression more frequently [28,29]. Interestingly, recent data suggest potential connections between CIOGD and peripheral neuropathy. There have been multiple reports of patients with neuropathy also showing dysosmia or dysgeusia [30,31]. A recent study found hypogeusia in 59% of patients receiving taxane-containing chemotherapy [32]. To date, the extent and relevance of CIOGD-associated peripheral neuropathy remains indistinct.

The aim of this study was to investigate olfactory and gustatory alterations in adult cancer patients receiving systemic chemotherapy using a longitudinal study design and standardized questionnaires as well as testing of olfaction and gustation. We evaluated associations with clinical characteristics such as age, sex, and anorexia, as well as with peripheral neuropathy. We assessed both quantitative and qualitative CIOGD during the course of our study as well as post-therapeutic recovery of olfactory and gustatory function.

2. Materials and Methods

This study was approved by the Charité—Universitätsmedizin Berlin ethical review committee (file reference: EA2/167/21) and was performed in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. Patients did not receive financial compensation for their participation.

2.1. Patients

This prospective, longitudinal, observational cohort study was conducted between July of 2021 and August of 2023. We determined the sample size using suspected gustatory and olfactory changes during chemotherapy. Pre-existing data showed mean threshold-identification scores of 21 points with a standard deviation of 5 points among healthy controls [33]. We suspected a decrease in olfactory performance to 18 points with a standard deviation of 10 points. The presumed power was set at 0.8, and the significance level was defined at $\alpha = 0.05$. This resulted in an effect strength of 0.35 and a necessary sample size of 70 patients. Anticipating a drop-out rate of 35%, we planned to recruit 108 patients.

Accordingly, we recruited 108 patients at the Department of Hematology, Oncology, and Tumor Immunology of Charité-Universitätsmedizin Berlin, Germany. Recruitment was performed prior to the first cycle of chemotherapy for either lymphoma, leukemia, or a gastrointestinal malignancy. Inclusion criteria for participation were (1) full capacity to consent to study participation; (2) physical condition at baseline of 0 or 1 regarding the ECOG-Score (Eastern Cooperative Oncology Group) [34]; (3) life expectancy of at least 12 months; (4) place of residence allowed anticipation of long-term participation; (5) age between 18 and 85 years; (6) able to read, speak, and understand German or English; (7) no previous or current symptomatic otorhinolaryngological comorbidities, including sinusitis and oral mucositis; (8) tobacco exposure of maximum 15 pack years; (9) no active COVID-19-infection or post-COVID-19-associated dysosmia or dysgeusia; and (10) no pre-existing diagnosis of neuropathy. Criteria for exclusion included (1) reduced capacity to consent; (2) physical condition at baseline of >1 regarding the ECOG-Score; (3) life expectancy < 12 months; (4) long-term treatment at our institution seems unlikely due to long distance to the patient's place of residence; (5) age < 18 years or >85 years; (6) insufficient capability to communicate in German or English; (7) previous or current symptomatic otorhinolaryngological diagnoses; (8) tobacco exposure of >15 pack years; (9) current COVID-19-infection or post-COVID-19-associated dysosmia or dysgeusia; and (10) pre-existing diagnosis of neuropathy.

2.2. Examination

Patients were screened prior to chemotherapy, which included taking a comprehensive medical history and performing a precise cancer classification within the TNM staging system before recruitment [35]. Participating patients were examined five times (T1 to T5) during a total time frame of 12 to 24 months. The first assessment (T1) was conducted prior to the first cycle of chemotherapy. Patients receiving temporary chemotherapy (i.e., curative intention) were examined a second time (T2) halfway through their regimen. Third assessment (T3) was taken at the end of the final cycle. We conducted the follow-up examinations 3 to 6 months (T4) as well as 6 to 12 months (T5) after completion of chemotherapy. No follow-up examinations were conducted in case of relapse because of chemotherapy re-challenge. Patients receiving perpetual chemotherapy (i.e., mostly with palliative intention) were assessed at 3 months (T2), 6 months (T3), 9 to 12 months (T4), and 12 to 18 months (T5) after baseline (Figure 1). We performed examinations during chemotherapy within the first 3 days of each particular cycle. Assessments during and after chemotherapy took place at the hospital or the outpatient department.

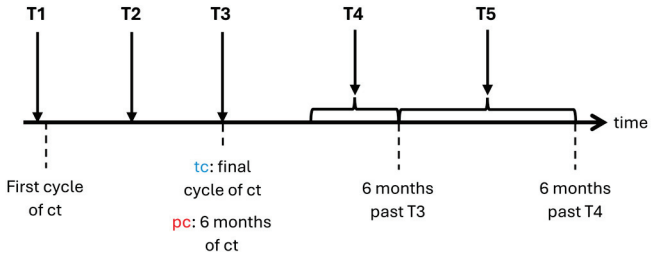


Figure 1. Timeline of examinations. ct: chemotherapy; tc: temporary chemotherapy; pc: perpetual chemotherapy; T1–T5: time points of examination.

Each examination consisted of a comprehensive questionnaire and a psychophysical examination of olfaction and gustation. First, we recorded sociodemographic parameters such as age, sex, body mass index, and profession. Second, we used the EORTC QLQ-C30 to assess patients' health-related quality of life, as well as potential side effects of chemotherapy, such as reduced performance, lower energy levels, or changes in food intake [36]. Third, we used a standardized neurology-focused questionnaire extension to inquire about neurological symptoms, including signs of neuropathy like paresthesia or dysesthesia. Fourth, we recorded taste and smell alterations, as well as qualitative disturbances (parosmia, phantosmia, parageusia, and phantogeusia), and asked patients to self-assess their current olfactory and gustatory function. Answers were recorded using the web application Research Electronic Data Capture System (REDCap) [37,38].

Next, olfactory function was tested using the "Sniffin' Sticks" [33]. These pen-like odor dispensers were used for a threshold and identification test. The "Sniffin' Sticks" can also be used for the discrimination test, which was not performed to keep examinations within a feasible time frame of a maximum of 60 min. We performed threshold testing using 16 triplets of pens, with only one pen of each triplet actually containing an odor. We repeatedly presented the odor in increasing and decreasing intensity until the individual olfactory threshold was determined. The identification test uses another set of 16 pens with each pen containing a different odor of strong intensity. Patients were asked to identify the correct odor among 4 options. Both olfactory scores were added and resulted in the threshold-identification score (TI score). Published data were used to compare TI scores and categorize patients into groups of anosmia, hyposmia, normosmia, and supersmellers [39].

Subsequently, gustatory function was tested using the "Taste Strips" [40]. Blindfolded patients were presented with impregnated paper strips on their tongue and asked to identify sweet, salty, sour, and bitter flavors of different intensities [41]. Again, we used already published data to compare and categorize patients' results into groups of hypogeusia and normogeusia. To date, gustatory testing using the "Taste Strips" does not offer a uniform definition of ageusia.

We determined peripheral neuropathy at T1, T3, and T5 using nerve conduction measurement. Additional examination included testing of general esthesia, thermoception, pallesthesia, muscle strength, and reflexes. Results were quantified by the total neuropathy score-reduced (TNSr), with higher scores indicating more symptoms [42].

2.3. Data Analysis

We performed a descriptive analysis of sociodemographic parameters using means, median, standard deviation, frequencies, and percentages. The Friedman test was used to evaluate longitudinal data regarding the development of CIOGD (i.e., results of the olfactory and gustatory testing) and results of nerve conduction studies. We analyzed differences in sociodemographic and clinical factors between groups by means of Mann–Whitney tests and Kruskal–Wallis tests. In addition, we used Mann–Whitney tests and Kruskal–Wallis tests to evaluate differences in olfactory and gustatory tests as well as in nerve conduction studies between groups. Post-hoc analyses were used in case of significant results among pairwise comparisons. Using Spearman's rank correlation, we evaluated correlations between self-assessments and psychophysical results.

Subsets of patients were compared and evaluated using multiple subgrouping variables such as age categories, sex, and BMI categories. Age was categorized according to previous studies into groups of 18 to 40 years, 41 to 60 years, and >60 years [41]. The official BMI categories were adopted to categorize patients into groups of underweight, healthy weight range, overweight range, obesity range class I, obesity range class II, and obesity range class III [43]. In addition, diagnoses were grouped and compared with each other. Also, characteristics regarding chemotherapy regimens served as subgrouping variables. Important distinguishing features were known as neurotoxicity and temporary vs. perpetual therapy. Data analysis was performed using SPSS Statistics version 28 (Chicago, IL, USA).

3. Results

3.1. Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics of all participating patients (n = 108) as well as of the two most important subsets—patients receiving temporary chemotherapy (i.e., most often following a curative intention of therapy; n = 58) and patients receiving perpetual chemotherapy (i.e., most often following a palliative intention of therapy; n = 50) are displayed in Table 1. Patients' median age at baseline was 54.5 years, while patients receiving temporary chemotherapy (tc) were younger and had predominantly been diagnosed with lymphomas. Patients receiving perpetual chemotherapy (pc) suffered more often from gastrointestinal malignancies and showed higher scores of BMI at baseline.

Table 1. Patient characteristics.

Parameter	All Patients	Patients Receiving tc	Patients Receiving pc
n	108	58	50
Mean age (SD) [years]	53.5 (17.6)	49.1 (19.1)	58.6 (14.1)
Female sex: n (%)	49.0 (45.4%)	22.0 (37.9%)	27.0 (54.0%)
Mean BMI (SD) [kg/m^2]	24.7 (4.4)	24.2 (3.9)	25.2 (5.0)
Reported anorexia: n (%)	23.0 (21.3%)	16.0 (27.6%)	7.0 (14.0%)
ECOG-Score of 0: n (%)	101.0 (93.5%)	56.0 (96.6%)	45.0 (90.0%)
NT-treatment: n (%)	88 (81.5%)	48 (82.8%)	40 (80.0%)
Entity: n (%)			
Lymphoma	49 (45.4%)	46 (79.3%)	3 (6.0%)
Leukemia	13 (12%)	3 (5.2%)	10 (20.0%)
Gastrointestinal	46 (42.6%)	9 (15.5%)	37 (74.0%)

ECOG: Eastern Cooperative Oncology Group; NT: neurotoxic.

Over the course of our study, BMI decreased insignificantly to 24.4 kg/m^2 at T4 and T5 among all patients. No differences were found between patients receiving tc and pc or other subsets of patients. However, the prevalence of anorexia showed a strong increase during chemotherapy from 21.3% at baseline to 65.9% at T2 and 80.5% at T3. From here, frequency diverged depending on the continuation of chemotherapy: in patients with tc frequency of reported anorexia dropped to 28.2% and 7.4% at T4 and T5, respectively. Among patients receiving pc, we documented anorexia in 70.8% and 88.2% of cases at T4 and T5, respectively.

Throughout our study, a number of reasons led to increasing drop-out rates; 20 patients discontinued their participation due to changes in residence or continuation of treatment closer to their residence, 17 patients experienced relapse or needed therapy adjustments, 11 patients passed away, and another 16 patients were too stressed to continue participation (Table 2). Applied chemotherapeutics varied between treatment groups depending on the patient's diagnosis (Tables 3 and 4).

Table 2. Number of participating patients at each examination.

Examination	All Patients	Patients Receiving tc	Patients Receiving pc
T1	108	58	50
T2	91	52	39
T3	82	49	33
T4	63	39	24
T5	44	27	17

Table 3. Chemotherapy regimen applied to patients receiving tc in absolute numbers.

Regimen	T1	T2	T3	T4	T5
BEACOPP	14	13	11	10	7
Rituximab + Bendamustine	7	5	4	3	2
Rituximab + CHOP	19	18	18	16	14
GMALL (lymphoma)	4	4	4	3	3
FLOT	1	1	1	1	1
FOLFOX	3	3	3	2	2
Cisplatin + Etoposid	3	2	2	0	0
mFOLFIRINOX	1	1	1	1	1

Table 4. Chemotherapy regimen applied to patients receiving pc in absolute numbers.

Regimen	T1	T2	T3	T4	T5
GMALL (leukemia)	5	5	5	5	4
Doxorubicin + Cytarabine	9	9	8	5	2
Gemcitabine + Nab-paclitaxel	3	3	3	3	1
Gemcitabine + Cisplatin	4	4	3	3	1
FOLFOX	9	7	5	4	3
mFOLFIRINOX	15	10	9	5	4
VCD	2	2	2	2	2

3.2. Olfactory and Gustatory Self-Assessment

At each examination, self-assessment of olfactory and gustatory function was obtained. At baseline, patients described their chemosensory function as "average" when compared to others. No significant differences were found between patients receiving tc and pc, between patients of different BMI categories, or between patients of different age groups. However, distinct differences showed between men and women (p-values for olfaction = 0.002; p-values for gustation = 0.053), with 30.6% of women describing their olfactory function as higher-than-average. The longer patients received chemotherapy, the worse their self-assessed functions became. However, olfactory function was still seen as "average" by the majority during chemotherapy. Overall, women and patients below 60 years of age evaluated their chemosensory function better than older patients did. Gustatory self-assessments showed similar dynamics; however, patients receiving tc described more decline during chemotherapy and showed stronger recovery after completion of chemotherapy. The percentage of patients with tc evaluating their taste sensation as "average" grew from 70% at T3 to over 80% at T4 and to over 90% at T5, while 42% and 30% of patients with pc described their taste sensation as moderately or severely below average at T4 and T5, respectively. Comparison of these results with chemosensory tests revealed lower sensitivity of self-assessment regarding both hyposmia and hypogeusia.

3.3. Olfactory Examination

We conducted an olfactory examination using the "Sniffin' Sticks". At baseline, patients scored a mean of 8.1 points on the threshold test and a mean of 14.5 points on the identification test. On average, they scored 22.6 out of 32 possible points (SD 2.6). Patients prospectively receiving tc (23.0 points) scored higher than patients prospectively receiving pc (22.2 points; *p*-values = 0.01). Also, significant differences were found between patients above 60 years of age and patients between 18 and 40, as well as 41 to 60 years (*p*-values = 0.002 and *p*-values = 0.01, respectively). Likewise, women and underweight patients scored higher than men and patients within healthy weight or overweight ranges. Overall, men above 60 years of age reached the lowest scores of 21.0 points in total.

Between baseline and T2, olfactory scores decreased from 22.6 to 18.7 points on average (*p*-values < 0.001). Again, men (17.7 points), patients above 60 years of age (16.8 points), overweight patients (18.2 points), patients reporting anorexia (17.9 points), and patients diagnosed with leukemia (18.1 points) reached lower scores. However, differences between temporary and perpetual chemotherapy (*p*-values = 0.71) as well as between neurotoxic and non-neurotoxic regimens did not reach significance (*p*-values among patients with tc = 0.71 and *p*-values among patients with pc = 0.25).

Reduction of olfactory function continued between T2 and T3. Again, olfactory scores decreased significantly from 18.7 to 16.6 points (*p*-values < 0.001). No significant differences were shown between temporary and perpetual chemotherapy (*p*-values = 0.54). The same was true for neurotoxic therapies among patients with tc (*p*-values = 0.88). However, among patients receiving pc, those with neurotoxic therapies scored significantly lower than those without (*p*-values = 0.023). In men (16.0 points), patients above 60 years of age (15.7 points), overweight patients (16.0 points), patients reporting anorexia (16.2 points), and patients diagnosed with leukemia (16.3 points) reached lower scores.

At T4, olfactory scores varied depending on the continuation of chemotherapy (*p*-values = 0.01). Patients who had finished tc showed olfactory recovery and scored 19.2 points on average. Among patients after tc, lower scores were reached by women (18.7 points), patients above 60 years of age (17.2 points), overweight patients (18.9 points), patients reporting anorexia (18.3 points), and patients diagnosed with gastrointestinal malignancies (17.7 points). In contrast, patients continuing pc showed further olfactory decline and scored 16.4 points at T4. Patients with neurotoxic therapy reached insignificantly lower olfactory levels than those without (*p*-values = 0.28). Again, men (15.2 points), patients above 60 years of age (15.0 points), overweight patients (15.1 points), patients reporting anorexia (15.7 points), and patients diagnosed with leukemia (15.6 points) reached lower scores.

This diverging trend continued at T5. Olfactory scores among patients after completion of tc increased to 20.3 points on average, while patients continuing pc scored 15.5 points (*p*-values < 0.001). Again, after tc, men scored higher than women, while women reached higher olfactory levels during pc. Other characteristics showed equivalent results as at T4.

In summary, the majority of patients suffered from olfactory dysfunction during treatment with chemotherapy. The degree and recovery of dysosmia varied depending on the duration of chemotherapy, sex, age, BMI, anorexia, cancer type, and chemotherapeutic neurotoxicity. In total, 90.2% of all patients experienced reduced olfaction during chemotherapy. In the case of tc, olfactory function recovered after completion of treatment. However, baseline levels were not reached within 6 to 12 months (Figure 2).

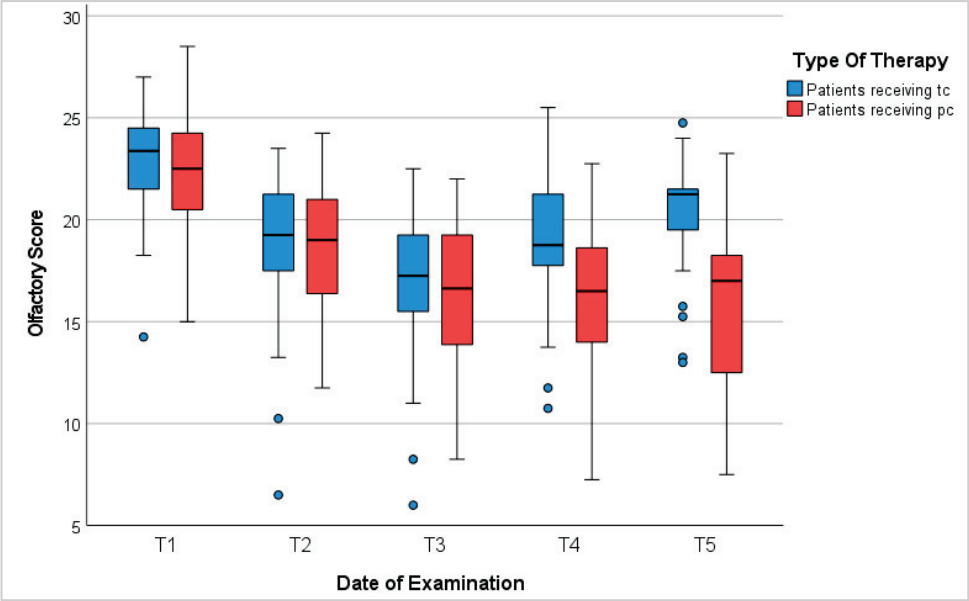


Figure 2. Olfactory score. T1: before chemotherapy; T2: halfway through tc or 3 months into pc; T3: at the end of tc or 6 months into pc; T4: 3–6 months after tc or 9–12 months into pc; T5: 6–12 months after tc or 12–18 months into pc; blue circles represent outliers.

3.4. Gustatory Examination

We conducted a gustatory examination using the "Taste Strips". At baseline, patients scored a mean of 13.4 out of 16 possible points. (SD 2.6). Patients prospectively receiving tc scored 13.9 points, while those prospectively receiving pc scored 12.9 points (p-values < 0.001). Similar to olfactory results, overweight patients reached the lowest gustatory levels among all BMI categories (13.1 points). In addition, patients above 60 years of age scored significantly lower than younger patients. Men above 60 years scored the lowest, reaching 11.8 points on average.

Between baseline and the second examination, gustatory scores decreased from 13.4 to 10.0 points on average (p-values < 0.001). Patients receiving tc scored insignificantly higher than patients receiving pc (p-values = 0.15). Similarly, no significant differences were observed between patients with and without neurotoxic chemotherapy regimens. We observed lower-than-average scores among men (9.1 points), patients above 60 years of age (8.5 points), overweight and obese patients (9.6 and 8.8 points, respectively), patients reporting anorexia (9.5 points), and patients diagnosed with leukemia and gastrointestinal malignancies (8.7 and 9.3 points, respectively).

Patients' gustatory function decreased further between T2 and T3, with average scores dropping from 10.0 to 8.6 points (p-values for patients receiving tc = 0.25; p-values for patients receiving pc = 0.06). Patients under perpetual treatment (7.1 points) scored significantly lower than patients at the end of temporary treatment (9.5 points; p-values = 0.01). No definite differences were shown between neurotoxic and non-neurotoxic chemotherapy regimens. Overall, lower gustatory scores were measured among men (7.6 points), patients above 60 years of age (6.5 points), and patients reporting anorexia (9.0 points). Results between BMI categories and diagnoses appeared ambiguous, with the exception of lymphoma patients who scored above average (10.4 points).

Like olfactory results, gustatory scores diverged between T3 and T4 depending on the continuation of treatment (p-values between groups < 0.001). Patients still receiving chemotherapy showed a further decrease to 7.0 points on average. Among these, women (8.5 points) scored higher than men (5.7 points); patients between 18 and 40 years (10.6 points) scored higher than patients between 41 and 60 years (7.4 points), and patients above 60 years of age (5.2 points). Patients suffering from lymphomas (10.2 points) scored higher than those suffering from leukemia (7.4 points) or gastrointestinal malignancies

(6.2 points). In addition, patients receiving neurotoxic chemotherapy scored 6.5 points, while those without scored 9.4 points (p-values = 0.1). In contrast, patients after completion of tc recovered to 11.4 points on average. Significant differences were observed between age groups (p-values for patients between 18 and 40 years compared to patients between 41 and 60 years = 0.02; p-values for patients between 18 and 40 years compared to patients above 60 years < 0.001) and patients reporting (12.0 points) and not reporting (9.9 points) anorexia (p-values = 0.04).

Between T4 and T5, gustatory results continued diverging between therapy groups. Post-therapy patients recovered from 11.4 points at T4 to 12.5 points at T5. Among these patients, men's scores (13.0 points) were higher than women's scores (11.5 points), and patients reporting anorexia (8.3 points) scored lower than patients with intact appetite (12.8 points). On the other hand, patients receiving pc scored 7.7 points on average at T5. Significant differences were only seen between sexes, with women's scores exceeding men's scores (p-values < 0.001). Additionally, patients above 60 years of age (6.1 points), as well as patients diagnosed with leukemia (5.8 points) scored below average.

In conclusion, 78% of patients in our study presented dysgeusia during receipt of chemotherapy. The degree of gustatory dysfunction depended mostly on the duration of therapy, sex, age, and anorexia. Gustatory recovery commenced post-therapy; however, patients did not reach baseline levels within 6 to 12 months (Figure 3).

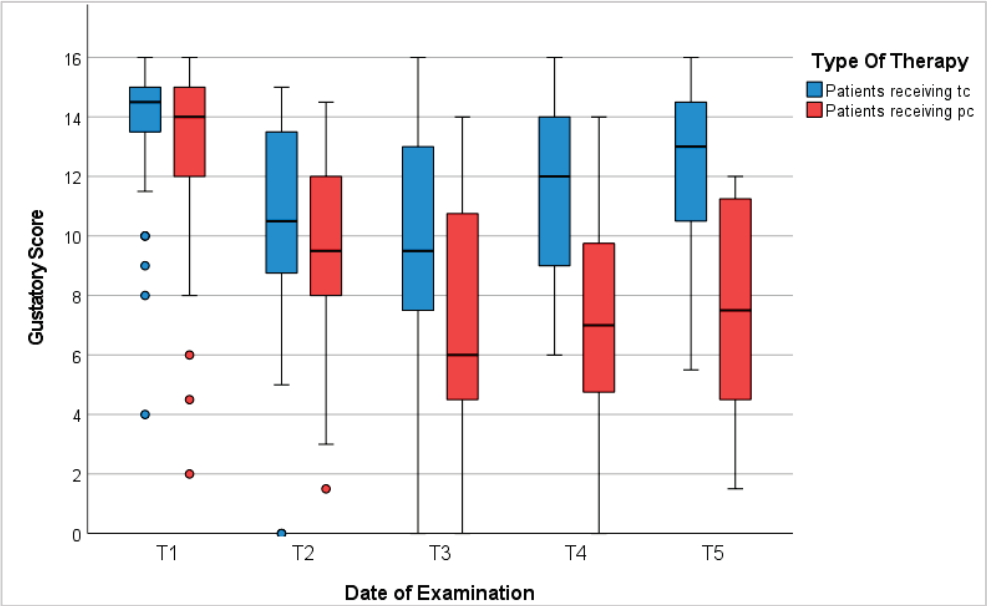


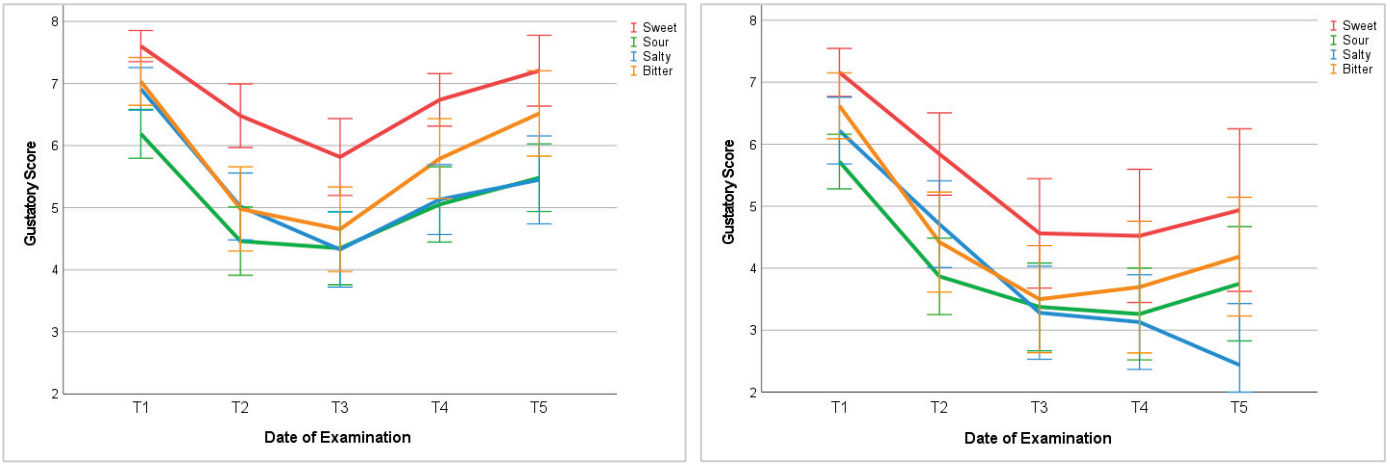
Figure 3. Gustatory score. T1: before chemotherapy; T2: halfway through tc or 3 months into pc; T3: at the end of tc or 6 months into pc; T4: 3–6 months after tc or 9–12 months into pc; T5: 6–12 months after tc or 12–18 months into pc; red/blue circles represent outliers.

Sensation of Basic Tastes

Gustatory examination included specific testing of sweet, sour, salty, and bitter tastes. Similar to overall gustatory function, the sensation of each particular taste decreased during chemotherapy and showed recovery among patients receiving tc after completion of chemotherapy. Throughout the entire study, patients identified sweet taste most sensitively. On the opposite, we identified sour taste the least during chemotherapy. However, the detection of salty taste showed the slowest recovery after chemotherapy had ended. We measured the strongest recovery regarding bitter taste; however, none of the basic tastes recovered entirely within 6 to 12 months compared to baseline levels.

Among patients receiving pc, the perception of each particular basic taste decreased stronger than among patients receiving tc and showed slight to no recovery between T3 and T5. Again, throughout the course of examinations, patients correctly detected sweet

taste more sensitively than other tastes. Between T3 and T5, patients' ability to identify sweet, sour, and bitter tastes slightly improved. However, salty was least detected at T3, T4, and T5 and showed a continuous decrease compared to each previous examination (Figure 4).



(**a**) Patients receiving tc (**b**) Patients receiving pc

Figure 4. Gustatory examination of basic tastes. T1: before chemotherapy; T2: halfway through tc or 3 months into pc; T3: at the end of tc or 6 months into pc; T4: 3–6 months after tc or 9–12 months into pc; T5: 6–12 months after tc or 12–18 months into pc.

3.5. Qualitative Dysfunctions of Olfaction and Gustation

During receipt of chemotherapy, patients also showed qualitative dysfunctions of olfaction and gustation. The number of patients reporting parosmia grew to over 20% at T2, T3, and T4. Among patients who had finished tc, parosmia was no longer reported 6 to 12 months after treatment. This was also true for phantosmia, which was reported by less than 15% of all patients at any given time.

Compared to parosmia and phantosmia, qualitative gustatory dysfunctions were observed more frequently in our study. The number of patients reporting phantogeusia grew to 30% during temporary chemotherapy and 40% during perpetual chemotherapy. Post-therapy, patients recovered to baseline levels within 6 to 12 months. Moreover, parageusia appeared as the most frequently reported qualitative chemosensory dysfunction, peaking at 50% at the end of temporary treatment as well as after 12 to 18 months of perpetual treatment. Like the aforementioned qualitative dysfunctions, patients showed signs of recovery from parageusia within 6 to 12 months after completion of chemotherapy.

3.6. Nerve Conduction Study

Neurological examinations at T1, T3, and T5 showed an increase in symptoms of peripheral neuropathy during chemotherapy (Figure 5). Average TNSr tripled from 1.4 points at T1 to 4.2 points at T3 (p-values < 0.001). Patients receiving tc scored 3.3 points on average at T3. Among these, patients with neurotoxic treatment scored higher than those without (p-values = 0.07), while analyses of sex, BMI, diagnosis, and reported anorexia showed inconclusive results. Patients receiving pc scored 5.2 points on average at T3 (p-values compared to patients receiving tc = 0.14). Again, patients with neurotoxic treatment scored higher than patients without (p-values 0.03). Further analyses of sex, BMI, and anorexia showed no significant differences. Noticeably, patients with gastrointestinal malignancies scored significantly higher than patients with lymphomas (p-values = 0.002). Regarding all patients, those above 60 years of age scored significantly higher than younger patients.

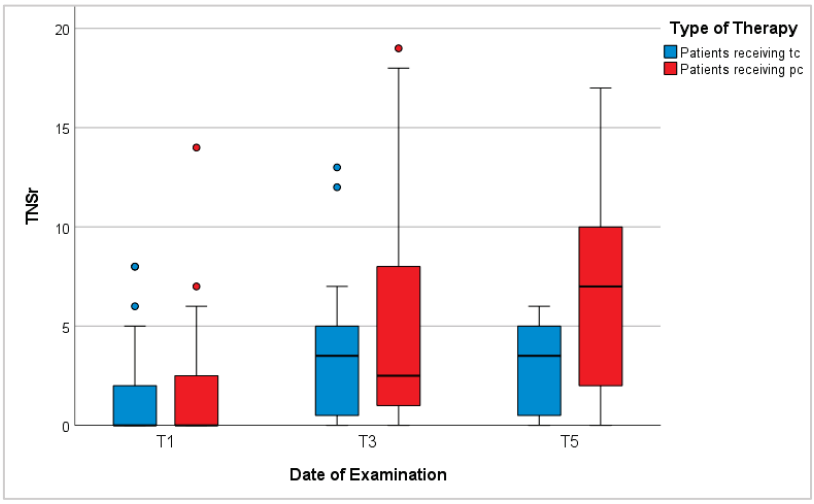


Figure 5. Total neuropathy score-reduced (TNSr). T1: before chemotherapy; T3: at the end of tc or 6 months into pc; T5: 6–12 months after tc or 12–18 months into pc; red/blue circles represent outliers.

Between T3 and T5, TNSr rose from 4.2 points to 4.9 points on average with patients receiving pc scoring significantly higher than those having finished temporary chemotherapy (*p*-values 0.04). Similar to results at T3, analyses of BMI and reported anorexia showed no significant differences. However, men's TNSr during receipt of pc were higher than women's but recovered more quickly after completion of tc. In addition, during continued pc, patients with gastrointestinal malignancies showed significantly higher TNSr than patients with lymphomas (*p*-values = 0.002). Again, regarding all patients, those above 60 years of age showed more signs of peripheral neuropathy than younger patients.

The comparison of neurological and chemosensory dysfunction revealed that patients without symptoms of peripheral neuropathy scored the highest points in olfactory and gustatory tests. Correspondingly, patients with dysosmia or dysgeusia showed symptoms of peripheral neuropathy more often. During and after treatment, patients with hyposmia and hypogeusia displayed higher TNSr than patients with regular chemosensory function. This proved especially true for patients receiving neurotoxic treatment (Figure 6).

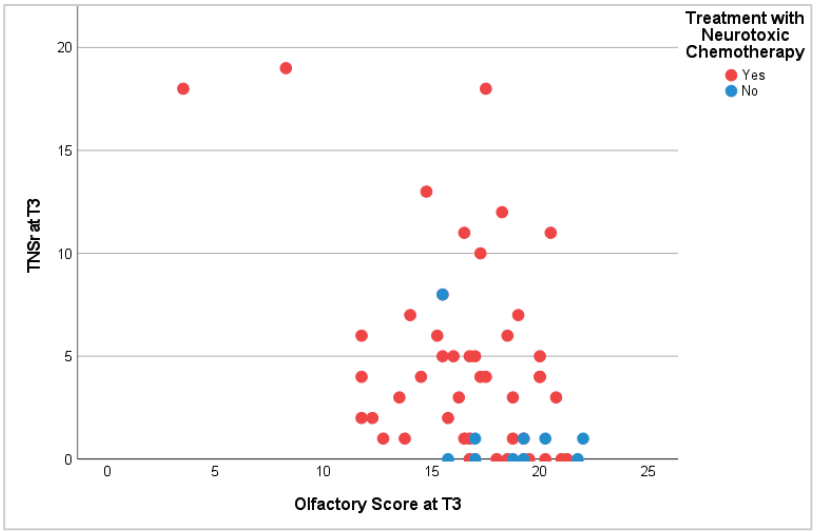


Figure 6. Olfactory score and TNSr at T3. T3: at the end of tc or 6 months into pc.

4. Discussion

Our data provide evidence to support the hypothesized correlation between the receipt of chemotherapy and dysfunctions of olfaction and gustation in adult cancer patients [17].

Current data based on both self-assessments and chemosensory testing are scarce [20]. This is one of few studies examining over 100 cancer patients for a minimum of 12 months in a longitudinal study design using standardized olfactory and gustatory tests as well as patient questionnaires. High rates of CIOGD were confirmed in our study, with approximately 4 out of 5 patients presenting TSA during chemotherapy. Additionally, to our knowledge, this is the first study to monitor peripheral neuropathy using neurological examination and nerve conduction studies to investigate potential correlations between chemosensory and neurological dysfunctions during receipt of chemotherapy. This potential correlation between dysosmia and peripheral neuropathy had previously emerged and was lately studied among patients receiving taxane-containing chemotherapy [31,32]. Here, 59% of patients reported dysgeusia, which was indeed correlated with symptoms of peripheral neuropathy. Our findings also suggest that cancer patients experiencing symptoms of peripheral neuropathy show gustatory and olfactory dysfunctions more often. This might indicate that chemosensory dysfunctions can be categorized as a neurotoxic side effect of chemotherapy that, in turn, could disclose new therapeutic approaches.

Olfactory and gustatory functions are frequently impaired during and after chemotherapy. In our study, psychophysical testing appeared to be more sensitive in the detection of CIOGD than self-assessment. Similar results were found in previous studies using the same chemosensory tests [44]. However, other data also show contrasting results, with self-assessed CIOGD being more frequent [45]. Sensitivity of self-assessment appears to strongly depend on the style in which questions are phrased [46]. Furthermore, patients above 60 years of age were generally affected more strongly, while men showed more CIOGD during chemotherapy but recovered more quickly after treatment. These findings are mostly consistent with previous data showing higher rates of TSA among older patients [47–49]; however, some studies describe female sex as a potential risk factor for dysgeusia [50], while others do not mention or did not find sex as a relevant risk factor [20,51]. In addition, patients reporting anorexia showed higher rates of CIOGD. This correlation between anorexia and dysgeusia has also been described previously [24,52]. These gustatory dysfunctions can lead to decreased liking of food and reduced health-related quality of life [26,53]. In addition, patients diagnosed with gastrointestinal malignancies and those receiving neurotoxic treatment seemed to present CIOGD more often. Although we did not identify distinct correlations with particular types of cancer in our study, cancer progress must also be discussed as a separate factor with a potential impact on anorexia and reduced olfactory or gustatory performance. This has also been difficult or inconsistent in previous studies [30].

Moreover, longitudinal testing enabled monitoring CIOGD post-therapy. We found that olfactory and gustatory functions commenced to recover after completion of treatment. However, baseline levels for both olfaction and gustation were not attained within 6 to 12 months. Previous data on the duration of recovery are heterogeneous. Some describe full recovery within weeks to 3 months [23,54], while others describe 6 or 12 months [55,56]. This variability in data is most likely due to different types of cancer as well as different chemotherapy regimens. Moreover, most studies on CIOGD have not monitored patients post-therapy, which leads to scarce and, thus, insufficient data on the process of recovery. Hence, our findings highlight the need for further investigation of recovery of gustatory and olfactory function after completion of chemotherapy.

Besides testing overall gustatory function, we also distinguished between the sensation of sweet, sour, salty, and bitter taste. Before, during, and after chemotherapy, sweet taste was perceived most frequently. Interestingly, the longer chemotherapy was received, the fewer patients were able to detect salty taste. In contrast, the sensation of bitter taste showed the strongest recovery, which might be due to its evolutionary importance as an indicator of toxins in foods [57]. These findings were consistent with numerous studies, though current data are not unambiguous yet. However, other studies that also used psychophysical tests also described the highest sensitivity for sweet taste, the lowest sensitivity for sour taste, and the strongest reduction for salty taste [45,58]. Patients need to be informed about

potential gustatory alterations to prevent the negative consequences of overusing sugar or salt [58]. There have also been reports of periodic dynamics of sensitivity during each chemotherapy cycle [23]. This could also lead to varying results between studies depending on differing study designs.

The qualitative assessment of CIOGD was performed using questionnaires and was found in 10 to 50% of patients during chemotherapy. Most often, patients reported parosmia or parageusia. These findings are consistent with previous studies, which also described higher rates as well as severe consequences of qualitative dysfunctions of olfaction and gustation during chemotherapy [51,59].

The strengths of our study involved the use of both self-assessments and standardized psychophysical tests to examine both taste and smell function. In addition, longitudinal examinations over the course of 12 to 18 months enabled us to monitor changes in olfactory and gustatory function during and after receipt of chemotherapy. Comparing groups with tc and pc offered additional information on long-term CIOGD as well as on chemosensory recovery post-therapy. In addition, we used neurological examinations and nerve conduction studies to identify correlations between chemosensory and neurological dysfunctions. These results convinced us to launch a follow-up study among patients diagnosed with lymphomas using olfactory interventions to assess the application of prevention and treatment strategies for CIOGD in the future.

However, our study also had several limitations. First, we conducted the vast majority of patient examinations at the hospital or the outpatient department. We connected these examinations with patients' regular appointments for treatment or follow-up. This, however, led to a certain variance regarding the exact timing and interval of examinations. Second, multiple reasons caused patients to drop-out throughout the course of our study, the most frequent being changes in residence or continuation of treatment at a hospital closer to their residence. Drop-outs rose to over 30% after T3. Third, we assessed qualitative dysfunctions only by means of questionnaires due to a lack of psychophysical examination methods. Fourth, we performed this study during the global pandemic of COVID-19. Although active infections were listed as exclusion criteria for participation and associated dysosmia or dysgeusia were conscientiously inquired, potential effects or overlap of chemosensory dysfunction cannot be ruled out entirely. Fifth, long-term chemotherapy regimens could be adjusted to better patients' overall health and alleviate side effects. This might have led to altering levels of neurotoxicity, which, however, was only evaluated as a dichotomous trait and thus may not reflect each patient's treatment in its entire complexity. Sixth, patients with various types of cancer were included in our study. This also led to greater heterogeneity in chemotherapy regimens, which did not allow for more precise analyses regarding correlations of CIOGD with particular types of cancer or chemotherapy regimens. Therefore, future research should focus on more homogeneous study cohorts of appropriate size in order to identify additional risk factors, such as type of cancer and chemotherapeutic substances with a high risk of CIOGD more accurately.

5. Conclusions

In sum, this study extends prior research on CIOGD in adult cancer patients. Receipt of chemotherapy led to high rates of dysosmia and dysgeusia (90% and 78% of patients, respectively). We identified age (especially above 60 years), male sex, as well as reported anorexia as important risk factors. By means of nerve conduction studies, we identified correlations between CIOGD and symptoms of peripheral neuropathy. These findings suggest that CIOGD might be a neurotoxic effect of chemotherapy, which could lead to new therapeutic prospects. Furthermore, olfactory and gustatory recovery commenced post-therapy; however, full restoration was not attained within 6 to 12 months. This long-term impairment can significantly reduce patients' quality of life and, therefore, requires future research to facilitate effective prevention and treatment strategies. Building upon our research results, we have launched the interventional "ImproverTox" trial to gain further insight and offer more support for patients suffering from CIOGD.

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Article

Past Happiness and Broken Future Horizon of Oncological Patients during Chemotherapy—A Quantitative Exploration of a Phenomenological Hypothesis

Magdalena Fryze [1], Patrycja Wisniewska [2], Jadwiga Wiertlewska-Bielarz [2] and Marcin Moskalewicz [2,3,4,5,*]

[1] Department of Psychology, Medical University of Lublin, 20-059 Lublin, Poland
[2] Philosophy of Mental Health Unit, Department of Social Sciences and the Humanities, Poznan University of Medical Sciences, 61-701 Poznań, Poland
[3] Phenomenological Psychopathology and Psychotherapy, Psychiatric Clinic, University of Heidelberg, 69115 Heidelberg, Germany
[4] Institute of Philosophy, Maria Curie-Sklodowska University, 20-400 Lublin, Poland
[5] IDEAS NCBR, Chmielna 69, 00-801 Warsaw, Poland
* Correspondence: moskalewicz@gmail.com

Simple Summary: Cancer significantly affects physical and mental health, evoking intense emotions and forcing life changes. Emotional responses to cancer treatment have an intrinsic connection with time, in particular with the positive memories of how life looked before the disease and the often grim and hopeless outlook on the future. This study found that patients in chemotherapy experience increased focus on the present, decreased focus on the future, and a sense of unpredictability, with a relatively short temporal horizon measured in weeks and months, not years. These experiences are prevalent regardless of the type of cancer, the length of treatment, and the sociodemographic background. It can be concluded that changed temporal experience during chemotherapy is a factor that can have an impact on patients' well-being and ability to cope with the disease.

Abstract: Understanding the impact of cancer on the experience of time is crucial in the context of hope and recovery. This study, a follow-up to a previous qualitative study of ovarian cancer patients – explored two types of such experiences—the memory of past happiness and the limited future planning. A sociodemographic questionnaire with nine questions about the experience of time was used on a convenience sample of 202 patients with various cancers, predominantly women with breast, ovarian, and cervical cancer. It was found that the respondents experienced increased focus on the present, decreased focus on the future, and a sense of unpredictability, with a relatively short temporal horizon measured in weeks and months, not years. Almost half of the respondents (46%) measured time during treatment by the rhythm of chemotherapy and check-ups, which thus appeared as the most meaningful events. The increase in the frequency with which patients underwent chemotherapy mildly affected their focus on the present ($R = 0.25$, $p < 0.05$), likely because of the discomfort of the side effects. The correlations between age and time in treatment, on the one hand, and the experience of time, on the other, were negligible. Changed temporal experience during chemotherapy is a factor that can have an impact on patients' well-being and ability to cope with the disease. It thus should be taken into account when planning oncology care.

Keywords: lived experience; phenomenology; time; time perception; temporality; quality of life; qualitative research; chemotherapy

1. Introduction

1.1. The Experience of Time in Cancer: Memories of the Past and Plans for the Future

Cancer is one of the most traumatic experiences that can befall a person. It affects physical and mental life, contributing significantly to the disruption of existence. From the

moment of diagnosis to daily struggle with the disease, patients experience a wide range of emotions that affect their well-being, including sadness, anxiety, anger, frustration, and uncertainty about the future. Chronic oncological conditions disrupt the sense of time and reorganize its experience, also due to the rhythmic nature of treatment [1–11].

This study is concerned with understanding how cancer patients during chemotherapy experience time, especially regarding their recollections and plans. Time can be understood in various ways, either as clock time or a sequence of consecutive events or, from a phenomenological perspective, as a stream of experience permanently linked to our presence in the world [1,12,13]. From this perspective, memories and plans for the future are inseparable from present existence and affect the lived experience of reality. Also, they are not merely passive but are actively constructed by current perceptions, emotions, and the meaning attributed to them. Recollections and anticipations are intrinsic to lived presence, and their meaning changes depending on the context and individual development [14,15]. In the absence of positive or negative stimuli, there is usually no awareness of the passing of time, so it ceases to be explicitly felt, while a person experiencing positive emotions might have the sense of time accelerating or, when experiencing negative emotions or exposed to unpleasant events, the sense of time dragging. A disturbed sense of time may translate into increased stress and discomfort and affect recovery [10,16].

In the context of cancer, memories and plans are vital. Memories are a source of meaning and significance, providing comfort and hope in difficult moments. Reinterpreting memories allows for discovering new meanings, enhances inner strength, and enables more effective coping with difficulties. Planning for the future is a motivating force, allowing patients to maintain hope and purpose in the face of illness, providing a sense of control and a focus on values and life goals. At the same time, people struggling with chronic illnesses often feel confused and discouraged as their life plans and objectives have to be adjusted to their new health reality. This can lead to losing control and hope of achieving their goals. Reflecting on the human condition in the face of illness allows one to search for the meaning of life, consider suffering, death, and transcendence, and ultimately help one find answers to questions of identity and values in the face of illness [5,12,13,17–23].

Memories and plans for the future can be a source of strength and motivation to fight. It can be helpful for patients to focus on positive memories, such as moments spent with loved ones, life accomplishments, and goals they still want to achieve. Planning for the future, even in the face of the disease, can give patients a sense of control and hope, which are crucial in the struggle against cancer. On the other hand, patients may experience difficult memories of medical procedures, loss of health, and the unpleasant emotions accompanying treatment. They often feel the loss of their previous identity when aspects of their lives are altered or reduced [3–5,11,24–31].

1.2. Lived Time in Ovarian Cancer: Qualitative Phenomenology

Our (MM and JWB) previous qualitative study explored the lived experience of time among ovarian cancer patients while in chemotherapy [13,32]. The research was based on Giorgi's method of phenomenological psychology and, among others, found two experiential structures affecting the lived experience of time, which we called "broken horizon" and "happiness closed off by regret".

A broken horizon is a sense of general uncertainty in life, which leads patients to focus on the narrow present and short-term goals. A broken horizon means that those affected by ovarian cancer do not plan very far into the future. Their perspective covers only a few days, and their dreams of recovery are not precisely defined. As one patient put it (P9): *Unpredictable life has taught me the humility not to look too far ahead* [13].

The structure of regret-closed happiness was described as a combination of regret, guilt, and nostalgia for a lost, happy past, which now seems distant and inaccessible. It is the time before diagnosis associated with better days, good health, and disease-free life, and it becomes integral to present life during illness and includes an element of longing for the happy past [13,32]. As one patient put it (P7): *I wish I could live the way I lived when I*

didn't have this problem(...) I had such a happy life [13]. A sense of regret, on the other hand, comes from reflecting on what was not realized before the disease and what will no longer be possible.

The aim of this study was to investigate whether these two experiential phenomena regarding temporal experience are observed in a more extensive and oncologically more diverse sample. We were interested in finding whether they occur in the lived experience of other types of cancer, also because they may be relevant to fighting the disease, maintaining hope, and coping more effectively with difficulties.

2. Materials and Methods

2.1. Objectives

This is the second part of a sequential (first qualitative, then quantitative) study, whose aim is to explore the lived experience of past and future during oncological treatment. Following our previous qualitative results, we hypothesized that individuals undergoing chemotherapy will have difficulty in planning for the future and accurately defining their life goals and that they will often return in thought to their life before treatment with a sense of grief over the loss as well as in the form of happy memories.

2.2. Objective Temporal Variables

In addition, we were interested in seeing if there was a relationship between how time is subjectively experienced during chemotherapy and objective temporal variables in the form of time elapsed since diagnosis and the beginning of treatment (objectified linear time) and the frequency of chemotherapy sessions (objectified circular time). This was because, except for our previous studies, there is no research on the effect of chemotherapy length and treatment rhythm on cancer patients' felt sense of time. In contrast, our previous studies showed that the treatment rhythm (rather than linear time) is critical to the experience of time [10,16,30].

2.3. Research Questionnaire

This study used a proprietary questionnaire that was designed to explore the experience of time in people being treated for cancer in accordance with hypotheses stemming from our previous qualitative study in a sequential manner (for the original version of the questionnaire, see the Supplementary Material). The questionnaire consisted of two parts. The first metrical part was designed to collect sociodemographic data and information directly related to the disease, such as the type of cancer, time passed since diagnosis and the beginning of chemotherapy, and the current frequency of chemotherapy courses. This part of the questionnaire made it possible to obtain context information for independent variables. The second part of the questionnaire contained seven statements about the reflective sense concerning the lived experience of time in the context of revisiting memories and planning for the future. These statements were directly related (as face-validated by MM and JWB) to the qualitative experiential structures from our previous study described in the introduction and called "broken horizon" and "happiness closed off by regret" [13]. Respondents were asked to rate the degree to which they agreed with each statement using a 7-point Likert scale. These statements were (translated here from Polish to English—see the Supplementary material for the original phrasing): "I don't think about the past because I focus on the present"; "Thoughts about my life before treatment often come back to me in the form of regrets. I regret that I did/did not do something that could have had negative consequences"; "Regardless of the above, thoughts of my life before treatment come back to me as happy memories"; "I live from day to day"; "I am not planning the future further than my next chemo"; "I have no concrete plans for the future after recovery, at most dreams"; and "I live with a constant sense that something unforeseen might happen." In addition, in the same section of the questionnaire, the study participants were asked to define their horizon of the future in calendar terms (days, weeks, months, years) and how they measured time during treatment. The latter question was phrased: "During treatment,

I measure time using," with the options of calendar values (such as weeks or months) as well as treatment-related values, such as chemotherapy courses or follow-up visits, for contrast. These nominal-scale questions were designed to add to the understanding of the respondents' lived experience of the future qualitatively explored in the previous study [13] by quantifying it in terms of calendar variables.

2.4. Data Collection

Data were obtained by engaging Polish-speaking patient groups from the social networking site Facebook, which were chosen based on their size and ongoing activity to maximize the response rate. The groups in question were as follows: Healed from cancer true stories; Beat cancer; Leukemia, lymphomas and other blood cancers support group; Patients and their loved ones—hematology department; Cancer is not a sentence. Join us if you have chosen to live for real; Cancer; Breast cancer—tame the fear. Support group for amazons; and Lung cancer. The Bioethics Committee of the Poznan University of Medical Sciences approved the study design as non-experimental. The entire study was conducted by the principles of the Declaration of Helsinki, and all participants gave their informed consent to participate.

2.5. Data Analysis

The values of the variables representing temporal experience phenomena on the ordinal scale were analyzed statistically and presented using the mean, median, and standard deviation, while the nominal-scale variables were presented using the count and percentage. In addition, quartiles were used to illustrate the characteristics of the group. A one-way analysis of variance (ANOVA) was performed to examine potential differences in the respondents' questionnaire responses according to gender, age, place of residence, education, and type of cancer. The normality of the distribution was assessed using the W Shapiro–Wilk test. The Mann–Whitney U test was used to compare independent groups, Spearman's R correlation was used to assess the relationship between linear time variables and ordinal scale temporal phenomena, and the chi-square test was used to compare groups with different cancers and different treatment frequencies and their temporal experience represented by the nominal-scale variables. A significance level of $p < 0.05$ was adopted for statistically relevant differences or relationships. Database and statistical tests were conducted using the STATISTICA 13.0 computer software (StatSoft, Kraków, Poland).

3. Results

3.1. Sample Characteristics

A group of 202 patients with a cancer diagnosis participated in this study. Women predominated among the respondents, accounting for 87.13% of the total group (n = 176), while men accounted for 12.87% (n = 26). A total of 15.84% (n = 32) of the participants were under 30 years old, 13.37% (n = 27) were between 31 and 40 years old, 31.68% (n = 64) were between 41 and 50 years old, 27.72% (n = 56) were between 51 and 60 years old, and only 11.39% (n = 23) were patients over 60 years old. The majority of the respondents had a high school (24.75%) or college education (41.09%). An overwhelming number of the participants lived in cities with a population of up to 500,000, accounting for 20.79% of the study group. In terms of family income, the majority of the respondents had an income of up to PLN 3000 (34.65%) or up to PLN 5000 (30.69%). In terms of the type of cancer, the largest number of respondents suffered from breast cancer (22.27%). High incidence rates were also recorded for ovarian cancer (10.89%) and cervical cancer (10.40%). In contrast, single cases included brain tumors (0.50%), anaplastic thyroid cancer (0.50%), nasopharyngeal cancer (0.50%), rectal cancer (0.50%), bladder cancer (0.50%), penile cancer (0.50%), and salivary gland cancer (0.50%)—see Table 1.

Table 1. Sample characteristics (n = 202).

		N (%)
Education level		
	Basic Education	11 (5.44)
	Vocational Education	33 (16.33)
	Secondary Education	50 (24.75)
	Higher Education	83 (41.09)
	PhD	18 (8.91)
	Higher Medical Education	7 (3.46)
Place of residence		
	>500 k	25 (12.38)
	<500 k	42 (20.79)
	<250 k	40 (19.80)
	<100 k	37 (18.32)
	<20 k	37 (18.32)
	<5 k	21 (10.39)
Age		
	<30	32 (15.84)
	31–40	27 (13.37)
	41–50	64 (31.68)
	51–60	56 (27.72)
	>60	23 (11.39)
Sex		
	Female	176 (87.13)
	Male	26 (12.87)
Chemotherapy frequency		
	4 weeks or more	25 (12.38)
	3 weeks	64 (31.68)
	2 weeks	57 (28.22)
	1 week	34 (16.83)
	Everyday	8 (3.96)
	Last	9 (4.46)
	Interrupted	2 (0.99)
	Starting	3 (1.49)
Type of cancer		
	Breast	45 (22.27)
	Ovarian	22 (10.89)
	Cervical	21 (10.40)
	Colorectal	19 (9.41)
	Leukemia	17 (8.41)
	Lung	12 (5.94)
	Kindey	11 (5.45)
	Hodgkin's	11 (5.45)
	Other (Testicular, Lumphotic, Liver, Multiple Myeloma, Prostate, Uterus, Melanoma, Pancreatic, Skin, In situ, AML, Penile, Salivary gland, Bladder, Nasopharyngeal, Anaplastic thyroid, Brain)	44 (21.78)

The most common chemotherapy administration regimen was a triweekly (31.68%) or biweekly (28.22%) cycle, with 16.83% of the patients receiving chemotherapy once a week and 3.96% receiving it daily.

The median time since diagnosis was 18 months (Me 18), with a mean of just over two years, while the time range varied significantly, indicating the heterogeneity of the respondents (M 25.63, SD 28.88). The median time from the beginning of chemotherapy was 7.5 months (Me 7.5), with a mean of about a year (M 12.53, SD 12.44). These differences

reflect the diversity of the patients' experiences of time in terms of their duration (in the linear sense of time), regardless of the content.

3.2. Happiness Closed off by Regret and Broken Future Horizon

Based on the assumption that the 7-point Likert scale was sensitive enough to represent the subtle differences among the respondents, even if the final numerical values merely concerned the level of agreement with the pre-given content (and were, therefore, not absolute), we looked at numbers above the median values of the 7-point Likert (i.e., representing neither agree nor disagree) as indicating an overall tendency to have the experience in question (as represented by each particular variable statement). A slight tendency to accept the statements representing the phenomena of happiness closed off by regret and broken future horizon was apparent, with all the responses' median values being higher than the means (see Table 2).

Table 2. Lived time phenomena and their representing statements.

Phenomenon	Statement	Value M, Me, SD, Q1, Q2, Q3
Being in the present	I don't think about the past because I focus on the present.	4.11, 5.00, 1.19, 3.00, 5.00, 5.00
Regret	Thoughts about my life before treatment often come back to me in the form of regrets. I regret that I did/did not do something that could have had negative consequences.	3.55, 4.00, 1.47, 2.00, 4.00, 5.00
Bygone happiness	Regardless of the above, thoughts of my life before treatment come back to me as happy memories.	4.29, 5.00, 1.00, 3.00, 5.00, 5.00
Living for today	I live from day to day.	4.05, 5.00, 1.37, 3.00, 5.00, 5.00
Future planning	I am not planning the future further than my next chemo.	3.51, 4.00, 1.58, 2.00, 4.00, 5.00
Dreams about future	I have no concrete plans for the future after recovery, at most dreams	3.99, 5.00, 1.36, 3.00, 5.00, 5.00
Unpredictable future	I live with a constant sense that something unforeseen might happen	4.14, 5.00, 1.18, 3.00, 5.00, 5.00

The median score of 5.0 regarding focusing on the present indicates that most participants experienced their lives during treatment in a continuous, day-to-day manner, which was also confirmed by the agreement with the statement on living from day to day, with a median score of 5.0. This may, however, suggest the patients' ability to enjoy the present moment despite difficulties. Reflections on life before treatment in the form of regrets were less intense, with a median score of 4.0. In contrast, the statement regarding the thoughts of life before treatment coming back as happy memories received a median score of 5.0. With regard to planning for the future, the median values were lower, with 4.0 for not planning further than the next chemotherapy treatment and 5.0 for not having any specific plans after recovery. The median score regarding living with a constant sense that something unforeseen might happen was 5.0, suggesting that half of the respondents experienced uncertainty related to the future (see Table 2).

The participants' future horizon specified in calendar terms was relatively short. A total of 23% of the respondents looked ahead no further than six months, while 20.79% looked ahead no further than the coming week. For 14.84%, the horizon reached the next

three months; for 12%, the upcoming chemotherapy; and for 9%, the next day only. Only one out of five respondents (19.31%) reached further than a year, including longer periods.

The dominant method of measuring time during treatment could not be identified in the study group. Nevertheless, the most common was the rhythm of check-ups (29%), the monthly cycle (26%), the schedule of chemotherapy courses (17%), the daily rhythm (15%), and the weekly rhythm (13%). It is noteworthy, however, that measuring time by non-calendar rhythms related to treatment, that is, chemotherapy and check-ups, applied to almost half of the respondents (46%), thus supporting our previous hypothesis [32].

Interestingly, no statistically significant differences were observed between the cancer groups and the responses to any of the questions on experienced temporal phenomena ($p > 0.05$). What is more, no sociodemographic variables showed statistically significant differences ($p > 0.05$) with the temporal variables representing the lived experience of time. In this context, it can be concluded that neither the type of cancer nor the social background was a significant factor in differentiating the temporal experience of the patients.

3.3. Correlations with Cyclic and Linear Time

The frequency with which the patients underwent chemotherapy only affected their focus on the present, and mildly (Being in the present; R = 0.25, $p < 0.05$), likely because of the discomfort of the side effects. The frequency of chemotherapy also did not differentiate the results of the responses to the question concerning how time is measured—which was our original hypothesis, confirmed in another study [16]—and the question concerning the length of the temporal horizon in calendar terms (Chi2, $p > 0.05$).

As far as linear time is concerned, there were significant but very weak relationships between age and three variables: Bygone happiness (R = 0.18, $p < 0.05$), Future planning (R = 0.16, $p < 0.05$), and Unpredictable future (R = 0.14, $p < 0.05$). No significant relationship was observed between age and the other statements ($p > 0.05$). Except for Dreams about the future (R = 0.17, $p < 0.05$), there were no correlations between the time passed since diagnosis or the beginning of chemotherapy and the rating of the statements (see Table 3).

Table 3. Spearman's R correlations between linear time variables and temporal phenomena.

Linear Time Variables	Being in the Present	Regret	Bygone Happiness	Living for Today	Future Planning	Dreams about Future	Unpredictable Future
Age	0.11	0.12	**0.18** *	0.10	**0.16** *	0.04	**0.14** *
Time since diagnosis	0.01	0.00	−0.04	−0.03	0.09	**0.17** *	0.00
Time since the beginning of chemotherapy	0.01	−0.02	0.01	−0.08	−0.11	0.01	−0.4

Bold * indicates statistically significant results ($p < 0.05$).

However, all of these correlations were negligible, which can be interpreted to mean that entering the cancer treatment stage reevaluates the attitude toward time regardless of the type of cancer, the age of the patient, and the length of the process in calendar time. In this sense, chemotherapy affects lived temporality totally and equally for everyone.

4. Discussion

At the outset, it should be noted that chemotherapy treatment is a traumatic experience for any patient, negatively affecting their mental state. The patient usually dramatically changes their attitude to their surrounding reality and social relations. This study aimed to explore, in a sequential manner, following our previous qualitative phenomenological study concerning ovarian cancer, how patients in a larger and more diverse sample experience time during chemotherapy in terms of their past memories and future plans.

The analysis showed that for almost half of the respondents, the rhythm of chemotherapy courses and check-ups was the means of measuring the passing of time—what we previously called the chemo-clock [32]. This both indicates the subjective significance

of treatment for the patients and potential adverse psychological effects. Frequent and meaningful hospital visits might lead to a sense of security and optimism and, in turn, positively influence the course of treatment and its outcomes. Still, they may also make patients more susceptible to worries and anxieties about aspects of treatment, such as the proper intake of medication, the body's readiness for subsequent doses, and concerns about the possible return of the disease.

The frequency of chemotherapy only mildly affected the respondents' perception of the present, with more frequent cycles likely leading to a focus on current aspects of the disease. But, even with frequent cycles, no significant differences were observed regarding other aspects of the lived experience of time. Nevertheless, a slight tendency to agree with all the questions points to how patients' temporal experience changes during treatment. The increased present focus might be a defensive element, in that by focusing on the current stage of treatment, they isolate themselves from negative memories of the past and an uncertain future. Focusing on the present is a way to cope with these emotional challenges [33]. Simultaneously, the respondents' narrowed future planning likely stems from the need to face treatment challenges and future uncertainties. Immediate goals and plans within their reach are what counts. It is worth noting that even slight differences in the tendency to think ahead can have a significant impact on the psychological state of patients. A sense of hope and control can be an important element in coping with the difficulties arising from the disease, affecting their ability to adapt to a new situation. A limited and unpredictable future horizon may lead to avoiding activities related to uncertainties about the disease and its treatment. Directing attention to the present may be due to physical ailments. Still, it is a way of coping with difficulties while also effectively counteracting negative emotions related to an uncertain future. In addition, research highlights the contrast between revisiting happy memories, where the past appears as a separate reality, and the present, where feelings of anxiety, apprehension, and uncertainty dominate. This may induce patients to cling to dreams instead of concrete plans, as uncertainty about the course of life complicates the formulation of realistic expectations. An interesting aspect is the observation of feelings of regret resulting from reflections on decisions made before the onset of the disease, decisions that could have potentially brought negative consequences. This phenomenon can be interpreted as a sense of deserved punishment for past behavior or a belief that there was a conscious cause for the onset of the disease.

This study identified some differences in temporal experience related to the type of cancer; however, they were not statistically significant. Respondents with blood and squamous cell cancers were more likely to agree with the statements regarding past happiness and living for today, and their temporal horizon was more limited by the upcoming chemotherapy. This is likely related to the rapid growth and expansion of these cancers, which requires a decisive therapeutic approach within a short period after diagnosis. Also, the long-term and chronic treatment of these types of cancer requires patients to be constantly monitored and controlled, potentially affecting their outlook on time. Focusing on the present may effectively cope with difficulties and counteract negative emotions about the future. The diagnosis of these types of cancer is often made at an advanced stage, which increases patients' awareness of the limitations and future difficulties. Reminiscence may be a way to cope with the disease and its consequences. It may provide a kind of escape from the anxiety associated with the possibility of recurrence. The aspect of past happiness is also relevant in the context of breast cancer, where anticancer therapies often require involvement in very invasive procedures, which can lead to visible effects on the body. Further studies in larger and more diverse samples are needed to confirm these hypotheses. Currently, the type of cancer does not appear to be a significant factor affecting the temporal experience during treatment.

In terms of linear time, elderly cancer patients experience more frequent horizon collapses. Lack of hope for recovery, worries about the future, and probably awareness of imminent death, as well as more frequent revisiting of the past, are more common among the elderly, although correlations are low. Arguably, cancer is a factor that usually compels

the patient to reflect on the past and related memories, both positive and difficult. The changed life situation places high demands on the ability to adapt and cope with daily life and redefine one's social roles. These changes involve a sense of existential change and looking at oneself differently. People also experience thoughts related to dying and death. More time is spent reflecting on life to date, living with cancer, and death [4,34–37]. The younger age of patients, on the other hand, mildly translates into a broader time perspective. Cancer is usually seen as a challenge to overcome or to live with. Young patients actively analyze the possibility of relapse and its potential impact on their family life, finances, image, sexual function, and future roles in the family. Faced with these uncertainties, they seek to flexibly shape their experiences, adjusting priorities in their professional and family lives. Planning for the future becomes a motivating force for them, enabling them to maintain hope, a sense of control, and focus on their values and life goals, which promotes effective coping [37–44]. Furthermore, in terms of the linear time passed since diagnosis and treatment, there are only subtle connections between the former and dreaming about the future. This may result from less hope for recovery caused by deterioration, chronicity of the disease, or related limitations. It is noteworthy that despite fears and anxieties about taking further doses of drugs or concerns about the body's readiness for therapy, the duration of chemotherapy did not affect how time was experienced.

Limitations

The main limitation of this study is the sample size and convenience sampling method, which is never representative. Another limitation is that the participants consisted of online cancer support groups only, with a possible overrepresentation of people with online access. Furthermore, there was a female tumor prevalence, namely breast, ovarian, and cervix. For these reasons, and also given that the questionnaire was constructed for the purpose of this study only in order to account for hypotheses stemming from our previous small-sample qualitative research, the results of this follow-up quantitative study should be treated as exploratory. Further studies in larger and more diverse cancer samples, and possibly directly collected data, are needed to confirm these results.

5. Conclusions

During chemotherapy, patients experience increased focus on the present, decreased focus on the future, and a sense of unpredictability with a relatively short temporal horizon. They also tend to measure time during treatment by the rhythm of chemotherapy and check-ups. The type of cancer and the length of treatment do not appear to be a significant factor affecting the temporal experience of patients. Changed temporal experience during chemotherapy should be considered when planning oncology care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16112124/s1.

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Review

Effects of Opioids in Cancer Pain: An Interplay Among Genetic Factors, Immune Response, and Clinical Outcomes—A Scoping Review

Kamil Adamczyk [1], Konrad Zuzda [1,*], Miłosz Jankowski [1], Rafał Świerczyński [1], Kamil Chudziński [1], Bartosz Czapski [2] and Konstanty Szułdrzyński [1]

[1] Department of Anesthesiology and Intensive Care, National Medical Institute of the Ministry of the Interior and Administration, 02-507 Warsaw, Poland; kamil.adamczyk@pimmswia.gov.pl (K.A.); milosz.jankowski@pimmswia.gov.pl (M.J.); rafal.swierczynski@pimmswia.gov.pl (R.Ś.); kamil.chudzinski@pimmswia.gov.pl (K.C.); konstanty.szuldrzynski@pimmswia.gov.pl (K.S.)
[2] Department of Neurosurgery, National Medical Institute of the Ministry of the Interior and Administration, 02-507 Warsaw, Poland; bartosz.czapski@pimmswia.gov.pl
* Correspondence: konrad.zuzda@pimmswia.gov.pl

Simple Summary: This review examines the relationship between cancer pain management, patients' genotype, and outcomes. The article highlights how genetic differences influence individual responses to pain treatments and opioid processing. The authors conclude that pain management in cancer care involves a delicate balance between treatment effectiveness and immune system impact, with genetic factors playing a crucial role in treatment response. To enhance the reliability of pain management practices, conducting further studies is essential for assessing the long-term effectiveness of novel genetic-based approaches.

Abstract: Background/Objectives: Managing cancer-related pain presents complex challenges involving the interplay between analgesic efficacy, immune system responses, and patient outcomes. **Methods**: Following the Scale for the Assessment of Narrative Review Articles (SANRA) criteria, we conducted a comprehensive literature search in Medline, Scopus, and Web of Science databases. The review synthesized evidence regarding opioid pain management modalities, genetic variations affecting pain perception, and associated drug metabolism. **Results:** The literature reveals significant associations between opioid administration and immune function, with potential implications for cancer progression and survival. Genetic polymorphisms in key genes influence individual responses to pain opioid metabolism and, finally, pain management strategies. The immunosuppressive effects of opioids emerge as a critical consideration in cancer pain management, potentially influencing disease progression and treatment outcomes. **Conclusions:** Genetic variants influence analgesic efficacy, while the interaction between opioid-induced immunosuppression and genetic factors impacts both pain control and survival outcomes. This emphasizes the need for personalized treatment approaches considering individual genetic profiles and immune function.

Keywords: cancer pain; opioids; immune response; genetic factors

1. Introduction

Oncology pain management is currently one of the key aspects of comprehensive cancer treatment, significantly contributing to better quality of life (QoL) and survival for patients. However, recent studies suggest a more complex connection between pain management and patient outcomes [1,2]. While pain relief is crucial, its potential effects on immune function and, consequently, tumor progression require careful consideration.

Studies on the interplay between pain, opioid consumption, and survival expectancy in cancer patients have profound implications for patient care. Chronic pain, a common symptom of malignancy, not only weakens patients physically but also impacts significant physiological effects that can alter the disease process and patients' coping mechanisms [3,4]. Personalized medicine increasingly emphasizes the genetic variations that affect both the opioid efficacy and host response, thereby leading to differences in chronic pain perception, opioid effects, and therapeutic outcomes [5,6]. Genes regulating drug transport and metabolism further affect the response to treatment, adding to the challenge of tailoring pain management strategies.

This review explores the relationship between pain, opioid use, and survival in cancer patients. It highlights the significance of genotyping and the impact of opioids on immune function. The authors hypothesize that opioid-related adverse effects, particularly immunomodulation and hyperalgesia, may negatively impact survival and other clinical outcomes in cancer patients.

2. Methodology

This narrative review followed the Scale for the Assessment of Narrative Review Articles (SANRA) criteria [7] to comprehensively evaluate the relationships between genetic factors, pain management, and survival outcomes in cancer patients.

A literature search was conducted using Medline, Scopus, and Web of Science databases. The initial search identified over 15,000 potentially relevant studies addressing three key domains: pain perception mechanisms, opioid metabolism pathways, and cancer-related pain processes. Search terms included variations of "cancer pain genetics", "opioid pharmacogenetics", and "cancer pain immunology".

The review synthesizes current evidence regarding genetic variations affecting three major pathways: pain perception, drug metabolism, and the host's immune response. Genetic polymorphism studies were the focus concerning their effects on clinical outcomes, including the effectiveness of pain control, opioid-related adverse effects, and patient survival.

3. Pain Perception, Opioid Use, and Survival

The complex interaction between pain perception, opioid usage, and overall survival outcomes is a key area of focus in oncology research, with significant implications for patient outcomes (Figure 1). Emerging evidence underscores pain perception as a critical, independent factor influencing prognosis in various oncological settings. A comprehensive systematic review by Zylla et al. revealed that pain at the time of diagnosis in advanced non-small cell lung cancer (NSCLC) was associated with shorter survival, with 80% of the analyzed studies affirming pain's prognostic importance [1]. The data described by Zheng and colleagues indicated that pain significantly predicts survival rates in different forms of cancer, which is especially evident in prostate cancer patients [2,8]. Moreover, Reyes-Gibby's team demonstrated that pain could serve as a key indicator of survival in head and neck cancer patients. These findings highlight the potential interplay between advanced pain management and improving cancer treatment outcomes [9]. Additionally, Boland and

Bennett described the undertreatment of pain as threatening patients' survival [10]. It is possible to improve the QoL, treatment adherence, and overall outcomes through adequate pain control, potentially extending patients' survival [11].

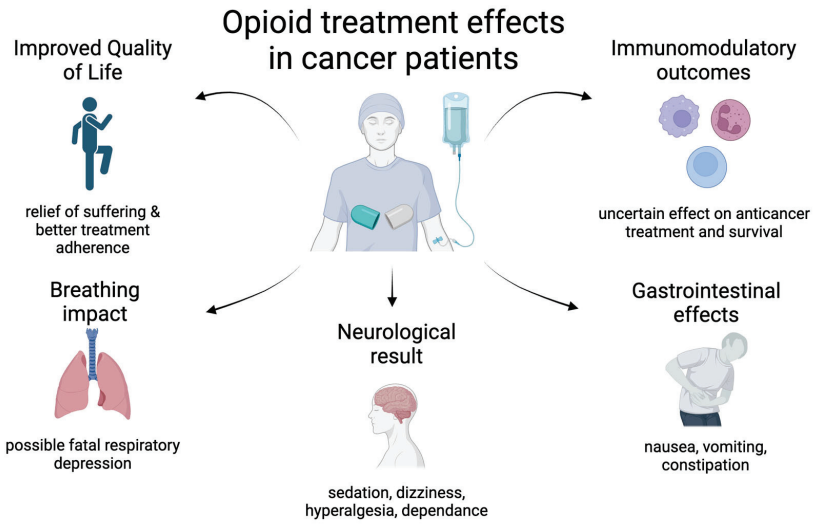

Figure 1. Opioid treatment effects in cancer patients—a graphical summary.

The immunomodulatory effects of opioid administration represent a complex and nuanced aspect of cancer care. Recent data indicate that opioid analgesics influence cancer progression through various mechanisms. Kavgaci et al. [12] highlighted immunological interactions concerning immune checkpoint inhibitor therapies (ICIT). It was proposed that modulation of the μ-opioid receptor significantly modifies the survival mechanisms, alters cancer progression, and affects the immune system's functioning. The activation of μ-opioid receptors in tumor and immune cells may cause tumor proliferation, suppression of apoptosis, and angiogenesis through pathways like EGFR and MAPK/ERK, among others. Opioids also inhibit the signaling of T cells by T-cell receptors, reduce CD8+ T cell effector activity, increase regulatory T cell populations, and potentially aid in forming an immunosuppressive tumor microenvironment [12]. Chancellor et al. demonstrated that prolonged opioid exposure correlates with reduced survival following lung cancer resection [13]. A comprehensive meta-analysis by Ju et al. further studied this relationship, revealing potential negative immunological consequences of opioid utilization in patients receiving ICIT [14]. Conversely, Zylberberg et al. recorded increased survival rates for elderly pancreatic cancer patients with opioid treatment [15].

The area that has evolved in recent years is the immunosuppressive effect of opioids. According to a study by Bradley and Boland [16], administration of opioids leads to immunological compromise by targeting immune cells expressing opioid receptors and through any central mechanisms that inhibit NK cell activity. These and other related mechanisms may predispose the individual to infections, including reduced cytotoxicity by NK cells and altered immune responses via opioid-induced activation of TLR-4. In addition, Shao et al. [17] reported that in advanced cancer patients, the risk of infection increased by approximately 2 percent for every 10 mg increase in the daily oral morphine equivalent (OME). It is important to note that while this association suggests a dose-dependent relationship, higher opioid dosages in these patients may also reflect a more advanced disease state or other confounding factors rather than being solely attributable to the immunomodulatory effects of opioids. Montagna et al. reported a significantly greater improvement in recurrence-free survival in patients with triple-negative breast

cancer who received intraoperative administration of opioids, where fentanyl was the primary opioid given. However, hydromorphone and morphine were also included and converted to oral morphine milligram equivalents (MME) for analysis [18], while Connolly et al. conversely documented shortened progression-free survival in advanced prostate cancer with increased opioid exposure [19].

4. Refractory Cancer Pain: Mechanisms and Consequences

4.1. Mechanisms Affecting the Response to Analgesics

The management of refractory cancer pain in advanced malignancies remains a significant clinical challenge due to its multifaceted etiology and complex pathophysiology. Cancer-related pain arises through diverse mechanisms, broadly classified as nociceptive or neuropathic. Nociceptive pain typically results from tumor invasion, leading to inflammation and direct tissue damage. In contrast, neuropathic pain stems from nerve injury or dysfunction, often aggravated by tumor progression or adverse effects of treatment modalities [20]. The interaction of several biological processes primarily determines the pathophysiology of cancer pain. Tumors can secrete inflammatory mediators sensitizing the nociceptors, which results in the increased recognition of pain. For instance, the cytokines, tumor necrosis factor-alpha (TNFα), and interleukin-1 beta (IL-1β), as well as the nerve growth factor (NGF), are some of the crucial molecules in the activation and sensitization of primary afferent nociceptors. The mediators, like bradykinin and endothelin-1 (ET-1), contribute to nociception. Proteases and protease-activated receptors (PARs) modulate further the pain response by making nociceptors more excitable in the cancer microenvironment. Thus, the impact of these inflammatory mediators is very complex and lies at the basis of chronicity, which often leads to resistance to pain in the end [21–24]. Additionally, peripheral nerve injury (PNI), due to tumor invasion, can lead to neuropathic pain, which is often more challenging to treat and can significantly impair the quality of life [25].

Research indicates that central sensitization is crucial in maintaining cancer pain [26]. This phenomenon involves changes in the central nervous system, particularly within the spinal cord, where synaptic plasticity can enhance pain-signaling pathways [27]. Studies have shown that bone cancer elicits, among its mechanisms, distinctive central sensitization effects such as enhanced synaptic transmission, increased excitability of dorsal horn neurons, and plastic changes in spinal sensory pathways [28]. These alterations result in generalized changes in spinal cord excitability, leading to chronic pain and hypersensitivity. Additionally, the activation of microglia and the production of pro-inflammatory mediators such as IL-18 and phosphorylated p38 MAPK (p-p38) have also been implicated in preclinical studies to persist in cancer pains. Those mediators are upregulated in spinal microglia during advanced cancer pain and contribute to neuronal hyperactivity and central sensitization. ATP, acting through the P2X7 receptors, further increases this inflammatory cascade by microglial release of IL-18, thereby amplifying nociceptive signaling pathways [29].

4.2. Consequences of Pain Refractory Pain to Conventional Treatment

The clinical management of refractory cancer pain often requires a multidisciplinary approach, as standard analgesic treatments, including opioids, may prove insufficient for many patients [30,31]. Approximately 10–15% of cancer patients experience pain that remains unmanageable despite high-dose opioid therapy [32]. This necessitates the exploration of alternative therapeutic strategies, such as intrathecal drug delivery systems, which have shown promise in managing refractory pain [33].

Importantly, uncontrolled pain can lead to significant immunosuppression by activating the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. This stress response

increases glucocorticoid levels and catecholamines, suppressing innate and adaptive immunity [34]. In this context, effective pain management with opioids may help preserve immune function by preventing pain-induced immunosuppression, despite opioids' direct immunosuppressive effects. While opioids can suppress immune responses directly, their ability to control pain may protect against the profound immunosuppressive effects of uncontrolled pain and chronic stress. Therefore, the net impact of opioid therapy on immune function likely depends on the balance between these competing effects in each patient.

Poorly controlled cancer pain is a significant clinical issue that can lead to a multitude of complications affecting both psychological and physical well-being, including daily functioning. Pain can interfere significantly with patients' ability to perform routine activities, leading to increased dependency on caregivers and a diminished sense of autonomy [35,36]. Research has shown that even mild pain, rated as low as two on a zero-to-ten numerical rating scale, has been found to impair daily functioning severely [36]. Furthermore, the psychological ramifications of unmanaged pain are substantial; patients often experience heightened levels of anxiety and depression [37]. The interplay between physical pain and psychological distress creates a vicious cycle that can lead to increased healthcare utilization and costs, as patients may seek more frequent medical interventions to manage their symptoms [38].

5. Immunosuppression Due to Opioid Treatment

Recent studies have demonstrated that opioid therapy can contribute to immunosuppression [39], potentially worsening cancer progression and patient survival [40]; however, the extent to which these outcomes are directly attributable to the immunomodulatory effects of opioids—as opposed to other risk factors inherent to patients requiring opioid treatment—remains uncertain [41].

Opioids exert their analgesic effects by binding to seven trans-membrane G protein-coupled receptors (GPCRs)—so-called opioid receptors. These receptors are classified as classical and non-classical. The classical group includes three main subtypes: μ, κ, and δ [42]. Although opioids can exert their pharmacological effects through κ and δ opioid receptors, most opioids act mainly on μ-opioid receptors (MORs), which is their primary analgesia mechanism [43]. Opioid binding and MOR activation inhibit excitatory neurotransmitter release from presynaptic neurons while hyperpolarizing postsynaptic neurons [44]. Analgesia is primarily mediated by opioid receptors in the central nervous system (CNS), although there is evidence that opioid receptors in the peripheral nervous system may also mediate analgesia [45].

Opioid receptors are expressed in neurons, neutrophils, macrophages, and T and B lymphocytes [44]. Their widespread distribution can lead to various side effects such as sedation, constipation, nausea, pruritus, physical dependence, vomiting, dizziness, respiratory depression, hyperalgesia, and shock due to histamine release, as well as immunosuppression and increased infection risk [46–48]. The effects of endogenous opioids on the immune system are complex and can be immunostimulatory or inhibitory, depending on the type of cells they affect [49].

Opioids impair innate and acquired immunity by directly interacting with immune cells or indirectly activating the central nervous system and hypothalamic–pituitary–adrenal axis, releasing immunosuppressive corticosteroids and hormones [50–54]. Recent controlled studies substantiate these findings. For example, Chen [55] demonstrated that repeated intraperitoneal injections of oxycodone in mice significantly reduced $CD4^+$ T cells dose-dependently. Similarly, McIlvriedd found that morphine treatment in tumor-bearing models diminished $CD4^+$ and $CD8^+$ T cell infiltration, reducing the efficacy of immune checkpoint inhibitors such as anti-PD-1; these effects were mediated via *OPRM1* sig-

naling in $CD8^+$ T cells and could be counteracted by peripherally acting *OPRM1* antagonists [56]. Supporting these preclinical findings on a broader scale, Mao et al. [57] reported that opioid use was associated with decreased response rates to immune checkpoint inhibitors (OR = 0.49) and increased risks of disease progression (HR = 1.61) and mortality (HR = 1.67).

Morphine activates MOR on various innate immune cells [50,51,58]. In macrophages, this results in reduced proliferation, recruitment, phagocytosis, and bactericidal activity, potentially via interaction with Toll-like receptors (TLRs) and altered signaling of the transcription factor NF-κB. Morphine inhibits neutrophil migratory function by interfering with IL-8 signaling and reduces neutrophil superoxide production, impairing their bactericidal activity [50,51,58]. Morphine, moreover, reduces mast cell activation, increasing intestinal permeability and the risk of infections [50,51,58].

Clinical observations lend further support to these mechanisms. Kc et al. [59] linked latent herpes simplex virus (HSV) reactivation to chronic morphine use, while Puzhko et al. [60] reported that opioid users face increased risks of infections such as hepatitis C and HIV [59,60]. Moreover, Kelty et al. [61] showed that prenatal opioid exposure may induce long-term immune dysregulation, predisposing children to diseases and conditions like eczema and asthma. Similarly, Kudrina [62] noted that chronic opioid use alters the intestinal microbiome and activates the HPA axis [61,62]. In oncology, Scarpa et al. [63] demonstrated that opioids—particularly morphine—impair the efficacy of immune checkpoint inhibitors by modulating RNA expression networks in $CD8^+$ T cells, underscoring the clinical impact of opioid-induced immunosuppression on cancer therapy.

6. Genetic Profiling

Genetic variations can significantly impact a patient's pain perception and response to pain medication, influencing treatment outcomes and QoL. Recent findings align with the broader applications of pharmacogenomics in pain management, supporting the development of personalized treatment protocols to optimize therapeutic efficacy while minimizing adverse effects [64]. By identifying specific genetic markers associated with pain sensitivity and analgesic response, clinicians can tailor treatments to individual patients, potentially improving pain control and reducing the risk of adverse effects [Table 1].

Table 1. Influence of Genes on Pain Perception, Opioid Therapy, and Analgesic Drugs.

Category	Gene/ Citation	Role	Impact on Pain Perception	Effect on Analgesic Drugs
Opioid Signaling Pathway	*OPRM1 OPRD1 OPRK1*	Encode classical opioid receptors μ-, δ-, and κ-, mediating opioid analgesic effects.	Variations may lead to differences in analgesic efficacy and pain control.	Influence opioid responsiveness, potentially causing inadequate pain relief or increased sensitivity.
	NOP	Encodes nociceptin/orphanin FQ receptor, involved in non-classical opioid signaling.	Modulates nociceptive neurotransmission, reducing pain perception.	Potential target for novel analgesics with fewer side effects compared to traditional opioids.
Pain Perception Modulators	*CACNA1B*	Encodes N-type calcium channel subunit, critical for neurotransmitter release.	Overexpression enhances pain sensation; linked to hyperalgesia.	Genetic variants may alter opioid efficacy; dysfunction affects analgesic responses.
	BCL2 BAX	Regulate cellular apoptosis; *BCL2* gene is anti-apoptotic, while BAX is pro-apoptotic.	Imbalance increases neuronal sensitivity to pain.	Targeting these pathways may reduce pain and modulate glial activation.
	FAAH	Enzyme degrading endocannabinoids, particularly anandamide.	Inhibition increases anandamide levels, reducing pain sensitivity.	*FAAH* [1] inhibitors may enhance analgesic effects; polymorphisms affect treatment responses.
	KCNJ6	Encodes GIRK2 [2] potassium channels, regulating neuronal excitability.	Variants influence pain sensitivity and opioid requirements.	Genetic variants may necessitate opioid dosage adjustments for effective analgesia.

Table 1. *Cont.*

Category	Gene/ Citation	Role	Impact on Pain Perception	Effect on Analgesic Drugs
Drug Metabolism Genes	*CYP2D6 CYP2B6 CYP3A4 CYP3A5 CYP2C19*	Enzymes involved in Phase I drug metabolism, including opioids.	No direct influence on pain perception.	Variants affect opioid metabolism, altering efficacy and risk of side effects like toxicity or inadequate relief.
	UGT2B7	Enzyme responsible for Phase II glucuronidation of opioids like morphine.	No direct influence on pain perception.	Polymorphisms impact opioid efficacy by altering metabolite levels; dosage adjustments may be required.
	COMT	Metabolizes catecholamines, affecting neurotransmitter levels.	Polymorphisms influence pain sensitivity and stress response.	Variants affect opioid dosage requirements; specific genotypes need higher or lower doses for effective pain control.
Transport and Regulatory Genes	*ABCB1*	Encodes P-glycoprotein, an efflux transporter affecting drug distribution and blood-brain barrier crossing.	Variants influence nociceptive processing and pain sensitivity.	Alters opioid transport, affecting drug efficacy and toxicity.
	SLC6A3 SLC6A4	Encode dopamine and serotonin transporters, regulating synaptic neurotransmitter levels.	Polymorphisms may influence pain modulation and emotional responses.	May affect efficacy of drugs modulating serotonergic or dopaminergic systems.
	DRD2	Encodes dopamine D2 receptor, involved in dopaminergic signaling.	Variants affect pain sensitivity and stress responses.	May influence opioid efficacy and risk of addiction.
	NLRs	Encode NOD-like receptors [3], involved in immune and inflammatory responses.	Activation amplifies nociceptive signaling through pro-inflammatory cytokines.	Potential therapeutic targets for reducing opioid tolerance and opioid-induced hyperalgesia.
Inflammatory Response Gene	*PTGS2*	Encodes COX-2 [4], essential for prostaglandin synthesis in inflammatory responses.	Variants linked to heightened pain sensitivity and inflammation.	Target for NSAIDs [5]; polymorphisms may affect anti-inflammatory drug efficacy.

[1] FAAH—Fatty-acid amide hydrolase-1, [2] GIRK2—G-protein-regulated inward-rectifier potassium channel-2, [3] NOD-like receptors—nucleotide-binding oligomerization domain-like receptors, [4] COX-2—Cyclooxygenase-2, [5] NSAIDs—Nonsteroidal Anti-Inflammatory Drugs.

6.1. OPRM1, OPRD1, and OPRK1 Genes

The genes OPRM1, OPRD1, and OPRK1, which encode for the classical opioid receptors (μ-, δ-, and κ-), have been implicated in the modulation of pain and potentially in the survival of cancer patients. Differential expression in chronic pain or opioid addiction suggests their utility as biomarkers [65,66]. Studies examining opioid response in cancer patients have highlighted the role of genetic polymorphisms, particularly in the OPRM1 gene. Variants in this gene can affect opioid metabolism and receptor sensitivity, influencing pain management [67,68]. For example, polymorphisms such as OPRM1 rs1799971 and rs677830 can affect opioid receptor sensitivity, which may increase the risk of side effects such as constipation and alter the effectiveness of pain relief.

Although some suggest that cancer patients require high opioid doses and rapidly develop tolerance, Schug et al. [69] demonstrated effective pain control with lower doses—dose increases were more often due to disease progression. In contrast, Gagnon et al. [70] observed escalating opioid needs in advanced stages, and Preux et al. [71] reported an 8% prevalence of opioid use disorder. In this context, μ-opioid receptor downregulation [72] and genetic variations, including OPRM1 rs9479757 and OPRK1 rs7824175 [73], may contribute to differences in analgesic efficacy. Poor pain management can increase emotional distress, anxiety, and depression, all of which are known to lower QoL and potentially shorten survival in oncology patients [74–76].

6.2. NOP Gene of the Nociceptin/Orphanin FQ Receptor

Activated by nociceptin/orphanin FQ (N/OFQ), the NOP receptor is present throughout the central and peripheral nervous systems, affecting pain modulation, emotional

responses, and stress regulation [77,78]. Its distinct pharmacological profile sets it apart from classical opioid receptors, making it a promising target for cancer-related pain management [79,80]. NOP receptor activation inhibits nociceptive neurotransmission by reducing cAMP production and altering calcium and potassium currents in neurons [81,82]. This is especially relevant for patients who suffer from complex pain due to tumor growth, metastasis, and treatment side effects. Selective NOP agonists, such as SR14150, SR16835, and Ro65-6570, have demonstrated significant analgesic effects in preclinical models of cancer-induced bone pain, suggesting targeted therapies that may reduce the side effects of traditional opioids [83,84]. NOP receptors located on spinal microglia cells play a key role in neuroinflammatory processes associated with cancer pain by regulating microglia activation and the production of pro-inflammatory cytokines. This modulation affects pain-signaling pathways, thereby contributing to the development and maintenance of cancer-related pain [85]. Modulating microglial activity through NOP signaling could mitigate pain and underlying inflammation in chronic cancer pain states [86]. In addition, combining NOP and μ-opioid receptor pathways using bifunctional ligands such as cebranopadol, buprenorphine, AT-121, or SR 16435 can increase analgesic efficacy through synergistic effects on both receptors. At the same time, this combination can reduce typical opioid side effects, such as tolerance development and addiction, making pain therapies safer and more effective [78,83].

Polymorphisms in the NOP gene can alter receptor expression or function, influencing pain experiences and analgesic efficacy [87]. Beyond pain modulation, NOP receptors regulate emotional and stress responses, which are often intensified in cancer patients [77,80]. NOP modulators also exhibit anxiolytic and antidepressant properties, benefiting cancer patients with anxiety and depression [79,87].

6.3. CACNA1B Gene

CACNA1B gene encodes the N-type calcium channel subunit CaV2.2. This gene is integral to the functioning of voltage-gated calcium channels, essential for neurotransmitter release in the nervous system, particularly in pain pathways [88]. The modulation of calcium influx through these channels is crucial for synaptic transmission and neuronal excitability, which are fundamental in processing pain signals [88]. The expression levels and functional variants of CACNA1B may influence how patients perceive pain and respond to analgesic treatments. For instance, overexpression of CACNA1B has been associated with enhanced neuronal excitability, which can exacerbate pain sensations and hyperalgesia [11]. In addition, specific genetic variants in the CACNA1B gene may alter opioid efficacy by affecting alternative splicing of CaV2.2 calcium channels. These variants may modify DNA methylation, which affects CTCF protein binding and, ultimately, the expression of more opioid-sensitive channel isoforms [89]. Activating MORs can inhibit N-type calcium channel activity, thereby reducing calcium influx and neurotransmitter release, a critical mechanism for pain modulation. Variations in the expression or function of CACNA1B may disrupt this balance, leading to altered responses to opioid analgesics and necessitating adjustments in pain management strategies for cancer patients [90].

6.4. BCL2 and BAX (Apoptosis-Related Genes)

BCL2, an anti-apoptotic gene, and BAX, a pro-apoptotic gene, maintain a balance that affects cellular responses to stress and pain. Their expression levels modulate pain pathways, where increased BAX and decreased BCL2 are associated with heightened pain sensitivity and chronic pain development. Pro-inflammatory cytokines like IL-1β and TNF-α upregulate BAX and downregulate BCL2, enhancing neuronal apoptosis and pain

perception [91–93]. The activation of microglia and the subsequent release of inflammatory mediators exacerbate this process, creating a vicious cycle of pain and inflammation [93]. In glial cells, dysregulation of BCL2 and BAX contributes to neuroinflammation and pain hypersensitivity in neuropathic pain models [94]. Targeting the BCL2/BAX pathway has been shown to reduce glial activation and pain behaviors [95,96]. Cancer treatments, particularly chemotherapy, often induce neuropathic pain, significantly impairing patients' QoL. Thymoquinone and mangiferin alleviate neuropathic pain by modulating the BCL2/BAX pathway, promoting neuronal survival, and reducing apoptosis [95,97]. Genetic polymorphisms in BCL2 and BAX influence individual pain sensitivity and responses to analgesic treatments, highlighting the potential for personalized pain management strategies [98]. In addition, non-pharmacological approaches such as electroacupuncture affect BCL2 and BAX expression by regulating the miR-206-3p/BDNF pathway, reducing levels of the pro-inflammatory cytokines IL-6 and TNF-α, and modulating apoptosis pathways, which offers integrative approaches to cancer pain management [99,100].

6.5. FAAH (Fatty Acid Amide Hydrolase) Gene

Fatty Acid Amide Hydrolase (FAAH) is essential for metabolizing endocannabinoids like anandamide, which modulates pain and inflammation. This makes FAAH inhibition a promising strategy for cancer pain management [101,102]. FAAH is responsible for the degradation of anandamide, an endocannabinoid that interacts with cannabinoid receptors to exert analgesic effects. Elevated levels of anandamide have been associated with reduced pain sensitivity, suggesting that FAAH inhibition may enhance analgesia by increasing the availability of this endocannabinoid. Cajanus et al. [103] demonstrated that common single-nucleotide polymorphisms (SNPs) in the FAAH gene can influence pain sensitivity in postoperative settings, indicating a genetic basis for individual variability in pain response. Moreover, the FAAH's role in pain modulation is further illustrated by the discovery of FAAH-OUT, a novel pseudogene that may regulate *FAAH* expression. FAAH-OUT expression could significantly change anandamide levels, affecting pain sensitivity and response to analgesics [104]. In a study by Nasirinezhad and team, FAAH inhibition significantly attenuated persistent pain-related behaviors in a rat model of human immunodeficiency virus (HIV) sensory neuropathy, suggesting that FAAH inhibitors could be beneficial for managing pain in diverse clinical contexts [105].

6.6. KCNJ6 (GIRK2) Gene

The KCNJ6 gene encodes the G-protein-regulated inward-rectifier potassium channel-2 (GIRK2) potassium channel. Polymorphisms in the KCNJ6 gene affect pain responses by modifying the function of GIRK2 channels that regulate opioid receptors, leading to changes in pain tolerance and opioid efficacy and affecting treatment outcomes and quality of life for cancer patients [102]. Variants in KCNJ6 are associated with pain-related phenotypes, such as pain intensity and opioid analgesic effectiveness. Ozberk et al. found that the KCNJ6 polymorphism rs2070995 affects methadone response in advanced cancer patients [106]. Elens et al. further demonstrated that specific KCNJ6 polymorphisms, along with other genetic factors, can lead to inadequate opioid-induced analgesia in preterm infants [107]. Langford's study showed that variations in potassium channel genes, including KCNJ6, are associated with preoperative breast pain in women with breast cancer [108]. Smith's review of potassium channels in neuropathic pain underscored KCNJ6's broader implications in pain management, suggesting that targeting sensory abnormalities linked to KCNJ6 could improve analgesic efficacy [109]. Jeremic et al. discussed the therapeutic potential of GIRK channels in the central nervous system, proposing that modulating these channels

can enhance pain pathway regulation and analgesic outcomes for cancer patients [110]. Additionally, Bony et al. [111] highlighted the interaction between GIRK channels and GABA_B receptors, indicating that activating GIRK channels via GABA_B agonists can reduce neuronal excitability and manage pain effectively.

6.7. CYP3A4 (Cytochrome P450 3A4) Gene

Cytochrome P450 3A4 (CYP3A4) is crucial for metabolizing various opioid analgesics, including fentanyl (to norfentanyl), sufentanil, alfentanil, and methadone through N-demethylation pathways. Genetic polymorphisms and environmental factors lead to significant variability in CYP3A4 activity, resulting in heterogeneous opioid plasma concentrations and diverse therapeutic outcomes [112]. In fentanyl metabolism, CYP3A4 facilitates the conversion to norfentanyl, significantly affecting fentanyl clearance and efficacy [113]. While CYP2B6 primarily metabolizes methadone, CYP3A4 contributes substantially to its biotransformation, influencing its pharmacokinetic profile and therapeutic effects [114]. Pharmacological interactions significantly impact CYP3A4-mediated opioid metabolism. CYP3A4 inhibitors such as ketoconazole can substantially elevate fentanyl plasma concentrations, potentially precipitating respiratory depression [113]. The interindividual variability in CYP3A4 activity, influenced by genetic polymorphisms and environmental factors, including dietary components, significantly impacts therapeutic responses [115].

6.8. CYP3A5 (Cytochrome P450 3A5) Gene

Cytochrome P450 3A5 (CYP3A5) is integral to the metabolism of several opioid analgesics, including alfentanil, fentanyl (via N-dealkylation), and methadone (via N-demethylation), as well as other therapeutic agents like midazolam and immunosuppressants [115]. Official international guidelines already include recommendations for adjusting the dosage of the immunosuppressant drug tacrolimus based on the CYP3A5 genotype [116]. Genetic variations in this gene result in distinct metabolizer phenotypes, leading to significant differences in the pharmacokinetics of opioids such as methadone and buprenorphine. Individuals with specific CYP3A5 variants may require tailored therapeutic adjustments to achieve optimal analgesic efficacy [112,117]. Notably, the CYP3A5*1 and CYP3A5*3 alleles are associated with functional enzyme expression, significantly impacting drug metabolism and therapeutic outcomes [118]. Patients with a single nucleotide polymorphism (SNP) of the CYP3A5*3 gene had plasma fentanyl concentrations approximately twice as high as patients with the wild-type gene polymorphism (*1*1) or patients with heterozygous gene polymorphism (*1*3) [119]. Personalized analgesic protocols based on CYP3A5 genotypes can enhance therapeutic precision and efficacy, particularly in populations with significant genetic variability affecting enzymatic activity [116,118].

6.9. CYP2C19 (Cytochrome P450 2C19) Gene

Cytochrome P450 2C19 (CYP2C19) is pivotal in metabolizing various pharmaceuticals, including proton pump inhibitors like omeprazole, antidepressants such as citalopram and imipramine, and anticonvulsants like S-mephenytoin. Additionally, CYP2C19 metabolizes barbiturates, diazepam, propranolol, clopidogrel, and other therapeutic agents [120,121]. In opioid metabolism, CYP2C19 facilitates the N-demethylation of methadone to EDDP, with genetic variants impacting metabolic efficiency and safety [122]. Genetic polymorphisms within the CYP2C19 gene manifest in distinct metabolic phenotypes, precipitating substantial pharmacodynamic responses and safety profile variations. Specific genetic variants,

including CYP2C192 and *CYP2C193*, result in reduced enzymatic activity, categorizing individuals as poor metabolizers [123].

6.10. UGT2B7 (UDP Glucuronosyltransferase Family 2 Member B7) Gene

The *UGT2B7* gene influences pain perception and therapeutic responses. Polymorphisms like rs7439366 are associated with variations in opioid efficacy and sensitivity, notably for morphine and fentanyl [124,125]. For instance, carriers of the mutant allele of rs7439366 exhibit a higher affinity for morphine metabolites, specifically morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which make them more sensitive to morphine [126]. Sastre et al. [127] found that UGT2B7*2 homozygotes exhibit higher morphine-6-glucuronide (M6G) to morphine ratios, enhancing analgesic potency [127]. Similarly, Muraoka et al. demonstrated that UGT2B7 variants affect fentanyl dosage requirements during painful procedures [124]. Ning et al. linked the UGT2B7 C802T polymorphism to morphine efficacy, highlighting genotyping's potential to optimize opioid therapy [128]. Margarit et al. observed genotype-dependent effects of UGT2B7 on opioid titration and pain intensity, though Gregori et al. noted COMT polymorphisms as stronger predictors of postoperative morphine needs, emphasizing the multifactorial nature of pain management [129,130]. UGT2B7 also impacts oxycodone metabolism. Li et al. reported superior pain relief in oxycontin users with the UGT2B7 802CC genotype compared to 802TT carriers, reinforcing the gene's role in opioid pharmacogenomics [131].

6.11. COMT (Catechol-O-Methyltransferase) Gene

Catechol-O-methyltransferase (COMT) is pivotal in pain management by metabolizing catecholamines—dopamine, norepinephrine, and epinephrine that influence pain perception and analgesic response. Genetic variations in COMT, particularly the single nucleotide polymorphism (SNP) rs4680, are associated with differences in pain sensitivity and opioid requirements among individuals [132–134]. Patients with the COMT rs4680 GG genotype, associated with the higher enzymatic activity of COMT responsible for metabolizing catecholamines such as dopamine, norepinephrine, and epinephrine, generally require higher doses of opioids for effective pain control compared to those with the AA genotype [132,133]. COMT polymorphisms influence not only opioid efficacy but also overall pain experience. Patients with the low-activity AA genotype may exhibit increased pain sensitivity, complicating pain management [135,136]. Conversely, those with the high-activity GG genotype might experience reduced pain responses, risking under-treatment if their higher opioid needs are not addressed [132]. Khan's research highlighted the significance of the COMT rs4680 SNP in predicting responses to tramadol, a commonly used postoperative analgesic, indicating that genetic testing can optimize analgesic selection and dosing [134,137]. Similarly, the RELIEF study demonstrated that genotyping for COMT variants can predict the most effective opioid for individual patients, improving pain control and minimizing side effects [132,138]. Anxiety and fear of pain have been shown to moderate the relationship between COMT genotypes and pain outcomes, particularly in chronic pain conditions like fibromyalgia [139].

6.12. ABCB1 (ATP-Binding Cassette Sub-Family B Member-1) Gene

The ABCB1 gene, or multidrug resistance protein 1 (MDR1), encodes P-glycoprotein, an essential ATP-dependent efflux transporter critical for opioid pharmacokinetics [140–142]. These differential therapeutic responses correlate with P-glycoprotein functional variations, which modulate opioid penetration across the blood-brain barrier, thereby influencing central analgesic effects [143]. Specific genetic variants in the ABCB1 gene associated with increased

susceptibility to opioid-induced respiratory depression include the CT and TT genotypes of the 062rs1045642 (C > T) polymorphism. These variants correlate with adverse reactions to oxycodone, with the T allele associated with a higher incidence of such effects [144,145]. This genotype-phenotype correlation emphasizes the fundamental importance of pharmacogenetic assessment in optimizing individual analgesic protocols while minimizing adverse effect profiles [146,147]. The ABCB1 C3435T polymorphism in perioperative medicine significantly affects postoperative pain and analgesic requirements. TT genotype carriers experience lower pain intensity and require fewer opioids compared to CC genotype individuals, supporting the use of genetic profiling for personalized pain management [148]. Beyond opioids, ABCB1 polymorphisms influence responses to non-steroidal anti-inflammatory drugs and other analgesics, impacting chronic pain management and adjunctive therapies [143,149]. Moreover, ABCB1 genetic variations affect nociceptive processing and opioid dependence pathways, aiding in the development of strategies to reduce dependence risk while optimizing pain relief [5,143].

6.13. SLC6A3 and SLC6A4 (Solute Carrier Family 6 Member 3 and 4) Gene

The SLC6A3 and SLC6A4 genes encode the dopamine and serotonin transporters, respectively, playing crucial roles in nociceptive processing and opioid therapeutic efficacy. SLC6A3 facilitates presynaptic dopamine reuptake and is integral to nociceptive signaling cascades. A study by Qadri et al. [150] demonstrated that specific polymorphic variants in SLC6A3 significantly influence acute nociceptive intensity following traumatic events, such as vehicular collisions, highlighting the direct correlation between dopaminergic transport and nociceptive processing. Similarly, SLC6A4, which encodes the serotonin transporter protein (5-HTT), plays a significant role in modulating both nociceptive processing and the associated emotional responses. By regulating serotonin reuptake from the synaptic cleft, 5-HTT influences the intensity and duration of serotonergic signaling, thereby affecting the transmission of pain signals within the central nervous system. Genetic variations in SLC6A4 can also alter serotonin availability, impacting mood regulation and the emotional perception of pain [151].

6.14. DRD2 (Dopamine Receptor D2) Gene

Dopamine receptor D2 (DRD2) is essential for nociceptive processing and opioid responses. The 957C > T variant significantly influences thermal pain sensitivity, with 957TT homozygotes exhibiting lower thermal detection thresholds, indicating heightened sensitivity [152]. The DRD2 SNP rs6276 also correlates with acute pain intensity, as A/A genotype carriers report lower pain scores than A/G or G/G individuals [150]. In opioid therapy, DRD2 polymorphisms show mixed associations with outcomes. Studies in opioid-dependent patients undergoing methadone maintenance therapy found no significant links between DRD2 variants and pain, withdrawal, or sleep parameters, suggesting potential population-specific effects [153]. Patients with DRD2 variations [150] may benefit from personalized analgesic protocols, including dopaminergic modulators within opioid-sparing regimens [154].

6.15. NLRs (NOD-like Receptors) Gene

Nucleotide-binding oligomerization domain-like receptors (NOD-like) receptors (NLRs), particularly the NLRP3 inflammasome, are key mediators in immune and pain pathways. Activation of the NLRP3 inflammasome in spinal microglial cells triggers the release of pro-inflammatory cytokines like IL-1β, amplifying nociceptive signaling and contributing to neuropathic pain [155]. Cellular stress and injury activate NLRP3, pro-

moting secretion of IL-1β and IL-18, which heighten pain perception and are associated with hyperalgesia, including opioid-induced hyperalgesia [156]. NLRs pathways are integral to the development of opioid tolerance, where prolonged opioid use paradoxically increases pain sensitivity. Prolonged opioid exposure activates NLRs, particularly the NLRP3 inflammasome, leading to the production of pro-inflammatory cytokines that increase pain perception. This inflammatory response mediated by NLR activation may counteract the analgesic effects of opioids. Zare's work highlights these NLR pathways as potential therapeutic targets to reduce hyperalgesia and improve opioid efficacy, suggesting that inhibiting NLR activation may improve pain outcomes [156]. Basu et al. identified microRNAs that downregulate NLRP3 expression, suggesting therapeutic potential in neuropathic pain management [157].

6.16. PTGS2 (Prostaglandin-Endoperoxide Synthase 2) Gene

The PTGS2 gene, encoding cyclooxygenase-2 (COX-2), plays a central role in pain perception and inflammation by regulating prostaglandin synthesis [158]. PTGS2 expression increases significantly after surgical interventions, with higher levels correlating with greater reported pain intensity. Genetic polymorphisms in PTGS2, such as rs1799964 and rs5277, influence pain sensitivity and therapeutic outcomes. These variants are linked to enhanced pain sensitivity, particularly in lung cancer survivors, and affect the efficacy of NSAID-based analgesics by modulating PTGS2 expression patterns [159,160]. Therapeutic inhibition of PTGS2 has demonstrated efficacy across various pain conditions. Meloxicam is an example that shows antiallodynic effects in diabetic neuropathy models [161]. PTGS2 is also implicated in complex regional pain syndrome (CRPS), where its expression correlates with inflammation-driven pain amplification [162]. Regulation of PTGS2 involves interactions with transcription factors such as ATF3, a negative regulator during acute inflammation, highlighting potential targets for therapeutic intervention [163].

7. Clinical Applications and Treatment Implications

The genetic variations discussed in this review have significant implications for clinical practice in cancer pain management. Understanding a patient's genetic profile can help predict both analgesic response and the risk of adverse effects, enabling more personalized treatment approaches. For example, patients with the OPRM1 rs1799971 A/A genotype [67,68] typically require lower opioid doses compared to G allele carriers, while those with CYP2D6 poor metabolizer status may need alternative analgesics instead of codeine or tramadol due to reduced drug activation. Genetic testing for COMT rs4680 [134,137] can guide initial opioid dosing, as GG genotype carriers generally require higher doses for effective pain control than AA carriers.

Implementation of genetic screening in clinical practice has shown promising results. Several studies report that genotype-guided therapy leads to better pain control and fewer adverse effects. For instance, the RELIEF study [132,138] demonstrated that selecting between morphine and oxycodone based on the COMT genotype improved pain outcomes. Similarly, screening for ABCB1 polymorphisms [5,143] has helped identify patients at higher risk for opioid-induced respiratory depression, allowing for more careful monitoring and dose adjustment.

However, genetic testing should be considered within the broader context of patient care. Age, organ function, comorbidities, and concurrent medications remain crucial in treatment decisions. The cost-effectiveness and availability of genetic testing must also be considered, though advancing technology continues to make testing more accessible. Integration of genetic information into electronic health records and clinical decision

support systems could facilitate the practical application of pharmacogenetic data in routine cancer pain management.

8. Conclusions

The evidence demonstrates that genetic variants in opioid receptors, drug metabolism enzymes, and pain perception modulators significantly influence analgesic efficacy in cancer patients. The complex interaction between opioid-induced immunosuppression and genetic factors affects both pain control and survival outcomes, highlighting the importance of personalized treatment approaches that consider individual genetic profiles and immune system function.

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Communication

"From Drowning to Treading Water": Adolescents and Young Adults Living with Incurable and Indolent Metastatic Soft Tissue Sarcoma for More than Two Years

Paul R. D'Alessandro [1,*], Caitlin E. Homanick [1], Brittany D. Cooper [1], Katelyn Ferguson [2], Hillary Rutan [1] and Joseph G. Pressey [1,3]

[1] Division of Oncology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA
[2] College of Medicine, University of Kentucky, Lexington, KY 40506, USA
[3] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA
* Correspondence: paul.dalessandro@saskhealthauthority.ca; Tel.: +1-306-844-1277

Simple Summary: This pilot study surveyed a rare cohort of adolescent/young adult (AYA) cancer patients who were living with incurable yet indolent metastatic soft tissue sarcomas. With increasing biological insight and successful use of targeted therapies, it is anticipated that this patient group will experience increasingly prolonged survival. Yet, given the rarity of the patient population, it is unclear how to best capture their experiences. Hence, we conducted a single-center pilot study using standardized symptom measures. We also asked patients to describe their illness experiences in their own words. We have included a medical summary of how they were treated. We anticipate that our research findings will be used to generate a conceptual framework that can be further studied in a larger multi-institutional study. The ultimate goal is to improve the experiences of other similar AYA patients when they interact with their health care teams.

Abstract: Introduction: Adolescent/young adult (AYA) patients with metastatic soft tissue sarcoma (STS) typically face a dismal prognosis. However, a subset of patients with incurable disease lives beyond two years. Due to the rarity of diagnoses and inherent heterogeneity within this population, a paucity of data exists regarding the experiences of AYAs with an indolent course (and how to best capture these experiences). With increasing biological insight and clinical experience, including the use of targeted or immune therapies, it is anticipated that more such patients will experience prolonged survival. Our pilot study aimed to describe the clinical characteristics and illness experiences of AYAs with incurable yet indolent metastatic STS who were living two years after their diagnoses. Our exploratory aim was to generate a conceptual framework that could subsequently be tested in a multi-center study with a larger cohort of patients. Materials and Methods: Patients with metastatic incurable STS, aged 15–39 years at diagnosis, and at least two years from diagnosis, were eligible. Patients were recruited over a two-year period at a quaternary children's hospital with a comprehensive AYA oncology program. Participants completed a demographic form and PROMIS short form questionnaires for seven domains and answered an open-ended question. Responses to open-ended questions were coded independently by two authors and utilized to generate themes. Clinical variables were collected from medical records. Results: Five patients completed questionnaires. Mean age was 29.4 years (18.5–39.8 years) at diagnosis and 34 years (23.2–45.7 years) at study. Three patients were female; two were male; four were White; and one was Black/African American. Diagnoses included *ASPSCR1::TFE3* alveolar soft part sarcoma;

WWTR1::CAMTA1 epithelioid hemangioendothelioma; INI-1 deficient epithelioid sarcoma; *EWSR1::NR4A3* extra-skeletal myxoid chondrosarcoma; and low-grade *ARHGAP23::FER* spindle cell malignancy, a novel fusion-driven sarcoma. Mean time since diagnosis was 4.5 years (2.6–6 years), and mean treatment duration was 4.2 years (1.5–6 years). On average, patients received 4.8 lines (range 2–8 lines) of antineoplastic therapy. All patients received at least one targeted therapy or immune checkpoint inhibitor. Patients reported increased fatigue and anxiety and decreased physical function compared to the standardized US reference population. Themes emerging from qualitative responses included managing physical symptoms, navigating feelings of guilt and inadequacy, self-reflection generating gratitude, and changing illness experiences over time. Conclusions: AYA patients living with incurable metastatic soft tissue sarcoma for more than two years were treated with multiple lines of antineoplastic therapy longitudinally. PROMIS data identified fatigue, anxiety, and decreased physical function within this population. Exploratory thematic analysis of qualitative responses generated concepts that could be further tested in an expanded cohort of patients.

Keywords: adolescents and young adults (AYA); oncology; psycho-oncology; sarcoma

1. Introduction

Approximately 89,000 adolescents and young adults aged 15–39 years (AYAs) in the United States and 900,000 AYAs worldwide are diagnosed with cancer annually [1,2]. AYAs represent a distinct population with unique care needs [1]. In particular, AYAs with metastatic soft tissue sarcoma (STS) typically face a dismal prognosis, with a median overall survival of 12–18 months [3,4]. While <20% of patients are alive at 2 years, long-term survival beyond 5 years (with or without disease present) is documented in 5–9% of patients [3,4].

Due to the rarity of diagnoses and heterogeneity within this population, a paucity of data exists regarding the illness experiences of AYAs with an indolent course. Additionally, because these patients are so few and unique, it is unclear how to best capture their experiences. These patients typically receive multiple lines of antineoplastic treatment, including precision-based therapies (i.e., targeted agents, immune checkpoint inhibitors) [3]. These therapies can have a delayed onset of action and prolonged antineoplastic effect after discontinuation, leading to clinical benefit for months to years [5–14]. Although patients are classified as long-term 'survivors', many are likely living with incurable metastatic disease [3]. Patient-reported outcome measures, mixed-methods research, and qualitative data have been utilized to describe the experiences of AYAs with sarcomas and other rare cancers [15,16]. However, robust measurement of the quality of life in patients with STS remains challenging due to the heterogeneity of diagnoses, subtypes, treatments, and prognoses [16,17]. Specifically, the experiences of STS patients who have a more indolent course may not be captured by existing measures. Most of these measures focus either on patients who are on active treatment for STS with acute symptoms or those who are off treatment in longitudinal surveillance programs focused on monitoring for recurrence or late effects [16,17]. A qualitative study of AYAs living with uncertain or poor cancer prognoses (UPCP) identified fluctuating needs related to physical and cognitive symptoms and psychosocial concerns over time [18]. AYAs with UPCP also described grief over their inability to achieve normative life milestones and anxiety related to future disease progression [18]. However, this study mostly included AYAs with low-grade glioma and a

smaller proportion of patients with sarcoma (without identifying STS subtypes). Moreover, it did not isolate patients who had been living with UPCP for a prolonged time. There have been no published studies to date that have exclusively focused on patients living with incurable metastatic STS more than two years from diagnosis.

The primary aim of this pilot study was to characterize the experiences of patients (AYAs aged 15–39 years at diagnosis) living with incurable and indolent metastatic soft-tissue sarcoma for more than two years, utilizing patient-reported outcome measures and a qualitative open-ended question. Given the rarity and uniqueness of this patient population, the additional exploratory aim was to generate a preliminary conceptual framework regarding those illness experiences that could be tested in an expanded cohort of patients in a multi-center study.

2. Materials and Methods

Patients were recruited at a quaternary care children's hospital with a comprehensive AYA oncology program. Recruitment lasted two years, from 31 January 2023 to 17 January 2025. All patients were enrolled at the onset of the study between 8 February 2023 and 12 May 2023. Patients aged 15–39 years at diagnosis who were living with incurable metastatic soft-tissue sarcoma for more than two years were eligible. Patients who were not fluent in English, and those with secondary neoplasms were excluded. Institutional outpatient clinic schedules were screened weekly, with eligible AYAs recruited during hospital visits. After obtaining informed consent, participants completed one in-person study visit that included a questionnaire and a demographic form. The questionnaire included patient-reported outcome measure information system (PROMIS) short-form questionnaires for seven domains and an open-ended question. Patient demographics and clinical variables were collected via medical record review.

2.1. PROMIS Measures

Patients completed quantitative PROMIS short-form questionnaires for seven domains. Domains were selected a priori following a literature review based on their strong psychometric properties and previous use in AYA sarcoma patients [19–22]. These included: Pain Interference Short Form 6a; Fatigue Short Form 7a; Physical Function Short Form 8a; Ability to Participate in Social Roles and Activities Short Form 6a; Emotional Distress Anxiety Short Form 7a; Sleep Disturbance Short Form; and Depression Short Form 6a.

2.2. Demographic and Clinical Information

Patient and clinical variables (age, sex assigned at birth, diagnosis, dates of diagnosis and treatments, active treatment status at time of study, and therapies received) were collected from medical records using a standardized data extraction form. Patient-reported variables (gender identity, sexual orientation, race, ethnicity, relationship status, parental status, education, employment, income, and insurance status) were obtained via a demographic form.

2.3. Analyses

PROMIS questionnaires were scored using standardized rubrics (US reference population normalized to T-score 50 ± 10). (https://www.healthmeasures.net/, first accessed on 1 August 2022). The proportion of patients with T-scores outside the reference range, indicating greater or less symptomatology, was reported for each domain. To supplement quantitative data, an open-ended question was asked: "Please describe your experience living with cancer. You may share any thoughts or feelings that you determine to be relevant". Qualitative responses were transcribed and summarized by the first author (P.R.D.). Two authors (P.R.D. and C.E.H.)

independently reviewed the responses to identify representative statements/quotations and generate keywords and codes. P.R.D. and C.E.H. reviewed the independently generated keywords and codes, resolved discrepancies through discussion, and generated themes that were incorporated into a preliminary conceptual framework. This process followed the inductive thematic analysis outline described by Naeem et al. 2023 [23,24].

3. Results

3.1. Patient Characteristics and Clinical Variables

Five patients were eligible, invited to participate, and completed questionnaires. Mean age was 29.4 years (18.5–39.8 years) at diagnosis and 34 years (23.2–45.7 years) at time of study. Three patients were female; two were male; four were White; and one was Black/African American. Diagnoses included low-grade *ARHGAP23::FER* spindle cell malignancy, a novel fusion-driven sarcoma [25]; *ASPSCR1::TFE3* alveolar soft part sarcoma (ASPS); INI-1 deficient epithelioid sarcoma (ES); *EWSR1::NR4A3* extra-skeletal myxoid chondrosarcoma (EMC); and *WWTR1::CAMTA1* epithelioid hemangioendothelioma (EHE).

Mean time since diagnosis was 4.5 years (2.6–6 years), and mean treatment duration was 4.2 years (range 1.5–6 years). Four patients were receiving therapy at the time of the study. On average, patients received 4.8 lines (range 2–8 lines) of antineoplastic therapy over 4.2 years (range 1.5–6 years). All patients received at least one targeted therapy or immune checkpoint inhibitor, monotherapy, or in combination. Four patients received multiple kinase or tyrosine kinase inhibitors, including pazopanib (n = 4); sunitinib (n = 2); axitinib (n = 2); and cabozantanib (n = 1). Two patients received conventional cytotoxic chemotherapy. The patient with low-grade *ARHGAP23::FER* spindle cell malignancy initially received two cycles of methotrexate and vinorelbine and was switched to lorlatinib (an ALK/ROS/FER inhibitor) once the actionable fusion was identified. The patient with INI-1-deficient epithelioid sarcoma received palliative liposomal doxorubicin as an eighth line of therapy after multiple unacceptable toxicities and disease progression events. Three patients received radiation therapy. Notably, the patient with EHE was enrolled in a clinical trial and received FLASH proton therapy for upper extremity bone pain [26]. In addition to targeted therapy, the patient with extra-skeletal myxoid chondrosarcoma underwent palliative below-knee amputation for burdensome disease as well as pulmonary metastatectomy (Table 1, Figure 1).

Table 1. Patient characteristics and clinical variables.

Patient Characteristics	n (%)
Age at diagnosis, years, mean (range)	29.5 (18.5–39.8)
Age at time of survey, years, mean (range)	34.0 (23.2–45.7)
Sex	
Male	2 (40)
Female	3 (60)
Race	
White	4 (80)
Black	1 (20)
Ethnicity	
Non-Hispanic	5 (100)
Sexual Orientation [a]	
Heterosexual	4 (100)

Table 1. *Cont.*

Patient Characteristics	**n (%)**
Relationship Status [a]	
Single	1 (25)
In a Relationship	3 (75)
Parental Status	
More than one child	3 (60)
No children	2 (40)
Highest Level of Education Completed	
High School	2 (40)
College/Vocational	1 (20)
Graduate/Doctoral Degree	2 (40)
Education Status, current	
Full-Time Student	1 (20)
Part-Time Student	1 (20)
Not Currently in School	3 (60)
Employment Status, current	
Full-Time Work (≥40 h per week)	1 (20)
Part-Time Work (<40 h per week)	1 (20)
Employed, but Not Working	1 (20)
Not Currently Employed	2 (40)
Self-Reported Income Quintile	
1st Quintile (<$27,000 USD)	1 (20)
2nd Quintile ($27,000–$51,999 USD)	1 (20)
3rd Quintile ($52,000–$84,999 USD)	1 (20)
4th Quintile ($85,000–$140,000 USD)	2 (40)
5th Quintile (>$140,000 USD)	0 (0)
Insurance Status	
Private	4 (80)
Public, including Medicaid	1 (20)
Uninsured	0 (0)
Treatment Characteristics	**n (%)**
Time since diagnosis, years, mean (range)	4.5 (2.6–6)
Active treatment duration, years, mean (range)	4.2 (1.5–6)
On active treatment	4 (80)
Incisional or excisional biopsy	5 (100)
Number of lines of therapy, mean (range) [b]	4.8 (2–8)
Conventional chemotherapy	2 (40)
Surgery	1 (20)
Radiation therapy, photon or proton	3 (60)
Targeted therapy and/or immune checkpoint inhibitor	5 (100)
Enrollment in clinical trial	1 (20)

[a] n = 1 missing; [b] including conventional chemotherapy, surgery, radiation therapy, targeted therapy, and immune checkpoint inhibitors, excluding biopsy.

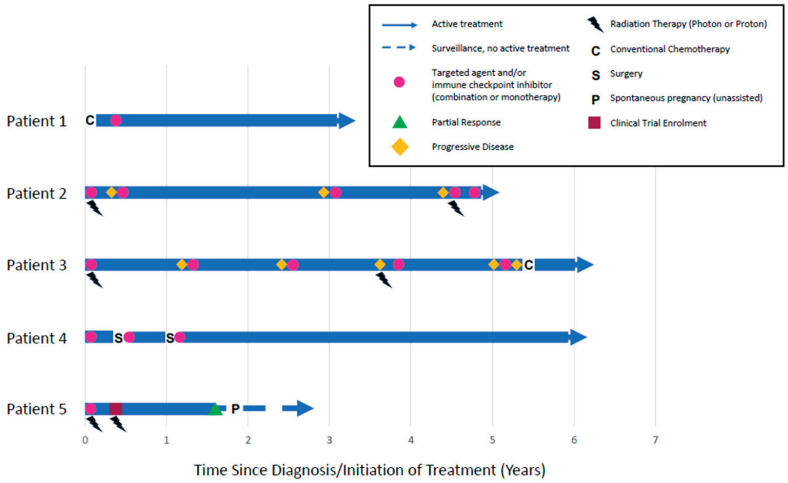

Figure 1. Swimmer plot describing the treatments for five patients living with incurable metastatic soft tissue sarcoma for more than two years. Diagnoses included low-grade *ARHGAP23::FER* spindle cell malignancy (Patient 1); *ASPSCR1::TFE3* alveolar soft part sarcoma (Patient 2); INI-1 deficient epithelioid sarcoma (Patient 3); *EWSR1::NR4A3* extra-skeletal myxoid chondrosarcoma (Patient 4); and *WWTR1::CAMTA1* epithelioid hemangioendothelioma (Patient 5). Mean time since diagnosis was 4.5 years (range 2.6–6 years), and mean treatment duration was 4.2 years (range 1.5–6 years). On average, patients received 4.8 lines (range 2–8 lines) of antineoplastic therapy over 4.2 years (range 1.5–6 years). All patients received at least one targeted therapy or immune checkpoint inhibitor.

3.2. T-Scores for PROMIS Measures

The T-scores for all patients and for all measures are summarized in Table 2. Patient 1, with *ARHGAP23::FER* malignancy, reported above-average functioning in terms of fatigue, physical functioning, and participation in social roles and activities. Patient 2, with ASPS, reported no symptoms outside of the U.S. adult reference normative ranges. Patient 3, with ES, reported increased pain and fatigue, decreased physical function, and greater sleep interference. Patient 4, with EMC, reported increased fatigue, anxiety, and depression, and decreased physical function and participation in social roles and activities. Patient 5, with EHE, reported increased anxiety.

Table 2. T-scores for PROMIS Measures. PROMIS measure T-score results for each patient and each domain are summarized. Questionnaires were scored using standardized rubrics (US reference population normalized to T-score 50 ± 10, https://www.healthmeasures.net/), first accessed on 1 August 2022). T-scores > 60 were considered having greater or worse symptomatology compared to the general US adult population, except for physical function and ability to participate in social roles and activities, which were scored in reverse (indicated in red). T-scores < 40 were considered as having lesser or improved symptomatology compared to the general US adult population, except for physical function and ability to participate in social roles and activities, which were scored in reverse (indicated in green).

	Pain T-Score	Fatigue T-Score	Physical Function T-Score	Social Participation T-Score	Anxiety T-Score	Sleep T-Score	Depression T-Score
Patient 1	52	**36.9**	**61.3**	**65**	52.6	41.7	38.4
Patient 2	58.2	57.8	41.9	51.9	49.9	50.4	59.3
Patient 3	**66.7**	**64.8**	**38.9**	41.6	55.1	**66.4**	48.3
Patient 4	50.7	**67.8**	**35.5**	**37.2**	**63.8**	56.8	**60.5**
Patient 5	54.5	55.1	43	45.6	**66.4**	50.4	53.2

3.3. Qualitative Responses

Two authors (P.R.D. and C.E.H.) independently reviewed the quotations to generate keywords and codes. P.R.D. generated 7 codes, and C.E.H. generated 8 codes. Agreement/overlap was reached for 12 of 15 codes (80%). Identified discrepancies (3/15 or 20% of codes) were resolved with discussion and consultation with the original data source. From these codes, four overarching themes were identified by both authors: managing physical symptoms related to disease and/or treatment side effects; navigating feelings of guilt and inadequacy; changing illness experience over time; and self-reflection generating gratitude. Themes, codes, and representative statements/quotations are summarized in Table 3. A concept map was then generated that included themes, codes, and keywords. As a final exploratory exercise, PROMIS measures that overlapped with the themes generated from the coding analysis were added into the concept map at the level of codes or keywords. For instance, pain, fatigue, and decreased physical function overlapped with "managing physical symptoms related to disease or treatment side-effects". Additionally, anxiety and participation in social roles and activities overlapped with "navigating feelings of guilt and inadequacy" under the grief/worry and social comparison codes, respectively (Figure 2).

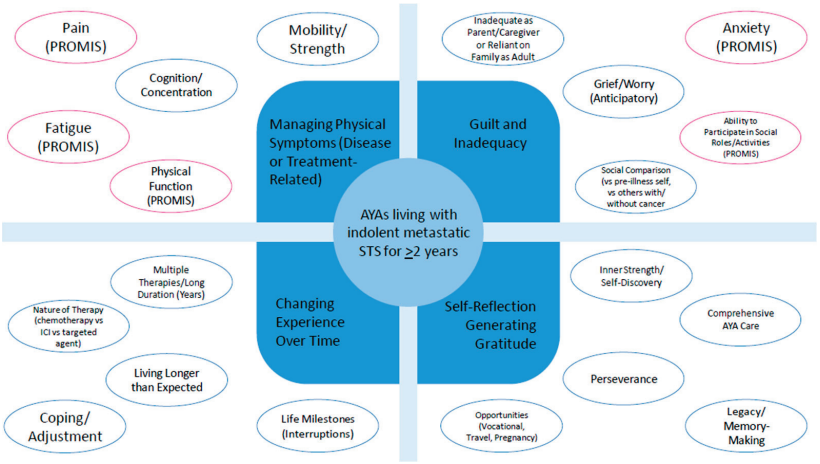

Figure 2. Concept map. An exploratory thematic analysis was conducted in order to generate themes that could be studied in a multi-center expansion cohort with a larger sample of patients. Four main themes were identified, with surrounding illustrative codes and keywords. PROMIS measures that overlapped with the codes or keywords were also inserted into the conceptual framework.

Table 3. Preliminary thematic analysis of responses to open-ended question, including codes and illustrative quotations/statements.

Theme	Code	Illustrative Quotations/Statements
Managing physical symptoms related to disease/treatment side effects	Disease-related symptoms	"I was constantly tired, in pain. I am upset because my mobility and my strength in my arm [are] very bad. [I experience] exhaustion. . ."
		"[Around the time of diagnosis], I lost my ability to walk. . .adjusting to my reduced mobility".
	Treatment-related side effects	"My main problem is the fatigue. My medicine affects how I feel, but I am usually tired. It clouds my thoughts and my words. A lot of times, I can't remember what I want to say mid-sentence. . ."

Table 3. *Cont.*

Theme	Code	Illustrative Quotations/Statements
Navigating feelings of guilt and inadequacy	Guilt	"I felt very down. . . I can't always get down on the floor and play with my children. . .I sometimes feel like I'm a bad mom". "I was shocked that I couldn't handle [my usual] tasks and responsibilities. . . my family was a great help in picking up the slack".
	Grief/worry (anticipatory)	"I do fear [for my family members] when we lose control of the disease. . .It's really tough to remember all the plans we had for our future". "I worry about being able to play [with my children] when they get older".
	Social comparison	"I miss working and being social at the same level as before. I try not to have a 'victim' mindset, but I do compare myself up against "normal" people without cancer or [to] others' cancer journeys. . . Several people I've seen on social media are like "woe is me".
Changing illness experience over time	Long treatment duration	"It's really still kind of crazy, even after almost 6 years. There are times when I forget that I have cancer. . .I never thought I'd live so long and feel ok".
	Changes to experience	"Personal experience can change over time. It was overwhelming at first; [and this feeling] continued for another year or two. . . After about 2.5–3 years of treatment, things stopped being overwhelming. Instead of feeling like I was . . . drowning, I [began to feel like I was] treading water and trying to stay afloat".
Self-reflection generating gratitude	Perseverance (inner strength)	"Cancer has shown me how far past my limits I can push myself. . . Real pain, real love, real discipline, real courage. Not just in me, but in others. . . especially the children I have met [at the children's hospital]. And my doctors. Champions all".
	Comprehensive AYA care (locus of care)	"I am grateful for my team here. I'm not sure I would be doing as well if I were somewhere else".
	Opportunities	"I also wanted more kids and didn't know if that was going to be possible". I try to take advantage of the good days. . . We. . . have been travelling. Recovery from travelling is tough, but the memories are worth it".

4. Discussion

The present study described a cohort of AYA patients living with indolent metastatic soft tissue sarcomas (STS) for at least two years. STS are a group of rare and heterogeneous tumors with more than 70 different histological subtypes, accounting for approximately 8% of AYA cancers [17,27]. Although prognosis for patients with metastatic STS is dismal, a subset of AYAs is alive beyond two years from diagnosis [4]. Despite a two-year recruitment period at a high volume center (approximately 100 new AYA diagnosis per year), only five patients were eligible. All were recruited at the start of the study period. No additional patients reached eligibility criteria of living for two years from diagnosis despite the two-year recruitment period. These data speak to the rarity and uniqueness of this subset of patients. In order to generate more robust and meaningful data, a larger multi-center study

will be required in order to recruit more patients. We present our preliminary data at this juncture with an iterative aim to generate concepts and hypotheses that could be further explored in a future collaborative study.

Each AYA patient in our cohort had a different histologic subtype of STS. In larger series, characteristics associated with long-term survival from diagnosis of metastatic STS included female gender; primary tumors < 5 cm; simple genetic alterations; and certain histologic subtypes, including EHE and low-grade tumors [3,4]. Some patients in our cohort exhibited better prognostic features, including three females; a patient with EHE; and a patient with low-grade spindle cell malignancy with a novel targetable fusion.

Our patients' treatments, with multiple lines of therapy over many years, were reflective of previously published literature. In a series of patients with STS who were alive five years after the diagnoses of metastases, 46% of patients were treated with five or more lines of treatment, and 20% of patients received eight or more lines of treatment, typically involving clinical trial enrollment [4]. Clinical trial enrollment has been associated with prolonged progression-free survival [12].

Molecular profiling of all but one tumor in our cohort was utilized to confirm the diagnosis and tailor therapeutic decisions. Consensus guidelines advise clinicians to test tumor tissue for specific genetic alterations and molecular fusions upfront or at relapse in STS patients with surgically unresectable or metastatic disease to identify targetable alteration(s) [8]. Such therapies can have a delayed onset of action and/or prolonged antineoplastic effect after discontinuation, leading to clinical benefit for months to years [5–14]. Some agents have been utilized as chronic maintenance therapy [5].

One patient in our cohort had treatment interrupted to facilitate a spontaneous pregnancy with healthy live birth at term (Figure 1). Despite persistent metastatic disease, she has now successfully carried a subsequent pregnancy to term. Women with metastatic cancer rarely consider pregnancy or parenthood because of uncertain life expectancy, fear of cancer progression, incompatible treatments, or uncertainty regarding the effects of cancer treatments on the fetus [4]. A case series described four women with metastatic, unresectable STS who started and carried first pregnancies while living with indolent disease [4]. Each patient was at least four years from diagnosis with good functional status. Two pregnancies were facilitated with in vitro fertilization. All women stopped systemic cancer treatment during pregnancy. Three women had documented disease progression during treatment interruption, but all had tumor control re-established after reintroduction of chemotherapy following pregnancy. All four patients were long-term survivors (20 months to two decades) [4]. These data highlight the possibility of treatment interruptions to facilitate pregnancy in highly selected subsets of female patients with metastatic STS.

PROMIS measures allowed comparison of each patient to a reference population to gauge symptom burden. Patients reported increased pain, fatigue, sleep interference, and anxiety, with decreased physical function and social participation. Pain, fatigue, and decreased physical function are commonly reported in patients with STS, regardless of diagnosis or treatment modality/duration, due to tumor location (i.e., often localized to an extremity) [17]. Anxiety is also a symptom that has been well described by other AYAs with UPCP. This anxiety is multifactorial, begotten by isolation, loneliness, and fear [18]. Patients describe fear—for self and for loved ones—related to future disease progression [18]. Of note, Patient 1 (with *ARHGAP23::FER* malignancy) achieved disease control with an oral targeted agent. This patient reported above-average function compared to the adult U.S. reference population in three measures (pain, physical function, and social participation, Table 2). As described above, such therapies may represent novel treatment strategies for

patients with STS and have been associated with long-term clinical benefit, particularly when used as chronic maintenance therapy [5]. Although all measures were endorsed by at least one patient, no measure was endorsed by more than two patients within the cohort. Though this may represent heterogeneity within the cohort, it is also possible that PROMIS measures were inadequate to capture the patients' illness experiences.

Responses to the open-ended question overlapped with some PROMIS domains but also revealed concepts that were not captured in the quantitative measures (Table 3). Common themes included: managing physical symptoms related to disease and/or treatment side effects; navigating feelings of guilt and inadequacy; changing illness experience over time; and self-reflection generating gratitude. Physical symptoms and treatment-related side effects included pain, strength/mobility, and fatigue. Additional cognitive symptoms related to medications were also reported. Patients' guilt and inadequacy not only related to their physical symptoms but were contextualized within their perceived self-image as AYAs. Some patients were parents/caregivers themselves and felt guilty that their own physical limitations prevented them from fully caring for their children (i.e., "I felt like a bad mom"). Other patients, diagnosed at a time when they sought more independence, felt "shocked" that they had to rely on their parents or family members for physical support. This inadequacy also extended to social comparisons, including comparisons to their pre-illness selves, other patients living with cancer, and other people who were not living with cancer (via social media). Patients described fluctuating illness experiences over time. One patient reported that they "never thought [they] would live so long", at times, "forget [ting] that they had cancer". Another patient likened their illness experience to "drowning" at the time of diagnosis and "treading water. . . to. . . stay afloat" several years later. Changing needs related to physical symptoms (i.e., disease or treatment-related side effects) and psychosocial concerns (i.e., persistent worry about disease progression or ongoing mortality confrontation) have been described in AYAs with STS and/or UPCP [18]. However, our cohort of patients described distinct mindset shifts after two years, characterized by adjustment and acceptance. This finding is particularly novel, as no studies to date have specifically described AYAs living with incurable, metastatic STS for such a long duration.

Lastly, patients reported that their long illness duration gave them perspective and time to reflect. These reflections manifested as both internal self-discoveries as well as external expressions of gratitude for opportunities that they did not expect to have (including personal and vocational goals). Although some AYAs with UPCP experience grief over their inability to achieve normative life milestones, others describe feelings of urgency to prioritize enjoyable activities (i.e., travel) or life goals [18]. Patients who reframe their situation to maximize "time they have left" often feel gratitude for that time [18]. For our patients, the "time they [had] left" was longer than they expected, which may have been a driving factor for these perceptions.

Our patients also extended gratitude to their multidisciplinary health care team, suggesting that they perceived benefit to receiving comprehensive care at a center with sarcoma and AYA expertise. One patient reflected: "Cancer has shown me how far past my limits I can push myself. . . Real pain, real love, real discipline, real courage. Not just in me, but in others. . . especially the children I have met [at the children's hospital]. And my doctors. Champions all". This patient cited their specific environment (surrounded by much younger pediatric cancer patients who were going through similar experiences) as particularly motivating and inspiring. Embedding AYA care within pediatric hospitals (i.e., treating AYAs with pediatric protocols at pediatric loci of care compared to pediatric protocols at adult loci of care) has been associated with improved survival outcomes for AYAs with leukemia at Canadian centers [28]. It is suggested that superior outcomes may relate

to expanded supportive care that AYAs receive within a comprehensive pediatric/AYA program [28]. It is possible that comprehensive supportive care designed to meet AYA needs at such unique loci of care also influences patient-reported illness experiences.

Although full qualitative analysis is beyond the scope of our preliminary study, these phenomena could be elucidated in further work that is expanded to other sites. Given the anticipated small sample size at individual sites, it is likely that several sites of comparable size would be needed for collaboration. The most feasible methods may be purely qualitative (i.e., interviews) conducted centrally via a study team at a single institution. In this instance, virtual participation may be needed.

Limitations

This study was limited by a small cohort of patients with inherently rare, heterogeneous STS. Two patients died after participation, limiting the ability to revise informed consent for study measures or conduct follow-up research with this cohort. Results may not be generalizable to larger AYA populations or other patients with STS. This study was not adequately powered to assess for differences in patient-reported outcomes based on clinical variables. Finally, this study was not designed to assess patients across multiple time points. Additional work is needed to understand the trajectory of symptoms and concerns in this population over time.

5. Conclusions

Despite a two-year recruitment period at a quaternary center, only five AYA patients living with incurable metastatic soft tissue sarcoma for more than two years were identified. Patients were treated with multiple lines of antineoplastic therapy longitudinally, including targeted agents and immune checkpoint inhibitors. Via PROMIS measures, patients reported increased pain, fatigue, and anxiety, with decreased physical function and ability to participate in social roles and activities. Exploratory thematic analysis of qualitative data identified additional common illness experiences, including feelings of guilt and inadequacy; distinct shifts in experiences over time; and self-reflection generating gratitude. These data can serve as the foundations for a larger, multi-center study with the aim of capturing the experiences and needs of this rare and unique subset of patients.

Author Contributions: P.R.D. and J.G.P. conceived and designed the study. P.R.D., B.D.C., C.E.H. and H.R. collected and curated the data. P.R.D. and C.E.H. analyzed and interpreted the data. P.R.D. drafted the manuscript. All authors (P.R.D., B.D.C., K.F., C.E.H., H.R. and J.G.P.) reviewed the manuscript critically. All authors agree to be accountable for all aspects of the work. We confirm that neither the manuscript nor any parts of its content are currently under consideration for publication with or published in another journal. All authors have read and agreed to the published version of the manuscript.

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