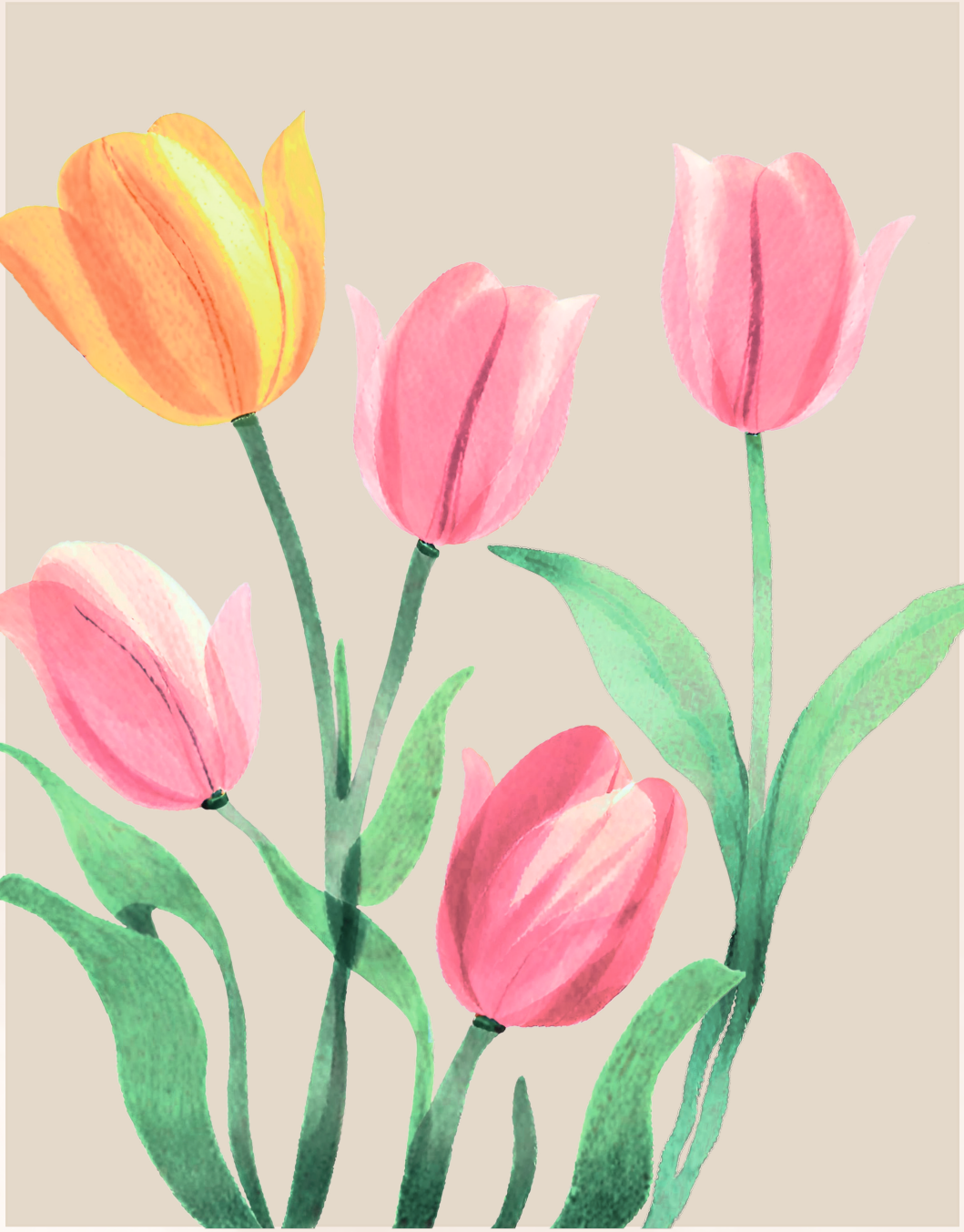
RARE VERSUS COMMON CANCERS IN THE NETHERLANDS



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Rare versus common cancers in the Netherlands

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TABLE OF CONTENTS

CHAPTER 1

General introduction

The shared challenges experienced by patients with a rare cancer and their healthcare professionals are evident: progress in diagnosis, treatment, and research in rare cancers lags behind that of common cancers. Yet, to further explore differences within the rare cancers group, and between patients with a rare cancer and patients with a common cancer, this thesis presents the epidemiological and psycho-oncological challenges faced within the field of rare cancers. Moreover, it provides valuable insights into differences between rare and common cancers regarding their epidemiology, psycho-oncology, and healthcare organisation.

EPIDEMIOLOGICAL OVERVIEW

What are rare cancers?

Rare cancers are a heterogeneous group of malignant tumours, defined as those with an annual incidence of less than 6 per 100,000 people according to the definition set by the Surveillance of Rare Cancers in Europe (RARECARE) consortium [1]. Despite being rare and less well-known compared to common cancer types, e.g., breast, lung, prostate, colorectal, and skin cancer, they make up a large proportion of the cancer burden and collectively account for more than any of the common cancer types alone. Although rare cancers belong to both groups of cancers and rare diseases, the definition of rare cancers differs from that of rare diseases: while rare diseases, due to their mostly chronic course, can be adequately described based on their prevalence, the more acute course of rare cancers requires a definition based on incidence.

Classification of rare cancers

The RARECARE consortium has provided a list of cancers based on topography and morphology codes in line with the International Classification of Disease for Oncology third edition (ICD-O-3) [2, 3]. This cancer list with 260 cancer types is organised into three tiers, namely:

• Tier 1: General categories of tumours which are similar in terms of healthcare organisation (i.e., same clinical expertise and patient referral structure) (e.g., epithelial tumours of nasal cavity and sinuses).

• Tier 2: Categories of tumours which are similar in terms of clinical decision making and research (e.g., squamous cell carcinoma with variants of nasal cavity and sinuses).

• Tier 3: WHO classification of individual cancer entities and corresponding ICD-O-3 topography and morphology codes.

The RARECARE definition is based upon Tier 2 entities [1]. In agreement with this, the European Reference Network for Rare Adult Solid Cancers (EURACAN) has classified rare adult solid cancers into 10 *domains*: head and neck cancer, digestive cancer, thoracic cancer, female genital cancer, male genital and urogenital cancer, skin cancers and non-cutaneous melanoma, sarcomas, neuroendocrine tumours, cancers of the endocrine organs, and cancers of the central nervous system [4].

The Joint Action on Rare Cancers (JARC) has proposed a new classification of rare cancers into *families*, comparable to the EURACAN domains [5]. The JARC families are defined upon Tier 1 entities, assuming that these families follow similar patient referral patterns and are treated by the same disease-based communities of healthcare providers. Although both RARECARE and JARC maintain the set threshold of less than 6 cases per 100,000 people per year, the JARC classification results in less cancers being classified as rare compared to RARECARE (i.e., 13% versus 22% of all cancer diagnoses, respectively) [1].

Cancer epidemiology in Europe and the Netherlands

In Europe, nearly 4.4 million new cancer cases were diagnosed in 2020 as reported by the International Agency for Research on Cancer [6]. Of those, 24% was represented by rare cancers [7], and more than 5.1 million people in Europe are currently living with a diagnosis of rare cancer [8]. Moreover, the 5-year survival rates for rare cancers are worse compared with common cancers (49% and 63%, respectively) [7]. In the Netherlands, where approximately 124,000 individuals were diagnosed with cancer in 2021 [9], similar epidemiological results were found. In a previous Dutch report on rare cancers, it was shown that one out of five cancer patients are diagnosed with a solid rare cancer, accounting for more than 20,000 rare cancer diagnoses annually [10]. Moreover, more than 100,000 Dutch people are currently living with the consequences of a rare cancer diagnosis. Out of the 260 cancer types represented in the RARECARE cancer list, 223 (86%) are rare according to the definition. In addition, the improvements in survival for rare cancers are lagging behind compared with those for common cancers: during the period 1995 to 2016, 5-year survival for rare cancers improved by 6% (from 50% to 56%) versus an improvement of 13% for common cancers (from 59% to 72%) (Figure 1). [10] Yet, an extensive overview of epidemiological measurements and outcomes for all rare cancers versus common cancers has not been given before.

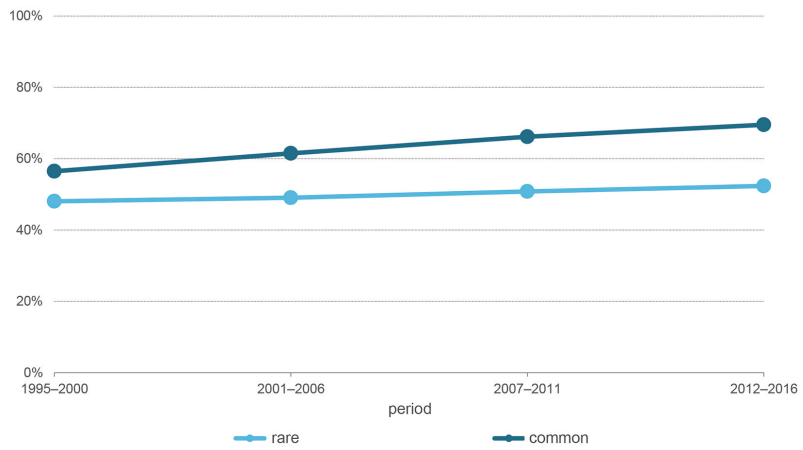

Figure 1. 5-year survival for rare versus common cancers [10]

Increasing burden and epidemiological challenges of rare cancers

The survival gap between rare and common cancers stresses the urgency to improve outcomes for patients with a rare cancer. A recent trend report published by the Netherlands Comprehensive Cancer Organisation (IKNL) showed that the overall cancer incidence and prevalence will increase considerably in the Netherlands, with an expected rise to 156,000 new cancer diagnoses per year and 1.4 million people living with or after cancer in 2032 [11]. This increase will result in more people having to deal with the consequences of a cancer diagnosis throughout their disease trajectory. Despite their heterogeneity in terms of cancer type and outcomes, the collective clinical and psychosocial burden of the total group of rare cancers is substantial. Moreover, patients with a rare cancer as well as the rare cancer care organisation share many challenges. For rare cancers, due to the low incidence rates, performing observational studies and clinical trials is often complex and costly. Alongside the logistical hurdles of recruiting a sufficient number of patients, small sample sizes pose difficulties in obtaining statistically powerful results. Further, cancer research grant opportunities are predominantly aimed at common cancers, and rare cancers consequently remain an underfunded field of research. [12] This not only hampers the development of highly needed evidence for rare cancers, but also asks for innovative strategies and international collaboration to overcome these epidemiological challenges. In this thesis, we will focus on the epidemiology of rare versus common cancers, incorporating estimates of incidence, prevalence, survival, and quality of life (QoL), using the nationwide Netherlands Cancer Registry.

PSYCHOSOCIAL FUNCTIONING AND SUPPORT

Psychosocial oncology

A cancer diagnosis not only impacts a person's physical functioning, but also their psychosocial functioning. The diagnosis of a life-threatening disease and its treatment may cause functional loss in behavioural and life domains (e.g., physical, emotional, occupational) and lead to specific psychosocial problems (e.g., distress, fear of recurrence). Consequently, functioning and QoL of a patient with cancer might be diminished, leading to an increased need for psychosocial supportive care throughout all phases of their disease. Efforts have been made to implement psychosocial care into routine oncology care, e.g., by the agenda of the International Psycho-Oncology Society Standard of Quality Cancer Care, stating that quality cancer care must integrate the psychosocial domain and distress screening into routine care [13]. A considerable body of evidence on the effectiveness of psychosocial interventions for patients with cancer and their families throughout the patient journey exists [14-17], and several evidence-based guidelines for psychosocial care have been published worldwide [18-20]. For rare cancers, however, research on the psychosocial impact of a diagnosis on patients and their caregivers is limited, and most psychosocial interventions are developed for patients with a common cancer. Further, despite the growing consensus and evidence that psychosocial care should be an integral part of oncology care, there is still unequal access to psychosocial care in Europe due to a lack of psychosocial resources and financial constraints within the healthcare systems [21]. Particularly for rare cancers, this additional challenge comes on top of the difficulties that those patients are facing during their already complex disease trajectory. However, the impact on their healthcare experiences has not been assessed before, and no comparison with the experiences of those with common cancer has been made.

Quality of life

A cancer diagnosis may have a profound effect on the QoL experienced by patients. QoL can be defined as an individual's perception of their physical, social, mental, and functional well-being [22] and is measured, for example, via generic QoL questionnaires, such as the European Organisation for Research and Treatment of Cancer QoL (EORTC QLQ-C30) questionnaire. For some cancer types, disease-specific questionnaires have been developed, such as the EORTC Breast Cancer-specific QoL questionnaire (QLQ-BR23), but the number of questionnaires specifically for rare cancers is limited. Several disease-related factors can affect a patient's QoL, including the emotional burden of being diagnosed with a life-threatening disease, and problems related to treatment such as physical discomfort, changes in social functioning, and disruptions in daily functioning [23]. Compared to the general population, patients with cancer often experience worse QoL, both on the short- and long-term [24-26]. For example, patients with colorectal

cancer (i.e., a common cancer) reported a decline in physical and functional QoL up to six months after diagnosis [24]. In a previous study in rare cancer survivors, it was shown that this group reported worse psychosocial outcomes (e.g., high levels of distress), including lower QoL, compared to common cancer survivors [27]. However, far less studies have investigated QoL among patients with a rare cancer, and the impact of the specific disease trajectory-related factors on their QoL has not been investigated before.

Healthy life expectancy

As a result of rising cancer incidence and improvements in survival rates, people are now living longer with and after their cancer diagnosis. In general, patients with a rare cancer often receive their diagnosis at a younger age and in a more advanced stage compared to patients with a common cancer. Consequently, they might experience a longer duration of poor health during their remaining lifetime. Since survival is worse for patients with a rare cancer, it is essential for these patients, as for all patients, to live their remaining life as much as possible in a state of relatively good health. Short- and long-term consequences of a cancer diagnosis should be addressed in order to promote a long and healthy life. Healthy life expectancy (HLE) has become a useful indicator for measuring population health [28]. HLE takes into account both QoL and life expectancy, providing insight into the number of remaining years of life spent in good health. Measuring HLE may help interpret the health of one population compared to another, changes in the health of populations, and quantification of health inequalities within populations [29]. Yet, the utility of the HLE measure among cancer survivors of both rare and common cancer types should be investigated further.

Unmet supportive care needs

Patients with a rare cancer face specific challenges during their disease trajectory, particularly during the diagnostic phase. These challenges might lead to specific unmet supportive care needs, which can differ from those experienced by survivors of common cancer. Unmet supportive care needs can be defined as a desire or requirement for support in managing the emotional, physical, and psychological impact of disease [30]. Unmet needs among patients with cancer are diverse and can impact many aspects of their life. For example, in a previous systematic review, patients with cancer reported high unmet needs throughout their disease trajectory with regard to psychological support (e.g., fears about cancer spread), information provision (e.g., being adequately informed about benefits and side effects of treatment), and coping with the physical consequences of the disease (e.g., not being able to do things you used to do) [31]. While these unmet needs were mainly reported by patients with a common cancer (i.e., breast, lung, prostate or skin cancer or mixed cancer diagnoses), the prevalence and broad range of unmet needs in supportive care for all patients with a rare cancer have not been reported before.

Challenges for patients with a rare cancer

The unique challenges for patients with a rare cancer might influence their psychosocial functioning and QoL. The challenges they face include a lack of a clear cancer pathway, disease-specific information and support, and recognition and understanding from their surroundings [32]. Moreover, patients with a rare cancer have less fellow sufferers to share their experiences with, and might have longer travel distances to receive expert care than patients with a common cancer [33, 34]. Consequently, patients with a rare cancer not only report a lower QoL compared to patients with a common cancer, but also experience feelings of insecurity, social isolation, and anxiety [27, 35]. In this thesis, we will focus on the experiences, needs, and QoL of this patient group to give a more comprehensive insight into these unique challenges faced by patients with a rare cancer.

HEALTHCARE ORGANISATION FOR PATIENTS WITH CANCER

Dutch healthcare system

Within the Dutch healthcare system, the cancer patient pathway usually starts with a visit to a general practitioner, who plays a crucial role as gatekeeper to specialised medical services. In case the general practitioner suspects cancer, the patient is referred to a hospital for diagnosis, staging, and treatment planning. Treatment is performed by a multidisciplinary team of healthcare professionals, and, in case of curative treatment, the patient receives regular check-ups afterwards during the follow-up care.

For common cancers, nationwide cancer screening programmes (e.g., for breast and colorectal cancer) have been implemented in the Netherlands, and a general practitioner regularly encounters a patient with a common cancer. However, for rare cancers, obtaining a correct diagnosis might be more challenging, since a Dutch general practitioner encounters approximately three new patients with a rare cancer per year [10]. Consequently, patients with a rare cancer are often confronted with a delayed diagnostic pathway as well as limited treatment options [1, 36, 37]. Moreover, finding expert care for patients with a rare cancer might be more difficult than for patients with a common cancer.

Centralisation of care for rare cancers

While treatment for patients with a common cancer is usually offered in every hospital, patients with a rare cancer might face barriers with access to treatment and care. To receive the best available care, patients with a rare cancer might need referral to a hospital specialized in their rare cancer type for treatment. Within such a centre of expertise, specialised multidisciplinary care, knowledge, and research are centralised

in order to provide comprehensive and high-quality care for patients with a rare cancer. In the Netherlands, developments in the field of rare cancers have been made in recent years with regard to improving the organisation of care for patients with a rare cancer, including networking (e.g., the initiation of the Dutch Rare Cancer Platform, and collaboration among regional and national working groups), introduction of expert panels, and the recognition of centres of expertise by the Dutch Ministry of Health, Welfare and Sport. Nevertheless, in a recent Dutch report from IKNL on the organisation of rare cancer expertise, it was pointed out that further improvements in terms of expert care and networking are needed. Access to high-quality expert care should be guaranteed through care from a centre of expertise or collaboration with a centre of expertise (e.g., treatment partly carried out in a centre of expertise or consulting advice from a centre of expertise and/or national expert panel) [38]. In line with this, reference networks for rare cancers have been implemented in Europe based on the 'hubs-and-spoke model', aiming to improve the management and survival of this patient group [5, 39]. This model might serve as an example of best practice, with close collaboration between reference centres ('hubs'), which provide expert and highly specialised services, and collaborating centres ('spokes'), which ensure the geographical accessibility of cancer care. Promising results have been shown for the French Sarcoma National Reference Network NETSARC+, where no geographical inequalities in survival of patients with sarcoma were found, suggesting that the reference network organisation is able to address the social and spatial inequalities in cancer management [40].

International developments within the field of rare cancers

The current challenges and issues within rare cancer care are present worldwide. Therefore, several international developments and initiatives have focused attention to improve care of rare cancers. For example, the International Rare Cancers Initiative (IRCI) has promoted research and clinical trials for rare cancers [41]. Within Europe, Rare Cancers Europe (RCE) has been initiated as a multi-stakeholder partnership to raise awareness of rare cancers, and to put rare cancers on the European policy agenda [42]. RCE has been involved in the launch of JARC, publication of the Rare Cancer Agenda 2030 [43], and establishment of European Reference Networks (ERNs) for rare diseases. [39] ERNs are virtual networks of selected, specialised hospitals across Europe, of which three have been dedicated to rare cancers: EURACAN (for adult solid rare cancers), PaedCan (for paediatric cancers), and EuroBloodNet (for rare haematological diseases). The ERNs aim to bring shared knowledge, expertise, care, and innovative and collaborative research from centres of expertise to all patients, regardless of the point of access through, e.g., tele-consultation, advancing research, and producing clinical-based practice guidelines. [39]

Challenges in healthcare organisation for patients with a rare cancer

The challenges within the healthcare organisation affect both the outcomes of and the provision of care for patients with a rare cancer. The survival gap between patients with a rare cancer and patients with a common cancer might be the result of a delayed or wrong diagnosis, due to limited expertise and awareness of rare cancers, leading to inappropriate or delayed treatment. Moreover, patients with a rare cancer are confronted with fewer available treatment options, insufficient access to appropriate clinical expertise, and limited opportunities to participate in clinical trials [1, 36, 37]. Within care of rare cancers, the low number of patients with a rare cancer complicates setting up evidence-based clinical guidelines, ensuring access to high-quality expert care, performing clinical studies, and developing new effective therapies [12, 37]. All these unique challenges for rare cancers impact the outcomes and overall well-being of patients with a rare cancer worldwide, and therefore should be further investigated.

The current disparities between rare and common cancer demonstrate that rare cancers establish a significant public health problem. Therefore, more attention should be devoted to rare cancers. The posed challenges from an epidemiological, psycho-oncological, and healthcare perspective indicate the urgency of accelerating research into rare cancers, especially regarding early diagnosis, developing new therapies, improving psychosocial functioning, and optimising organisation of healthcare. Current and future accomplishments in research into rare cancers will not only benefit patients with a rare cancer, but will also contribute to improvement of healthcare and outcomes for all patients with cancer, both rare and common. In this thesis, this will be further explored to gain a better understanding of the outcomes of patients with a rare cancer and to provide directions for improvements and future research.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to investigate the differences between rare cancers and common cancers, both from an epidemiological and a psycho-oncological perspective. Accordingly, this thesis is subdivided into two parts: Part I, **Chapters 2-5**, focuses on epidemiology, and Part II, **Chapters 6-8**, focuses on psychosocial functioning and support. Both perspectives are intertwined with the healthcare organisation of rare cancers, which will be addressed throughout this thesis.

First, in **Chapter 2**, an epidemiological overview of rare and common solid cancers in adults in the Netherlands is presented. Within this population-based study, incidence, prevalence, and survival rates are provided and trends in survival evaluated for both rare and common cancers, and individual (Tier 2) rare cancer entities within EURACAN domains and JARC families are compared. In **Chapter 3**, expected lifetime and QoL are combined, by describing the proportion of remaining life that survivors with a subset of rare cancers and common cancer spend in good health (i.e., HLE), and the

determinants of poor perceived health in rare cancer survivors. In **Chapter 4**, the difference in QoL between patients with a rare and common cancer is assessed, and the association between disease trajectory-related factors and QoL in patients with a rare cancer is examined.

In **Chapter 5**, a systematic review is described exploring the unmet supportive care needs of patients with a rare cancer during the phases of their disease trajectory, presented per rare cancer subdomain. Furthermore, predictors of these unmet needs are identified. In **Chapter 6.** the differences in healthcare experiences between patients with a rare and common cancer are described regarding diagnosis and treatment in multiple hospitals, hospital choice, medical expertise, second opinions, and travel distance to care. In **Chapter 7**, experiences, needs, and QoL of patients with a rare and common cancer are explored and compared throughout the disease trajectory by conducting a focus group study.

In **Chapter 8,** the General Discussion of the main findings of this thesis is depicted, and implications for practice and future research are provided.

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PART I:
Epidemiological focus

CHAPTER 2

The gap between rare and common cancers still exists: Results from a population-based study in the Netherlands

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European Journal of Cancer 2022; 167: 103-111

ABSTRACT

Introduction: Epidemiological discrepancies exist between rare and common cancers. The aim of this population-based study was to compare rare versus common adult solid cancers in the Netherlands, by providing incidence, prevalence and survival rates, evaluating trends in survival, and comparing individual entities within domains and families.

Methods: All adult patients with malignant solid cancers in the Netherlands between 1995-2019 were identified from the Netherlands Cancer Registry. Data on patient, tumour, and treatment characteristics were collected, and relative survival and survival trends were analysed.

Results: A total of 170,628 patients with rare adult solid cancers and 806,023 patients with common adult solid cancers were included. Rare cancers accounted for 18% of all cancer diagnoses (mean incidence), and 15% of the total ten-year cancer prevalence during 2010-2019. Overall 5-year survival was worse for rare cancers than for common cancers (52.0% vs. 68.7%). Between 1995-1999 and 2015-2019, 5-year survival rates for rare cancers increased to a lesser extent (from 46.2% to 52.6%, i.e., 6.4%) than for common cancers (56.9% to 70.1%, i.e., 13.2%), and for most rare cancer domains compared to common cancer domains. The majority of rare cancer entities did not show an improvement in 5-year survival. Differences for individual entities between domains and families were found.

Conclusion: Differences in survival between rare and common cancers indicate major challenges for rare cancer care and emphasize that improvement is highly needed. Observed inequalities need to be overcome by investing in early diagnosis, novel therapies, scientific research, and in establishing centres of expertise.

INTRODUCTION

In the Netherlands, the incidence of cancer has increased over the past 30 years to an annual number of 124,000 new cases in 2021 [1]. Approximately 25,000 of these new cases are identified as rare cancers [2], and defined as those with an incidence of <6/100,000 people per year, according to the Surveillance of Rare Cancers in Europe (RARECARE) project [3].

Rare cancers (RC) pose challenges within health care for both clinicians and patients [4]. That is, knowledge and expertise are not widely available, and information regarding RC is limited, due to the lack of scientific studies and the small number of patients available for inclusion in these studies. Limited knowledge and expertise may lead to misdiagnosis and delay in diagnosis. Further, the lack of access for patients to appropriate therapies may be a consequence of deficient concentration in healthcare and expertise [5]. Consequently, disease outcomes for patients with RC are worse than for common cancer (CC) patients [3, 6].

Nowadays, more than 5.0 million people with a diagnosis of RC are living in the European Union (EU), as reported by RARECARE and RARECARENet [3, 7]. The RARECARENet project showed that RC represent 24% of all cancers diagnosed in the EU in 2000-2007, and that the 5-year relative survival for RC is 49% compared to 63% for CC [6]. Because of these high incidence rates and adverse outcomes, priority should be given to improving such outcomes and healthcare in general for patients with RC.

In the European Reference Network called EURACAN, established in 2017, adult solid RC entities were grouped into ten 'domains'. In 2020, the Joint Action on Rare Cancers (JARC) published a consensus paper in which RC entities were partitioned into RC 'families' [8], comparable to the EURACAN domains. Yet, while the EURACAN domains correspond to the RARECARENet list, in which RC are defined upon Tier 2 entities (i.e., relevant for clinical decision making and research), JARC families are defined upon Tier 1 entities[1] (i.e., relevant for health care organisation). Potential implications of the adjusted partitioning and whether there will be widespread adherence to the modification still has to be explored. A comparison of RC entities as grouped within the EURACAN domains and within the JARC families is needed as a first step.

So far, no overview has been given over the past 25 years, regarding epidemiological measurements (incidence and prevalence) and outcomes (survival), between adult solid RC and CC in the Netherlands, and a comparison between entities within domains and families has not been made. Therefore, the aim of this study was to present population-based data on the incidence, prevalence and survival for adult solid RC versus CC

1 ICD-O-3 entities are grouped into categories (Tier 2) of cancers, considered to require similar clinical management and research. These categories are further grouped into general categories of tumours (Tier 1), considered to involve the same clinical expertise and patient referral structure.

entities in the Netherlands from 2010 to 2019, to evaluate trends in survival from 1995-1999 to 2015-2019, and to compare individual entities within domains and families.

METHODS

Study population and quality control

Patients in this population-based study were selected from the Netherlands Cancer Registry (NCR). The NCR is a nationwide registry including all newly diagnosed malignant cancer cases within the Netherlands (i.e., 17.4 million inhabitants) [9]. Specially trained registrars routinely collect patient information from medical records in all Dutch hospitals. Data quality is assured due to thorough training of the registrars and systematic consistency checks [10]. The NCR registers topography and morphology codes according to the International Classification of Diseases for Oncology version 3 (ICD-O-3) [11]. The International Agency for Research on Cancer multiple primary coding rules have been applied for reporting data on cancer incidence and survival [12]. Cancer stage is based on the TNM Classification of Malignant Tumours [13-15], and is converted to the Extent of Disease (EoD) [16] classification, distinguishing localised (TNM stage I-II), regional (TNM stage III) and metastatic disease (TNM stage IV).

For the current study, all Dutch patients aged ≥18 years diagnosed with solid malignant tumours during 2010-2019 were selected from the NCR to obtain incidence, prevalence, and survival rates. A 10-year period was chosen to account for fluctuations in incidence over time. In addition, patients diagnosed during 1995-2019 (25-year period) were selected to evaluate survival trends (1995-1999 vs. 2015-2019). Population data and cancer mortality data (i.e., date of death) were accessed by linkage to the Dutch Municipal Personal Records Database.

Systematic data checks were routinely performed, and standard data quality indicators (e.g., percentage of microscopically verified cases, percentage of topography codes not otherwise specified (NOS)) were calculated to assess the quality of the NCR data (Supplementary Table S1).

Cancer list, definition, and classification

In this study, Tier 1 and Tier 2 cancer entities are presented and based on the ICD-O-3 topography and morphology codes in concordance with the updated version (February 2019) of the RARECARENet cancer list [17]. Furthermore, RC are defined as those Tier 2 entities with an annual incidence rate of <6/100.000 according to the RARECARE definition [18], and this definition has been applied to the Dutch situation. The heterogenous group of adult solid RC and CC entities are primarily presented according to the EURACAN domains [19]. Breast cancer has been added as an additional domain,

due to the high incidence of breast cancer in the Netherlands [20], in accordance with the national organisation of cancer care.

In addition to the EURACAN domains, entities within the JARC families are presented as a comparison. Within the JARC families, RC are defined as those Tier 1 entities with an annual incidence rate of <6/100,000 according to the JARC partitioning [8]. In Supplementary Table S2, all estimates of incidence, prevalence and survival for Tier 1 and Tier 2 entities are shown.

Statistical analyses

For this study, patient, tumour and treatment characteristics were described, and differences in characteristics, both within domains and families, were tested using Chi-square tests. Incidence, prevalence, survival (trends) were calculated for both domains and families. Incidence rates of RC and CC were calculated as the annual number of new cases arising in 2010-2019, divided by the total person-years in the general Dutch population (both male and female). Further, the number of prevalent cases in 2019 and the 10-year prevalence per 100,000 at the index date of 1st January 2020 were calculated. Relative 5-year survival was calculated using the Ederer II method [21]. To establish differences in relative survival (RS) by domain for RC and CC, and to evaluate trends in survival by domain, family, and for RC entities, a generalised linear model adjusted for age, sex and year of diagnosis was used. The model assumed that the observed number of deaths were Poisson-distributed and produced the excess risks of death. [22] Trends in survival were evaluated for the Tier 2 RC entities whose survival rates changed significantly over time, and were evaluated by log-rank tests. Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed using STATA (version 14.2, Stator LP, College Station, TX).

RESULTS

Sample characteristics

Between 2010 and 2019, 170,628 newly diagnosed patients with RC and 806,023 with CC (domain categorisation) were registered by the NCR. Patient, tumour and treatment characteristics by domain and family are presented in Table 1.

Table 1. Patient, tumour and treatment characteristics of patients aged ≥18 years, diagnosed with rare and common solid cancer entities in the Netherlands between 2010-2019

	Domains (EURACAN)[a]		**Families (JARC)**[a]	
	Rare cancers (*n* = 170,628)	Common cancers (*n* = 806,023)	Rare cancers (*n* = 118,504)	Common cancers (*n* = 859,002)
Age at diagnosis (median years, IQR)	64 (55-75)	68 (61-77)	65 (54-75)	69 (60-77)
Age at diagnosis (%)				
18-34 years	5.9	0.9	7.1	1.1
35-49 years	11.7	7.0	12.0	7.3
50-64 years	28.5	27.0	28.6	27.0
65-79 years	39.3	46.3	38.0	46.1
>80 years	14.5	18.8	14.3	18.3
Gender (%)				
Male	48.4	52.6	58.4	51.0
Female	51.7	47.4	41.6	49.1
Extent of disease (%)				
Localised	45.2	55.0	45.2	54.5
Regional	17.7	16.0	14.0	16.6
Metastatic	22.7	20.4	21.2	20.8
Unknown	14.4	8.5	19.6	8.1
Treatment[b] (%)				
Surgery (+/- PPT)	58.7	62.2	60.6	61.7
Systemic[c] (+/- RT)	14.9	16.3	12.1	16.5
RT	9.0	4.7	10.5	4.7
Other	2.3	1.8	2.6	1.8
None	15.2	15.1	14.2	15.2
Hospital type[d] (%)				
Academic[e]	41.4	11.4	44.3	12.8
Top clinical[f]	39.5	52.6	37.9	52.0
General	19.0	34.8	17.6	34.0
Other	0.2	1.3	0.2	1.2

IQR, interquartile range; PPT, pre- or posttreatment; RT, radiation therapy
[a] All P < 0.001. Chi-square test.
[b] In case of multiple treatments, treatment is presented in the order of surgery (+/- pre- or posttreatment), systemic therapy (+/- radiotherapy), radiotherapy and other
[c] Systemic treatment includes chemotherapy, targeted therapy, hormonal therapy and immune therapy
[d] Hospital type has been classified according to the Dutch health care system, and cancer care is given in all hospitals
[e] Including all eight academic teaching hospitals, affiliated to universities, and the Antoni van Leeuwenhoek hospital (specialised in oncology)
[f] Top clinical hospitals are non-academic teaching hospitals that provide complex care in addition to basic care

Compared to patients with CC, patients with RC (domain categorisation) were more often diagnosed at a younger age (median 64 years vs. 68 years; *P*<0.001). Most cancers in patients up to 34 years were RC, and CC became increasingly prominent in patients aged 35 and older. Further, RC patients were less often diagnosed with a localized EoD (45.2 vs. 55.0%; *P*<0.001), but more often with an unknown EoD (14.4 vs. 8.5%; *P*<0.001) than CC patients. RC patients were also more often treated in an academic hospital (41.4% vs. 11.4%; *P*<0.001), and received more often radiotherapy (9.0% vs. 4.7%; *P*<0.001) compared to CC patients. Within the families, RC patients were more often male and diagnosed with an unknown EoD compared to RC patients within the domains.

Incidence

In Table 2, incidence, prevalence and survival rates of adult solid RC and CC by domain and family are shown. The crude incidence of all RC (domain categorisation) was 100.7 patients per 100,000 per year (SE 1.2), compared with 475.6 patients per 100,000 per year (SE 10.0) for all CC. Overall, RC accounted for 18% of all adult solid cancers diagnosed in the Netherlands during 2010-2019. RC constituted 63% of incident female genital cancers, and 12% of incident digestive cancers. RC were <10% of incident cancers within other domains (in those domains in which CC were present as well). Within the families, RC accounted for 12% of all cancer diagnoses. In addition, RC entities within the families comprised 11% of incident female genital cancers, and <10% in all other families.

Prevalence

The 10-year prevalence of all adult solid RC (domain categorisation) was 516.5 patients per 100,000 (SE 5.2), compared with 2958.6 patients per 100,000 (SE 27.7) for all adult solid CC. In total, RC were 15% of the total cancer prevalence in the Netherlands during 2010-2019. The prevalence estimates of RC were higher than those of CC for the female genital tract (92.5 per 100.000 vs. 75.7 per 100.000). The prevalence rates of RC were lower than those of CC for all other domains (in those domains in which CC were present as well). Within the families, RC entities were 12% of the total cancer prevalence (Table 2).

Table 2. Estimates of incidence, prevalence and survival for rare and common adult solid cancers in the Netherlands by domain and family, 2010-2019

		Entities	Crude incidence per 100,000 people per year	SE	10-year prevalence per 100,000	SE	5-year relative survival (%, 95% CI)[a]	SE
Digestive cancers	Domain	RC	16.1	0.6	46.2	1.0	**24.0 (23.4-24.6)**	0.3
		CC	115.2	2.2	553.7	5.8	**51.7 (51.5-52.0)**	0.1
	Family	RC	7.1	0.2	22.3	0.4	**27.6 (26.7-28.6)**	0.5
		CC	124.3	2.4	578.3	6.4	**49.5 (49.3-49.8)**	0.1
Thoracic cancers	Domain	RC	6.9	0.4	11.9	0.3	**13.7 (13.0-14.4)**	0.4
		CC	72.2	1.6	181.6	4.7	**20.6 (20.3-20.8)**	0.1
	Family	RC	3.7	0.0	6.9	0.2	**12.1 (11.1-13.0)**	0.5
		CC	75.3	1.2	187.0	4.8	**20.4 (20.1-20.6)**	0.1
Breast cancer	Domain	RC	4.2	0.1	34.8	0.1	**92.8 (91.7-94.0)**	0.6
		CC	81.2	0.6	678.3	2.8	**90.2 (89.9-90.4)**	0.1
	Family	RC	-	-	-	-	**-**	-
		CC	85.4	0.6	713.0	2.9	90.3 (90.1-90.5)	0.1
Female genital cancers	Domain	RC	16.8	0.3	92.5	1.1	**53.8 (53.1-54.5)**	0.4
		CC	9.7	0.1	75.7	0.3	**85.9 (85.2-86.7)**	0.4
	Family	RC	2.9	0.1	19.2	0.2	**72.8 (71.0-74.5)**	0.9
		CC	23.6	0.2	127.3	0.8	**64.8 (64.2-65.3)**	0.3
Male genital and urogenital cancers	Domain	RC	9.0	0.2	63.1	0.4	**72.6 (71.8-73.5)**	0.4
		CC	99.2	1.8	698.3	5.6	**80.3 (80.0-80.6)**	0.2
	Family	RC	8.4	0.2	61.1	0.4	**75.4 (74.5-76.2)**	0.4
		CC	100.0	1.9	701.3	5.6	**80.0 (79.7-80.3)**	0.2
Skin cancers and non-cutaneous melanoma	Domain	RC	2.6	0.0	17.8	0.1	**76.8 (75.0-78.6)**	0.9
		CC	98.1	6.2	771.0	9.2	**93.4 (93.1-93.7)**	0.2
	Family	RC	2.6	0.0	18.0	0.1	**76.9 (75.0-78.7)**	0.9
		CC	98.2	6.3	772.2	9.3	**93.4 (93.1-93.7)**	0.2
All cancers	Domain	RC	100.7	1.2	516.5	5.2	**52.0 (51.7-52.3)**	0.1
		CC	475.6	10.0	2958.6	27.7	**68.7 (68.6-68.9)**	0.1
	Family	RC	69.9	1.0	378.4	3.6	**55.7 (55.3-56.0)**	0.2
		CC	506.8	10.3	3079.1	29.2	**67.2 (67.1-67.3)**	0.1

SE, standard error; CI, confidence interval; RC, rare cancer; CC, common cancer.
[a] Bold numbers indicate statistical significance ($P < 0.05$).

Relative survival

The 5-year RS of all adult solid RC (domain categorisation) was 52.0% (95% CI 51.7-52.3), compared with 68.7% (95% CI 68.6-68.9) for all adult solid CC (P<0.001) (Table 2). Compared to CC patients, higher survival rates were found in RC patients with breast cancer (92.8% (95% CI 91.7-94.0) vs. 90.2% (95% CI 89.9-90.4)) (P<0.001). The survival rates of RC were lower than those of CC for all other domains (P<0.001). Site-specific RS differences for RC and CC can be found in Supplementary Table S2 (e.g., within female genital cancers, RS for rare Tier 2 entities of epithelial tumours of corpus uteri is lower than for CC entities). Domains including RC only had a 5-year RS ranging from high (>75%), for cancers of the endocrine organs (84.7% (95% CI 83.6-85.8)), to intermediate (50-75%), for sarcomas (66.9% (95% CI 65.9-67.9)), cancers of head and neck (HNC) (62.9% (95% CI 61.5-62.9)), and neuroendocrine tumours (60.1% (95% CI 59.1-61.1)), and low (<50%) for cancers of the central nervous system (CNS) (20.0% (95% CI 19.3-20.9)) (data not shown). The 5-year RS of all RC entities within the families were higher than those within the domains, except for thoracic cancers (12.1% vs 13.7%, respectively) and breast cancer (i.e., not considered rare within the family). Comparing RC entities within the families to the domains, a major difference in 5-year RS was seen for female genital cancers (72.8% vs. 53.8%, respectively).

Trends in survival

The 5-year RS of all adult solid RC (domain categorisation) increased from 46.2% (95% CI 45.8-46.7) in 1995-1999 to 52.6% (95% CI 52.1-53.0) in 2015-2019 (i.e., 6.4%), compared to an increase from 56.9% (95% CI 56.7-57.2) in 1995-1999 to 70.1% (95% CI 69.9-70.3) in 2015-2019 (i.e., 13.2%) for CC (Fig. 1). Smaller or no survival improvements were found for all RC domains in comparison to CC domains, except for skin cancers and non-cutaneous melanoma, in which a larger survival improvement was found for RC versus CC patients (from 70.3% to 78.5% vs. from 88.4% to 94.0%). From 1995-1999 to 2015-2019, the 5-year survival rates increased for all domains including RC only. Similar results were found for RC entities within families, although the 5-year RS rates were higher compared to the domains. In addition, a deterioration in 5-year RS was seen for RC entities within the family male genital and urogenital cancers (from 77.7% to 74.8%) (data not shown).

In Fig. 2, the survival trends for statistically significant Tier 2 RC entities (domain categorisation) diagnosed in 1995-1999 vs. 2015-2019 are presented. Although large improvements in 5-year RS (≥20%) were seen for five entities (i.e., Mammary Paget's disease of breast, malignant/immature teratomas of ovary, soft tissue sarcoma of retroperitoneum and peritoneum, gastrointestinal stromal sarcoma, and oligodendroglial tumours of central nervous system), the improvement in 5-year RS was small (≤10%) in 63% of the RC entities. A decrease in 5-year RS was observed in four entities (i.e., Mullerian mixed tumour of corpus uteri, transitional cell carcinoma of pelvis and ureter, soft tissue sarcoma of viscera, and soft tissue sarcoma of skin).

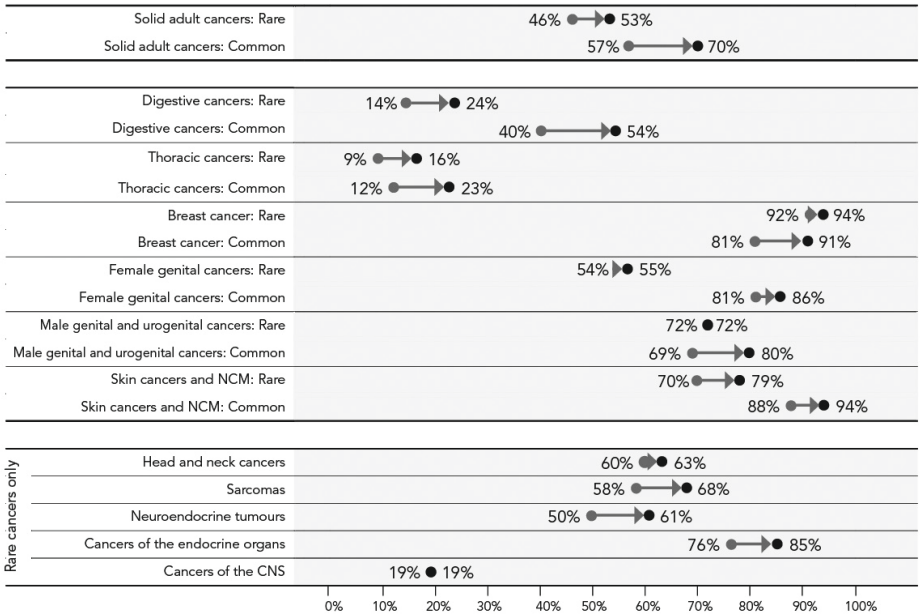

Fig. 1. Survival trends for rare and common adult solid cancers by domain, 1995-1999 vs. 2015-2019. NCM, non-cutaneous melanoma; CNS, central nervous system.

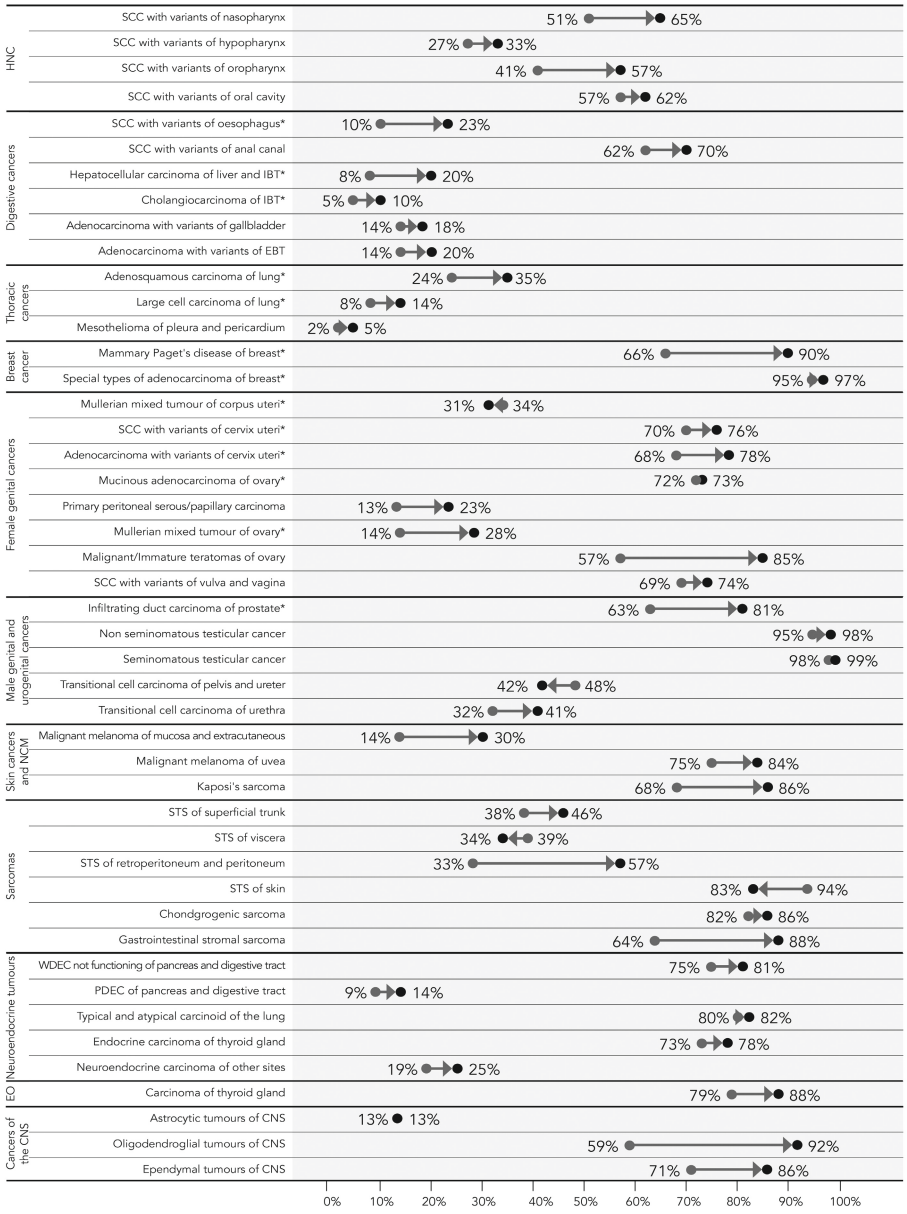

Fig. 2. Statistically significant survival trends for rare Tier 2 cancer entities, 1995-1999 vs. 2015-2019. HNC, head and neck cancer; SCC, squamous cell carcinoma; IBT, intrahepatic bile tract; EBT, extrahepatic bile tract; NCM, non-cutaneous melanoma; STS, soft tissue sarcoma; WDEC, well differentiated endocrine carcinoma; PDEC, poorly differentiated endocrine carcinoma; EO, endocrine organs; CNS, central nervous system.
Log rank test. A *P*-value < 0.05 was considered statistically significant.
* Considered common according to the rare cancer 'families' from the Joint Action on Rare Cancers (JARC), based on the Tier 1 entities with incidence rate >6/100,000.

DISCUSSION

In this population-based study, we have shown that adult solid RC were 18% of the total solid cancer incidence and 15% of the total solid cancer prevalence in the Netherlands during 2010-2019. This finding on incidence is partly in line with previous studies using the RARECARE definition, demonstrating that RC represent 24% of cancer diagnoses in Europe (period: 2000-2007), 20% of cancers in the United States (period: 2009-2013), 16-24% of cancers in Asia (period: 2011-2015), and 17% of cancers in Canada (period: 2006-2016) [6, 23-25]. If haematological and childhood cancers had been included in our study, as those previous studies all did, RC would have accounted for 21% of the total cancer incidence in the Netherlands (period: 2010-2019) (data not shown). Our finding on prevalence contrasts with previous findings from a study by Gatta et al. (2011), in which RC were estimated at 24% of the total cancer prevalence in Europe [3]. However, contrary to our study, complete prevalence was used, and haematological cancers were included here as well, pushing up the prevalence rates of RC. Still, our findings on incidence and prevalence indicate that solid RC comprise a large proportion of the cancer burden in the Netherlands.

As previously reported in studies in Europe and the United States [6, 23], it has been confirmed in our study that overall 5-year survival for solid RC was worse than for solid CC in adults (52.0% vs 68.7%). This survival gap might be explained by differences in biological tumour behaviour, and inadequacies of care or treatment for RC, including lack of expertise, diagnostic delays, lack of adequate treatments, and lack of evidence-based clinical guidelines [3, 26]. A general consensus emerged that care for patients with RC should be centralised within Centres of Expertise (CoE) to ensure multidisciplinary expertise, and patients' access to clinical studies [27]. It has been suggested that centralisation of care, including networking and establishing international ERNs and national CoE for all RC patients, will improve disease outcomes for RC [28]. Up to now, centralisation of care for RC is still suboptimal in Europe [6], while centralisation seems crucial to reduce the disparities between RC and CC.

Over a 25-year period, 5-year survival increased to a lesser extent for adult solid RC (from 46.2% to 52.6%) than for adult solid CC (from 56.9% to 70.1%), and for all RC domains compared with CC domains, except for skin cancers and non-cutaneous melanoma. Similar findings on survival improvements in RC versus CC were found in Europe [6], implying that investments regarding, e.g., diagnostic approaches, treatment, and scientific studies, were predominantly aimed at CC. No previous studies have assessed the survival trends by domain. The larger survival improvement for RC versus CC patients with skin cancers and non-cutaneous melanoma can largely be explained by the survival improvement for Kaposi sarcoma (+19%) due to the more effective treatment for HIV and decline of AIDS-related Kaposi sarcoma incidence rates [29].

Regarding survival trends for RC entities, it has been shown that improvements in survival rates were large (≥20%) for a number of RC entities, but this degree of improvement was not visible for the majority of the RC entities. Besides, only statistically significant

survival trends for RC entities have been presented here, and for more than two-thirds of the RC entities we were unable to show significant results due to the low number of cases. These large improvements in 5-year RS can be explained by the introduction of new and effective treatment (for malignant/immature teratomas of ovary and gastrointestinal stromal sarcomas (GIST) [30, 31]), improved diagnosis and centralisation of care (for GIST and soft tissue sarcoma of retroperitoneum and peritoneum [32]), and a possible reduced diagnostic delay due to improved detection and early diagnosis (for Mammary Paget's disease of breast and malignant/immature teratomas of ovary). Developments in these particular RC entities can serve as an example for other RC, aiming at investments within diagnostics, treatment, scientific research, and organisation of care.

With regard to the partitioning of adult solid RC entities, differences were found between the grouping within the EURACAN domains and within the JARC families. In our study, RC accounted for 18% of all cancers as grouped within EURACAN domains (i.e., defined upon Tier 2 entities), while RC correspond to 12% within the partitioning of the JARC families (i.e., defined upon Tier 1 entities). These findings are in line with the JARC consensus paper [8]. Consequently, certain rare Tier 2 entities are partitioned as 'common' within the JARC families in contrast to the EURACAN domains, resulting in a shift in gender, EoD, and RC estimates.

Main strengths of this study are the analysis of trends in survival by domain and for Tier 2 RC entities, the use of population-based nationwide data with high national coverage, and the extensive study period, resulting in a representative and recent study population. Limitations include the changes within the ICD-O classification over time and the lack of specificity of morphology NOS codes which might have led to an underestimation of the true incidence and prevalence of Tier 2 entities. For this study, 6% of the RC patients had missing morphology codes (i.e., M8000-M8001), and could only be classified to a Tier 1 category. A possible explanation for this might be the difficulty of obtaining an accurate histological diagnosis by pathologists, because of the rarity and heterogeneity of these tumours.

Future research should examine more in-depth comparisons between solid RC and CC, e.g., taking into account trends and patterns in incidence and prevalence, stage and/or grade, tumour biology, hospital type, type of treatment, treatment volumes, and degree of centralisation of care. Furthermore, the clinical impact of the adjusted partitioning of RC entities into families instead of domains should be explored into further detail. Regarding clinical practice, (inter)national collaboration should be further stimulated by, e.g., establishing CoE, accessible to all RC patients. Those CoE should be part of clinical networks to stimulate knowledge sharing and research development (e.g., interventions for prevention, early diagnosis, and treatment) in the field of RC. In the Netherlands, the initiation of the Dutch Rare Cancer Platform (DRCP) ensures national and multidisciplinary collaboration for optimal diagnostics, increased participation in clinical studies, and timely treatment. In addition, although grouping RC entities into families would be relevant for health care organisation and patient referral, certain RC patients will be at disadvantage in terms of medical expertise.

CONCLUSION

To our knowledge, this is the first study, in which a comparison between adult solid RC and CC in the Netherlands has been made, regarding data on incidence, prevalence, survival (trends), and the partitioning of entities within domains and families. RC survival improvements are still lagging behind CC. Although some progress in 5-year survival rates was seen for most RC domains and several RC entities, further improvement in diagnosis, treatment and management of solid RC is urgently needed to offer the best possible care for all patients with RC.

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SUPPLEMENTARY

Table S1. Standard data quality indicators (e.g., percentage of microscopically verified cases, percentage of topography codes NOS) were calculated to assess the quality of the NCR data

Number of malignant tumours (N)	Data quality indicators						
	Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Bases of diagnoses unknown (%)	Cases 2010-2019 censored before 5 years (%)	Morphology codes NOS* (%)	Topography codes NOS* (%)
976,651	0.0	0.0	95.0	0.0	0.4	4.9	0.0

NOS, not otherwise specified
Morphology codes NOS: 8000, 8001
Topography codes NOS : C140, C260, C268, C269, C390, C398, C399, C559, C579, C639, C689, C729, C762, C763

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	Head and neck cancers							
	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	0.68	0.01	4.13	0.04	701	64.6	1.8
R	– Squamous cell carcinoma with variants of nasal cavity and sinuses	0.58	0.01	3.62	0.03	614	66.9	1.9
R	– Lymphoepithelial carcinoma of nasal cavity and sinuses	0.00	NE	0	NE	0	NE	NE
R	– Undifferentiated carcinoma of nasal cavity and sinuses	0.02	0.00	0.13	0.00	22	47.5	8.8
R	– Intestinal type adenocarcinoma of nasal cavity and sinuses	0.05	0.01	0.34	0.01	58	65.7	6.8
	EPITHELIAL TUMOURS OF NASOPHARYNX	0.41	0.01	2.51	0.02	426	63.7	2.1
R	– Squamous cell carcinoma with variants of nasopharynx	0.35	0.01	2.20	0.02	373	64.7	2.3
R	– Papillary adenocarcinoma of nasopharynx	0.00	NE	0	NE	0	NE	NE
	EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	1.42	0.04	9.46	0.08	1604	72.6	1.2

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Epithelial tumour of major salivary glands	0.98	0.03	6.34	0.06	1075	69.9	1.5
R	– Salivary gland type tumour of head and neck	0.44	0.02	3.13	0.02	529	78.5	2.0
	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	5.30	0.09	29.58	0.24	5014	60.7	0.7
R	– Squamous cell carcinoma with variants of hypopharynx	1.18	0.03	4.35	0.07	740	34.8	1.2
R	– Squamous cell carcinoma with variants of larynx	3.99	0.07	24.90	0.17	4219	69.5	0.7
	EPITHELIAL TUMOURS OF OROPHARYNX	3.75	0.06	20.24	0.23	3435	53.4	0.7
R	– Squamous cell carcinoma with variants of oropharynx	3.69	0.06	20.13	0.23	3417	54.0	0.7
	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	5.84	0.08	34.97	0.24	5925	66.1	0.6
R	– Squamous cell carcinoma with variants of oral cavity	4.68	0.06	26.88	0.23	4558	60.8	0.7
R	– Squamous cell carcinoma with variants of lip	1.13	0.06	8.02	0.02	1356	90.4	1.4
	EPITHELIAL TUMOURS OF EYE AND ADNEXA	0.07	0.01	0.54	0.01	92	85.1	5.0

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Squamous cell carcinoma with variants of eye and adnexa	0.05	0.01	0.43	0.01	73	90.1	5.6
R	– Adenocarcinoma with variants of eye and adnexa	0.02	0.00	0.10	0.00	17	70.4	10.9
	EPITHELIAL TUMOURS OF MIDDLE EAR	0.02	0.00	0.12	0.00	21	59.8	9.1
R	– Squamous cell carcinoma with variants middle ear	0.02	0.00	0.11	0.00	18	59.4	9.8
R	– Adenocarcinoma with variants of middle ear	0.00	0.00	0.02	0.00	3	77.2	22.3
	Digestive cancers							
	EPITHELIAL TUMOURS OF OESOPHAGUS*	13.14	0.34	37.40	0.84	6371	23.6	0.3
R	– Squamous cell carcinoma with variants of oesophagus	3.90	0.07	10.15	0.23	1729	21.5	0.6
C	– Adenocarcinoma with variants of oesophagus	8.84	0.28	26.82	0.61	4568	25.1	0.4
R	– Salivary gland type tumour of oesophagus	0.00	0.00	0.02	0.00	3	NE	NE
R	– Undifferentiated carcinoma of oesophagus	0.04	0.00	0.05	0.00	8	10.0	4.1

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	EPITHELIAL TUMOURS OF STOMACH*	9.93	0.27	22.86	0.47	3889	20.4	0.4
C	– Adenocarcinoma with variants of stomach	9.53	0.26	22.43	0.46	3816	20.8	0.4
R	– Squamous cell carcinoma with variants of stomach	0.05	0.01	0.12	0.00	20	20.0	4.6
R	– Salivary gland-type tumour of stomach	0.00	0.00	0.01	0.00	1	NE	NE
R	– Undifferentiated carcinoma of stomach	0.02	0.00	0.06	0.00	11	22.8	7.9
	EPITHELIAL TUMOURS OF SMALL INTESTINE	1.15	0.05	3.54	0.07	603	27.5	1.2
R	– Adenocarcinoma with variants of small intestine	1.03	0.03	3.36	0.06	571	29.1	1.3
R	– Squamous cell carcinoma with variants of small intestine	0.00	0.00	0.00	0.00	0	0.0	0.0
	EPITHELIAL TUMOURS OF COLON (including appendix)*	58.59	1.35	346.61	3.46	58789	66.5	0.2
C	– Adenocarcinoma with variants of colon	56.33	1.41	343.02	3.39	58176	68.5	0.2
R	– Squamous cell carcinoma with variants of colon	0.01	0.00	0.05	0.00	8	69.4	14.6

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Fibromixoma and low-grade mucinous adenocarcinoma (pseudomyxoma peritonei) of the appendix	0.29	0.02	1.89	0.02	321	66.2	2.7
	EPITHELIAL TUMOURS OF RECTUM*	23.55	0.88	146.06	1.12	24745	68.0	0.3
C	– Adenocarcinoma with variants of rectum	23.20	0.89	145.52	1.11	24653	68.7	0.3
R	– Squamous cell carcinoma with variants of rectum	0.02	0.00	0.08	0.00	13	37.5	10.2
	EPITHELIAL TUMOURS OF ANAL CANAL	1.34	0.06	9.06	0.10	1538	68.6	1.2
R	– Squamous cell carcinoma with variants of anal canal	1.25	0.07	8.67	0.09	1471	70.1	1.2
R	– Adenocarcinoma with variants of anal canal	0.08	0.01	0.35	0.00	59	53.2	5.8
R	– Paget's disease of anal canal	0.00	NE	0	NE	0	NE	NE
	EPITHELIAL TUMOURS OF PANCREAS*	14.45	0.41	13.67	0.67	2345	4.0	0.2
C	– Adenocarcinoma with variants of pancreas	9.59	0.32	11.33	0.56	1943	4.6	0.2

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Squamous cell carcinoma with variants of pancreas	0.01	0.00	0.02	0.00	4	9.5	6.4
R	– Acinar cell carcinoma of pancreas	0.03	0.00	0.08	0.00	13	17.6	6.4
R	– Mucinous cystadenocarcinoma of pancreas (invasive)	0.01	0.01	0.05	0.00	9	40.7	12.4
R	– Intraductal papillary mucinous carcinoma invasive of pancreas	0.05	0.01	0.15	0.00	26	38.6	6.3
R	– Solid pseudopapillary carcinoma of pancreas	0.01	0.00	0.11	0.00	19	101.3	0.0
R	– Serous cystadenocarcinoma of pancreas	0.00	0.00	0.00	0.00	0	0.0	0.0
R	– Carcinoma with osteoclast-like giant cells of pancreas	0.00	0.00	0.02	0.00	3	19.3	16.6
	EPITHELIAL TUMOURS OF LIVER AND INTRAEPATIC BILE TRACT (IBT)*	4.57	0.35	11.13	0.34	1901	17.4	0.5
R	– Hepatocellular carcinoma of liver and IBT	3.54	0.25	9.41	0.27	1606	20.0	0.6
R	– Hepatocellular carcinoma, fibrolamellar	0.01	0.00	0.04	0.00	6	49.2	13.3
R	– Cholangiocarcinoma of IBT	0.66	0.06	1.21	0.05	208	10.2	1.1

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Adenocarcinoma with variants of liver and IBT	0.36	0.05	0.47	0.03	81	5.4	1.1
R	– Undifferentiated carcinoma of liver and IBT	0.00	0.00	0	NE	0	NE	NE
R	– Squamous cell carcinoma with variants of liver and IBT	0.00	NE	0	NE	0	NE	NE
R	– Bile duct cystadenocarcinoma of IBT	0.00	0.00	0	NE	0	NE	NE
	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	4.62	0.12	9.57	0.29	1633	15.4	0.5
R	– Adenocarcinoma with variants of gallbladder	0.73	0.02	1.66	0.04	283	19.3	1.3
R	– Adenocarcinoma with variants of EBT	2.72	0.10	7.08	0.21	1209	19.0	0.7
R	– Squamous cell carcinoma of gallbladder and EBT	0.02	0.00	0.02	0.00	3	8.4	6.9
	Thoracic cancers							
	EPITHELIAL TUMOURS OF TRACHEA	0.06	0.01	0.24	0.00	40	43.7	5.5

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Squamous cell carcinoma with variants of trachea	0.03	0.00	0.09	0.00	15	31.2	6.8
R	– Adenocarcinoma with variants of trachea	0.01	0.00	0.03	0.00	5	48.4	16.8
R	– Salivary gland type tumour of trachea	0.02	0.00	0.12	0.00	20	80.8	9.8
	EPITHELIAL TUMOURS OF LUNG*	75.30	1.21	186.60	4.76	31823	20.4	0.1
C	– Squamous cell carcinoma with variants of lung	15.13	0.27	41.60	0.84	7081	25.2	0.3
C	– Adenocarcinoma with variants of lung	30.05	1.00	89.23	2.19	15215	24.4	0.2
R	– Adenosquamous carcinoma of lung	0.42	0.01	1.44	0.04	246	29.8	2.1
R	– Large cell carcinoma of lung	2.28	0.43	2.34	0.02	396	10.9	0.6
C	– Poorly differentiated endocrine carcinoma of lung	11.31	0.12	15.85	0.56	2709	8.7	0.2
R	– Salivary gland type tumour of lung	0.07	0.01	0.41	0.01	70	67.6	5.2
R	– Sarcomatoid carcinoma of lung	0.36	0.02	0.82	0.02	0	20.0	1.8
	EPITHELIAL TUMOURS OF THYMUS	0.35	0.02	2.44	0.03	414	70.3	2.3

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Malignant thymoma	0.29	0.02	2.13	0.02	360	77.4	2.4
R	– Squamous cell carcinoma of thymus	0.04	0.01	0.25	0.01	42	40.3	7.1
R	– Adenocarcinoma with variants of thymus	0.01	0.00	0.00	0.00	0	0.0	0.0
	MALIGNANT MESOTHELIOMA	3.31	0.03	4.25	0.21	730	4.9	0.4
R	– Mesothelioma of pleura and pericardium	3.14	0.03	3.94	0.20	677	4.4	0.4
R	– Mesothelioma of peritoneum and tunica vaginalis	0.17	0.01	0.31	0.01	53	13.3	2.4
	Breast cancer							
	EPITHELIAL TUMOURS OF BREAST*	85.44	0.61	713.05	2.88	120689	90.3	0.1
C	– Invasive carcinoma of no special type-NST (obs Invasive ductal carcinoma of breast)	68.45	0.49	580.47	2.19	98238	91.2	0.1
C	– Invasive lobular carcinoma of breast	10.30	0.23	84.30	0.55	14281	89.5	0.4
R	– Mammary Paget's disease of breast	0.23	0.02	1.84	0.01	310	88.6	2.6
R	– Special types of adenocarcinoma of breast	3.50	0.06	29.34	0.11	4964	95.7	0.6

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Metaplastic carcinoma of breast	0.44	0.03	3.05	0.04	518	71.6	2.2
R	– Salivary gland type tumour of breast	0.07	0.01	0.57	0.01	96	94.4	3.7
	Female genital cancers							
	EPITHELIAL TUMOURS OF CORPUS UTERI*	11.38	0.11	83.93	0.45	14213	79.6	0.4
C	– Adenocarcinoma with variants of corpus uteri	9.41	0.10	74.39	0.27	12588	87.0	0.4
R	– Squamous cell carcinoma with variants of corpus uteri	0.01	0.00	0.03	0.00	5	23.7	11.6
R	– Adenoid cystic carcinoma of corpus uteri	0.00	NE	0	NE	0	NE	NE
R	– Clear cell adenocarcinoma, NOS	0.29	0.02	1.83	0.03	312	58.3	2.9
R	– Serous (papillary) carcinoma	1.01	0.11	5.31	0.13	906	45.0	1.6
R	– Mullerian mixed tumour	0.56	0.02	2.17	0.03	369	36.8	1.8
	EPITHELIAL TUMOURS OF CERVIX UTERI*	4.42	0.11	33.13	0.22	5612	75.5	0.6
R	– Squamous cell carcinoma with variants of cervix uteri	3.33	0.08	25.16	0.16	4261	76.2	0.7

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Adenocarcinoma with variants of cervix uteri	0.90	0.03	6.79	0.05	1150	75.6	1.3
R	– Undifferentiated carcinoma of cervix uteri	0.01	0.00	0.02	0.00	4	0.0	0.0
R	– Mullerian mixed tumour of cervix uteri	0.01	0.00	0.01	0.00	2	NE	NE
	EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE*	7.78	0.08	32.06	0.48	5447	37.1	0.5
R	– Adenocarcinoma with variants of ovary	5.23	0.08	21.25	0.35	3613	36.0	0.6
R	– Mucinous adenocarcinoma of ovary	0.53	0.02	3.71	0.02	628	71.6	1.8
R	– Clear cell adenocarcinoma of ovary	0.39	0.02	2.36	0.03	401	58.1	2.3
R	– Primary peritoneal serous/ papillary carcinoma	0.75	0.03	2.01	0.04	343	20.7	1.3
R	– Mullerian mixed tumour of ovary and fallopian tube	0.16	0.01	0.48	0.02	81	25.4	3.1
R	– Adenocarcinoma with variants of fallopian tube	0.31	0.02	1.64	0.03	279	44.0	2.6

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	NON-EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE	0.21	0.03	1.80	0.03	305	88.1	2.0
R	– Sex cord tumour of ovary	0.08	0.02	0.68	0.02	116	90.9	3.6
R	– Malignant/immature teratoma of ovary	0.08	0.01	0.69	0.01	116	83.8	3.4
R	– Germ cell tumour of ovary	0.05	0.01	0.43	0.01	73	90.9	3.3
	EPITHELIAL TUMOURS OF VULVA AND VAGINA	2.67	0.06	16.88	0.16	2863	71.2	0.9
R	– Squamous cell carcinoma with variants of vulva and vagina	2.55	0.06	16.28	0.16	2761	72.2	1.0
R	– Adenocarcinoma with variants of vulva and vagina	0.05	0.01	0.26	0.01	44	42.4	6.7
R	– Paget's disease of vulva and vagina	0.04	0.01	0.26	0.00	44	84.4	7.1
R	– Undifferentiated carcinoma of vulva and vagina	0.00	0.00	0.01	0.00	1	45.8	39.7
R	– Mullerian mixed tumour of vulva and vagina	0.00	0.00	0.00	0.00	0	0.0	0.0
	TROPHOBLASTIC TUMOURS OF PLACENTA	0.05	0.01	0.43	0.01	72	94.9	2.7
R	– Choriocarcinoma of placenta	0.04	0.01	0.39	0.01	65	94.4	2.9

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	Male genital and urogenital cancers							
	EPITHELIAL TUMOURS OF PROSTATE*	67.99	1.53	528.04	3.75	89476	89.8	0.2
C	– Adenocarcinoma with variants of prostate	65.60	1.40	518.63	3.51	87869	91.1	0.2
R	– Squamous cell carcinoma with variants of prostate	0.00	0.00	0.01	0.00	1	0.0	0.0
R	– Infiltrating duct carcinoma of prostate	0.19	0.02	1.40	0.02	238	81.5	3.7
R	– Transitional cell carcinoma of prostate	0.00	NE	0	NE	0	NE	NE
R	– Basal cell adenocarcinoma of prostate	0.00	0.00	0.01	0.00	1	58.2	41.2
	TESTICULAR AND PARATESTICULAR CANCERS	4.47	0.10	42.58	0.13	7203	98.0	0.2
R	– Paratesticular adenocarcinoma with variants	0.00	NE	0	NE	0	NE	NE
R	– Non seminomatous testicular cancer	1.85	0.04	17.60	0.05	2976	97.6	0.3
R	– Seminomatous testicular cancer	2.46	0.07	23.58	0.08	3988	98.8	0.3

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Spermatocytic seminoma	0.04	0.01	0.37	0.00	63	96.7	4.8
R	– Teratoma with malignant transformation	0.00	0.00	0.01	0.00	1	NE	NE
R	– Testicular sex cord cancer	0.03	0.00	0.21	0.00	36	74.5	7.7
	EPITHELIAL TUMOURS OF PENIS	0.92	0.04	5.98	0.07	1015	73.4	1.7
R	– Squamous cell carcinoma with variants of penis	0.90	0.04	5.93	0.07	1007	74.6	1.7
R	– Adenocarcinoma with variants of penis	0.01	0.00	0.02	0.00	3	26.9	18.9
	EPITHELIAL TUMOURS OF KIDNEY*	14.40	0.36	89.27	0.91	15145	66.4	0.4
C	– Renal cell carcinoma with variants	11.82	0.22	79.62	0.68	13500	71.9	0.4
R	– Squamous cell carcinoma spindle cell type of kidney	0.00	0.00	0.00	0.00	0	0.0	0.0
R	– Squamous cell carcinoma with variants of kidney	0.01	0.00	0.00	0.00	0	0.0	0.0
	EPITHELIAL TUMOURS OF PELVIS AND URETER	2.72	0.11	10.64	0.20	1811	38.1	0.9

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Transitional cell carcinoma of pelvis and ureter	2.39	0.09	10.00	0.18	1701	41.1	1.0
R	– Squamous cell carcinoma with variants of pelvis and ureter	0.03	0.01	0.07	0.01	12	21.7	6.3
R	– Adenocarcinoma with variants of pelvis and ureter	0.01	0.00	0.04	0.00	7	38.2	11.3
	EPITHELIAL TUMOURS OF URETHRA	0.17	0.01	0.80	0.01	136	45.6	3.8
R	– Transitional cell carcinoma of urethra	0.13	0.01	0.58	0.01	99	43.5	4.5
R	– Squamous cell carcinoma with variants of urethra	0.02	0.00	0.13	0.00	22	49.7	9.6
R	– Adenocarcinoma with variants of urethra	0.02	0.00	0.09	0.00	15	54.7	10.6
	EPITHELIAL TUMOURS OF BLADDER*	17.48	0.17	83.11	0.96	14107	52.8	0.4
C	– Transitional cell carcinoma of bladder	16.40	0.14	80.76	0.92	13707	54.9	0.4
R	– Squamous cell carcinoma with variants of bladder	0.36	0.02	0.83	0.01	141	23.9	2.0
R	– Adenocarcinoma with variants of bladder	0.17	0.01	0.71	0.01	120	38.4	3.4

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Salivary gland type tumour of bladder	0.00	NE	0	NE	0	NE	NE
	EXTRAGONADAL GERM CELL TUMOURS	0.13	0.01	0.96	0.01	163	78.2	3.1
R	– Non seminomatous germ cell tumour	0.05	0.00	0.31	0.00	53	58.4	5.7
R	– Seminomatous germ cell tumour	0.04	0.00	0.37	0.00	63	99.7	2.7
R	– Germ cell tumour of CNS	0.02	0.00	0.21	0.00	36	91.4	5.1
	Skin cancers and non-cutaneous melanoma							
	MALIGNANT SKIN MELANOMA*	33.84	1.20	291.12	1.93	49322	93.0	0.2
C	– Malignant skin melanoma	33.84	1.20	291.12	1.93	49322	93.0	0.2
	MALIGNANT MELANOMA OF MUCOSA AND EXTRACUTANEOUS	0.27	0.02	0.73	0.01	125	23.9	2.4
R	– Malignant melanoma of mucosa and extracutaneous	0.27	0.02	0.73	0.01	125	23.9	2.4
	MALIGNANT MELANOMA OF EYE	1.24	0.03	9.31	0.08	1579	81.3	1.2
R	– Malignant melanoma of conjunctiva	0.08	0.01	0.64	0.01	109	92.9	4.8

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Malignant melanoma of uvea	1.16	0.03	8.65	0.07	1466	80.7	1.3
	EPITHELIAL TUMOURS OF SKIN*	342.09	18.49	2606.01	51.05	448949	98.8	0.0
C	– Basal cell carcinoma of skin[a]	277.9	16.7	2126.1	46.1	367439	100.0	0.0
C	– Squamous cell carcinoma with variants of skin	64.18	5.18	479.55	7.36	81510	93.6	0.2
	ADNEXAL CARCINOMAS OF SKIN	0.75	0.02	5.17	0.03	875	85.0	1.9
R	– Adnexal carcinoma of skin	0.75	0.02	5.17	0.03	875	85.0	1.9
	KAPOSI'S SARCOMA	0.32	0.02	2.60	0.03	440	86.3	2.0
R	– Kaposi's sarcoma	0.32	0.02	2.60	0.03	440	86.3	2.0
	Sarcomas							
	SOFT TISSUE SARCOMA	5.22	0.08	29.77	0.27	5048	59.9	0.7
R	– Soft tissue sarcoma of head and neck	0.17	0.01	0.90	0.01	153	58.5	4.0
R	– Soft tissue sarcoma of limbs	1.44	0.04	9.40	0.08	1594	69.8	1.2
R	– Soft tissue sarcoma of superficial trunk	0.57	0.02	2.46	0.03	417	42.8	1.9
R	– Soft tissue sarcoma of mediastinum	0.03	0.01	0.12	0.00	20	30.2	6.6
R	– Soft tissue sarcoma of heart	0.02	0.00	0.06	0.01	11	12.0	7.1

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Soft tissue sarcoma of breast	0.20	0.01	1.25	0.01	212	67.4	3.2
R	– Soft tissue sarcoma of uterus	0.49	0.01	2.20	0.02	373	43.1	2.0
R	– Soft tissue sarcoma of paratestis	0.07	0.01	0.49	0.01	84	85.9	5.5
R	– Soft tissue sarcomas of other genitourinary tract (vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra)	0.10	0.01	0.44	0.01	75	41.4	4.3
R	– Soft tissue sarcoma of viscera	0.21	0.01	0.65	0.01	110	27.5	2.8
R	– Soft tissue sarcoma of retroperitoneum and peritoneum	0.34	0.02	1.70	0.03	289	50.2	2.5
R	– Soft tissue sarcoma of pelvis	0.24	0.01	1.20	0.01	203	52.8	3.1
R	– Soft tissue sarcoma of skin	0.93	0.04	7.14	0.05	1210	86.6	1.5
R	– Soft tissue sarcoma of paraorbit	0.00	0.00	0.02	0.00	4	69.3	24.4
R	– Soft tissue sarcoma of brain and other parts of the nervous system	0.19	0.01	1.03	0.01	175	57.3	3.1
R	– Embryonal rhabdomyosarcoma of soft tissue	0.02	0.00	0.08	0.00	13	39.3	9.3

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Alveolar rhabdomyosarcoma of soft tissue	0.02	0.00	0.07	0.00	12	15.4	8.3
R	– Ewing's sarcoma of soft tissue	0.05	0.01	0.31	0.01	53	60.5	5.8
	BONE SARCOMA	1.20	0.13	9.04	0.09	1523	78.4	1.1
R	– Osteogenic sarcoma	0.20	0.01	1.16	0.01	196	57.3	3.1
R	– Chondrogenic sarcoma	0.77	0.12	6.57	0.11	1104	90.7	1.0
R	– Notochordal sarcoma, chordoma	0.10	0.01	0.63	0.01	107	72.0	4.7
R	– Vascular sarcoma	0.02	0.00	0.05	0.00	9	18.1	6.9
R	– Ewing's sarcoma	0.05	0.00	0.28	0.01	47	46.7	5.9
R	– Other high-grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0.00	0.00	0.01	0.00	2	68.0	27.8
	GASTROINTESTINAL STROMAL SARCOMA	1.16	0.03	8.86	0.08	1503	85.9	1.2
R	– Gastrointestinal stromal sarcoma	1.16	0.03	8.86	0.08	1503	85.9	1.2

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	Neuroendocrine tumours							
	NET GEP	4.59	0.27	30.10	0.35	5110	67.8	0.7
R	– Well differentiated not functioning endocrine carcinoma of pancreas and digestive tract	3.57	0.21	27.62	0.29	4686	81.1	0.7
R	– Well differentiated functioning endocrine carcinoma of pancreas and digestive tract	0.10	0.02	0.91	0.02	155	89.3	3.7
R	– Poorly differentiated endocrine carcinoma of pancreas and digestive tract	0.91	0.04	1.55	0.05	264	12.7	1.0
R	– Malignant mixed pancreatic endocrine and exocrine tumour	0.01	0.00	0.03	0.00	5	54.8	18.3
	NET LUNG	0.91	0.05	7.15	0.07	1213	81.8	1.3
R	– Typical and atypical carcinoid of the lung	0.91	0.05	7.15	0.07	1213	81.8	1.3
	NET OTHER SITES	2.96	0.04	11.76	0.15	1996	41.1	0.9
R	– Pheochromocytoma, malignant	0.05	0.01	0.33	0.01	56	74.4	6.1
R	– Paraganglioma	0.00	NE	0	NE	0	NE	NE

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
R	– Endocrine carcinoma of thyroid gland	0.21	0.01	1.67	0.01	283	82.6	2.4
R	– Neuroendocrine carcinoma of skin	0.87	0.04	4.73	0.08	803	62.2	1.9
R	– Neuroendocrine carcinoma of other sites	1.83	0.03	5.03	0.07	854	25.9	0.9
	Cancers of the endocrine organs							
	CARCINOMAS OF PITUITARY GLAND	0.00	0.00	0.01	0.00	1	NE	NE
R	– Carcinomas of pituitary gland	0.00	0.00	0.01	0.00	1	NE	NE
	CARCINOMAS OF THYROID GLAND	3.85	0.12	32.17	0.17	5448	87.1	0.5
R	– Carcinoma of thyroid gland	3.85	0.12	32.17	0.17	5448	87.1	0.5
	CARCINOMAS OF PARATHYROID GLAND	0.02	0.00	0.17	0.00	29	95.0	7.1
R	– Carcinoma of parathyroid gland	0.02	0.00	0.17	0.00	29	95.0	7.1
	CARCINOMAS OF ADRENAL CORTEX	0.18	0.01	0.67	0.01	114	34.2	3.1
R	– Carcinoma of adrenal cortex	0.18	0.01	0.67	0.01	114	34.2	3.1

Table S2. Estimates of incidence, prevalence and survival for rare and common malignant solid cancers in the Netherlands, 2010-2019 *(continued)*

Rare or common		Crude incidence per 100,000 per year	SE incidence	10-year prevalence per 100,000	SE prevalence	Prevalent cases	Relative 5-year survival (%)	SE survival (%)
	Cancer of the CNS							
	TUMOURS OF CNS	7.40	0.14	18.66	0.40	3175	19.9	0.4
R	– Astrocytic tumours of CNS	5.35	0.06	11.59	0.34	1977	14.2	0.4
R	– Oligodendroglial tumours of CNS	0.35	0.02	2.76	0.02	468	83.3	1.9
R	– Ependymal tumours of CNS	0.20	0.01	1.69	0.01	286	86.0	2.3
R	– Neuronal and mixed neuronal-glial tumours	0.00	0.00	0.02	0.00	3	25.2	15.4
R	– Choroid plexus carcinoma of CNS	0.00	0.00	0.01	0.00	1	50.1	35.5
R	– Malignant meningiomas	0.05	0.00	0.18	0.01	30	41.7	6.4
R	– Tumours of the pineal gland	0.02	0.00	0.12	0.00	20	70.7	8.8
	EMBRYONAL TUMOURS OF CNS	0.05	0.01	0.27	0.01	45	54.8	6.1
R	– Embryonal tumour of CNS	0.05	0.01	0.27	0.01	45	54.8	6.1

C = common; CNS = central nervous system; NE = not estimated; NET = neuroendocrine tumours; R = rare; SE = standard error.
Tier 1 is not the exact sum of Tier 2, because 'not otherwise specified' (NOS) morphology codes (i.e., M8000-M8001) are only part of Tier 1.
* Considered common according to the rare cancer 'families' from the Joint Action on Rare Cancers (JARC), based on the Tier 1 entities with incidence rate >6/100,000.
[a] The presented data of basal cell carcinoma of the skin is based upon years 2017-2019, because the registration of basal cell carcinoma in the Netherlands has been nationally covered since 2017.

CHAPTER 3

The utility of measuring healthy life expectancy: a population-based study among a subset of rare and common cancer survivors

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ABSTRACT

Introduction: As the survival proportions for rare cancers are on average worse than for common cancers, assessing the expected remaining life years in good health becomes highly relevant. This study aimed to estimate the healthy life expectancy (HLE) of a subset of rare and common cancer survivors, and to assess the determinants of poor perceived health in rare cancer survivors.

Methods: To calculate HLE, survival data from the population-based Netherlands Cancer Registry of survivors of a rare cancer (i.e., ovarian cancer, thyroid cancer, Hodgkin lymphoma, non-Hodgkin lymphoma) (n = 21,376) and a common cancer (i.e., colorectal cancer (CRC)) (n = 76,949) were combined with quality of life (QoL) data from the PROFILES registry on a random sample of the rare (n = 1,025) and common cancer (n = 2,400) survivors. A flexible parametric relative survival model was used to estimate life expectancy (LE) and years of life lost, and multivariate logistic regression was applied to determine factors related to reported poor perceived health.

Results: Patients previously diagnosed with a rare cancer had an average LE of 8 to 36 years and spent ≥67% of their remaining life in good health. CRC survivors had an average LE of 10 years with approximately 65% of their remaining life spent in good health. For all cancer types, those aged ≥65 years or with stage IV had the lowest HLE. Low socioeconomic status, advanced stage, and having received radiotherapy were important predictors of poor perceived health among rare cancer survivors.

Conclusion: HLE can provide meaningful perspective for patients and practitioners for all cancer types, including rare cancers. Yet, data on QoL for rare cancers should be routinely collected, as such will serve as an indicator for monitoring and improving cancer care, and for enabling HLE measurements in cancer survivors.

INTRODUCTION

Nearly 4.4 million new cancer cases were diagnosed in Europe in 2020 [1], with an expected relative rise by almost 50% in 2035 [2]. There have been improvements in cancer survival through earlier detection, better access to care, and improved treatment [3]. However, survival improvements for rare cancers, defined by the Surveillance of Rare Cancers in Europe (RARECARE) consortium as those with an incidence of <6 per 100,000 people per year [4], are lagging behind. A large, and still increasing, survival gap was found between rare cancers (49%) compared to common cancers (63%) [5]. In Europe, rare cancers comprise 24% of all cancer diagnoses [5] and currently 4.3 million people are living with a diagnosis of rare cancer [4]. While most rare and common cancer survivors are faced with long-term physical and psychosocial impacts of their cancer diagnosis and treatment, affecting their quality of life (QoL), insight in how much of their remaining life they spent in good health is missing. Patients with a rare cancer are on average diagnosed at a younger age and at a more advanced stage than common cancer survivors and, hence, might be more at risk for long-term sequelae [6].

In line with the World Health Organization's goal on 'healthy ageing' (i.e., to develop and maintain functional ability to enable well-being for all), there should be a focus on managing long-term health consequences of cancer and promoting a long and healthy life for cancer survivors. Whether cancer survivors spend their lives after diagnosis in good or poor health, can be measured by indicators, such as healthy life expectancy (HLE). HLE is a population health outcome measure combining expected lifetime and QoL, and indicates the number of remaining years of life spent in good health [7]. Previous studies on HLE have shown that cancer has a major impact on life expectancy (LE) and HLE [8-10]. For example, HLE among Canadians at age 65 was estimated to be 7 years for those diagnosed with cancer compared to 16 years for those without cancer (i.e., 9 total years of life lost (YLL) for cancer survivors) [8].

Since the number of cancer survivors is growing, ensuring a high HLE is of great importance for cancer survivors' QoL, psychosocial functioning, and daily life activities [11]. Moreover, in previous systematic reviews, it has been shown that promoting healthy lifestyle behaviour benefits cancer survivors' health and QoL in their remaining years of life [12, 13]. Only few studies have studied HLE in cancer survivors [14, 15]. For example, colorectal cancer survivors were found to have a HLE of approximately 75% [15]. Yet, no comparison between rare and common cancer survivors has been made so far, and as such, an initial comparison among a subset of rare and common cancers is valuable to showcase the utility of the HLE measure.

Therefore, the aim of this study was to estimate the LE and proportion of remaining life that selected rare cancer and common cancer survivors spend in good health by making use of HLE estimates, and to assess determinants of poor perceived health in rare cancer survivors.

METHODS

Design and data collection

Cancer patient data were obtained from the population-based Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Organization. The NCR is a nationwide registry including all newly diagnosed malignant cancer cases in the Netherlands since 1989. Cancer data are recorded in the registry after notification by the national automated pathology archive and the National Registry of Hospital Discharge Diagnosis. Follow-up information on vital status is obtained through a yearly linkage with the Municipal Personal Records Database (BRP).

Data on QoL were obtained through the Patient Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry [16]. PROFILES includes data on short- and long-term cancer survivors, through which the physical and psychosocial impact of cancer and its treatment can be studied. The registry started data collection in 2008, comprising data of several randomly selected cohorts of Dutch cancer survivors, and is linked to the NCR. In each cohort, participants are informed about the particular study via a letter by their involved medical specialist. The letter includes a link to a secure website and credentials, so that interested patients can provide informed consent and complete self-report questionnaires online (or, if preferred, receive the paper-and-pencil version). No follow-up questionnaires are administered. A detailed description of the PROFILES registry has been described previously [16].

Study sample

We included all adult patients diagnosed between 2009 and 2014 from the NCR with one of four selected malignant rare cancers, i.e., ovarian cancer, thyroid cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) [17], and one common cancer type, i.e., colorectal cancer (CRC). Included patients from the NCR were followed until death or end of the study (31 December 2022). Such a subset of cancer types was chosen to showcase the utility of the HLE measure, and to make an initial comparison between rare and common cancer.

Similarly, we derived relevant cohorts from the PROFILES registry including data from survivors of ovarian cancer, thyroid cancer, HL, NHL (together: rare), and CRC (common). QoL assessment was performed in a random sample of the NCR selection of adult cancer survivors (n = 1,025 rare; n = 2,400 common). All survivors in the PROFILES registry were diagnosed between 2000 and 2014 and completed the PROFILES' questionnaires between April 2009 and April 2014. Ethical approval was obtained for each cohort separately from local certified Medical Ethics Committees.

Study measures

Sociodemographic data were obtained from the NCR and included date of birth, sex, and socioeconomic status (SES). Clinical data obtained from the NCR included date of cancer diagnosis, tumour type, stage, and primary treatments received. Tumour type was classified according to the third International Classification of Diseases for Oncology (ICDO-O-3) [18]. Stage was classified according to tumour-node-metastasis (TNM) [19-22], International Federation of Gynaecology and Obstetrics (FIGO) (ovarian cancer) [23] or Ann Arbor classification (HL and NHL) [24, 25]. Primary treatments received were classified into surgery (+/- systemic therapy), systemic therapy (i.e., chemotherapy, targeted therapy, immune therapy, and hormone therapy) (+/- radiation therapy), radiation therapy, other, and no treatment. Patients' vital status at time of analysis and date of death were obtained from the BRP and were last verified on January 31, 2022.

QoL was assessed by the validated 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), consisting of cancer-specific measures of health-related QoL in cancer survivors [26]. In this study, only the Global Health Status/Quality of Life (GHS/QoL) score of the questionnaire was used. GHS/QoL scores were linearly transformed to a score between 0 and 100, with a higher score indicating a better perceived health [27].

Statistical analyses

HLE was calculated in two steps. First, LE and YLL for each tumour type were estimated by extrapolating survival from a flexible parametric relative survival model, using the approach defined by Andersson et al. [28]. In this step, the baseline cumulative excess hazard was modelled with 5 degrees of freedom. The model included age at diagnosis, sex, SES, stage, and interactions among these covariates. Age was modelled using restricted cubic splines with 4 degrees of freedom and the effect of age was kept constant in the upper and lower 2 percentiles of the data (i.e., winsorizing) to improve model stability [29]. Time-dependent effects with between 1 and 3 degrees of freedom (as flexible as possible) were enabled for age, sex, stage, and SES to allow for non-proportional excess hazards. A period analysis was performed with the window set from April 2009 to April 2014 for all models, thus only including the person time within this period window in the analysis [30]. The expected survival was obtained from population mortality data by BRP and stratified by age, year of death, and sex. Second, by using the Sullivan method [31], the proportion of HLE for each tumour type, sex, age, SES, and stage was calculated by combining the LE estimates derived from the first step with the GHS/QoL scores. For each tumour type and stage of the disease, weights were applied to the GHS/QoL scores, differentiating between the diagnosis and initial treatment phase and follow-up phase [32], and corrections were made if GHS/QoL scores were statistically different from the normative population (i.e., multiplying the percentage difference to the GHS/QoL scores).

In order to assess determinants of HLE in the subset of rare cancer survivors, a multivariate logistic regression was used to measure the association of perceived health (GHS/QoL) scores with the estimated HLE. The GHS/QoL score was dichotomized to good (GHS>50) and poor health (GHS≤50). Adjustments were made for sociodemographic factors including age (18-39, 40-64, ≥65 years), sex, and SES (high, middle, low) and clinical factors including years since diagnosis (≤5 years, >5 years), tumour type (ovarian cancer, thyroid cancer, HL, NHL), stage at diagnosis (I, II, III, IV, unknown), and treatment (surgery, systemic therapy, radiotherapy, other, none). All statistical analyses were performed using Stata (version 17.0, StataCorp LLC, College Station, TX).

RESULTS

Sample characteristics

Between 2009 and 2014, 21,376 newly diagnosed patients with ovarian cancer, thyroid cancer, HL and NHL (i.e., rare cancers) and 76,949 with CRC (i.e., common cancer) were registered in the NCR (Table 1). Most thyroid cancer survivors were female (72.0%), while for HL, NHL, and CRC the majority were male (58%, 61%, and 56%, respectively). Age at diagnosis was lowest in HL survivors (median 42 years) and highest in CRC survivors (median 71 years). Moreover, almost half of thyroid cancer survivors and almost two-thirds of HL survivors were aged 18-49 years, while three-quarters of the CRC survivors was aged over 65 years. Most cancer survivors were diagnosed in stage III or IV (72% ovarian cancer, 52% HL and 52% CRC survivors), except for thyroid cancer and NHL survivors (35% and 44%, respectively).

Table 1. Characteristics of selected rare and common cancer patients diagnosed between 2009 and 2014 in the Netherlands

	Rare cancers (n = 21,376)				**Common cancer** (n = 76,949)
	Ovarian (n = 7,389)	**Thyroid** (n = 3,529)	**HL** (n = 2,489)	**NHL** (n = 7,969)	**CRC** (n = 76,949)
Gender (n, %)					
Male	0 (0.0)	998 (28.0)	1,439 (57.8)	4,819 (60.5)	42,834 (55.7)
Female	7,389 (100.0)	2,540 (72.0)	1,050 (42.2)	3,150 (39.5)	34,115 (44.3)
Age at diagnosis (median years, IQR)	67 (58-75)	53 (40-66)	42 (28-60)	64 (53-73)	71 (63-78)
Age at diagnosis (n, %)					
18-34 years	108 (1.5)	514 (14.6)	950 (38.2)	416 (5.2)	328 (0.4)
35-49 years	672 (9.1)	1,025 (29.1)	572 (23.0)	1,101 (13.8)	3,533 (4.6)
50-64 years	2,422 (32.8)	997 (28.3)	485 (19.5)	2,571 (32.3)	19,360 (25.2)
65-79 years	3,117 (42.2)	750 (21.3)	380 (15.3)	3,008 (37.8)	38,074 (49.5)
>80 years	1,070 (14.5)	243 (6.9)	102 (4.1)	873 (11.0)	15,654 (20.3)
Socioeconomic status (n, %)					
Low	2,217 (30.0)	1,086 (30.8)	815 (32.7)	2,403 (30.2)	23,894 (31.1)
Middle	2,954 (40.0)	1,308 (37.1)	913 (36.7)	3,053 (38.3)	31,218 (40.6)
High	2,218 (30.0)	1,135 (32.2)	761 (30.6)	2,513 (31.5)	21,837 (28.4)
Stage[a] (n, %)					
I	1,302 (17.6)	1,850 (52.4)	339 (13.6)	879 (11.0)	14,179 (18.4)
II	581 (7.9)	365 (10.3)	1,019 (40.9)	795 (10.0)	20,827 (27.1)
III	3,623 (49.0)	523 (14.8)	592 (23.8)	1,425 (17.9)	23,055 (30.0)
IV	1,663 (22.5)	723 (20.5)	510 (20.5)	2,685 (33.7)	16,995 (22.1)
Unknown/NA	220 (3.0)	68 (1.9)	29 (1.2)	2,185 (27.4)	1,893 (2.5)
Treatment[b] (n, %)					
Surgery (+/- ST)	5,691 (77.0)	3,174 (89.9)	9 (0.4)	277 (3.5)	63,819 (82.9)
ST[c] (+/- RT)	935 (12.7)	7 (0.2)	2,221 (89.2)	4,430 (55.6)	6,473 (8.4)
RT	2 (0.0)	77 (2.2)	108 (4.3)	683 (8.6)	1,093 (1.4)
Other	19 (0.3)	10 (0.3)	5 (0.2)	228 (2.9)	880 (1.1)
None	742 (10.0)	261 (7.4)	146 (5.9)	2,351 (29.5)	4,684 (6.1)

IQR, interquartile range; NA, not applicable; ST, systemic therapy; RT, radiation therapy
This cohort (*n* = 98,325, 22% rare cancers) was used to calculate life expectancy and years life lost. They were diagnosed with cancer between 2009 and 2014 in the Netherlands.

[a] According to TNM [20-22]. FIGO was used for ovarian cancer [23] and Ann Arbor Code was used for Hodgkin lymphoma and Non-Hodgkin lymphoma [24, 25].
[b] In case of multiple treatments, treatment is presented in the order of surgery (+/- systemic therapy), systemic therapy (+/- radiotherapy), radiotherapy and other.
[c] Systemic treatment includes chemotherapy, targeted therapy, hormonal therapy, and immune therapy.

Healthy life expectancy

LE, YLL, and HLE estimates for rare and common cancer survivors, presented by cancer type, are shown in Table 2 and Fig. 1. Among rare cancer survivors, an ovarian cancer survivor had on average a LE of 8 years, 14 YLL in total, and 5 years spent in good health (HLE 66%). Higher LE and HLE estimates were found for thyroid cancer survivors (LE 24 years, HLE 87% (males) and LE 30 years, HLE 89% (females)), HL survivors (LE 31 years, HLE 90% (males) and 36 years, HLE 91% (females)), and NHL survivors (LE 14 years, HLE 80% (males) and 16 years, HLE 80% (females)). These cancer survivors also had lower YLL due to cancer (3-4 years, both 6 years, and both 9 years for, respectively, male and female thyroid, HL, and NHL survivors). On the other hand, common cancer survivors (i.e., CRC survivors) had an average LE of 9 years, 7 YLL, and 63% HLE for males and 10 years, 7 YLL, and 67% HLE for females.

Age greatly determined LE, YLL and HLE within both groups (i.e., rare and common). The oldest age group (65 and older) had a LE of 4-7 years for rare cancer survivors (vs. 26-51 years for the youngest age group (18-29 years)) and a LE of 7 years for common cancer survivors (vs. 24 years for the youngest age group). The oldest age group also showed the lowest HLE both for rare cancer (ovarian 50%, thyroid 60%, HL 56%, and NHL 60%) and common cancer survivors (CRC 53%). In comparison, those in the youngest age group had higher HLE (ovarian 87%, thyroid 93%, HL 93%, and NHL 90%).

LE was slightly lower among rare cancer survivors with low SES compared to those with high SES, but YLL was similar for all SES groups among rare cancer survivors. In line with this, HLE was lowest for survivors with a low SES, in particular for ovarian cancer and NHL survivors. For example, on average, an ovarian cancer survivor with a low SES had a HLE of 58% vs. 62% among survivors with a high SES. For common cancer survivors, LE and HLE were slightly lower for survivors with a low SES.

Stage at diagnosis had a strong influence on LE, YLL and HLE within both rare and common cancer survivors. Among rare cancer survivors, those diagnosed with stage I lived on average for another 20-41 years as compared to 3-26 years for those with stage IV. Rare cancer survivors with stage IV also had the lowest HLE (ovarian 2%, thyroid 63%, HL 87%, and NHL 74%). For common cancer survivors, LE and HLE differed by stage at diagnosis as well: LE 15 years and HLE 77% for those diagnosed with stage I vs. LE 2 years and HLE 0% for those with stage IV.

Table 2. Life expectancy (LE), years of life lost (YLL), and healthy life expectancy (HLE) among rare and common cancer survivors

	Rare cancer survivors												Common cancer survivors		
	Ovarian (n = 308)			Thyroid (n = 158)			HL (n = 205)			NHL (n = 354)			CRC (n = 2,400)		
	LE (years)	YLL (years)	HLE (years, %)	LE (years)	YLL (years)	HLE (years, %)	LE (years)	YLL (years)	HLE (years, %)	LE (years)	YLL (years)	HLE (years, %)	LE (years)	YLL (years)	HLE (years, %)
Gender															
Male	NA	NA	NA	24	4	21 (87.3)	31	6	28 (89.6)	14	9	12 (80.0)	9	7	6 (63.4)
Female	8	14	5 (65.5)	30	3	27 (89.2)	36	6	32 (90.8)	16	9	12 (79.5)	10	7	7 (66.6)
Age at diagnosis															
18-39	26	25	23 (87.2)	51	1	47 (93.4)	49	6	46 (93.2)	35	17	31 (90.3)	24	24	21 (85.6)
40-64	11	19	8 (72.2)	28	4	25 (88.7)	24	8	21 (86.5)	19	10	16 (83.9)	15	12	12 (77.1)
>65	4	9	2 (50.4)	7	5	4 (60.0)	7	6	4 (55.9)	7	6	4 (60.0)	7	4	4 (53.3)
Socioeconomic status															
Low	8	14	4 (57.5)	28	4	25 (89.2)	31	7	28 (90.2)	14	9	11 (78.3)	9	7	6 (64.1)
Middle	8	14	5 (62.2)	28	4	24 (88.3)	33	6	30 (89.9)	15	8	12 (80.0)	10	7	7 (65.7)
High	9	14	5 (61.8)	29	3	26 (89.2)	35	5	32 (90.5)	15	9	12 (78.4)	10	7	7 (65.4)
Stage[a]															
I	21	6	17 (84.0)	41	1	38 (91.7)	34	3	30 (89.2)	20	3	17 (84.9)	15	2	11 (76.8)
II	14	9	11 (77.9)	25	1	22 (88.6)	39	5	35 (91.7)	16	7	13 (81.2)	12	4	9 (72.3)
III	4	16	2 (33.6)	18	4	15 (83.2)	29	8	26 (88.8)	14	8	11 (77.9)	11	7	8 (69.6)
IV	3	17	0 (1.8)	8	10	5 (62.6)	26	10	23 (86.5)	12	11	9 (73.9)	2	15	0 (0.0)

Random sample of living cancer survivors within the NCR in the period 2009-2014 (n = 1,025 rare cancer survivors; n = 2,400 common cancer survivors)

Fig. 1 Percentage of HLE presented per cancer type and per gender, age at diagnosis and stage

Determinants of poor perceived health in rare cancer survivors

Among rare cancer survivors only, poor perceived health (i.e., GHS/QoL score) was significantly associated with SES, tumour type, stage, and treatment (Table 3). Survivors with a low SES were two times more likely to have a poor perceived health compared to those with a high SES (odds ratio (OR) 2.10, 95% confidence interval (CI) 1.35-3.25). Moreover, survivors of HL and NHL were less likely to have a poor perceived health compared to survivors of ovarian cancer (OR 0.19, 95% CI 0.05-0.65; OR 0.25; 95% CI 0.08-0.80). Furthermore, stage was significantly associated with poor perceived health. Survivors with stage II, III, IV, and unknown were all more likely to report poorer health compared to those with stage I (OR 1.90, 95% CI 1.07-1.35; OR 2.48, 95% CI 1.49-4.13; OR 2.51, 95% CI 1.15-5.33). Finally, survivors who received radiotherapy only were five times more likely to report poor perceived health compared to those who had surgery (+/- systemic therapy) (OR 4.99, 95% CI 1.31-19.06).

Table 3. Perceived health in rare cancer survivors in 2009-2014

	Rare cancer survivors (n = 1,025)		
	Good (n, %)	**Poor (n, %)**	**OR[d] (95% CI) for poor perceived health**
Gender (n, %)			
Male	302 (36)	65 (34)	1
Female	531 (64)	127 (66)	0.99 (0.65-1.52)
Age at diagnosis (%)			
18-39	113 (14)	14 (7)	1
40-64	408 (49)	84 (44)	0.86 (0.50-1.49)
>65	312 (38)	94 (49)	1.16 (0.64-2.09)
Socioeconomic status (n, %)			
High	295 (37)	51 (28)	1
Middle	341 (43)	73 (41)	1.27 (0.85-1.89)
Low	159 (20)	56 (31)	**2.10 (1.35-3.25)**
Years since diagnosis (n, %)			
≤5 years	630 (76)	148 (77)	1
>5 years	203 (24)	44 (23)	1.08 (0.72-1.61)
Tumour type (n, %)			
Ovarian cancer	236 (28)	72 (38)	1
Thyroid cancer	131 (16)	27 (14)	0.84 (0.48-1.46)
HL	178 (21)	27 (14)	**0.19 (0.05-0.65)**
NHL	288 (35)	66 (34)	**0.25 (0.08-0.80)**
Stage[a]			
I	276 (33)	41 (21)	1
II	169 (20)	33 (17)	**1.90 (1.07-3.35)**
III	194 (23)	63 (33)	**2.48 (1.49-4.13)**
IV	146 (18)	41 (21)	**2.51 (1.38-4.54)**
Unknown/NA	48 (6)	14 (7)	**2.48 (1.15-5.33)**

Table 3. Perceived health in rare cancer survivors in 2009-2014 *(continued)*

	Rare cancer survivors (n = 1,025)		
	Good (n, %)	**Poor (n, %)**	**OR[d] (95% CI) for poor perceived health**
Treatment[b]			
Surgery (+/- ST)	359 (43)	91 (47)	1
ST[c] (+/- RT)	350 (42)	78 (41)	2.85 (0.92-8.86)
RT	52 (6)	13 (7)	**4.99 (1.31-19.06)**
Other	16 (2)	2 (1)	1.50 (0.23-9.99)
None	56 (7)	8 (4)	1.72 (0.44-6.79)

OR, odds ratio, CI, confidence interval; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; ST, systemic treatment; RT, radiation therapy
Random sample of living cancer survivors within the NCR in the period 2009-2014 (*n* = 1,025 rare cancer survivors)
[a] According to TNM. FIGO was used for ovarian cancer and Ann Arbor Code was used for Hodgkin lymphoma and Non-Hodgkin lymphoma.
[b] In case of multiple treatments, treatment is presented in the order of surgery (+/- pre- or posttreatment), systemic therapy (+/- radiotherapy), radiotherapy and other.
[c] Systemic treatment includes chemotherapy, targeted therapy, hormonal therapy, and immune therapy.
[d] Multivariate analysis adjusted for gender, age, socioeconomic status, tumour type, time since diagnosis, stage, treatment
Bold value indicates $p < 0.05$

DISCUSSION

Main findings

Survivors of a rare cancer (i.e., ovarian cancer, thyroid cancer, HL, and NHL) had an average LE of 8 to 36 years and spent ≥67% of their remaining life in good health. Survivors of a common cancer (i.e., CRC) had an average LE of 10 years with about 67% of their remaining life spent in good health. For both rare and common cancer survivors, LE and HLE were mainly determined by age and stage at diagnosis as cancer survivors in the oldest age group and those diagnosed with stage IV had the lowest HLE. Furthermore, having a low SES, being diagnosed in an advanced stage, and receiving radiotherapy were important predictors of poor perceived health among rare cancer survivors.

Interpretation of findings

Rare and common cancer survivors in this study spent more than 65% of their remaining life in good health. HLE was comparable between survivors of all cancer types included in this study. This is not in line with our expectations and, partly, in contrast with previous studies on survival and QoL, showing that patients diagnosed

with rare cancer have lower survival rates [5] and reported worse QoL outcomes when compared to common cancer patients [33, 34]. It is important to recognise that QoL and HLE are related but distinct measures, since HLE incorporates both life expectancy and QoL. In addition, these previous studies included a wide range of rare cancers, while in our study, only a subset of rare cancers was included. Indeed, the majority of rare cancer survivors in our study were diagnosed with highly curable cancers and with generally good prognosis (i.e., thyroid cancer, HL and NHL), positively affecting the HLE estimates. In contrast, for ovarian cancer survivors with on average a poorer prognosis, the HLE is somewhat lower (66% for ovarian vs. 89% for thyroid cancer (females)). Yet, the HLE of the good prognosis rare cancers closely resembles that of the general population in Europe (i.e., HLE at birth 80%) [35], while the HLE of the poorer prognosis rare cancers is found to be similar to that of women with diabetes (i.e., HLE 67%) [36]. The similar HLE estimates suggest that patients – specifically those with a good prognosis – can expect similar QoL for their remaining life as the general population. This could be partly explained by the adoption of healthier lifestyle among survivors, leading to improved overall health and QoL [37, 38]. As such, programmes that encourage survivors to adopt healthier lifestyles should be incorporated in survivorship planning.

For both rare and common cancer survivors, those aged 65 years and older at diagnosis had lower HLE than those in the younger age groups (50-60% vs. 86-93%, respectively). These findings are in concordance with previous studies on HLE in oral squamous cell carcinoma [14] and CRC survivors [15], showing that HLE became significantly shorter with increasing age. This might be explained by both the ageing process, i.e., increasing prevalence of multimorbidity and diminished treatment tolerance, and the effect of cancer and its' treatment, i.e., physiologic changes and long-term complications in older adults. For example, patients diagnosed with ovarian cancer at older ages show a reduced response to chemotherapy [39], which may adversely affect their LE and HLE. Moreover, a previous study in adults aged ≥65 years has shown that HLE was negatively associated with typical geriatric symptoms, including frailty, depression, and poor physical and cognitive function [40]. Consequently, both aspects might increase the vulnerability of the older cancer population in terms of losing functional independence and necessitating long-term care, which in turn negatively impacts their HLE. Assessing and addressing the QoL needs as part of integrated survivorship care are key to improve HLE for survivors, including those at older ages [41].

Our study also showed that those diagnosed with stage IV had lower HLE than those diagnosed with early-stage cancer. These findings are in line with previous studies on HLE in cancer survivors [14, 15]. Advanced disease stage is often associated with decreased physical functioning, compounding the effect of cancer on disability among cancer survivors. Despite improvements in diagnostics and treatment, physical functioning, self-rated health, and QoL outcomes are in particularly poor for cancer survivors with more advanced stage [42]. In our study, ovarian cancer and CRC survivors with stage IV had specifically low LE with hardly any years spent in good health. Those

survivors might receive more aggressive treatments and thus experience diminished QoL due to persistent symptoms and treatment effects such as fatigue, insomnia, and pain [43-46]. Our findings indicate the negative and long-lasting effect of advanced disease stage on HLE, and also stress the importance of improving early diagnosis and detection.

Low SES, advanced stage at diagnosis, and receiving radiotherapy are important predictors of poor perceived health among rare cancer survivors. Similar to our finding, lower SES has been associated with poorer health in survivors of ovarian cancer [47], thyroid cancer [48] and lymphoma [49]. In general, lower SES has been associated with poorer health due to a lack of knowledge regarding healthy lifestyle behaviours, limited access to health care services, poorer living conditions, and increased psychological stress [50, 51]. This finding is, however, probably not specific for rare cancer survivors, since similar results have been found among common cancer survivors [52]. This indicates that low SES remains an important predictor of poor perceived health for all cancer patients, regardless of the cancer type. Regarding treatment, having had radiotherapy was an important predictor of poor perceived health predominantly among NHL survivors (findings not shown). Radiotherapy is known to cause diverse long-term effects in patients with common cancer [53, 54], thereby negatively affecting QoL. For NHL survivors, a previous study reported that NHL survivors with a comorbidity at diagnosis reported lower QoL if they received radiotherapy [55]. Radiotherapy treatment in this survivor group might increase the risk of cardiovascular problems [56], which could adversely impact their health status. Therefore, special programmes to increase adoption of healthier lifestyle and tailored social support might be beneficial for those patients at a higher risk of a poor health.

Strengths and limitations

Strengths of this study include the use of population-based data, and the linkage with QoL data based on patient-reported outcomes from the same population. This linkage provides valuable insights into the health status of cancer patients during their expected remaining life. Moreover, HLE has become an important population health measure worldwide [7], and, with our subset of cancer types, we were able to showcase its utility for the cancer patient population and clinical practice. Several limitations should be considered as well. First, this explorative study only took into account a subset of cancer types. Due to the large number of rare cancer types, we decided to pick a subset of solid and haematological cancers to showcase the value of this HLE estimate for other cancer types. The included tumour groups are not representative for all rare or common cancer survivors, and therefore should be interpreted with caution. Second, QoL data from 2009-2014 (i.e., when the patients filled in the questionnaire) were used, since there are currently no more recent data on QoL for these patient groups. LE and HLE might change during different disease phases due to the influence of demographic and disease-related factors, including long-term sequelae, recurrence, or diagnosis of comorbid diseases after cancer. Third, the assessment

of QoL is based on a subjective measure of health, posing a risk of underestimation, and by the use of a cross-sectional questionnaire, while QoL and health perceptions might change over time. Finally, although QoL has been assessed throughout the different stages, no (possible) long-term effects of the cancer diagnosis on QoL have been considered.

Implications for research and practice

Future research should investigate the utility of the HLE measure among a wide range of cancer types, both rare and common, to gain a complete understanding of HLE among cancer survivors. Additionally, longitudinal data is needed, as repeated QoL measurements will give insights into the change in QoL, throughout the different disease phases. Finally, comorbidities at time of diagnosis should be taken into account, since they are likely to affect patient outcomes and thus HLE estimates.

Regarding clinical practice, HLE among cancer survivors can become a clinically meaningful measure, as it incorporates both duration of life and QoL. As such, HLE can be used as an important tool for clinical decision-making in cancer management, with the emphasis on spending the remaining years in good health. Current efforts in cancer research, e.g., within drug development, are predominantly aimed at prolonging duration of life with as little side effects as possible. However, since an increasing number of people are expected to live with and after cancer [57], more attention should be aimed at cancer survivors spending their remaining years in good health. Poor health among cancer survivors will enormously impact society as a whole, leading to adverse effects on work capacity, activities of daily living, financial stability and emotional well-being [58]. Therefore, HLE must be considered, e.g., for treatment decisions, and healthcare professionals should support cancer survivors living their life in the best possible health.

CONCLUSION

HLE estimates applied to a subset of rare and common cancer types showcased the utility of this health outcome measure for patients and clinical practice. Yet, data on QoL for all rare cancers should be collected routinely, as this can serve as an important indicator for monitoring and improving cancer care, and for enabling HLE measurements in cancer survivors. The current increasing trends in incidence and the number of people living with and after cancer indicate the need to improve HLE, which could be achieved through earlier diagnosis and healthier lifestyle.

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CHAPTER 4

Quality of life of patients with rare cancer: a comparison with patients with colorectal cancer and the association with disease trajectory-related factors

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ABSTRACT

Purpose: Differences in quality of life (QoL) between patients with rare and common cancer might be explained by the specific challenges patients with rare cancer face during their disease trajectory, but research is scarce. This study aimed to: (1) assess the difference in QoL between patients with rare and common cancer (i.e., colorectal cancer (CRC)), and (2) examine the association between disease trajectory-related factors and QoL in patients with rare cancer.

Methods: Cross-sectional data was collected among adults with rare cancer by a nationwide online survey in the Netherlands. For comparison with patients with CRC, data from the Prospective Dutch Colorectal Cancer (PLCRC) cohort were used. Associations were assessed by linear regression analyses.

Results: Data from 1,525 patients with rare cancer and 1,047 patients with CRC were analysed. Having a rare cancer was significantly associated with a lower QoL compared to having CRC (p<0.001). Disease trajectory-related factors significantly associated with QoL in patients with rare cancer were: time till diagnosis, misdiagnoses, information on best treatment options, information on late and/or long-term effects, and both satisfaction with physician and specialized nurse care (all: p<0.05).

Conclusion: Patients with rare cancers have a lower self-reported QoL than patients with CRC, and several disease trajectory-related factors are associated with QoL in patients with rare cancer.

Implications for Cancer Survivors: To improve QoL of patients with rare cancer, appropriate guidance and support by healthcare professionals throughout the disease trajectory is needed, as well as early diagnosis and proper referral to centres of expertise.

INTRODUCTION

Rare cancers are cancer types with an annual incidence of less than six per 100,000 people, as defined by the RARECARE initiative [1]. In the Netherlands, approximately 124,000 patients are diagnosed with cancer every year, of whom 21% are affected by a rare form of cancer [2,3]. Out of the 260 cancer types, 86% is rare in the Netherlands [2]. According to a recent study, patients with rare cancer have a lower five-year survival rate than those with common cancer, 52% vs. 69% respectively [4] Although significant improvement in survival is seen in patients with common cancer in recent years, e.g., breast and colorectal cancer (CRC), hardly any development is seen in the prognosis of patients with rare cancer [2,4].

Having a rare cancer may impair a patient's physical and emotional health, consequently affecting their quality of life (QoL) [2,5,6]. Only few studies have focused on QoL in patients with rare cancer [2]. For example, in a study of patients with sarcoma in Germany it was discovered that they have significantly worse health-related QoL than the general population [7]. In a study in Brazil, on QoL in patients with rare cancer, they found that these patients have worse QoL and higher degrees of distress than those with common cancer types [6]. However, information on QoL of patients with rare cancer in general, compared to QoL of patients with common cancer, is largely lacking [2].

Differences in QoL between patients with rare and common cancer might be explained by the specific challenges patients with rare cancer face during their disease trajectory (i.e., the period from pre-diagnosis to aftercare) [2]. These challenges include missed or delayed diagnosis, limited and less effective treatment options, scattered and less clinical expertise, missing guidelines on clinical decision-making, and a lack of disease-specific information [2,8-11]. As a result, patients with rare cancers are frequently diagnosed at more advanced stages, resulting in a worse prognosis than patients with common cancers [12]. In a recent study, healthcare experiences between patients with rare and common cancer were found to differ during the diagnostic and treatment phase [13]. For example, patients with a rare cancer were more likely to receive their diagnosis and treatment in different hospitals than patients with a common cancer, and had more negative experiences when they were treated in multiple hospitals (e.g., patients with rare cancer indicated more often that they did not feel supported by their physician when referred to another hospital).

Previous research on the impact of disease trajectory-related factors (e.g., diagnostic delay and lack of disease-specific information) on QoL is limited, focusing primarily on patients with common cancer, or specific rare tumour types. For example, Robinson et al. showed that longer total diagnostic delay was associated with reduced QoL in patients with ovarian and endometrial cancer [14]. Other disease trajectory-related factors that were shown to be associated with QoL in patients with common cancer are information provision [15,16] and satisfaction with care [17,18]. Despite the fact that patients with rare cancer often face specific challenges in their disease trajectory, the impact of these disease trajectory-related factors on QoL in patients with rare cancer

remains unknown. Therefore, the aims of this study were to: (1) assess the difference in QoL between patients with rare and common cancer (i.e., CRC), and (2) examine the association between disease trajectory-related factors and QoL in patients with rare cancer.

METHODS

Study design and participants

A nationwide cross-sectional survey on experiences regarding the disease trajectory among adult patients with rare cancer was conducted by the Dutch Federation of Cancer Patients Organisations (NFK) [19]. From the 9th of March 2020 to the 1st of February 2021, data were collected through an online survey in the Netherlands. Respondents were asked to self-report their rare cancer type from a predetermined list based on the RARECARENet cancer list, applied to the Dutch situation [1]. If respondents reported their diagnosis as 'other', it was checked whether the diagnosis corresponded with a type of rare cancer from the predetermined list. In a previous study it was concluded that the ability of self-reporting a prior cancer diagnosis is high for any patient with cancer [20]. Participation in the online survey was anonymous and participants were informed about privacy policies. Only participants who completed the entire questionnaire were included. The medical ethical committee of the VU University Medical Centre issued the Medical Research Involving Human Subjects act (WMO) as not applicable, so no ethical approval was required (2021.0722).

To make a comparison with patients with common cancer, a cohort of patients with CRC was chosen to represent common cancer, due to availability of data on a group of patients with a common cancer type that occurs in both men and women. Moreover, CRC is the third most common cancer in both men and women [21]. Data from the Prospective Dutch Colorectal Cancer (PLCRC) cohort were used [22]. PLCRC is a prospective Dutch observational cohort in which adult patients who have a histologically confirmed or strong clinical suspicion of CRC can be included [22]. Participants with a rare CRC type, such as pseudomyxoma peritonei (PMP), were excluded from this study. In PLCRC, patients provided informed consent at inclusion to use their clinical data for scientific research and to receive questionnaires on health-related issues. PLCRC was registered at ClinicalTrials.gov (NCT02070146), and approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht (NL47888.041.14).

Survey: experiences of patients with rare cancer

The online survey was developed by NFK, the Platform Rare Cancer Patients (PZK) (www.zeldzamekankers.nl), national experts on rare cancer, and representatives of the Dutch Rare Cancer Platform (DRCP). The Dutch survey consisted of 37 questions,

of which 30 were quantitative questions and seven were open-ended questions (Supplementary Survey 1). A number of questions were conditional (i.e., based on previous answers, questions were skipped due to irrelevance). Only the quantitative questions were used in this study.

The survey started with a question to select respondents who have (had) rare cancer, followed by three sociodemographic questions (i.e., gender, year of birth, and educational level). The remaining questions focused on various aspects of the disease trajectory, including diagnostic trajectory, treatment options, information provision, and support of the physician and/or specialized nurse. All quantitative questions on these aspects either had several answer alternatives or a 10-point Likert scale ranging from 1 (very dissatisfied) to 10 (very satisfied). Finally, respondents were asked to rate their QoL in the previous week on a 7-point Likert scale ranging from 1 (very poor) to 7 (excellent). This item was derived from the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) and is part of the global health status/QoL scale [23].

Data collection

With regard to patients with rare cancer, data were obtained using the online tool 'Survey Monkey' [24]. As almost the whole Dutch population has internet access [25], no problems with dissemination through the internet were anticipated. The questionnaire was nationally distributed through the 'Doneer Je Ervaring' (Donate Your Experience) website of NFK (www.nfk.nl/doneer-je-ervaring) and social media (e.g., Facebook, Twitter and LinkedIn). The participating cancer patient organizations, affiliated with NFK, were asked by email to distribute the survey amongst their members. All members of the 'Doneer Je Ervaring' panel received an invitation to fill out the survey. All patients who have (had) cancer can register online for this panel. In addition, a few hospitals actively recruited respondents. Partner organizations (e.g., The Dutch Cancer Society (KWF), and Kanker.nl) spread the questionnaire through their own channels. Participants' personal details (e.g., name, address, email) were not collected.

For the comparison with patients with common cancer, data from the PLCRC cohort and the Netherlands Cancer Registry (NCR) were used. Within PLCRC, patient-reported outcomes like QoL are collected. Measurement of QoL included the EORTC QLQ-C30 item on QoL in the previous week on a 7-point Likert scale ranging from 1 (very poor) to 7 (excellent). Clinical data, such as time since diagnosis and treatment information, were obtained by linking the PLCRC cohort with the NCR [26]. EORTC QLQ-C30 data reported in 2020 were obtained, in accordance with the data collection of the rare cancer questionnaire. The 18-month follow-up moment of the PLCRC cohort was chosen as most optimal match in sample size and average treatment time in both groups, resulting in a diverse cohort (i.e., ranging from tumour-free to metastasized).

Statistical analyses

Characteristics of both groups were described by means of descriptive analyses. This included sociodemographic variables and disease-related variables. To assess between-group differences in characteristics, t-tests and chi-squared tests were performed. Linear regression analysis was performed to compare QoL of patients with rare cancer and CRC. The 7-point Likert scale was transformed to a 0-100 scale, in line with scoring of the EORTC QLQ-C30 scales [27]. Confounding by age and gender was taken into account [2,28-31]. An additional adjusted analysis was performed to check whether differences in the dependent variable (i.e., QoL) between the groups could be explained by between-group differences in demographic and treatment-related factors. To examine the association between disease trajectory-related factors and QoL in patients with rare cancer, linear regression analyses were performed. Subsequently, all variables with a statistically significant association with QoL were combined into one explanatory model to assess which factors remained statistically significant. Confounding by age, gender, and educational level was taken into account [6,7].

Continuous variables are reported as mean and standard deviation (SD), when the data were normally distributed. For non-normally distributed data, continuous variables are reported as median and interquartile range (IQR). Categorical variables are reported as numbers and percentages. For all analyses, a p-value < 0.05 was considered statistically significant. Continuous independent variables were categorized if no linear relationship with the dependent variable existed. All analyses were performed using IBM SPSS Statistics Version 25.

RESULTS

Sample characteristics

A total of 2,666 participants started the survey for patients with a rare cancer, with 2,037 completing the entire questionnaire. After exclusion of participants who gave duplicate responses (i.e., if the exact same answers in both the open and closed fields were identified) or could not be classified into a rare cancer group of the RARECARENet cancer list, 1,525 participants with a rare cancer were eligible for analysis. In the rare cancer group, the majority was diagnosed with haematological cancer (40%), digestive cancers (11%) or sarcomas (11%). Regarding the PLCRC cohort, data from 1,047 participants with CRC, who completed the QoL questionnaire at 18-month follow-up in 2020, were available.

Patients with rare cancer were on average younger (57 years, SD 12.9) than patients with CRC (65 years, SD 10) (p<0.001). Patients with CRC were more likely to be men compared to patients with a rare cancer (65% vs. 38% respectively) (p<0.001). Information on educational level was unavailable for the CRC patients at the 18-month

follow-up moment. The majority of patients with a rare cancer had a high educational level (53%). The median time since diagnosis differed significantly between the rare cancer and CRC group (4 vs. 2 years respectively) (p<0.001). Except for chemotherapy (p=0.967), other received treatment types (i.e., surgery, radiotherapy, targeted and/or immunotherapy, and active surveillance/wait and see) differed significantly between the groups (all: p<0.001) (Table 1).

Table 1. Characteristics of the study sample by cancer type (total *n* = 2,572)

Characteristics	Rare cancer (*n* = 1,525)	CRC (*n* = 1,047)	*p*-value
Age in years, mean (SD)	57.07 (12.89)	64.91 (10)	<0.001
Gender – male	572 (37.5%)	676 (64.6%)	<0.001
Educational level			NA
Low	127 (8.3%)	-	
Medium	562 (36.9%)	-	
High	800 (52.5%)	-	
Years since diagnosis, median (IQR)	4 (6)	2 (1)	<0.001
Treatment			
Surgery	779 (51.1%)	904 (92.5%)	<0.001
Chemotherapy	628 (41.2%)	401 (41%)	0.967
Radiotherapy	469 (30.8%)	216 (22.1%)	<0.001
Targeted- and/or immunotherapy	237 (15.5%)	48 (4.9%)	<0.001
Active surveillance/wait and see	206 (13.5%)	NA	NA
Cancer domain*			NA
Sarcomas	163 (10.7%)	NA	
Female genital cancers	137 (9%)	NA	
Male genital and urogenital cancers	79 (5.2%)	NA	
Neuroendocrine tumours	73 (4.8%)	NA	
Digestive cancers	165 (10.8%)	1047 (100%)	
Cancers of the endocrine organs	88 (5.8%)	NA	
Head and neck cancers	94 (6.2%)	NA	
Thoracic cancers	33 (2.2%)	NA	
Skin cancers and non-cutaneous melanoma	30 (2%)	NA	
Cancers of the central nervous system	47 (3.1%)	NA	
Haematological cancers	616 (40.4%)	NA	

Table 1. Characteristics of the study sample by cancer type (total *n* = 2,572) *(continued)*

Characteristics	Rare cancer (*n* = 1,525)	CRC (*n* = 1,047)	*p*-value
Current disease phase			NA
I do not have cancer anymore	721 (47.3%)	-	
I will (probably) get better	167 (11%)	-	
I will (probably) not get better	637 (41.8%)	-	
Quality of life score, mean (SD)	71.04 (22.98)	80.98 (17.90)	<0.001

n, number; CRC, colorectal cancer; SD, standard deviation; IQR, interquartile range
*Based on EURACAN classification [55], supplemented with haematological cancer

Comparison of QoL between patients with rare cancer and CRC

The mean QoL scores of participants with rare cancer and CRC were 71.04 (SD 22.98) and 80.98 (SD 17.90) (p<0.001), respectively (Table 1). Having a rare cancer was significantly associated with a lower QoL score after adjusting for confounding by age and gender (β=-8.967; p<0.001) and after adjusting for between-group differences (i.e., age, gender, time since diagnosis, and treatment) (β=-7.814; p<0.001), compared to having CRC.

Disease trajectory-related factors associated with QoL in patients with rare cancer

Several factors from the diagnostic phase (i.e., time till diagnosis, misdiagnoses, and verbal vs. verbal and written information on diagnosis) were significantly associated with QoL score (all: p<0.05). In addition, several factors regarding (effects of) treatment were significantly associated with QoL score (all: p<0.05). These factors included: receiving information on the best treatment options, on expertise/experience of the physician regarding treatment, on reduction in complaints and symptoms, on short-term complications and side effects, and on late and/or long-term effects of treatment. No significant associations were found between type of hospital of cancer treatment and QoL score. Finally, multiple factors throughout the whole disease trajectory (i.e., satisfaction with physician care, having a specialized nurse, and satisfaction with specialized nurse care) were significantly associated with QoL score (all: p<0.05) (Table 2).

Table 2. Associations between disease trajectory-related variables and QoL in patients with rare cancer determined using crude and adjusted linear regression analyses

		Crude analysis		Adjusted analysis*		
		β	*p-value*	*β*	*95%-CI*	*p-value*
Time till diagnosis	<1 month	Ref.	-	-	-	-
	1-6 months	1.128	0.472	1.363	[-1.681; 4.406]	0.380
	>6 months	-4.970	0.039	-5.343	[-10.015; -0.672]	0.025
Misdiagnoses	0	Ref.	-	-	-	-
	1	-3.903	0.012	-4.297	[-7.316; -1.279]	0.005
	>1	-4.406	0.020	-4.314	[-7.985; -0.643]	0.021
Information on diagnosis	Verbal only	Ref.	-	-	-	-
	Verbal and written	3.105	0.015	3.668	[1.179; 6.157]	0.004
Type of hospital of cancer treatment	Academic/ specialized	Ref.	-	-	-	-
	Top-clinical	-0.331	0.805	-0.436	[-3.041; 2.170]	0.743
	General	0.277	0.882	-0.059	[-3.684; 3.566]	0.975
Information on expertise	Yes	Ref.	-	-	-	-
	No	-5.315	<0.001	-5.421	[-7.892; -2.949]	<0.001
Information on reduction in complaints and symptoms	Yes	Ref.	-	-	-	-
	Partially	-7.878	<0.001	-7.319	[-10.262; -4.376]	<0.001
	No	-7.027	<0.001	-7.817	[-11.283; -4.351]	<0.001
Information on best treatment options	Yes	Ref.	-	-	-	-
	Partially	-12.202	<0.001	-11.737	[-15.683; -7.791]	<0.001
	No	-13.990	<0.001	-14.424	[-19.565; -9.284]	<0.001
Information on short-term complications and side effects	Yes	Ref.	-	-	-	-
	Partially	-8.487	<0.001	-8.087	[-10.942; -5.232]	<0.001
	No	-5.891	<0.001	-5.963	[-9.358; -2.567]	<0.001
Information on late and/or long-term effects	Yes	Ref.	-	-	-	-
	Partially	-4.694	0.001	-4.501	[-7.341; -1.662]	0.002
	No	-8.707	<0.001	-8.664	[-11.341; -5.987]	<0.001
Satisfaction with physician care**	Insufficient	Ref.	-	-	-	-
	Sufficient/ good	13.453	<0.001	13.199	[9.394 ;17.003]	<0.001
	Excellent	19.516	<0.001	18.804	[14.983; 22.625]	<0.001
Specialized nurse	Yes	Ref.	-	-	-	-
	No	-4.217	<0.001	-4.770	[-7.169; -2.372]	<0.001

Table 2. Associations between disease trajectory-related variables and QoL in patients with rare cancer determined using crude and adjusted linear regression analyses *(continued)*

		Crude analysis		Adjusted analysis*		
		β	*p-value*	*β*	*95%-CI*	*p-value*
Satisfaction with specialized nurse care**	Insufficient	Ref.	-	-	-	-
	Sufficient/ good	1.955	0.204	2.667	[-0.326; 5.659]	0.081
	Excellent	9.227	<0.001	9.641	[6.695; 12.587]	<0.001

*Adjusted for confounding by age (18-39, 40-49, 50-59, 60-69 and ≥70 [56]), gender and educational level
**Categorized as insufficient (<5.5), sufficient/good (5.5 - <8.5) and excellent (≥8.5) [35]

After aggregating all significantly associated factors with QoL in one model, several factors remained significant. These factors include: a time till diagnosis of more than six months compared to a time till diagnosis of less than a month (p=0.015), receiving one misdiagnosis compared to no misdiagnosis (p=0.033), receiving no or only partial information on the best treatment options compared to receiving this information (both: p<0.05), receiving no information on late and/or long-term effects compared to receiving this information (p=0.035), and scoring sufficient/good or excellent on either satisfaction with physician care or satisfaction with specialized nurse care throughout the disease trajectory (all: p<0.05) (Table 3).

Table 3. Crude and adjusted multivariable model assessing the association between disease trajectory-related factors and QoL in patients with rare cancer

		Crude analysis		Adjusted analysis*		
		β	*p-value*	*β*	*95% CI*	*p-value*
Time till diagnosis	<1 month	Ref	-	-	-	-
	1-6 months	2.054	0.233	2.468	[-0.871; 5.807]	0.147
	>6 months	-6.431	0.018	-6.553	[-11.831; -1.275]	0.015
Misdiagnoses	0	Ref	-	-	-	-
	1	-2.977	0.079	-3.589	[-6.887; -0.292]	0.033
	>1	-1.629	0.433	-1.902	[-5.933; 2.129]	0.355
Information on diagnosis	Verbal only	Ref	-	-	-	-
	Verbal and written	-0.144	0.917	0.554	[-2.142; 3.250]	0.687
Information on expertise	Yes	Ref	-	-	-	-
	No	0.380	0.800	0.145	[-2.768; 3.057]	0.922

Table 3. Crude and adjusted multivariable model assessing the association between disease trajectory-related factors and QoL in patients with rare cancer *(continued)*

		Crude analysis		Adjusted analysis*		
		β	*p-value*	*β*	*95% CI*	*p-value*
Information on reduction in complaints and symptoms	Yes	Ref	-	-	-	-
	Partially	-2.624	0.149	-2.012	[-5.541; 1.517]	0.264
	No	-0.943	0.695	-0.477	[-5.160; 4.206]	0.842
Information on best treatment options	Yes	Ref	-	-	-	-
	Partially	-7.274	0.001	-6.923	[-11.254; -2.593]	0.002
	No	-6.458	0.049	-6.645	[-13.033; -0.257]	0.041
Information on short-term complications and side effects	Yes	Ref	-	-	-	-
	Partially	-2.015	0.280	-1.643	[-5.260; 1.975]	0.373
	No	4.300	0.083	4.384	[-0.431; 9.199]	0.074
Information on late and/or long-term effects	Yes	Ref	-	-	-	-
	Partially	-2.423	0.158	-2.892	[-6.244; 0.460]	0.091
	No	-3.719	0.052	-4.005	[-7.732; -0.277]	0.035
Satisfaction with physician care**	Insufficient	Ref	-	-	-	-
	Sufficient/ good	9.005	<0.001	8.539	[3.345; 13.734]	0.001
	Excellent	11.983	<0.001	10.816	[5.076; 16.556]	<0.001
Specialized nurse	Yes	Ref	-	-	-	-
	No	4.942	0.090	5.073	[-0.590; 10.736]	0.079
Satisfaction with specialized nurse care**	Insufficient	Ref	-	-	-	-
	Sufficient/ good	6.362	0.041	7.113	[1.061; 13.164]	0.021
	Excellent	8.002	0.013	8.915	[2.599; 15.231]	0.006

*Adjusted for confounding by age, gender, and educational level
**Categorized as insufficient (<5.5), sufficient/good (5.5 - <8.5) and excellent (≥8.5) [35]

DISCUSSION

Main findings

Patients with rare cancer showed a lower QoL than patients with CRC in the Netherlands. Regarding patients with rare cancer, several factors throughout the disease trajectory were associated with QoL. In the diagnostic phase, patients with rare cancer who had a longer time till diagnosis (i.e., > 6 months vs. < 1 month) had a lower QoL, as well as those who received a misdiagnosis compared to no misdiagnosis. Regarding treatment, patients with rare cancer who reported they did not or only partially receive information on the best treatment options had a lower QoL than those who reported they did receive this information. Additionally, patients with rare cancer who did not receive information on late and/or long-term effects of treatment had a lower QoL than those who did receive this information. Finally, throughout the whole disease trajectory, patients with rare cancer who gave a higher score (sufficient/good or excellent vs. insufficient) to either physician care or specialized nurse care had a higher QoL.

Interpretation of findings

Our study showed that patients with rare cancer had a statistically significant lower QoL score than patients with CRC, which is in line with the only previous study that compares QoL of patients with rare and common cancer [6]. Furthermore, research on differences in QoL between patients with a rare disease and patients with a common disease also confirm our finding, as they report a significantly lower QoL in patients with a rare disease [32,33]. The difference in QoL may be explained by the lasting impact of the difficult disease trajectory on patients with rare cancer, related to factors such as stage at diagnosis and diverse treatments, potentially caused by delays in this trajectory. This might imply that the overarching challenges that come with having a rare disease have a great impact on these patients' QoL compared to patients with a common disease, even several years after diagnosis [32].

Regarding the diagnostic phase of patients with rare cancer in our study, both time till diagnosis and misdiagnoses were found to be statistically significant associated with QoL. Although not previously reported in patients with rare cancers, a previous study in patients with ovarian and endometrial cancer found, in line with our findings, that longer total diagnostic delay was associated with reduced QoL [14]. On the contrary, a systematic review in a range of different cancer types on the association between time till diagnosis and better clinical and psychological outcomes found that there was only moderate consensus between, and even within, specific cancer types on the existence of an association [34]. The inconsistency between this review and our findings may be explained by the fact that, in the review, diagnostic delay was studied mostly in patients with common cancer, while patients with rare cancer more often face misdiagnoses and diagnostic delay [2,8-11]. Therefore, our findings might be

explained by the struggle patients with rare cancer often face during the diagnostic phase, possibly accompanied by feelings of insecurity, resulting in a lower QoL [2,11,35]. In a study by Bogart et al., on QoL of patients with rare diseases, it was found that having symptoms for a longer time was associated with lower QoL, whereas being diagnosed for a longer time was associated with better QoL [32]. This stresses the importance of receiving a timely diagnosis, as a diagnosis paves the way to treatment and support [32]. Another interesting finding of our study was that receiving multiple misdiagnoses was not statistically significant associated with lower QoL compared to receiving no misdiagnosis. Although speculative, this might imply that the first misdiagnosis has the greatest impact on QoL of rare cancer patients. Another explanation might be that getting multiple misdiagnoses creates the patient's understanding that it is something that is difficult to interpret (i.e., that it concerns a rare diagnosis).

Considering treatment-related variables, our finding that receiving no or only partial information on the best treatment options was statistically significant associated with lower QoL can be explained by previous literature. Due to a lack of clinical expertise for patients with a rare disease in general, those patients often have to become their own expert [36]. Therefore, these patients may have indicated that they, in retrospect, did not receive information on the best treatment options, due to their acquired knowledge about their disease and its treatment options. In our study, patients with rare cancer who did not receive information on late and/or long-term effects had a significantly lower QoL than patients who did. In line with our finding, a previous study in childhood cancer survivors showed the specific need for information on possible late effects, and that a lack of information was associated with a lower QoL [37]. Since the rare cancer group in our study was generally several years after diagnosis, their QoL might have been adversely affected by late treatment effects at the time they completed the questionnaire. Together with the lack of information on late treatment effects for rare cancer [38], this may explain our finding that patients with rare cancer who did not receive information on late and/or long-term effects had a lower QoL. Remarkably, although not statistically significant, was the reverse association between receiving information on short-term complications and side effects and QoL (i.e., no information was associated with higher QoL). This could be explained by the fact that not receiving information on short-term complications results in less concerns on potential complications and side effects, and therefore a better QoL [39].

With regard to the whole disease trajectory, being satisfied with both physician and specialized nurse care was statistically significant associated with better QoL. Although no previous studies focused specifically on satisfaction with the provided care of the physician and/or specialized nurse, patient satisfaction with the overall provided care and the association with QoL is well known [17,18]. Moreover, several factors in our study on information in the diagnostic and treatment phase (i.e., information on diagnosis, expertise, reduction in complaints and symptoms as an effect of treatment, and short-term complications and side effects of treatment) did not remain statistically significant associated with QoL. This may be explained by the

factors on satisfaction, indicating that the impact on QoL depends on satisfaction with (the quality and content of) information rather than solely information provision. An association between satisfaction with information and a better QoL has been supported by previous studies [15,16]. In contrast to previous studies, having a specialized nurse as main point of contact was not statistically significant associated with QoL [40-42]. However, satisfaction with specialized nurse care was significantly associated with QoL in our study, implying that satisfaction with a specialized nurse is of more importance than solely having a specialized nurse as main point of contact for improvement of QoL.

Strengths and limitations

To our knowledge, this is the first explorative study on differences in QoL between patients with rare cancer and a common cancer type, as well as on disease trajectory-related factors associated with QoL in patients with rare cancer. Another strength of this study is the large sample size of the rare cancer group. As research in patients with rare cancer is often challenging due to the fact that each specific rare cancer type has a small patient population [2,43], studying QoL in an aggregated cohort containing multiple types of rare cancers made it possible to perform analyses that otherwise would not have been feasible [5].

A number of study limitations must be addressed as well. First, regarding generalizability, data of patients with rare cancer were collected through a convenience sample, and therefore may not be representative for all patients with a rare cancer in the Netherlands. In the rare cancer group, there is an overrepresentation of female patients, patients with haematological cancers, and patients with a higher educational level. Moreover, as the Netherlands has a high treatment volume and centralisation pattern compared to other European countries [44], the burden of rare cancer in the Netherlands may differ from other European countries. Therefore, the results of this study may not be generalizable to other countries and non-Western cultures. Second, CRC was used as a representative for common cancer in order to make a comparison with rare cancer. The choice for CRC was made based on availability of data on a group of patients with a common cancer type including both men and women. Therefore, conclusions on differences in QoL between patients with rare and common cancer in general have to be drawn with caution. In addition, no comparisons with the CRC group based on stage and intensity of treatment could be made, which might have affected the observed differences in QoL between both groups. Third, in this study, QoL was measured with a single-item on a 7-point scale, instead of the whole EORTC QLQ-C30 or the two-item global health status/QoL scale. The 7-point scale was analysed according to the EORTC QLQ-C30 manual (i.e., linear transformation to a 0-100 scale), in order to make a cautious comparison to other literature based on global health status/QoL score. Additionally, previous studies found that a single-item to measure QoL is often more feasible for patients, has high correlations with multi-item scales, and therefore is reliable to assess overall QoL in large samples [45-48]. Fourth, only associations, and

no causal relations, were established in this cross-sectional study. QoL was measured for the week previous to filling in the questionnaire, while information on disease trajectory-related factors might have been from years ago based on information on time since diagnosis and disease phase. However, QoL might still be impacted by these factors, as it was found in previous literature that the QoL of patients with cancer is impacted on the long-term (i.e., even after a decade) [49-52].

Implications for research and practice

Future research should include groups of patients with rare and common cancer to assess the difference in QoL between these groups and the impact of disease trajectory-related variables on QoL. These groups should accurately represent the rare and common cancer population based on sociodemographic variables (e.g., gender, age, educational level) and cancer-related variables (e.g., cancer types, treatment). Further, measurement of QoL should be performed by a whole multi-item scale, e.g., the EORTC QLQ-C30, to measure QoL as comprehensive as possible. Additionally, longitudinal research is needed to establish causal relationships between disease trajectory-related factors and QoL in patients with rare cancer. This way, the impact of these factors on QoL of recently diagnosed patients versus long-term survivors can also be assessed. Finally, differences in the impact of disease trajectory-related factors may exist between various types and/or domains of rare cancers, so individual types and/or domains of rare cancers may need to be studied as well.

The results of this study provide input for supportive care (i.e., care aimed at assisting the patient and his or her family in dealing with cancer and its treatment throughout the disease trajectory [53]) to maintain or improve the QoL of patients with rare cancer. Appropriate guidance and support should be provided by healthcare professionals throughout the whole disease trajectory to improve QoL, by improving satisfaction with care. This, for example, includes considering the patient's medical and personal situation, informing about and caring for short-term complications and side-effects as well as long-term and/or late effects of treatment, having overview over the entire disease trajectory, and discussing all available treatment options with the patient. This also applies to specialized nurses, as just having a specialized nurse as main point of contact is not enough for a positive impact on QoL. Yet, satisfaction with the care provided by the specialized nurse is. In addition, misdiagnoses and the time till the correct diagnosis have an impact on QoL of patients with rare cancer. This calls for more scientific understanding and clinical expertise on early diagnosis of rare cancers, as well as better recognition and education among healthcare professionals (e.g., recognition leading to referral to a centre of expertise) and more awareness among patients themselves. (Inter)national cooperation between hospitals, clinicians, and researchers is required to reduce diagnostic intervals and prevent misdiagnoses for patients with a rare cancer. For example, tools like next-generation sequencing may be used for early diagnosis of rare cancers, as well as for deciding on optimal available treatment methods [54].

CONCLUSION

The results of this study showed that a difference in self-reported QoL between patients with rare cancer and CRC exists, and that several disease trajectory-related factors are associated with poor QoL in patients with rare cancer. Future longitudinal studies with groups of patients with rare and common cancer are needed to determine the difference in QoL, and to determine causal relationships between disease trajectory-related factors and QoL in patients with rare cancer. To improve QoL of patients with rare cancer, appropriate guidance and support by healthcare professionals throughout the whole disease trajectory is needed, as well as further improvement of early diagnosis of rare cancer types and proper referral to centres of expertise.

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SUPPLEMENTARY

SURVEY 1:

1. This questionnaire is intended for people who have (had) a rare* cancer. You can participate if you have (had) one of the following diagnoses**. Which type of rare cancer do/did you have?
   If you have (had) multiple types of rare cancer, then choose in the most recent type of cancer.
   **To determine the target group for this questionnaire, we consulted the list of the 'Information Network on Rare Cancers' and the report 'Kankerzorg in beeld: zeldzame kanker' of the Netherlands Comprehensive Cancer Organisation. The list of rare cancers for this question is based on these.*
   ***Please note: for some cancers, the (sub)forms that are not rare are indicated in the brackets. Do you have one of these (sub)forms? Then this questionnaire does not apply to you. Then choose 'my type of cancer is not rare' at the very bottom.*

About you

2. What is your sex?
   a. Male
   b. Female
   c. Other
   3. What is your year of birth?
   4. What is your highest level of education?
   a. No education achieved
   b. Primary school (primary education)
   c. Lower vocational secondary education (e.g., LTS, LHNO, huishoudschool, VMBO-basis beroepsgericht, VMBO-kader beroepsgericht, LEAO)
   d. Secondary general education (e.g., ULO, MULO/MAVO, 3-jaars HBS, VMBO-T)
   e. Secondary vocational education (MBO)
   f. Senior general secondary education/pre-university education (e.g., HAVO, VWO, gymnasium, HBS, MMS)
   g. Higher professional education (HBO, bachelor, post-HBO)
   h. University education (university, master, doctoral degree)
   i. I would rather not say
   j. Otherwise, namely: ...

About your disease and hospital

5. In which year were you diagnosed with [Q1]?

6. In which hospital were you diagnosed with [Q1]?

7. In which hospital were you treated* for [Q1]?

*Have you been treated in several hospitals? Then assume the hospital that was your first point of contact** for your treatment.*

**By treatment we mean: surgery, chemotherapy, radiation, hormonal therapy, immunotherapy, targeted therapy, stem cell transplantation, wait and see, active surveillance or watchful waiting, stoma placement or any other form of treatment or medication aimed at treating or reducing the symptoms/complaints of cancer.*

***By the hospital that is your first point of contact for your treatments, we mean the hospital where you have the most checks and conversations. The medical specialist, who has an overview of all your treatments as well as treatments in other hospitals, also works in this hospital. Over time, this role may shift from one hospital to another, in which case, choose the most recent hospital that fulfils the role of first point of contact in your treatment.*

8. Which of the following descriptions matches your situation (at this moment) the most, regarding [Q1]?
   a. I (probably) do not have cancer anymore
   b. I will (probably) get better
   c. I will (probably) not get better

About your diagnostic trajectory

9. How did you find out that you have/had [Q1]?

Choose the answer that fits your situation best.

   a. I had symptoms and went to see my GP. He (eventually) referred me to the hospital. After that, the diagnosis was made.
   b. I had complaints and was therefore immediately hospitalised. Then I was diagnosed.
   c. I had no complaints. During a medical examination or hospital admission for something else, it happened to be discovered that something was wrong. Then I was diagnosed.
   d. I had no complaints. During a population screening, it was discovered that something was wrong. Then I was diagnosed
   e. I do not know
   f. Otherwise, namely: ...

10. How much time passed between the first conversation with your GP about your symptoms/complaints and the moment you were referred to a hospital?
   a. Less than three days
   b. Three till seven days
   c. One to two weeks
   d. Two to four weeks
   e. One to three months
   f. Three to six months
   g. Six to twelve months
   h. More than twelve months
   i. I do not know anymore

11. How much time passed between the first conversation with a physician in a hospital about your symptoms/complaints and the moment you heard that you had [Q1]?
    a. Less than three days
    b. Three till seven days
    c. One to two weeks
    d. Two to four weeks
    e. One to three months
    f. Three to six months
    g. Six to twelve months
    h. More than twelve months
    i. I do not know anymore

12. How did you experience the time between the first conversation with your GP about your symptoms/complaints and the moment you heard that you have/had [Q1]?
    a. Not uncertain
    b. Somewhat uncertain
    c. Uncertain
    d. Very uncertain

Give an explanation if necessary: ...

13. How much time passed between the first conversation with a physician in a hospital (about your symptoms/complaints or the suspicion of cancer) and the moment you heard that you had [Q1]?
    a. Less than three days
    b. Three till seven days
    c. One to two weeks
    d. Two to four weeks
    e. One to three months
    f. Three to six months
    g. Six to twelve months
    h. More than twelve months
    i. I do not know anymore

14. How did you experience the time between the first conversation with a physician in a hospital (about your symptoms/complaints or the suspicion of cancer) and the moment you heard that you have/had [Q1]?
    a. Not uncertain
    b. Somewhat uncertain
    c. Uncertain
    d. Very uncertain

Give an explanation if necessary: ...

15. How did the diagnosis of [Q1] go?
    a. The first diagnosis [Q1] I was told was the correct one.
    b. The first diagnosis I was given was an incorrect one. After that, the correct diagnosis [Q1] was made.
    c. I was first given several incorrect diagnoses. After that, the correct diagnosis [Q1] was made.
    d. I do not know

Give an explanation if necessary: ...

16. Have you received any treatment, therapy, or medication for the incorrect diagnosis?
    a. Yes
    b. No
    c. I do not know/not applicable

Give an explanation if necessary: ...

17. In how many hospitals were you examined* before the correct diagnosis [Q1] was made?
    a. One
    b. Two
    c. Three
    d. Four
    e. More than four

    **By examination in a hospital we mean all the research needed to reach the correct diagnosis. For example, an ultrasound scan, X-ray photo, scan, puncture/biopsy, scopy, examination of blood, urine, stool or other bodily fluids*

18. Did a physician and/or a specialized nurse* in the [Q7] give you information/explanation on [Q1]?

Answer possibilities: yes, partially, no, I do not know/not applicable
    a. Verbal information/explanation
    b. Written information/explanation (e.g., leaflet or brochure)
    c. Digital information/explanation (e.g., website)

    Give an explanation if necessary: ...

    **By specialized nurse, we mean the nurse in the hospital who you (usually) see around the time you are diagnosed with cancer, during your treatment, and afterwards. For example, an oncology nurse, nursing specialist, physician assistant, specialized nurse, nurse director or nursing consultant.*

19. How satisfied are you with the information/explanation you received from your physician and/or specialized nurse in the [Q7] about [Q1]?
Please give a score for each healthcare professional between 1 and 10 (1=very dissatisfied – 10=very satisfied, I do not know/not applicable).

Give an explanation if necessary: ...

20. Do you have anything to share about the period preceding the diagnosis [Q1]?
You can do this below

About your treatment options and the information you received about them

21. Which treatment(s) did you have for [Q1]?

Multiple answers possible.

a. Surgery
b. Chemotherapy
c. Radiation
d. Hormonal therapy
e. Immunotherapy
f. Targeted therapy
g. Stem cell transplantation
h. Wait and see
i. Active surveillance or watchful waiting
j. Stoma placement
k. Pain-relieving treatment
l. I do not know which treatment I have had
m. I did not have any treatment
n. Otherwise, namely: ...

22. Are you informed about the expertise/experience of your physician in the [Q7], with regard to the treatment* of [Q1]?
Did you have several physicians in this hospital? If so, please choose the physician you had the most contact with.

a. Yes
b. No
c. I do not know/not applicable

**By treatment we mean: surgery, chemotherapy, radiation, hormonal therapy, immunotherapy, targeted therapy, stem cell transplantation, wait and see, active surveillance or watchful waiting, stoma placement or any other form of treatment or medication aimed at treating or reducing the symptoms/complaints of cancer.*

23. Have you sought information about the expertise/experience of your physician in the [Q7], regarding the treatment of [Q1]?

Did you have several physicians in this hospital? If so, please choose the physician you had the most contact with.

a. Yes
b. No
c. I do not know/not applicable

Give an explanation if necessary: ...

24. What information did you received about the expertise/experience of your physician in the [Q7], regarding the treatment of [Q1]? And who gave you this information?

25. Did a physician and/or specialized nurse at the [Q7] discuss the following effects of the treatment(s) for [Q1] with you?

Answer possibilities: yes, partially, no, I do not know/not applicable

a. Life extension and/or cure
b. Reduction of complaints and symptoms
c. Complications and short-term side effects*
d. Late and/or long-term effects**

Give an explanation if necessary: ...

**By complications and side effects that arise shortly after cancer treatment(s) we mean complaints that occur immediately or within a few weeks after treatment, for example nausea, tingling in hands/feet, fatigue, hair loss, pain or diarrhoea.*

***By late and/or long-term effects of the cancer treatment(s) we mean complaints that occur months or sometimes years after treatment. For example, fatigue, sexual problems, problems with eating or drinking, problems with memory and concentration, psychological problems, tingling in hands/feet, lymphedema, incontinence and impotence.*

26. Has a physician and/or specialized nurse at the [Q7] discussed treatments in research setting for [Q1] with you?

For example, participation in a study/trial/experiment/scientific research/(new) non-registered medicine.

a. Yes, one treatment in a research setting
b. Yes, several treatments in a research setting
c. No
d. I do not know/not applicable

27. Where were the treatment(s) in research setting for [Q1] offered?

a. Only at the [Q7]
b. Both in the [Q7] as in another hospital
c. Only in another hospital, not in the [Q7]
d. I do not know/not applicable

28. In retrospect, do you think that the discussed treatment options were the best treatment options for [Q1] at that time in the Netherlands?
Please consider all the treatment options discussed in all the hospitals you have visited, including the treatments in research setting.
    a. Yes
    b. Partially
    c. No
    d. I do not know/not applicable

29. Why do you think (in retrospect) that the discussed treatment options were not, or were only partially, the best treatment options for [Q1] in the Netherlands?

30. Do you have anything to share about the treatment options for [Q1] that have been discussed with you?
You can do this below

About the support you received

31. How satisfied are you with your physician in the [Q7], regarding his/her support of your entire disease trajectory of [Q1]?
Please give a score between 1 and 10 for each part (1=very dissatisfied – 10=very satisfied, I do not know/not applicable).
Did you have several physicians at this hospital? If so, please choose the physician you had the most contact with.
    a. Substantive knowledge of my type of cancer
    b. Expertise/experience with treatment of my cancer type
    c. Aware of my medical situation
    d. Consideration of my personal situation
    e. Care for short-term complications and side effects of my treatment(s)*
    f. Care for late and/or long-term effects of my treatment(s)**
    g. Overview of my entire diagnostic, treatment, and aftercare trajectory
    h. Proactive thinking about treatment options, also outside the [Q7]

    Give an explanation if necessary: ...
    **By complications and side effects that arise shortly after cancer treatment(s) we mean complaints that occur immediately or within a few weeks after treatment, for example nausea, tingling in hands/feet, fatigue, hair loss, pain, or diarrhoea.*
    ***By late and/or long-term effects of the cancer treatment(s) we mean complaints that occur months or sometimes years after treatment. For example, fatigue, sexual problems, problems with eating or drinking, problems with memory and concentration, psychological problems, tingling in hands/feet, lymphedema, incontinence, and impotence.*

32. Did you have a specialized nurse* as your main point of contact** in the [Q7] regarding your diagnosis [Q1]?
    a. Yes
    b. No
    c. I do not know/not applicable

    **By specialized nurse, we mean the nurse in the hospital who you (usually) see around the time you are diagnosed with cancer, during your treatment, and afterwards. For example, an oncology nurse, nursing specialist, physician assistant, specialized nurse, nurse director or nursing consultant.*
    ***By a main point of contact we mean a care provider who has an overview of your entire disease trajectory and supports and guides you where necessary. The main point of contact knows you as a person and is easily accessible.*

33. How satisfied are you with your specialized nurse in the [Q7], regarding his/her support of your entire disease trajectory of [Q1]?
    Please give a score between 1 and 10 for each part (1=very dissatisfied – 10=very satisfied, I do not know/not applicable).
    Did you have several specialized nurses at this hospital? If so, please choose the specialized nurse you had the most contact with.
    a. Substantive knowledge of my type of cancer
    b. Expertise/experience with treatment of my cancer type
    c. Aware of my medical situation
    d. Consideration of my personal situation
    e. Care for short-term complications and side effects of my treatment(s)*
    f. Care for late and/or long-term effects of my treatment(s)**
    g. Overview of my entire diagnostic, treatment, and aftercare trajectory

    Give an explanation if necessary: ...
    **By complications and side effects that arise shortly after cancer treatment(s) we mean complaints that occur immediately or within a few weeks after treatment, for example nausea, tingling in hands/feet, fatigue, hair loss, pain, or diarrhoea.*
    ***By late and/or long-term effects of the cancer treatment(s) we mean complaints that occur months or sometimes years after treatment. For example, fatigue, sexual problems, problems with eating or drinking, problems with memory and concentration, psychological problems, tingling in hands/feet, lymphedema, incontinence, and impotence.*

34. Did a physician or specialized nurse in the [Q7] offer you (peer) contact with other people with [Q1]?
    Multiple answers possible.
    a. Yes, I have been made aware of a patient organisation for people with my type of cancer.
    b. Yes, I have been made aware of the Platform Rare Cancer Patients (PZK)
    c. Yes, I have been made ware of other online (peer) contact for people with my type of cancer.

d. Yes, I have been put in touch with other people with my type of cancer in the [Q7]
e. Yes, I have been made aware of a centre where people with my cancer type go to
f. No
g. I do not know/not applicable
h. Otherwise, namely: ...

Finally

Below are three final questions on various topics.

35. This question is about your overall quality of life. This is a question that is often used in international scientific research. To enable comparison with scientific research, we have added this question. How would you rate your overall 'quality of life' during the past week?
Give a score between 1 and 7 that applies most to you (1=very poor – 7=excellent)

36. We would like to improve our Donate Your Experience. It helps us to know how people get into our questionnaires. How did you get into this questionnaire?
Multiple answers possible.
    a. I am member of the Donate Your Experience panel
    b. Through a cancer patient organization
    c. Through (the newsletter of) Platform Rare Cancer Patients (PZK)
    d. Through (the newsletter of) nfk.nl
    e. Through a hospital
    f. Through the general practitioner
    g. Through social media
    h. Through Kanker.nl
    i. Through KWF
    j. Through an advertisement (for example online, on paper, waiting-room screen)
    k. Through family/friends/acquaintances
    l. Otherwise, namely: ...

This is the last question. Do you have anything to share about your experience with rare cancer?

PART II:

Psycho-oncological focus

CHAPTER 5

Unmet supportive care needs of patients with rare cancer: A systematic review

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ABSTRACT

Objective: Patients with rare cancers may experience different unmet needs than those with common cancer. The objective of this systematic review was to: (1) investigate unmet supportive care needs of rare cancer patients throughout the disease trajectory and (2) identify predictive factors for these unmet needs.

Methods: PubMed, PsycINFO, CINAHL were searched for publications (January 2011-March 2021) focusing on unmet needs of patients with rare cancer. Two reviewers independently selected studies, extracted data, and performed quality assessment. Findings were synthesized.

Results: The search yielded 4,598 articles, of which 59 articles met eligibility criteria, and 57 were of medium or high quality. Rare cancer patients most frequently reported unmet needs in the healthcare system and information domain (up to 95%), followed by the psychological domain (up to 93%), and the physical and daily living domain (up to 80%). Unmet needs were mainly reported in the posttreatment phase. The most frequently identified predictors were higher anxiety, younger age, and higher neuroticism.

Conclusion: Patients with rare cancer have unmet needs throughout their disease trajectory. Supportive care needs of rare cancer patients should be addressed individually, depending on the rare cancer subdomain and phase of disease, and from diagnosis onwards.

INTRODUCTION

In Europe, 3.9 million people are diagnosed with cancer each year [1], of whom 22% are affected by a rare cancer [2]. Rare cancers are defined by the Surveillance of Rare Cancer in Europe (RARECARE) as those with an incidence of <6/100,000 people per year [2]. Patients who have been diagnosed with a rare cancer have lower survival rates than those with common cancers, i.e., 49% versus 63% respectively [3], experience lower quality of life (QoL) and higher levels of distress compared to common cancer patients [4]. Therefore, delivering high-quality cancer care for both rare and common cancer patients not only involves anti-cancer treatment, but also attention for patients' supportive care needs.

Supportive care needs can be defined as care that helps the patient and his/her family to cope with cancer and its treatment, from pre-diagnosis through the process of diagnosis and treatment to cure, continuing illness or death and into bereavement [5]. Supportive care needs are broad in dimension, and range from psychological to sexual needs of an individual cancer patient [6]. Unmet needs are those supportive care needs that are not addressed and require additional service or support for an individual in order to achieve optimal well-being [7, 8]. By assessing unmet needs, it can be determined how well needs have been met. Needs that remain unmet can be identified among a variety of domains, indicating the multidimensional impact of cancer [8-10]. Cancer patients reported high levels of unmet needs regarding information provision throughout the cancer pathway [8, 11, 12], psychological and psychosocial support [8, 12-14], coping with the physical effects of the disease and treatment [8, 15, 16], and practical issues (e.g., transportation) [17, 18]. The presence and broad range of unmet supportive care needs among cancer patients stress the importance of addressing these needs.

Patients with rare cancer face difficulties during their disease trajectory, including delayed and/or incorrect diagnosis, lack of disease-specific information, and limited access to clinical expertise, treatment options, and (pre)clinical research [19-22]. These difficulties might differ between rare cancer subdomains, e.g., rare digestive cancer, rare gynaecological cancer, and rare haematological cancer [23, 24]. Moreover, rare cancer patients might experience more, but also different unmet needs, compared to patients with common cancer. In previous studies on rare cancers, a high prevalence of unmet supportive care needs was shown among patients with sarcomas and with brain tumours [25, 26]. For example, in the study focusing on patients with sarcomas, patients reported a lack of information about their disease and treatment, and expressed a need for a community and contact with fellow-sufferers [25].

In patients with common cancers, highest unmet needs were reported in the daily living, psychological, information, and physical domains [8, 27]. For example, patients with colon and/or rectum cancer indicated a high need for emotional support and reassurance, particularly regarding cancer recurrence [28]. It has been shown that unmet needs of common cancer patients appear to be highest during the treatment and posttreatment phase [27]. This might have to do with the intensive phase of active

treatment for the patient, or because most studies on unmet needs have been conducted in these phases. Further, in a previous systematic review, it was shown that predictors of unmet needs in common cancer patients include advanced disease stage, poor health status, geographical isolation from health services, and lack of social support networks [27]. However, there is a lack of information about unmet needs in the specific disease trajectory phases, per rare cancer subdomain, and about predictors of these needs in patients who have been diagnosed with a rare cancer type.

To provide optimal supportive care for rare cancer patients, it is necessary that healthcare professionals have knowledge regarding the differences of unmet needs between rare and common cancer patients. Since one out of five cancer patients are diagnosed with a form of rare cancer, providing an overview of the unmet needs of rare cancer patients is relevant as healthcare professionals are likely to encounter this patient group. To our knowledge, no systematic review on unmet supportive care needs of patients with rare cancer at different stages of the disease trajectory has been conducted so far. Therefore, the aim of the current systematic review was to: (1) explore unmet supportive care needs of rare cancer patients during the phases of their disease trajectory, for each rare cancer subdomain, and (2) identify predictors of these unmet needs.

METHODS

Protocol registration and report

This systematic review was registered in the "International Prospective Register of Systematic Reviews" (PROSPERO) in 2020 (registration number CRD42020183601), and the protocol is available upon request. The review was performed in accordance with the recommendations of the "Preferred Reporting Items For Systematic Reviews and Meta-Analyses" (PRISMA) statement [29].

Search strategy

A systematic search was performed in the databases PubMed, PsycINFO, and CINAHL, restricted to studies published from January 2011 until March 2021. This period was chosen because of the definition of rare cancers, which has been published and adopted in the European Union since 2011 [2]. Studies were identified using search strings based on the PubMed strategy, which uses a combination of MeSH terms and free text terms. The terms used were related to cancer (e.g., neoplasms, cancer, and tumour) and unmet supportive care needs (e.g., psychological, physical, and information needs). The search string included broad terms on cancer to cover all studies that included data on both rare and common cancers. Subsequently, the search syntax was adapted per database,

including different or additional search terms where necessary (Supplementary Table S1, S2, and S3).

Both quantitative and qualitative studies were eligible for inclusion if they evaluated unmet supportive care needs for rare cancer patients of adult age (i.e., ≥18 years) regardless of cancer site and stage of disease. Rare cancers were defined as those with an incidence of <6/100,000 people per year [2]. An overview of the rare cancer types, based on an updated version (February 2019) of the RARECARENet list [30], can be found in Supplementary Table S4. Studies were excluded if: (1) the study population consisted of mixed rare and common cancer types, i.e., information on unmet needs could not be distinguished between rare and common cancer patients; (2) the unmet needs of children, adolescents and young adults (<18 years), caregivers, or those at high risk of developing cancer were explored; (3) nutritional needs only were explored; and/or (4) other reasons for ineligibility were present (e.g., full-text not available, studies published in other language than English).

All titles and abstracts were screened by two involved researchers (EdH, AF), and papers considered as irrelevant to this review (i.e., out of scope or not meeting the inclusion criteria) were eliminated. If title and abstract did not fully provide information for enabling selection, full-text articles were retrieved and screened. The remaining studies were assessed on eligibility, and disagreements about the selection of articles were discussed until consensus was reached. In case there was no consensus between the two authors, a third author (SD) was involved to decide if the article should be included in the review. Reference lists of relevant articles were checked to identify additional studies.

Data extraction

Two researchers (EdH, MR) independently extracted data from each publication, including: (1) general information (e.g., year of publication, country); (2) study characteristics (e.g., design, setting); (3) study population characteristics (e.g., number of participants, age, gender); (4) disease and treatment characteristics (e.g., tumour type, cancer stage, treatment); (5) unmet needs (e.g., measurement, domain); and (5) predictors. Tumour types were categorised into cancer subdomains according to EURACAN and EuroBloodNet [23, 24], with the exception of male breast cancer, which is included separately, as it is not represented in one of these rare cancer subdomains (Supplementary Table S4). Unmet needs were classified into fourteen predominantly studied domains: communication, disease-specific, economic, emotional, family-oriented, healthcare system and information, patient care and support, physical and daily living, psychological, psychosocial, supportive care, sexuality, transportation, and work-related [27, 31, 32]. Phases of the disease trajectory were divided into diagnostic, treatment and posttreatment phase. The two researchers (EdH, MR) compared the extracted data and discussed findings until consensus was reached. In case of no consensus, disagreements were resolved by arbitration with a third researcher (SD).

Quality assessment

The quality of the included studies was assessed independently by two researchers (EdH, MR), using checklists from the Critical Appraisal Skills Program (CASP) [33] (for qualitative and cohort studies) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [34] (for cross-sectional studies). The quality of the studies was indicated as low, medium or high quality, based on items from the checklist, e.g., a clear statement of aims, appropriate research design, appropriate recruitment strategy, description of the method of analysis, and a clear data description. Qualitative and cohort studies were classified as 'high quality', if scores were ≥80% on CASP criteria, 'medium quality' if scores were between 60-79%, and 'low quality' if scores were <60% [35, 36]. Cross-sectional studies were considered to be of 'high quality', if scores were ≥75% on STROBE criteria, 'medium quality' if scores were between 50-74%, and 'low quality' if scores were <50% [37, 38]. Inconsistencies in scoring were discussed and resolved by consensus by two researchers (EdH, MR). If consensus was not achieved, the opinion of another involved researcher (SD) was inquired for final assessment.

RESULTS

Study characteristics

After initial screening of 4,598 articles, 120 potentially eligible articles were retrieved and examined in full-text (Fig. 1). Finally, 57 articles met the inclusion criteria, including two additional articles that were identified after screening the reference lists of included articles [32, 39-94].

Studies were conducted in Europe (N=19), Australia/New Zealand (N=13), Asia (N=9), Canada (N=9), United States (N=5), and Africa (N=2). Twenty-eight studies had a cross-sectional design, fourteen had a qualitative design, four had a mixed methods design, and eleven had a prospective cohort design, with follow-up periods ranging from three months to two years. Two mixed method studies [84, 93] used two designs (i.e., quantitative and qualitative design), which are separately presented in Table 1. The other two mixed method studies [72, 79] presented findings on unmet needs only in the qualitative section. One study on haematological cancer patients was reported in two articles, with the first focusing on the course of unmet needs [67], and the other reporting the influence of unmet needs on QoL [68]. In total, 12,399 patients (aged 18-94 years) were included across all studies. Cancer subdomains of research were rare HNC (N=22), rare gynaecological cancer (N=8), rare haematological cancer (N=6), rare CNS cancer (N=5), NET (N=4), endocrine cancer (N=4), rare digestive cancer (N=3), rare male genital and urogenital cancer (N=3), rare skin cancer/eye melanoma (N=1), and male breast cancer (N=1). Most patients received surgery, radiotherapy, chemotherapy or a combination of these treatments. The majority of the studies used questionnaires

(N=43) to gather data on unmet needs, including the Supportive Care Needs Survey (SCNS) (N=15) and the Cancer Survivors Unmet Needs (CASUN) instrument (N=6), but also interviews (N=18) were conducted. Further details on the characteristics of the included studies have been provided in Table 1.

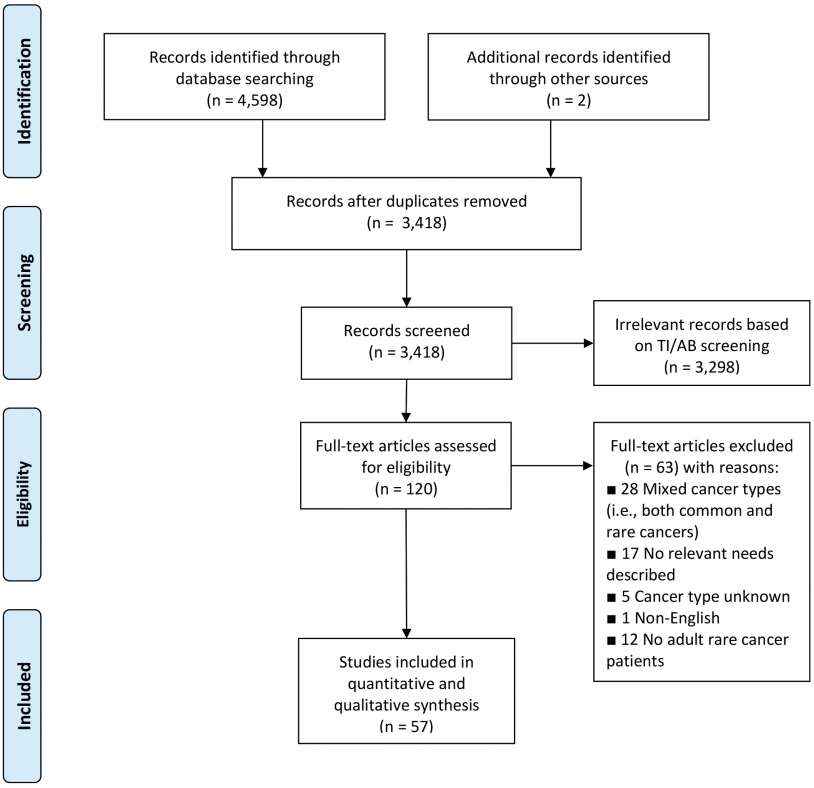

Fig. 1 PRISMA flow diagram of systematic search and selection procedure

Table 1. Characteristics of included studies on unmet needs in rare cancer patients

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Rare CNS cancer											
Halkett et al., 2015 [1]	Australia	Cross-sectional	Rare CNS (glioma)	116	Mean 56 (SD 13.3) (range 18-86)	71%	High grade (III and IV)	ns	CRT	Questionnaire; SCNS-SF34, BrTSCNS	H
Langbecker et al., 2016 [2]	Australia	Prospective cohort (3 mo)	Rare CNS (diverse brain tumours)	40	Median 55 (42-65)	58%	Low grade (I or II) and high grade (III or IV)	3 mo	Surgery, RT, CT	Questionnaire; SCNS-SF34, BrTSCNS	M
Piil et al., 2018 [3]	Denmark	Mixed methods (1 y)	Rare CNS (glioma)	30	Median 57.9 (range 29-79)	63%	High grade	1 y	Surgery, CT, RT	Interview	M
Reinert et al., 2018 [4]	Germany	Cross-sectional	Rare CNS (diverse brain tumours)	172	Mean 51.4 (range 20-84)	44%	Low grade / WHO I / WHO II, WHO III and high grade / WHO IV	ns	ns	Questionnaire; self-developed	M
Renovanz et al., 2017 [5]	Germany	Cross-sectional	Rare CNS (glioma)	173	Mean 50.9 (SD 13.9) (range 21-78)	53%	Low grade (I or II) and high grade (III or IV)	Median 33 mo (range 2-287)	Surgery, CT	Questionnaire; SCNS-SF34-G	H
Rare digestive cancer											
Gillespie et al., 2017 [6]	Canada	Cross-sectional	Rare digestive (HPB cancer)	36	72% 61-80y	58%	56% no metastatic disease	ns	Surgery	Questionnaire; adapted from Papadakos et al.	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Henselmans et al., 2012 [7]	The Netherlands	Qualitative	Rare digestive (oesophageal cancer)	20	Mean 62	70%	Stage I-IVA	ns	Surgery	Interview	M
Shun et al., 2018 [8]	Taiwan	Prospective cohort (2 mo)	Rare digestive (HCC)	90	Mean 62.5 (SD 10.6)	72%	BCLC stage (B, 1; A, 0) (C, 1; A, 0)	Mean 43.8 mo (SD 36.54) (range 1-149)	RFA, TACE	Questionnaire; SCNS-SF34	H
Endocrine cancer											
Goldfarb et al., 2014 [9]	USA	Cross-sectional	Endocrine (thyroid cancer)	673	40+	17%	ns	Mean 5.11 y (SD 7.02)	Surgery, radioactive iodine	Questionnaire; self-developed	M
Henry et al., 2018 [10]	Canada	Qualitative	Endocrine (thyroid cancer)	17	Mean 45.2 (SD 16.5)	29%	ns	ns	Surgery	Interview	H
Husson et al., 2014 [11]	The Netherlands	Cross-sectional	Endocrine (thyroid cancer)	306	Mean 56.4 (SD 14.5)	25%	Stage I-IV	Mean 9.6 y (SD 5.5)	Surgery, RT, radioactive iodine, other (ns)	Questionnaire; EORTC QLQ-INFO25	H
B. Lee et al., 2016 [12]	Korea	Qualitative	Endocrine (thyroid cancer)	29	Range 30-69	0%	ns	ns	Surgery	Interview	M
Rare gynaecological cancer											
Beesley et al., 2013 [13]	Australia	Prospective cohort (2 y)	Rare gyn (ovarian cancer)	185	Mean 59 (SD 10)	0%	Early (I-II) and late (III-IV) FIGO	Range 6-12 mo	ns	Questionnaire; SCNS-SF34	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Kebede et al., 2017 [14]	Ethiopia	Qualitative	Rare gyn (cervical cancer)	12	Mean 42.3 (range 25-67)	0%	ns	ns	RT, CT, CRT, surgery	Interview	L
Long et al., 2016 [15]	South Africa	Qualitative	Rare gyn (cervical cancer)	28	Range 30-73	0%	Stage I-III	ns	RT	Interview	H
Philp et al., 2017 [16]	Australia	Qualitative	Rare gyn (vulvar cancer)	12	Mean 60 (range 51-60)	0%	ns	ns	Surgery	Interview	H
Putri et al., 2018 [17]	Indonesia	Cross-sectional	Rare gyn (cervical, ovarian cancer)	153	118 ≤55y, 35 > 55y	0%	Stage I-IV	ns	CT	Questionnaire; SCNS-SF34	M
Rietveld et al., 2018 [18]	The Netherlands	Cross-sectional	Rare gyn (ovarian cancer)	185	Mean 63 (range 28-91)	0%	FIGO stage I-IV	Mean 6.2 y (range 1.9-12.3)	Surgery, CT, other (ns)	Questionnaire; CaSUN	H
Vermeer et al., 2015 [19]	The Netherlands	Cross-sectional	Rare gyn (cervical cancer)	343	Mean 48.7 (SD 8.9)	0%	85% FIGO ≤ stage IIA	ns	RT, CT, surgery, CRT	Questionnaire; self-developed	H
Zeng et al., 2017 [20]	China	Qualitative	Rare gyn (cervical cancer)	31	Range 18-60; female only	0%	Stage IA-IVA	ns	Surgery, CT, RT, CRT	Interview	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Rare HNC											
Badr et al., 2016 [21]	USA	Qualitative	Rare HNC (diverse)	6	Mean 55.3 (SD 5.9) (range 51-67)	83%	Stage I and IV	ns	RT, surgery, CRT	Interview	H
Brennan et al., 2019 [22]	Canada	Prospective cohort (1 y)	Rare HNC (diverse)	175	Mean 62.5 (SD 10.2)	83%	TNM stage T1-T4 and N0-N3	ns	Surgery, RT, CRT	Questionnaire; adapted from de Bock et al.	H
Chen et al., 2013 [23]	Taiwan	Prospective cohort (6 mo)	Rare HNC (oral cavity cancer)	82	Mean 50.1 (SD 10.83)	98%	Stage II, III and IV	ns	RT, CRT	Questionnaire; CNQ-SF-hn	H
Giuliani et al., 2016 [24]	Canada	Cross-sectional	Rare HNC (diverse)	158	Median 64 (range 19-89)	63%	ns	ns	Surgery, RT, CT	Questionnaire; CaSUN	H
Hansen et al., 2013 [25]	Denmark	Prospective cohort (14 mo)	Rare HNC (ns)	125	ns	ns	ns	ns	ns	Questionnaire; self-developed	H
Henry et al., 2020 [26]	Canada	Prospective cohort (3 mo)	Rare HNC (diverse)	145	Mean 63.3 (SD 10.2)	70%	Stage I-IV	ns	CT, RT, surgery	Questionnaire; SCNS-SF34	H
Holm et al., 2012 [27]	Denmark	Prospective cohort (14 mo)	Rare HNC (ns)	125	ns	ns	ns	ns	ns	Questionnaire; self-developed	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Jabbour et al., 2017 [28]	Australia	Cross-sectional	Rare HNC (diverse)	597	Mean 58, median 62 (range 21-94)	48%	Stage I-IV	ns	Surgery, RT, CRT, radioactive iodine, CT	Questionnaire; self-developed	H
Jansen et al., 2018 [29]	The Netherlands	Cross-sectional	Rare HNC (ns)	283	Mean 70 (SD 9)	84%	ns	ns	Surgery, RT, CRT	Questionnaire; SCNS-SF34, SCNS-HNC	H
Lin et al., 2020 [30]	Taiwan	Cross-sectional	Rare HNC (nasopharyngeal cancer)	145	Mean 49.2 (SD 10.3)	68%	Stage I-IV	ns	59% in-treatment	Interview	L
M.S. Lee et al., 2016 [31]	USA	Cross-sectional	Rare HNC (oral cancer)	342	Mean 56.4 (SD 10.5)	53%	Stage I-IV	Mean 5.56 y (SD 4.15)	RT, surgery, CT	Questionnaire; SUNS	H
Manne et al., 2016 [32]	USA	Cross-sectional	Rare HNC (oral, oropharyngeal cancer)	92	Mean 62.1 (SD 8.9) (range 33.4-79.0)	74%	Stage I-IV	Mean 41.3 mo (SD 6.4) (range 23.1-70.0)	Surgery, CT, RT	Questionnaire; SCNS-SF34	H
Moore et al., 2014 [33]	Australia	Qualitative	Rare HNC (diverse)	8	Mean 60 (range 51-60)	88%	ns	Mean 4.25 y (range 1-8)	CRT, RT, surgery, RT	Interview	H
O'Brien et al., 2017 [34]	Ireland	Cross-sectional	Rare HNC (diverse)	583	Mean 62.9 (SD 11.3)	67%	Early and late stage	50% less than 5 y, 50% 5+ y	CT, RT, surgery	Questionnaire; SCNS-SF34	H
Pateman et al., 2015 [35]	Australia	Qualitative	Rare HNC (diverse)	6	Mean 61.3 (range 50-72)	67%	ns	ns	CRT, surgery, RT	Interview	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Peeters et al., 2018 [36]	The Netherlands	Qualitative	Rare HNC (diverse)	13	Median 60 (range 48-73)	67%	Stage II-IV	ns	CT, RT	Interview	H
Pongthavornkamol et al., 2019 [37]	Thailand	Cross-sectional	Rare HNC (ns)	26	Mean 60.5 (SD 10.1)	81%	ns	2.7 y (SD 1.8)	CT, surgery, RT, hormone therapy	Questionnaire; CaSUN	H
Richardson et al., 2015 [38]	New Zealand	Qualitative (6 mo)	Rare HNC (diverse)	83	Mean 61 (SD 13)	75%	Stage TI-T4	ns	ns	Interview	M
Saroa et al., 2018 [39]	Canada	Mixed methods	Rare HNC (oral, oropharyngeal cancer)	205	Mean 58 (SD 6.5) (range 35-71)	85%	ns	ns	ns	Questionnaire; HaNiQ	H
So et al., 2019 [40]	China	Mixed methods	Rare HNC (diverse)	285	Mean 55.3 (SD 12.3)	77%	Stage I-III	8.0 mo (SD 3.8)	RT, surgery, CT	Questionnaire; SCNS-SF34	H
			Rare HNC (diverse)	53	Mean 51.8 (SD 10.5)	76%	Stage I-III	8.1 mo (SD 3.4)	Surgery, CT, RT	Interview	H
Sperling et al., 2014 [41]	Denmark	Cross-sectional	Rare HNC (ns)	177	ns	ns	ns	ns	Surgery, RT, CT	Questionnaire; self-developed	H
Wells et al., 2015 [42]	UK	Cross-sectional	Rare HNC (diverse)	280	Mean 64.5 (SD 11.4)	73%	Stage I-IV	9% <1y, 66% 1-4 y, 25% 4–5 y	Combination therapy, surgery	Questionnaire; PCI	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Rare male genital and urogenital cancer											
Bender et al., 2012 [43]	Canada	Cross-sectional	Rare male genital and urogenital (testicular cancer)	204	Mean 35.6 (SD 10.5)	100%	ns	Mean 2.2 y (SD 1.1)	Surveillance, CT, RT, RPLND	Questionnaire; CaSUN	H
Skoogh et al., 2013 [44]	Sweden	Cross-sectional	Rare male genital and urogenital (testicular cancer)	974	Mean 41, median 39	100%	Stage I-IV	Mean 11 y, median 9 y (range 3-26)	Surgery, RT, other	Questionnaire; self-developed	M
Smith et al., 2013 [45]	Australia	Cross-sectional	Rare male genital and urogenital (testicular cancer)	244	Mean 38.3 (SD 10.3) (range 21-68)	100%	36% metastatic	ns	Surveillance, surgery, RT, CT	Questionnaire; CaSUN	H
NET											
Beesley et al., 2018 [46]	Australia	Cross-sectional	NET (diverse sites)	111	39% <60y, 61% 60+ y	56%	Grade 1-2	Range 2 mo-27 y	Surgery, RT, hormone therapy, CT, targeted therapy	Questionnaire; SCNS-SF34	H
Feinberg et al., 2013 [47]	Canada	Qualitative	NET (diverse sites)	18	Median 63 (range 45-77)	54%	ns	Range 0-12 y	ns	Interview	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
Singh et al., 2017 [48]	Canada	Cross-sectional	NET (diverse sites)	1928	Mean 56.8	26%	Grade 1-3, 58% metastatic disease at time of diagnosis	Mean 5.2 y	Surgery	Questionnaire; self-developed	M
Wolin et al., 2017 [49]	Australia	Cross-sectional	NET (diverse sites)	758	Mean 57	28%	Grade 1-3	Mean 5.3 y	Surgery, CT, other	Questionnaire; self-developed	M
Rare skin cancer/eye melanoma											
Williamson et al., 2018 [50]	USA	Prospective cohort (3 mo)	Rare skin/eye melanoma (eye melanoma)	107	Mean 59.0 (SD 12.8)	54%	ns	1 week and 3 mo	RT	Questionnaire; CNQ-SF	H
Rare haematological cancer											
Boland et al., 2014 [51]	UK	Cross-sectional	Rare haema (MM)	32	Median 60 (range 41-71)	53%	ns	Median 5.5 y (range 2-12)	SCT, antimyeloma therapy	Questionnaire; SPARC	M
Molassiotis et al., 2011 [52]	UK	Cross-sectional	Rare haema (MM)	132	Mean 62 (SD 8.8) (range 35-83)	61%	ns	Mean 67.7 mo (SD 52.2) (range 12-269)	CT, SCT	Questionnaire; CaSUN	H
Nørskov et al., 2019 [53]	Denmark	Qualitative	Rare haema (AL)	18	Mean 52 (range 19-72)	44%	ns	Mean 11 weeks (range 4-16)	CT	Interview	H

Table 1. Characteristics of included studies on unmet needs in rare cancer patients *(continued)*

Author, year [ref]	Country	Design (follow-up)	Cancer subdomain† (type)	N	Age	Gender, % male	Cancer stage	Time since diagnosis	Treatment‡	Measurement§	QA¶
D. Oberoi et al., 2017 [54]	Australia	Prospective cohort (15 mo)	Rare haema (DLBCL, MM)	414	Mean 64.4 (SD 10.44) MM, mean 63.3 (SD 11.38) DLBCL	57%	ns	Mean 6.9 mo (SD 1.9) MM; Mean 6.5 mo (SD 1.9) DLBCL	RT, CT, SCT; RT, CT	Questionnaire; SCNS-SF34	H
D.V. Oberoi et al., 2017 [55]	Australia	Prospective cohort (15 mo)	Rare haema (DLBCL, MM)	414	Mean 63.82 (SD 11.08)	57%	ns	Mean 6.71 mo (SD 1.98)	CT, RT, SCT	Questionnaire; SCNS-SF34	H
Yu et al., 2017 [56]	China	Cross-sectional	Rare haema (AL)	311	Median 36.4 (SD 14.7) (range 18-78)	60%	ns	81.2% <12mo, 5.1% 13-18mo, 12.7% >18mo	ns	Questionnaire; SCNS-SF34	H
Male breast cancer											
Bootsma et al., 2020 [57]	The Netherlands	Mixed methods	Male breast cancer	12	Mean 66 (range 49-88)	100%	8% in situ, 92% invasive	Range 2-25y	Surgery, RT, CT, anti-hormonal therapy	Interview	H
			Male breast cancer	77	Mean 66.9 (10.9) (range 44-89)	100%	7% in situ, 94% invasive	Mean 66.9 mo (SD 10.8) (range 41-86)	Surgery, RT, CT, anti-hormonal therapy, immuno-therapy	Questionnaire; EORTC QLQ-BR23, B-force, EORTC QLQ-INFO25	H

† Cancer subdomain: Rare haema, rare haematological cancer; rare HNC, rare head and neck cancer; rare gyn, gynaecological cancer; NET, neuroendocrine tumours
Cancer subdomains are presented in concordance with the domains of EURACAN and EuroBloodNet, except for male breast cancer.
Tumour types: AL, acute leukaemia; DLBCL, diffuse large B-cell lymphoma; HCC, hepatocellular carcinoma; HPB cancer, hepato-pancreato-biliary cancer; MM, multiple myeloma.
‡ Treatment: Given treatments are listed here, but it can also involve combinations of these treatments. CRT, chemoradiotherapy; CT, chemotherapy; RFA, radiofrequency ablation; RLND, retroperitoneal lymph node dissection; RT, radiotherapy; SCT, stem cell transplantation; TACE, transarterial chemoembolization.
§ Measurement: BrTSCNS, Brain Tumour Specific Supportive Care Needs Scale; CASUN, Cancer Survivors Unmet Needs instrument; CNQ-SF, Cancer Needs Questionnaire Short Form; EORTC QLQ-BR23, EORTC Quality of Life Questionnaire – breast cancer specific; EORTC QLQ-INFO25, EORTC Quality of Life Questionnaire - Information Module; HaNiQ, Head and Neck Information Needs Questionnaire; PCI, Patient Concerns Inventory; SCNS-HNC, Supportive Care Needs Survey-Head & Neck Cancer; SCNS-SF, Supportive Care Needs Survey-Short Form; SPARC, Sheffield Profile for Assessment and Referral for Care; SUNS, Survivors Unmet Needs Survey
¶ QA, quality assessment; H, high quality; M, medium quality.
Mo, months; ns, not specified; SD, standard deviation; y, year

Quality assessment

With regard to the methodological quality assessment, 45 articles were assessed as being of "high quality", and twelve articles of "medium quality" (Table 1). Two studies [57, 92] were considered as "low quality" and were excluded from further review. Criteria less described in the included studies were: the adequate consideration of the relationship between the researcher and the participants (i.e., in qualitative studies), potential sources of bias (i.e., in cohort studies), the lack of indication of the study design in the title or abstract, and potential sources of bias (i.e., in cross-sectional studies).

Quantitative studies

A total of 42 studies reported quantitative results regarding unmet needs of patients with rare cancer (Table 2). Unmet needs are presented per cancer subdomain, beginning with 'general supportive care needs', as these needs are broad in dimension. The subsequent unmet need domains are presented in order from most prevalent unmet needs to least prevalent unmet needs, based on mean percentages.

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Rare CNS cancer				
Supportive care (1)	General: At least one unmet need		91% [1]	
Psychological (3)	General	45.8 (25.1)† [1]	35.6 (27.5)† [1]	
	Fears about the cancer spreading		56% [5]	
	Uncertainty about the future		45% [5]	
		27% [2]	30-44% [1,2]	
	Worry that results of treatment are beyond your control		37% [5]	
	Learning to feel in control of your situation		32% [5]	
	Feelings about death and dying		31% [5]	
	Feeling down or depressed		28% [5]	
			28% [1]	
	Concerns about the worries of those close to you		27% [5]	
		27% [2]	39% [1]	
	Feelings of sadness		26% [5]	
			24% [1]	
	Anxiety		25% [5]	
			28-47% [1,2]	
	Keeping a positive outlook		24% [5]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Physical and daily living (3)	General	47.9 (26.3)† [2]	38.9 (27.6)† [2]	
	Lack of energy/tiredness		31% [5]	
		24% [2]	26-50% [1,2]	
	Pain		19% [5]	
	Not being able to do the things you used to do		18% [5]	
		25% [2]	36-50% [1,2]	
	Work around the home		17% [5]	
	Feeling unwell most of the time		15% [5]	
			24% [1]	
Healthcare system and information (4)	General	37.9 (17.4)† [2]	27.8 (16.5)† [2]	
	Information about medical and supportive treatment		30% [4]	
	Information about things to help get well		28% [5]	
			24% [1]	
	Access to professional counselling		28% [5]	
	Information about cancer under control or diminishing		24% [5]	
			23% [1]	
	Personalised treatment		18% [5]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Information about test results as soon as feasible		17% [5]	
			27% [1]	
	Information about important aspects of care		17-19% [4,5]	
	Explanations of tests		17% [5]	
	One member of hospital staff to talk to		16-25% [4,5]	
	Information about benefits and side-effects of treatment		16% [5]	
	Information about managing illness at home		15-20% [4,5]	
	Information about legal issues, funding, and career		15% [4]	
Sexuality (1)	General	34.8 (28.6)† [2]	29.2 (35.3)† [2]	
	Changes in sexual feelings		23% [5]	
	Changes in sexual relationships		18% [5]	
	Information about sexual relationships		14% [5]	
Transportation (1)	Easy car parking at the hospital		36% [1]	
	Access to transport service to and from the hospital		10% [1]	
Disease specific (2)	General	32.5 (19.6)† [2]	21.9 (16.1)† [2]	
	Not feeling like the same person before the tumour	50% [2]	47% [2]	
	Information on developments in research and treatment		28% [1]	
	Physical side effects from tumour and/or treatment		24% [1]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Financial assistance/advice		21% [1]	
	Testing and advice about mental thinking abilities		17% [1]	
	Rehabilitation services		16% [1]	
	Internet/email to receive information and/or support		16% [1]	
	Legal assistance/advice		14% [1]	
	Change in mental or thinking ability		14% [1]	
	Talking to other people with a similar experience		12% [1]	
Economic (1)	Allowance for travel, treatment, equipment expenses		22% [1]	
Patient care and support (1)	General	30.4 (13.2)† [2]	13.0 (16.4)† [2]	
	Hospital staff attending promptly to physical needs		20% [5]	
	Reassurance that the way of feeling is normal		14% [5]	
	Acknowledgement/sensitivity to emotional needs		13% [5]	
	More choice about which cancer specialists to see		11% [5]	
	More choice about which hospital to attend		8% [5]	
Rare digestive cancer				
Healthcare system and information (2)	General		28.9 (15.0)† [8]	16.2 (12.6)† [8]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Information about likelihood of a cure		94% [6]	
	Information about dealing with pain		92% [6]	
	Information about whether family members are at risk of this cancer		91% [6]	
	Information about surgical procedure		91% [6]	
	Information about possible side effects after surgery		89% [6]	
	Information about caring for yourself after surgery		89% [6]	
	Information about managing possible bowel changes		89% [6]	
	General information about your cancer		86% [6]	
	Information about results of medical tests		86% [6]	
	Information about managing changes in daily activities		86% [6]	
	Information about likely outcomes of surgery		86% [6]	
	Information about symptoms		83% [6]	
	Information about other types of treatment		83% [6]	
	Information about possible risks associated with surgery		82% [6]	
	Information about possible side effects of other treatment		82% [6]	
	Information about coping with fears of recurrence		81% [6]	
	Information about managing nausea and vomiting		80% [6]	
	Information about managing feeling tired		78% [6]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Information about preparing for surgery	77% [6]		
	Information about drug coverage options	74% [6]		
	Information about how your relationship with your partner may be affected	73% [6]		
	Information about managing illness at home	72% [6]		
	Information about legal issues	71% [6]		
	Information about returning to work	71% [6]		
	Information about help from healthcare workers	69% [6]		
Physical and daily living (1)	General		27.4 (21.7)† [8]	20.1 (18.1)† [8]
Psychological (1)	General		33.0 (18.1)† [8]	15.1 (18.1)† [8]
Patient care and support (1)	General		22.1 (20.7)† [8]	4.5 (14.5)† [8]
Sexuality (1)	General		3.4 (9.6)† [8]	0.6 (4.0)† [8]
Endocrine cancer				
Psychological (1)	General	>80% [9]		
Physical and daily living (1)	General	>65 [9]		

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Healthcare system and information (1)	General			34% [11]
	Information about complications and long-term effects of treatment and medication use			67% [11]
	Information about aftercare and rehabilitation options			19% [11]
	General information about thyroid cancer			18% [11]
	Information about the cause of their cancer			11% [11]
Patient care and support (1)	General	<30% [9]		
Rare gynaecological cancer				
Supportive care (2)	General: At least one unmet need		59% [13]	65% [13]
Patient care and support (3)	General		75% [17], 15‡ [13]	
	Addressing of any complaints			61% [18]
	Knowledge about intercollegial consultation between caregivers			52% [18]
	Access to healthcare services when required			47% [18]
	Best medical care			43% [18]
	Access to complementary or alternative therapy services			34% [18]
Physical and daily living (2)	General		80% [17], 15‡ [13]	15‡ [13]
	Lack of energy/tiredness		18% [13]	15% [13]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Sexuality (3)	General		35% [17], 8‡ [13]	51% [19]
	Information about sexuality and cancer			83% [19]
Psychological (2)	General		72% [17], 25‡ [13]	23‡ [13]
	Fears about the cancer spreading		25% [13]	21% [13]
	Concerns about the worries of those close to you		20% [13]	18% [13]
	Uncertainty about the future		19% [13]	19% [13]
	Anxiety		17% [13]	15% [13]
	Worry that results of treatment are beyond your control		16% [13]	18% [13]
	Keeping a positive outlook		15% [13]	10% [13]
	Feelings of sadness		15% [13]	12% [13]
Healthcare system and information (2)	General		71% [17], 20‡ [13]	11‡ [13]
	Information about things to help get well		20% [13]	6% [13]
	Information about cancer under control or diminishing		16% [13]	5% [13]
	One member of hospital staff to talk to		16% [13]	3% [13]
	Information about test results as soon as feasible		16% [13]	16% [13]
	Personalised treatment		15% [13]	4% [13]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Rare HNC				
Supportive care (8)	General: At least one unmet need		62% [25]	
		40.9 (12.4)† [23]	39.7(13.3)† [23]	30.2 (9.5)† [23], 11.0 (10.4)† [37], 61-82% [24,26,29,39,42]
Disease-specific (5)	General	48.8 (19.5)† [23]	46.3 (19.4)† [23]	38.7 (13.4)† [23], 53% [29]
	Information on side effects of oral cancer treatment			59% [32]
	Information on oral cancer follow-up tests			58% [32]
	Information on prompting oral cancer symptoms			58% [32]
	Information on problems with chewing and/or swallowing			34% [32]
	Information on getting or maintaining insurance			33% [32]
	Information on maintaining good oral health			33% [32]
	Information on managing anxiety about recurrence			32% [32]
	Problems with social eating			30% [29]
	Problems with mobility of neck or shoulders			28% [29]
	Difficulty eating			26% [29]
	Information on dealing with changes in appearance			24% [32]
	Problems with coughing			23% [29]
	Information on dealing with social life			20% [32]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Information on dealing with effects on relationships			19% [32]
	Feeling better about appearance			19% [26]
	Problems with chewing and/or swallowing			18-26% [29,42]
	Difficulty speaking			17-28% [29,42]
	Problems with hearing			17% [29]
	Problems with chewing/eating			14% [42]
	Information on nutrition			13-41% [29,32]
	Problems with dry mouth and/or sticky saliva			12-27% [29,42]
	Loss of appetite			12% [29]
	Problems with weight			11-19% [29,42]
	Pain in head and neck/elsewhere			10% [42]
	Problems with taste and olfaction			9-35% [29,42]
	Problems with breathing			9-24% [29,42]
	Problems with memory			9% [42]
	Oral hygiene/dental health			8-18% [29,42]
	Smoking cessation			5% [26]
	Alcohol cessation			2% [26]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Healthcare system and information (8)	General	48.9 (21.0)† [23]	38.5 (21.6)† [23]	31.3 (14.0)† [23], 21-63% [26,29, 34,40]
	Routine blood tests			69% [22]
	Imaging			66% [22]
	Information on risk factors			57% [22]
	Information on heredity			51% [22]
	Information on fatigue/pain			43% [22]
	Information of long-term effects of treatment		33% [28]	
				84% [22]
	Information on type and stage of cancer	31% [28]		
	Information on prognosis	28% [28]		95% [21]
	Information on staying healthy		23% [28]	27-67% [22,28]
	Information on treatment options	26% [28]		
	Information on changes in eating and speaking			26% [28]
	Information on length of recovery			25% [28]
	Ongoing case manager to go to for services			21% [24]
	Up-to-date information			21% [24]
	Understandable information			21% [24]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Information on patient support groups		20% [28]	
				36% [22]
	Information on coping with stress and anxiety		20% [28]	
	Information on nutrition and maintaining weight		20% [28]	
	Information on coping with side effects of treatment			20-30% [23,26]
	Information on coping with cosmesis			20% [28]
	One member of hospital staff to talk to			18-41% [26,29,32,40]
	Information on effects of treatment on ability to work		18% [28]	
	Information on psychosexual health	17% [28]		
	Information relevant for family and/or partners			16% [24]
	Information about things to help get well			15-41% [26,29,32,40]
	Information about cancer under control or diminishing			15-33% [26,29,40]
	Information about test results as soon as feasible			15-29% [26,29,32,40]
	Information about benefits and side-effects of treatment			14-24% [26,29,32,40]
	Explanations of tests			14-22% [26,29,32,40]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Access to professional counselling			14-17% [26,29,32,40]
	Information about important aspects of care			13-16% [26, 29,32,40]
	Information on how to support family and/or partner			13% [24]
	Brochures about services and benefits for patients			13% [40]
	Personalised treatment			11-20% [26,29,40]
	Treatment in a physically pleasant hospital			11-17% [26,29,32,40]
	Information about managing illness at home			11-16% [29,32,40]
Psychological (8)	General	43.2 (15.1)† [23]	43.0 (15.8)† [23]	33.7 (15.4)† [23], 32-57% [26,29, 34,40]
	Concerns about cancer coming back			26% [24,42]
	Fears about the cancer spreading			19-37% [26,29,32,34,40]
	Reducing stress			17-22% [24, 34]
	Coping with others not acknowledging the impact of cancer had on their lives			17% [24]
	Concerns about the worries of those close to you			16-28% [26,29,34,40]
	Coping with changes to belief about life			16% [24]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Finding meaning and purpose in life			16% [26]
	Dealing with expectations as a "cancer survivor"			15% [24]
	Worry that results of treatment are beyond your control			13-41% [26,29, 34,40]
	Uncertainty about the future			13-36% [24,26,29,32, 34,40]
	Learning to feel in control of your situation			13-27% [26,29,40]
	Making life count			13% [24]
	Anxiety			12-21% [26,29,32,40,42]
	Feeling down or depressed			10-23% [26, 29,32,34,40,42]
	Feelings about death and dying			9-16% [26,29,32,40]
	Keeping a positive outlook			8-32% [26,29,32,40]
	Feelings of sadness			7-23% [26,29,34,40]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Physical and daily living (9)	General		38% [25]	
		30.2 (11.0)† [23]	34.9 (13.3)† [23]	26.7 (8.3)† [23], 31-55% [26,27, 29,34,39,41]
	Not being able to do the things you used to do			14-28% [26,29,32,34,40]
	Problems with sleeping			14% [42]
	Lack of energy/tiredness			11-22% [26, 29,32,34,40,42]
	Pain			9-38% [26,29,32,34,40]
	Feeling unwell most of the time			9-26% [26,29,32,40]
	Work around the home			3-20% [26,29,32,40]
Economic (6)	General		31% [25]	
				50% [27]
	Allowance for travel, treatment, equipment expenses			24% [40]
	Worry about earning money			23% [31]
	Obtaining life and/or travel insurance			21% [24]
	Help with financial support and/or state benefits			14-18% [24,42]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Patient care and support (7)	General	34.8 (18.4)† [23]	37.2 (18.8)† [23]	25.7 (14.2)† [23], 14-35% [26,29,34,40]
	Knowing that all my doctors talk to each other to coordinate my care			31% [24]
	Access to healthcare services when required			23% [24]
	Feeling like managing health together with medical team			22% [24]
	Managing side effects and/or complications of treatment			20% [24]
	Addressing of any complaints			20% [24]
	Best medical care			20% [24]
	Changes in quality of life as a result of cancer			19% [24]
	Provision of emotional support			19% [24]
	Access to complementary or alternative therapy services			19% [24]
	24-hr telephone support and cancer advisory service			19% [40]
	Adjusting to the body changes			17% [24]
	Talking to other people with a similar experience			17-21% [24,31]
	Handling cancer in social and/or work situations			15% [24]
	Moving on with life			14% [24]
	Reassurance that the way of feeling is normal			10-16% [26,29,32,40]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Impact of cancer on relationship with partner			12% [24]
	Help with developing new relationships after cancer			12% [24]
	More choice about which cancer specialists to see			10-24% [26,29,40]
	Help with access to legal services			10% [24]
	Acknowledgement/sensitivity to emotional needs			9-16% [26, 29,32,40]
	Hospital staff attending promptly to physical needs			9-15% [26, 29,32,40]
	Help with exploring spiritual beliefs			9% [24]
	Assistance with getting and/or maintaining employment			7% [24]
	Help with having a family due to fertility problems			5% [24]
	More choice about which hospital to attend			4-13% [26,29,32,40]
Family-oriented (2)	General		32% [25]	
				42% [27]
Communication (1)	General	35.8 (18.7)† [23]	33.2 (16.9)† [23]	31.3 (13.9)† [23]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Emotional (4)	General		47% [25]	
				61% [42]
	Dealing with feeling tired			35% [27]
	Dealing with changes in physical ability			23% [31]
	Dealing with feeling stressed			22% [31]
	Dealing with feeling worried/anxious			21% [31]
	Dealing with not feeling able to set future goals			21% [31]
	Dealing with losing confidence in abilities			20% [31]
	Coping with having a bad memory or lack of focus			20% [31]
Work-related (2)	General		28% [25]	
				29% [27]
Sexuality (9)	General		38% [25]	
				5-64% [26,27,29,34,40]
	Information about sexual relationships			9-15% [26,29,40]
	Changes in sexual feelings			3-20% [26,29,40]
	Changes in sexual relationships			1-19% [24, 26,29,32,40,42]
Transportation (2)	Easy car parking at the hospital			8-23% [24,40]
	Transport service to and from hospital			7% [40]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Rare male genital and urogenital cancer				
Supportive care (2)	General: At least one unmet need			63-66% [43,45]
Healthcare system and information (1)	Information about crisis and stress after diagnosis		59% [49]	
Psychological (3)	Access to psychological counselling		42% [49]	
	Reducing stress			24-27% [43,45]
	Concerns about cancer combing back			16-25% [43,45]
	Coping with others not acknowledging the impact of cancer had on their lives			13-26% [43,45]
	Dealing with expectations as a "cancer survivor"			12% [45]
Economic (2)	Help with financial support and/or state benefits			16-28% [43,45]
	Help with obtaining life and/or travel insurance			15% [45]
Patient care and support (2)	Adjusting to the body changes			28% [43]
	Access to complementary or alternative therapy services			22% [43]
	Access to community support services			21% [43]
	Handling cancer in social and/or work situations			21% [43]
	Changes in quality of life as a result of cancer			19% [43]
	Moving on with life			19% [43]
	Talking to other people with a similar experience			12-20% [43,45]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Provision of emotional support			12% [45]
Sexuality (1)	Changes in sexual relationships			18% [45]
Transportation (1)	Easy car parking at the hospital			12% [45]
NET				
Supportive care (1)	General: At least one unmet need			63% [46]
Healthcare system and information (3)	General			28% [46]
	Clearer information on longer-term impact of disease		66% [48]	
	More immediate access to NET experts		63% [48]	
	Wider range of treatment options		60% [48]	
				68% [49]
	Better direction on where to find NET information	58% [49]		
	Better access to NET experts/centre of expertise		56% [48]	
				62% [49]
	Clearer idea of treatment options available	50% [49]		
	Information about/opportunity to participate in trials		48% [48]	
	More knowledgeable NET medical providers		47% [48]	
		58% [49]		59% [5149
	Understanding test results	46% [49]		

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	More treatments available "in my country that I see in other countries"	45% [48]		
			60% [49]	
	Better coordinated/aligned NET medical team	45% [48]		
		39% [49]	50% [49]	
	Immediate transfer to a centre of expertise	42% [49]		
	More information brochures from NET medical providers	37% [48]		
			37% [49]	
	Clearer information on the diagnostics tests	32% [49]		
Physical and daily living (1)	General			38% [46]
	Lack of energy/tiredness			33% [46]
	Not being able to do the things you used to do			24% [46]
	Work around the home			17% [46]
Patient care and support (2)	General			11% [46]
	Immediate access to NET patient support groups	48% [49]		
	Provision of emotional support	31% [49]		
	More positive outlook from the HCPs during diagnosis	18% [49]		
Transportation (1)	Less travel to different healthcare professionals	27% [49]		
Psychological (1)	General			44% [46]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Feelings of sadness			28% [46]
	Fears about the cancer spreading			26% [46]
	Concerns about the worries of those close to you			26% [46]
	Uncertainty about the future			26% [46]
	Feeling down or depressed			19% [46]
	Anxiety			17% [46]
	Worry that results of treatment are beyond your control			17% [46]
Sexuality (1)	General			17% [46]
Rare skin cancer/eye melanoma				
Supportive care (1)	General: At least one unmet need	99% [50]	86% [50]	
Healthcare system and information (1)	General	92% [50]	77% [50]	
	Information about cancer remission	87% [50]	70% [50]	
	Information about things to help get well	87% [50]	66% [50]	
	Information about test results as soon as feasible	86% [50]	65% [50]	
	Information about the odds of treatment success	83% [50]	66% [50]	
	Information about benefits and side-effects of treatment	80% [50]	63% [50]	
	Explanations of tests	79% [50]	61% [50]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Psychological (1)	General	93% [50]	69% [50]	
	Fears about the cancer spreading	85% [50]	61% [50]	
	Fears about further physical disability or deterioration	73% [50]	48% [50]	
	Fears about the possible pain and suffering	72% [50]	41% [50]	
Patient care and support (1)	General	70% [50]	52% [50]	
Physical and daily living (1)	General	67% [50]	54% [50]	
Communication (1)	General	49% [50]	23% [50]	
Rare haematological cancer				
Supportive care (1)	General: At least one unmet need			27% [52]
Healthcare system and information (4)	General		56% [56]	
			24-42% [54,55]	32-42% [54]
	Information about test results as soon as feasible		66% [56]	
	Information about things to help get well		64% [56]	
	Information about cancer under control or diminishing		63% [56]	
	Information about benefits and side-effects of treatment		62% [56]	
	Information about managing illness at home		60% [56]	
	One member of hospital staff to talk to		60% [56]	
	Explanations of tests		56% [56]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Provision of materials about nursing service for disease		53% [56]	
	Access to professional counselling		52% [56]	
	Treatment in a physically pleasant hospital		40% [56]	
	Personalised treatment		35% [56]	
	Ongoing case manager to go to for services			28% [52]
	Information relevant for family and/or partners			24% [52]
	Information on how to support family and/or partner			21% [52]
Psychological (5)	General		46% [56]	
			30-55% [54,55]	42-47% [54]
	Concerns about the worries of those close to you		64% [56]	
				40% [51]
	Fears about the cancer spreading		63% [56]	
				30% [52]
	Worry that results of treatment are beyond your control		61% [56]	
	Uncertainty about the future		53% [56]	
				24% [52]
	Feeling down or depressed		46% [56]	
	Feelings of sadness		42% [56]	

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Anxiety		42% [56]	
				9% [51]
	Feelings about death and dying		34% [56]	
	Learning to feel in control of your situation		32% [56]	
	Maintaining decent appearance		26% [56]	
	Feeling like everything is an effort			25% [51]
	Reducing stress			25% [52]
	Dealing with expectations as a "cancer survivor"			23% [52]
	Coping with others not acknowledging the impact of cancer had on their lives			21% [52]
Physical and daily living (4)	General		37% [56]	
			30-48% [54,55]	32-42% [54]
	Feeling unwell most of the time		45% [56]	
	Lack of energy/tiredness		42% [56]	
				50% [51]
	Not being able to do the things you used to do		40% [56]	
	Daytime somnolence			37% [51]
	Pain		31% [56]	
				44% [51]
	Problems sleeping at night			31% [51]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
	Work around the home		28% [56]	
				25% [51]
	Worries about long-term effects of treatment			28% [51]
	Feeling weak			25% [51]
Patient care and support (5)	General		36% [56]	
			11-24% [54,55]	20-34% [54]
	More choice about which cancer specialists to see		40% [56]	
	More choice about which hospital to attend		38% [56]	
	Acknowledgement/sensitivity to emotional needs		38% [56]	
	Managing side effects of treatment			34% [51]
	Hospital staff attending promptly to physical needs		33% [56]	
	Reassurance that the way of feeling is normal		33% [56]	
	Knowing that all my doctors talk to each other to coordinate my care			24% [52]
	Talking to other people with a similar experience			23% [52]
	Changes in quality of life as a result of cancer			21% [52]
	Provision of emotional support			6% [51]
	Help with personal affairs			6% [51]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Sexuality (5)	General		16% [56]	
			9-23% [54,55]	14-17% [54]
	Information about sexual relationships		18% [56]	
	Changes in sexual relationships		15% [56]	
				31% [51]
	Changes in sexual feelings		15% [56]	
				21% [52]
Economic (1)	Obtaining life and/or travel insurance			39% [52]
	Help with financial support and/or state benefits			21% [52]
Transportation (1)	Easy car parking at the hospital			40% [52]
Male breast cancer				
Healthcare system and information (1)	Information on acute effects of treatment		65% [57]	
	Information on late effects of treatment			56% [57]
	Information on psychosocial problems		20% [57]	
	Information on sexuality		17-23% [57]	23-25% [57]
	Information on treatment side effects		17-18% [57]	23% [57]

Table 2. Unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory *(continued)*

Unmet needs (# studies)	Items	Prevalence rates per phase [ref]		
		Diagnostic	Treatment	Posttreatment
Disease-specific (1)	Male-specific information on symptoms and diagnosis, treatment, side effects, psychosocial impact, peer group support, and research		36% [57]	

† Presented as: Mean (SD)
‡ Presented as: Median

Diagnostic
Treatment
Post-treatment
Diagnostic/treatment
Treatment/posttreatment
Diagnostic/treatment/posttreatment

Unmet needs of patients with rare CNS cancer

Four studies [50, 58, 75, 76] were identified that quantified unmet supportive care needs of persons diagnosed with rare CNS cancer (i.e., primary brain tumour). Unmet needs were highest in the psychological domain (24-56%), followed by the physical and daily living domain (15-50%), and the healthcare system and information domain (15-30%), and these needs were reported throughout the whole disease trajectory. The highest score was found for needing help, in the diagnostic phase, with 'uncertainty about the future' (27%), in the treatment phase with 'not being able to do the things you used to do' (50%) and with 'fears about the cancer spreading' (56%) over all phases. In the treatment phase, 91% of the patients reported at least one unmet need. No unmet needs of these rare cancer patients were specifically reported in the posttreatment phase only.

Unmet needs of patients with rare digestive cancer

Two studies [47, 80] reported the presence of unmet needs of patients with rare digestive cancer. The unmet needs were most prevalent in the healthcare system and information domain (69-94%; mean 28.9 and 16.2, in respectively the treatment and posttreatment phase), followed by the physical and daily living domain (mean 27.4 and 20.1, in respectively the treatment and posttreatment phase), and the psychological domain (mean 33.0 and 15.1, in respectively the treatment and posttreatment phase), and these needs were reported throughout the whole disease trajectory. In the diagnostic and treatment phase, the need for 'information about the likelihood of a cure' (94%) had the highest score. No specific unmet needs were reported in one of the separate phases only.

Unmet needs of patients with endocrine cancer

In two studies [49, 54] in this review, unmet needs of patients with endocrine cancer were described. Unmet needs were highest in the psychological domain (>80%), followed by the physical and daily living domain (>65%), and the healthcare system and information domain (11-67%), and these needs were reported throughout the whole disease trajectory. In the posttreatment phase, 'information about complications and long-term effects of treatment and medication use' (67%) was the most prominent need. No specific unmet needs of these rare cancer patients were reported in the diagnostic and treatment phase only.

Unmet needs of patients with rare gynaecological cancer

Three studies [40, 74, 78] reported the presence of unmet supportive care needs of patients with rare gynaecological cancer. Patients most frequently reported unmet needs in the patient care and support domain (34-75%), followed by the sexuality domain (35-83%), and the physical and daily living domain (15-80%), and these needs were reported in the

treatment and posttreatment phase. In the treatment phase, needing help with 'fears about cancer spreading' (25%) was the highest ranked need, and in the posttreatment phase, 'information about sexuality and cancer' (83%) scored highest. Of all patients with rare gynaecological cancer, 59% reported at least one unmet need in the treatment phase, and 65% at least one unmet need in the posttreatment phase. No unmet needs of these rare cancer patients were specifically reported in the diagnostic phase only.

Unmet needs of patients with rare HNC

Fifteen studies [32, 44, 45, 48, 51, 55, 56, 60, 62, 66, 73, 84-86, 94] assessed unmet needs of patients with rare HNC. Unmet needs were highest in the disease-specific domain (2-59%), followed by the healthcare system and information domain (11-84%), and the psychological domain (7-41%), and these needs were reported throughout the whole disease trajectory. The highest need score, in the diagnostic phase, was reported for 'information on type and stage of cancer' (31%), in the treatment phase for 'information on staying healthy' (23%), in the posttreatment phase for 'information on prognosis' (95%), and for 'information of long-term effects of treatment' (33%) over all phases. During the treatment and posttreatment phase, 64% of the rare HNC patients reported at least one unmet need, and 61-82% reported at least one unmet need during the posttreatment phase.

Unmet needs of patients with rare male genital and urogenital cancer

In three studies [42, 82, 83] in this review, unmet needs of patients with rare male genital and urogenital cancer were described. Unmet needs were most prevalent in the healthcare system and information domain (59%), followed by the psychological domain (12-42%), and the economic domain (15-28%), and these needs were reported throughout the whole disease trajectory. The highest reported need, in the diagnostic and treatment phase, was found for 'information about crisis and stress after diagnosis' (59%), and for 'help with financial support and/or state benefits' (16-28%) in the posttreatment phase. In the posttreatment phase, 63-66% of the patients reported at least one unmet need. No specific unmet needs of these male genital and urogenital cancer patients were reported in the diagnostic or treatment phase only.

Unmet needs of patients with NET

Three studies [41, 81, 88] assessed unmet needs of patients with NET. Unmet needs were highest in the healthcare system and information domain (32-68%), followed by the physical and daily living domain (17-38%), and the patient care and support domain (11-48%), and these needs were reported throughout the whole disease trajectory. The highest need score, in the diagnostic phase, was reported for 'better direction on where to find NET information' and 'more knowledgeable NET medical providers' (both 58%), in the treatment phase for 'wider range of treatment options' (68%), in the diagnostic and

treatment phase for 'clearer information on longer-term impact of disease' (66%), and in the posttreatment phase, for help with 'lack of energy/tiredness' (38%). At least one unmet need was reported by 63% of the patients in the posttreatment phase.

Unmet needs of patients with rare skin cancer/eye melanoma

One study [87] was identified that quantified the unmet needs of patients with eye melanoma. Unmet needs were highest in the healthcare system and information domain (61-92%), followed by the psychological domain (41-93%), and the patient care and support domain (52-70%), and these needs were reported in the diagnostic and treatment phase. The highest levels of need, in the diagnostic phase, were found for 'information about cancer remission' and 'information about things to help get well' (both 87%), and 'information about cancer remission' (70%) in the treatment phase. At least one unmet need was reported by 99% of the patients in the diagnostic phase, and by 86% of the patients in the treatment phase. No unmet needs of these rare cancer patients were specifically reported in the posttreatment phase only.

Unmet needs of patients with rare haematological cancer

Five studies [43, 63, 67, 68, 89] were found that assessed unmet supportive care needs of patients with rare haematological cancer. Unmet needs were most frequently reported in the healthcare system and information domain (21-66%), followed by the psychological domain (9-64%), and the physical and daily living domain (6-50%), and these needs were reported in the treatment and posttreatment phase. In the treatment and posttreatment phase, 'information about test results as soon as feasible' (66%) was the most prominent need and in the posttreatment phase, need for help with 'lack of energy/tiredness' (50%) scored highest. In the posttreatment phase, 27% of the rare haematological patients reported at least one unmet need. No unmet needs of these rare cancer patients were specifically reported in the diagnostic or treatment phase only.

Unmet needs of patients with male breast cancer

One study [93] was found that assessed unmet needs in patients with male breast cancer. Unmet needs were reported in the healthcare system and information domain (17-65%), and in the disease-specific domain (36%). The highest need score, in the treatment phase, was reported for 'information on acute effects of treatment' (65%), in the posttreatment phase for 'information on late effects of treatment' (56%), and for 'male-specific information on symptoms and diagnosis, treatment, side effects, psychosocial impact, peer group support, and research' (36%) over all phases. No specific unmet needs of these male breast cancer patients were reported in the diagnostic treatment phase only.

Qualitative studies

A total of seventeen studies reported qualitative results regarding unmet needs of patients with rare cancer.

In one study in patients with rare CNS cancer [72], supportive care, informational, and rehabilitation needs in the diagnostic and treatment phase were described. Needs included, e.g., strategies for managing psychological symptoms, the exchange of experiences with other patients, and better access to specialists throughout the disease trajectory.

Posttreatment information needs regarding health-related QoL, medical care, and prognosis were reported in a single study for patients with rare digestive cancers [53].

In two studies in patients with endocrine cancer [52, 59], information needs in the treatment and posttreatment phase were found, i.e., detailed information on treatment procedures and on QoL after treatment.

High unmet supportive care and information needs were reported in three studies in patients with rare gynaecological cancer throughout the disease trajectory [61, 71, 90]. Needs were reported regarding the provision of disease- and treatment related information, but also concerns regarding sexuality, support from other fellow-sufferers, and strategies for managing symptoms were mentioned.

Seven studies in patients with rare HNC [39, 64, 69, 70, 77, 79, 84] reported supportive care, information, psychological, and psychosocial needs mainly during the posttreatment phase. Needs frequently described were related to managing the side effects of treatment, support for dealing with posttreatment consequences, organised patient care, and the need for returning to a normal life. The most frequently reported healthcare system and information needs were related to information on symptoms of recurrence, information on cure, information on adverse treatment effects, access to health resources (e.g., dental oncology services), timeframes for treatment and recovery, and posttreatment rehabilitation. Social support and sharing experiences and emotions with fellow-sufferers were mentioned as psychosocial needs, and psychological needs included managing concerns about recurrence, managing concerns about the future, and strategies for coping with HNC.

In a study in patients with NET [46], patients reported difficulties with access to appropriate care, and the need for disease-specific support and information on the disease and treatment.

Patients with haematological cancer [65] mentioned a need for social support from healthcare professionals, their social network, and other fellow-sufferers in the posttreatment phase.

Finally, in the male breast cancer study [93], information needs were reported regarding symptoms and (delay of) diagnosis, treatments, psychological impact and coping, genetics and family, research and raising awareness.

Table 3. Predictive factors for unmet supportive care needs in rare cancer patients during the diagnostic, treatment and posttreatment phase of their disease trajectory

Predictive factors† (# studies)	# Studies per phase [ref]		
	Diagnostic	Treatment	Posttreatment
Higher anxiety score (4)		1 [23]	
		1 [13]	
			2 [22,26]
Younger age (2)		1 [8]	
			1 [26]
Higher neuroticism (2)	1 [50]		1 [26]
Higher educational level (1)		1 [23]	
Higher overall physical symptom severity (1)		1 [23]	
Higher functional level (1)		1 [23]	
Without religious beliefs (1)		1 [23]	
High uncertainty (1)		1 [8]	
Advanced disease (1)		1 [13]	
Depression (1)		1 [13]	
Less social support (1)		1 [13]	
Older age (1)		1 [13]	
Insomnia (1)		1 [13]	
Receiving chemotherapy (1)		1 [54]	
Greater social network (1)	1 [50]		
Lower instrumental social support (1)	1 [50]		
Lower QoL score (1)			1 [22]
Lower performance status (ECOG) scores (1)			1 [22]
More stressful life events in the year pre-diagnosis (1)			1 [26]
Being female (1)			1 [27]

† The predictive factors are presented in order from most studies to least studies reporting on the predictive factor

Diagnostic
Treatment
Post-treatment
Diagnostic/treatment
Treatment/posttreatment
Diagnostic/treatment/posttreatment

Predictive factors for unmet needs throughout the rare cancer disease trajectory

In the diagnostic phase, predictive factors associated with a higher number of unmet needs in patients with rare cancers included: higher neuroticism, lower instrumental social support, and greater social network [87]. Predictive factors for unmet needs during treatment and posttreatment phase were somewhat inconsistent and included both younger age [80] and older age [40], but also higher anxiety score [40], high uncertainty [80], advanced disease [40], and depression [40]. Predictors for unmet needs posttreatment included higher anxiety score [44, 94], younger age [94], higher neuroticism [94], lower QoL score [44], more stressful life events in the year pre-diagnosis [94], and being female [32]. Predictive factors for unmet needs throughout the disease trajectory included higher anxiety score, higher educational level, and higher overall physical symptom severity [45]. In Table 3, the overview of all predictive factors can be found.

DISCUSSION

Main findings

Prevalence of unmet supportive care needs in rare cancer patients varied strongly over all need domains, across all rare cancer subdomains and throughout all phases of disease. Unmet needs were most frequently reported in the healthcare system and information domain, followed by the psychological domain, and the physical and daily living domain. Specific unmet needs were present in patients with rare female genital organ cancer, namely in the sexual domain, in patients with rare male genital and urogenital cancer, namely in the economic domain, and in patients with rare HNC, namely in the disease-specific domain. Unmet needs were primarily reported in the posttreatment phase, and over all phases, the most frequently identified predictors were higher anxiety score, younger age, and higher neuroticism.

Interpretation of findings

In this study, highest unmet needs of rare cancer patients were identified, throughout the disease trajectory, in the healthcare system and information domain. This contrasts with previous findings in patients with common cancer [27, 95, 96]. That is, in several reviews focusing on common cancer types, e.g., breast and lung cancer, needs in the psychological domain and physical and daily living domain were most frequently reported. Due to the lack of a clear cancer care pathway in some rare cancer types, it is not surprising that patients with these diagnoses request more information about their disease and treatment and enhanced organisation of care. Related to this, a plea for personalised treatment and one member of hospital staff to talk to has been

made. In addition, in this review, high prevalence rates were found for rare cancer patients reporting at least one unmet need. The lowest rate, for at least one unmet need, was found in rare haematological cancer patients (i.e., 27%), and rates in all other cancer subdomains ranged from 59% to 99%. A possible explanation for the low rate in rare haematological cancer patients might be that needs were only assessed in the posttreatment phase, while unmet needs during treatment, when symptom burden is expected to be higher, were not examined. Further, in another systematic review in cancer survivors posttreatment [97], prevalence rates of at least one unmet need alternated from 24% to 88%, but no rates of haematological cancer patients were described here. The fact that rare cancer patients more often express at least one unmet need than common cancer patients might be explained by healthcare providers being more alert and responsive to patients' needs they encounter regularly, whereas the needs of rare cancer patients might be recognised to a lesser extent, and herewith potentially remain unmet.

Regarding the identified needs in specific rare cancer subdomains, patients with rare female genital organ cancer, patients with rare male genital and urogenital cancer, and patients with rare HNC should be noted. That is, the first group of patients reported high unmet needs in the sexuality domain, which is in concordance with previous studies [98, 99]. A diagnosis and treatment of gynaecological cancer significantly affects sexual functioning. Especially women with vulvar cancer, undergoing extensive surgery, experience the most sexual problems [99]. Reasonably, the sexual function of patients with this rare form of gynaecological cancer is often impaired by the removal of, or changes to, their reproductive organs, resulting in high unmet sexuality needs. In addition, patients with rare male genital and urogenital cancer reported high unmet needs in the economic domain, i.e., help with financial support and/or state benefits, and with obtaining insurance. Since this type of cancer, specifically testicular cancer, mainly affects young men under the age of 40, these patients are at working age and potentially the breadwinner of the family, which may result in financial worries due to impaired work ability. This has been described by Gupta et al. as well, explaining the negative impact of cancer-related financial stress on patient's overall well-being during emerging adulthood [100]. Furthermore, rare HNC patients reported high unmet needs in the disease-specific domain, namely needs for help with and information on chewing, swallowing, eating, and speaking. Similarly, it has been shown in previous studies [101, 102], that this specific patient group is highly and negatively affected by these short- and long-term effects in the head and neck area, significantly impacting their physical functioning and QoL.

As previously reported for common cancer patients [27], in our review, it has been confirmed that unmet needs of patients with rare cancer are predominantly identified in the treatment and posttreatment phase. That said, it is rather surprising that studies focusing on the unmet needs early in the disease trajectory of rare cancer patients are lacking. Moreover, patients with rare cancer are likely to experience high unmet needs, in the diagnostic phase, regarding (the delay in) obtaining the correct diagnosis

and finding information about (specific treatment for) their rare cancer type. While the implementation of psychosocial supportive care in common cancer patients has progressed over the last decades, and is integrated from diagnosis up to long-term cancer survivorship [103], this seems to lag behind in rare cancer patients.

Finally, in this study, it has been found that higher anxiety scores, younger age, and higher neuroticism can be predictive factors for increased unmet supportive care needs. High level of anxiety, and younger age were also found to be predictive for unmet needs in patients with common cancer [27, 104]. Moreover, in both cancer patient groups, advanced disease, higher educational level, higher physical symptom severity, and low social support have been found to influence unmet needs [27, 104]. These similarities between groups are not unsurprising as sociodemographic, clinical, and psychosocial factors are found to influence QoL in cancer patients [105-107]. Further, while higher neuroticism was found to be predictive for increased unmet needs in rare cancer patients, this has not been found in common cancer patients. This is in line with the finding that patients with rare cancer, in general, report higher distress levels and impaired QoL than common cancer patients [4]. These findings highlight the relevance of addressing unmet needs of rare cancer patients throughout the disease trajectory. Also, screening for predictive factors, such as anxiety, depression, age, and neuroticism may facilitate the identification of high-risk patients, likely to benefit most from early targeted psychosocial care.

Strengths and limitations

The main strength of this systematic review is that this is the first review exploring the unmet supportive care needs, and related predictive factors, in rare cancer patients at different phases of their disease trajectory. Also, it can be considered a strength that both quantitative and qualitative studies were included. This resulted in an overview of all available studies on unmet needs in adult patients within different rare cancer subdomains.

A limitation of this systematic review is that findings on unmet needs are difficult to compare between countries due to possible differences in the provision of supportive care during the disease trajectory. Although psychosocial oncology is seen as an integral part of comprehensive cancer care, it has not been fully integrated into oncological care worldwide yet [108, 109]. In addition, in this review, a proportionate distribution of rare cancer types is missing. That is, the majority of the studies reported unmet needs within the rare HNC domain. Some studies (e.g., in sarcoma patients) might have been excluded based on our applied criteria. Lastly, specific unmet needs might have been missed due to the general measures used to assess the unmet needs in patients with a rare cancer type. Because of these limitations, results should be interpreted with caution.

Implications for practice and research

The findings of this review may guide healthcare professionals, working in the field of rare cancers, in their support of patients within a specific rare cancer subdomain during each phase of the disease trajectory. Specifically, healthcare professionals should be aware that patients with rare cancer require information about their disease and treatment, and transparency about the organisation of care for their specific type of rare cancer. Knowledge in healthcare professionals should be increased, and access to clinical expertise for rare cancer patients should be improved. By establishing regional clinical networks for rare cancers, including centres of expertise, unmet needs can be identified and purposely addressed from diagnosis onwards. Such a network could play an important role in ensuring guidance and support throughout the cancer care pathway for patients with rare cancer. Since patients with rare cancer are known to face difficulties especially during diagnosis and treatment [20, 21], more attention should be given to and research should be performed on unmet needs during these phases of the disease trajectory. Further, there is a lack of literature on unmet needs in several rare cancer subdomains, specifically in adult patients with sarcomas, rare urinary tract cancer, rare thoracic cancer, and rare skin cancer. Research on the unmet needs in those specific rare cancer subdomains is warranted, since those patients may have different unmet needs compared to patients from the other rare cancer subdomains. In addition, only a few studies used disease-specific questionnaires, which implies the need for development of disease-specific instruments, measuring unmet needs of patients with a rare cancer. Finally, appropriate supportive care strategies within patients with common cancer might also be applicable to patients with rare cancer. However, those strategies are likely to be different per cancer type, and therefore should be tailored according to the patient group and should be further investigated.

CONCLUSION

Patients with rare cancer have unmet supportive care needs throughout the disease trajectory, with the highest reported needs in the healthcare system and information domain. The most frequently identified predictors of unmet needs in rare cancer patients were higher anxiety, younger age, and higher neuroticism. Healthcare professionals should be aware of the different unmet needs per rare cancer subdomain, and these unmet needs should be recognized and individually addressed starting from diagnosis onwards. Future studies are needed to determine further unmet needs of patients in all rare cancer subdomains, in order to help healthcare professionals in providing tailored supportive care and improving QoL in rare cancer patients.

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SUPPLEMENTARY

Table S1. PubMed Search Strategy

Search	Query	Hits
#1	Neoplasms[Mesh]	3432815
#2	Cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab] OR sarcoma*[tiab] OR oncolog*[tiab]	3547933
#3	#1 OR #2	4511020
#4	Needs Assessment[Mesh]	31125
#5	Unmet[ti] AND need*[ti]	3408
#6	Need*[ti] AND assess*[ti]	6514
#7	Perceived[ti] AND need*[ti]	950
#8	Support*[ti] AND care[ti] AND need*[ti]	795
#9	Psycho*[ti] AND need*[ti]	2359
#10	Physical[ti] AND need*[ti]	728
#11	Information[ti] AND need*[ti]	2927
#12	(Patient[ti] AND need*[ti]) OR (patient[ti] AND experience*[ti])	10128
#13	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	53425
#14	#3 AND #13	5920
#15	Search (#4) Filters: Humans, Published since 01-01-2011	3007

Table S2. PsycINFO Search Strategy

Search	Query	Hits
#1	exp neoplasms/	51488
#2	(Cancer* or tumor* or tumour* or carcinoma* or neoplasm* or adenocarcinoma* or malignan* or sarcoma* or oncolog*).ti,ab.	79834
#3	1 or 2	83086
#4	Needs assessment/	4224
#5	Unmet need*.ti.	598
#6	Need* assess*.ti.	1055
#7	Perceived need*.ti.	340
#8	Support* care need*.ti.	118
#9	Psycho* need*.ti.	1069
#10	Physical need*.ti.	5
#11	Information need*.ti.	414
#12	(Patient need* or patient experience*).ti.	410
#13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	7251
#14	3 and 13	615
#15	Limiters: Human, Publication year: 2011 – Current	392

Table S3. CINAHL Search Strategy

Search	Query	Hits
#1	MH neoplasms	81657
#2	TI (Cancer* OR tumor* OR tumour* OR carcinoma* OR neoplasm* OR adenocarcinoma* OR malignan* OR sarcoma* OR oncolog*)	422559
#3	S1 OR S2	451806
#4	MH needs assessment	18603
#5	TI unmet need*	2131
#6	TI need* assess*	3749
#7	TI perceived need*	753
#8	TI support* care need*	534
#9	TI psycho* need*	1238
#10	TI physical need*	412
#11	TI information need*	2037
#12	TI (Patient need* OR patient experience*)	5370
#13	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	30805
#14	S3 AND S13	2757
#15	Limiters: Human, Published Date: 20110101 – 20200518	1199

Table S4. Rare cancer subdomains and cancer types

Rare cancer subdomain	Rare cancer type*
Rare CNS cancer	Tumours of central nervous system (CNS)
	Embryonal tumours of CNS
Rare digestive cancer	Epithelial tumours of oesophagus
	Epithelial tumours of small intestine
	Epithelial tumours of anal canal
	Epithelial tumours of liver and intrahepatic bile tract
	Epithelial tumours of gallbladder and extrahepatic bile tract
Endocrine cancer	Carcinoma of pituitary gland
	Carcinoma of thyroid gland
	Carcinoma of parathyroid gland
	Carcinoma of adrenal cortex
Rare gynaecological cancer	Epithelial tumours of cervix uteri
	Epithelial tumours of ovary and fallopian tube
	Non epithelial tumours of ovary and fallopian tube
	Epithelial tumours of vulva and vagina
	Trophoblastic tumours of placenta

Table S4. Rare cancer subdomains and cancer types *(continued)*

Rare cancer subdomain	Rare cancer type*
Rare head and neck cancer (HNC)	Epithelial tumours of nasal cavity and sinuses
	Epithelial tumours of nasopharynx
	Epithelial tumours of major salivary glands and salivary-gland type tumours
	Epithelial tumours of hypopharynx and larynx
	Epithelial tumours of oropharynx
	Epithelial tumours of oral cavity and lip
	Epithelial tumours of eye and adnexa
	Epithelial tumours of middle ear
Rare male genital and urogenital cancer	Testicular and paratesticular cancers
	Epithelial tumours of penis
	Epithelial tumours of pelvis and ureter
	Epithelial tumours of urethra
Neuroendocrine tumours	NET GEP
	NET lung
	NET other sites
Sarcomas	Soft tissue sarcomas
	Bone sarcoma
	Gastrointestinal stromal sarcoma
Rare skin cancer/eye melanoma	Malignant melanoma of mucosa and extracutaneous
	Malignant melanoma of eye
	Adnexal carcinomas of skin
	Kaposi's sarcoma
Rare thoracic cancers	Epithelial tumours of trachea
	Epithelial tumours of thymus
	Malignant mesothelioma
Rare haematological cancer	Lymphoid diseases *(except other non-Hodgkin, Mature B cell lymphoma)*
	Acute myeloid leukaemia and related precursor neoplasms
	Myeloid and lymphoid neoplasms
	Myeloproliferative neoplasms
	Myelodysplastic syndrome and myelodysplastic/ myeloproliferative diseases
	Histiocytic and dendritic cell neoplasms
Male breast cancer	Male breast cancer

* Based on an updated version (February 2019) of the list of cancer types from RARECARENet.

CHAPTER 6

Differences in health care experiences between rare cancer and common cancer patients: results from a national cross-sectional survey

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ABSTRACT

Background: Patients with rare cancers face challenges in the diagnostic and treatment phase, and in access to clinical expertise. Since studies on health care experiences of these patients in comparison to patients with more common cancers are scarce, we aimed to explore these differences.

Methods: Data were cross-sectionally collected among (former) adult cancer patients through a national online survey in the Netherlands (October 2019). Descriptive statistics were reported and subgroups (rare vs. common patients) were compared.

Results: In total, 7,343 patients (i.e., 1,856 rare and 5,487 common cancer patients) participated. Rare cancer patients were more often diagnosed and treated in different hospitals compared to common cancer patients (67% vs. 59%, $p<0.001$). Rare cancer patients received treatment more often in a single hospital (60% vs. 57%, $p=0.014$), but reported more negative experiences when treated in multiple hospitals than common cancer patients (14% vs. 9%, $p<0.001$). They also more often received advise from their physician about the hospital to go to for a second opinion (50% vs. 36%, $p<0.001$), were more likely to choose a hospital specialized in their cancer type (33% vs. 22%, $p<0.001$), and were more willing to travel as long as necessary to receive specialized care than common cancer patients (55% vs. 47%, $p<0.001$).

Conclusions: Rare and common cancer patients differ in their health care experiences. Health care for rare cancer patients can be further improved by proper referral to centers of expertise and building a clinical network specifically for rare cancers.

INTRODUCTION

Cancer represents the second most common cause of death in Europe [1]. The International Agency for Research on Cancer estimated that there were 3.9 million new European cancer cases in 2018 [2]. In the Netherlands, there were 118,500 new cancer diagnoses in 2019 [3]. About 24% of these are rare cancers, defined as those with an incidence of <6/100,000 people per year, according to the Surveillance of Rare Cancer in Europe (RARECARE) consortium [4]. In Europe, the five-year survival rates for rare cancers are lower than those for common cancers (49% vs. 63%, respectively) [5]. Therefore, rare cancers pose specific challenges on our health care system, both in the diagnostic and treatment phase, but also regarding access to clinical expertise [6, 7]. In their rare cancer trajectory, patients may be confronted with delayed or wrong diagnoses, conflicting treatment recommendations, logistical difficulties including coordination among multiple physicians and hospitals, and inadequate evidence to guide clinical decision-making [7-10]. Also, some patients with rare cancer (RC) might have longer travel distances in order to receive the necessary and best treatment [11]. Specifically, RC patients might – more than patients with common cancers (CC) – need treatment in centers of expertise (CoE), with multidisciplinary teams focusing specifically on their tumor type.

In the Netherlands, the health care system is based on universal health care access, in which all Dutch residents are entitled to a comprehensive basic health insurance package [12]. the general practitioner (GP) is generally the first access point for patients when they encounter physical complaints. Patients with suspected cancer are referred by the GP to the hospital for diagnosis, staging, and a treatment plan developed in multidisciplinary team meetings. Treatment might take place in the hospital of diagnosis, depending on the type of cancer and patient's request. However, patients with RC are often referred to a CoE. Moreover, patients might purposely choose for treatment or second opinion in such a hospital as well. After treatment, patients receive follow-up care to check for possible recurrence, to ensure patients' rehabilitation and to support their quality of life. [13, 14] All Dutch cancer patients are registered in the Netherlands Cancer Registry (NCR) since 1989 [15].

Research regarding experiences of patients with RC within the health care system is limited, and till now, mostly focused on individual types of rare cancers [16, 17]. Since RC patients jointly pose certain known challenges within health care [7-11], we hypothesize that they differ in health care experiences compared to patients with CC. To our knowledge, no explorative study on health care experiences of adult patients with RC has been published so far, and no comparison with experiences of adult patients with CC has been made. Therefore, in a national survey, we aimed to explore differences in health care experiences between patients with RC and patients with CC regarding diagnosis and treatment in multiple hospitals, hospital choice, medical expertise, second opinions, and travel distance to care. Further, objective data from the NCR were used to verify some of the subjective findings.

METHODS

Study design and participants

A cross-sectional survey was performed among (former) adult cancer patients. Data were collected amongst patients through an explorative national online survey in the Netherlands. The survey was open for two weeks in October 2019. In the survey, participants self-reported their type of cancer by selecting it from a predefined list. The ability of participants to self-report their cancer type accurately was shown to be quite high [18] The exact classification of a cancer being either rare or common was done afterwards based on the definition of a rare cancer [4] and on the classification used in a previous report on rare cancers in the Netherlands [19].

All participants within this study provided consent, and were informed about privacy policies, in accordance with the General Data Protection Regulation (EU) 2016/679. As they were not involved in an intervention, it was concluded that the Medical Research Involving Human Subjects Act (WMO) does not apply, and according to WMO, ethical approval is not required (2020.257).

Survey development and content

The explorative online survey was developed by the Dutch Federation of Cancer Patients Organizations (NFK), the Dutch umbrella organization for 19 cancer patient organizations. A project group consisting of a project leader, a researcher, three oncologists (MGB, MIvBH, CMLvH), and five cancer patient organizations' advocates experienced in quality of care was responsible for the development of the questionnaire's content, since no validated survey for the aim of this study was available. The final survey (in Dutch) consisted of 29 questions: 27 quantitative and 2 open questions (Supplementary Survey 1). In this study, the open questions were not qualitatively analyzed, but used to exemplify experiences of patients. Numerous questions were conditional, i.e., these questions were skipped when irrelevant for the respondent based on previous answers.

The survey started with a selection question to identify respondents who have (had) cancer and three general questions on sociodemographic characteristics. The remaining 25 questions were subdivided into overarching themes: diagnosis and treatment, hospital (choice), second opinion, and traveling to the hospital(s). All questions consisted of multiple answer options, except one question related to the rating of trust in medical expertise, which was scored on a 10-point scale ranging from 1 (no trust at all) to 10 (maximum trust). No personal information of participants was collected, and all data were analyzed anonymously. Only patients who completed the questionnaire at least up to and including the first question on health care experiences were included in the analyses.

Data collection

Data were collected through the online tool "Survey Monkey" [20]. The questionnaire was nationally distributed through four different channels. First, NFK asked affiliated cancer patient organizations to distribute the survey amongst their members and donors. This was done either directly by mail, or indirectly through their newsletter, website or social media. Second, an invitation was sent to all members of the "Doneer Je Ervaring" (Donate Your Experience) panel comprising (former) cancer patients. Third, an open link to the survey was spread through social media and websites of NFK and some relevant partner organizations (e.g., The Dutch Cancer Society, and website: www.kanker.nl). Last, respondents were actively recruited in several hospitals by means of posters, distribution of flyers, and a movie display in waiting rooms. In the Netherlands, the percentage of inhabitants with Internet access is high, i.e., 97% in 2019 [21]. Objective data was obtained via the NCR and included information on age, gender, type of cancer, number of types of treatment, hospital of diagnosis, hospital of treatment, and the number of hospitals patients were treated in. Hospital of diagnosis and hospital of treatment have been classified according to the Dutch health care system.

Statistical analyses

Analyses were defined a priori for testing, and applied at patients with RC and CC after data collection. Subgroups were defined based on type of cancer (rare vs. common) [19]. Differences between the subgroups were compared by an independent sample t-test for continuous variables or the Pearson's chi-square test for categorical variables. Nominal variables are presented as numbers and percentages. Continuous variables are presented as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. The number of prevalent cases was calculated at the index date of 1st October 2019 (10-year prevalence). For all analyses, a p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 25.

RESULTS

Sample characteristics

In total, 8,969 participants started the online survey. Of these participants, 556 did not meet the inclusion criteria (i.e., they did not have cancer), 966 did not complete the questionnaire at least up to and including the first question on health care experiences, and 104 could not be classified into a rare or common cancer group or gave duplicate

responses. After these exclusions, 7,343 participants were eligible for the analysis (i.e., 1,856 adult patients with RC and 5,487 adult patients with CC) (Table 1).

Patients with RC who participated in the survey were on average younger (61 years, SD 11.9) than patients with CC (63 years, SD 10.3) (p<0.001) (age range 18 to 95 years). Patients with RC were more likely to be men (39% vs. 33%, respectively) (p<0.001) and more often had a high educational level (43% vs. 38%, respectively) (p=0.001) compared to the participating patients with CC. The majority of patients with RC was diagnosed with hematological cancer (37%), female genital organs and breast cancer (15%), or cancer of the digestive tract (15%), while CC patients were mostly diagnosed with female genital organs and breast cancer (43%), male genital organ and urological cancer (19%), or cancer of the digestive tract (19%) (p<0.001). Most patients with RC received two types of treatment (36%), while most patients with CC received more than two types of treatment (43%) (p<0.001). Finally, patients with RC were more often in an incurable stage of the disease at time of survey completion compared to patients with CC (38% vs. 21%, respectively) (p<0.001) (Table 1). A selection of responses on the qualitative questions can be found in Table 2.

Table 1. Characteristics of the study population by cancer type (total *n* = 7,343)

	Rare cancer *n* = 1,856	**Common cancer *n* = 5,487**	**P-value**
Age in years, mean (SD)	61 (11.9)	63 (10.3)	0.001**
Sex, *n* (%)			0.001**
Male	723 (39%)	1,828 (33%)	
Female	1,121 (61%)	3,645 (67%)	
Educational level, *n* (%)			0.001*
High	781 (43%)	2,027 (38%)	
Medium	770 (43%)	2,413 (45%)	
Low	261 (14%)	874 (16%)	
Type of cancer, *n* (%)			0.001**
Sarcomas	216 (12%)	0 (0%)	
Female genital organs and breast cancer	284 (15%)	2,343 (43%)	
Male genital organ and urological cancer	65 (4%)	1045 (19%)	
Neuroendocrine tumors	28 (2%)	0 (0%)	
Cancer of digestive tract	270 (15%)	1,034 (19%)	
Cancer of endocrine organs	84 (5%)	0 (0%)	
Cancer of head and neck	143 (8%)	0 (0%)	
Thoracic cancer	34 (2%)	361 (7%)	
Melanoma of skin and eye	1 (0%)	237 (4%)	

Table 1. Characteristics of the study population by cancer type (total *n* = 7,343) *(continued)*

	Rare cancer *n* = 1,856	**Common cancer *n* = 5,487**	**P-value**
Cancer of central nervous system	50 (3%)	0 (0%)	
Hematological cancer	681 (37%)	467 (9%)	
Current phase of the disease, *n* (%)			0.001**
Cancer-free	904 (54%)	3,551 (70%)	
Curable	132 (8%)	489 (10%)	
Incurable	642 (38%)	1,056 (21%)	
Number of (types of) treatment[a], *n* (%)			0.001**
No treatment	58 (3%)	60 (1%)	
1 type of treatment	580 (31%)	1,393 (25%)	
2 types of treatment	672 (36%)	1,677 (31%)	
>2 types of treatment	546 (29%)	2,357 (43%)	
Years since last treatment, median (range)	2 (0-55 years)	2 (0-56 years)	0.06
Hospital of diagnosis[b], *n* (%)			0.001**
Academic or cancer-specialized hospital	481 (27%)	714 (13%)	
Top-clinical hospital	811 (45%)	2,571 (48%)	
General hospital	520 (29%)	2,092 (39%)	
Hospital of treatment[b], *n* (%)			0.001**
Academic or cancer-specialized hospital	1,020 (56%)	1,334 (25%)	
Top-clinical hospital	550 (30%)	2,431 (45%)	
General hospital	249 (14%)	1,597 (30%	

n, number; *SD*, standard deviation
The missing value rate was low (range 0-3%), with one exception, i.e., current phase of disease (8%).
[a] Types of treatment include surgery, radiation, chemotherapy, hormonal therapy, targeted therapy, stem cell transplantation, active surveillance and wait-and-see.
[b] Hospital of diagnosis and hospital of treatment have been classified according to the Dutch health care system.
* P<0.01.
** P<0.001.

Table 2. Selection of illustrative quotes from rare cancer patients

Topic	Quotes
Experiences regarding diagnosis and treatment in multiple hospitals	*"Bad communication from hospital X to hospital Y. Information was regularly missing, which almost led to crucial mistakes regarding treatment several times."*
Experiences regarding hospital choice	*"It is difficult to find out if another hospital would be better. You get into a crazy merry-go-around in the hospital where the diagnosis is made. Then you only want one thing, and that is to start treatment as soon as possible."*
Experiences regarding medical expertise and second opinions	*"The pathologist of hospital X asked for a second opinion himself, because of the rarity of angiosarcomas and thus I was immediately referred to hospital Y."*
Experiences regarding travel distance to care	*'If your life is at stake and you want maximum care, travel time is a secondary problem to be solved.'*

Experiences regarding diagnosis and treatment in multiple hospitals

Patients with RC more often received their diagnosis and treatment in different hospitals compared to patients with CC (67% [95% CI 65-69] vs. 59% [95% CI 57-60], respectively) (p<0.001). Diagnosis most often took place in a top-clinical hospital for both RC and CC patients (45% [95% CI 43-47] vs. 48% [95% CI 46-49], respectively) (p<0.001), while treatment for patients with RC mostly took place in an academic or cancer-specialized hospital (56% [95% CI 54-58]) and in a top-clinical hospital for patients with CC (45% [95% CI 44-47]) (p<0.001). For patients with CC, the hospital of diagnosis more often continued to remain their first point of contact and their treating hospital during the whole cancer trajectory compared to patients with RC (78% [95% CI 77-79] vs. 61% [95% CI 58-63], p<0.001).

Focusing specifically on treatment, a significant difference was found between RC and CC patients regarding the number of hospitals they were treated in (p=0.014). Patients with RC were more often treated in one hospital compared to patients with CC (60% [95% CI 58-62] vs. 57% [95% CI 55-58], p=0.014). In case patients with RC were treated in multiple hospitals, they reported more negative experiences than patients with CC (14% [95% CI 12-17] vs. 9% [95% CI 8-10], p<0.001). That is, patients with RC more often than patients with CC indicated that they did not feel supported by their physician when referred to another hospital (19% [95% CI 16-22] vs. 16% [95% CI 15-18], p=0.024), that their medical files were not available on time in the other hospital (18% [95% CI 15-21] vs. 13% [95% CI 12-15], p=0.001), and that their health care providers were not well informed about their situation (18% [95% CI 15-21] vs. 15% [95% CI 13-17], p=0.046).

Experiences regarding hospital choice

More than half of the RC and CC patients (51% [95% CI 48-53] vs. 52% [95% CI 51-53], respectively) never thought about the most suitable hospital regarding their cancer treatment (p=0.424). Of the patients who did think about which hospital was most suitable for them, 73% ([95% CI 70-76]) of the patients with RC and 71% ([95% CI 69-73]) of the patients with CC indicated that they have searched for information and/or have discussed this with someone (p=0.313). Patients with RC were more likely to choose a hospital, because it was specialized in their type of cancer than patients with CC (33% [95% CI 31-35] vs. 22% [95% CI 21-24], p<0.001). In retrospect, one in every six patients with RC (16% [95% CI 14-18]) and one in every five patients with CC (20% [95% CI 19-21]) would have done something in a different way regarding their choice of treatment hospital for their type of cancer (p<0.001), such as figuring out better what the best hospital for their type of cancer was or asking for a second opinion.

Experiences regarding medical expertise and second opinions

Differences between RC and CC patients were found regarding trust in medical expertise concerning their treatment. That is, respectively 66% ([95% CI 64-68]) and 61% ([95% CI 60-63]) gave, on a 0-10 scale, an 'excellent' score (range 9-10), 30% ([95% CI 29-31]) and 35% ([95% CI 34-35]) gave a 'sufficient to good' score (range 6-8), and 4% of both RC and CC patients gave an 'insufficient' score (range 1-5) ([95% CI 3-4]; [95% CI 4-4], respectively) (p=0.004). Further, patients with RC had slightly more often a second opinion compared to patients with CC (23% [95% CI 21-25] vs. 22% [95% CI 21-23], p=0.211). Patients with RC more often indicated to have been advised by their physician about the hospital to go to for a second opinion, compared to patients with CC (50% [95% CI 45-55] vs. 36% [95% CI 33-39], p<0.001).

Experiences regarding travel distance to care

Patients with RC were more often willing to travel as long as necessary to receive care from a hospital specialized in their cancer type in comparison to patients with CC (55% [95% CI 53-58] vs. 47% [95% CI 45-48], p<0.001). Patients with CC were more likely to choose a hospital close to home than patients with RC (65% [95% CI 64-67] vs. 46% [95% CI 44-49], p<0.001). Patients with RC (54% [95% CI 51-56]) more often travelled half an hour or longer to the hospital of treatment than patients with CC (35% [95% CI 33-36]) (p<0.001). Furthermore, significant differences were found between RC and CC patients regarding their travel experience; 67% ([95% CI 65-69]) of the patients with RC indicated that they never experienced problems with travelling compared to 79% ([95% CI 78-80]) of the patients CC (p<0.001). Of the patients who had problems with travelling to the hospital, both RC and CC patients explained that they were (sometimes) too sick or in too much pain (14% [95% CI 12-15] vs. 8% [95% CI 8-9], respectively), considered it as a

burden to travel to the hospital for treatment frequently (14% [95% CI 12-15] vs. 8% [95% CI 7-9], respectively), and experienced it as a burden for the ones who came with them (12% [95% CI 10-13] vs. 7% [95% CI 6-7], respectively) (all p<0.001).

Comparison of cancer registry and survey data

With respect to gender, data from the NCR showed that RC and CC patients are more often male (48% and 49%, respectively) compared to RC and CC patients who participated in the survey (39% and 33%, respectively) (Table 3). Patients with RC in the NCR are less often diagnosed with hematological cancer than patients in the survey (18% vs. 37%, respectively), while patients with CC in the NCR are less often diagnosed with female genital organs and breast cancer than patients in the survey (26% vs. 43%, respectively). Furthermore, both RC and CC patients in the NCR (45% and 40%, respectively) receive more often one type of treatment than participating patients in the survey (31% and 25%, respectively). According to the NCR data, the hospital of treatment for patients with RC is less often an academic or cancer-specialized hospital when compared to the survey (43% vs. 56%, respectively). In addition, diagnosis and treatment of patients with RC and patients with CC more often take place in one hospital according to the NCR data (52% and 64%, respectively), compared to data resulting from the survey (33% and 42%, respectively).

Table 3. Comparison of survey and NCR data (10-year prevalence) for rare and common cancer patients

	Rare cancer		**Common cancer**	
	Survey	**NCR**	**Survey**	**NCR**
Age in years, mean	61	58	63	65
Gender, %				
Male	39%	47%	33%	48%
Female	61%	53%	67%	52%
Type of cancer, %				
Sarcomas	12%	8%	0%	0%
Female genital organs and breast cancer	15%	20%	43%	26%
Male genital organ and urological cancer	4%	10%	19%	22%
Neuroendocrine tumors	2%	7%	0%	0%
Cancer of digestive tract	15%	6%	19%	17%
Cancer of endocrine organs	5%	5%	0%	0%
Cancer of head and neck	8%	16%	0%	0%
Thoracic cancer	2%	2%	7%	6%
Melanoma of skin and eye	0%	3%	4%	24%

Table 3. Comparison of survey and NCR data (10-year prevalence) for rare and common cancer patients *(continued)*

	Rare cancer		Common cancer	
	Survey	**NCR**	**Survey**	**NCR**
Cancer of central nervous system	3%	5%	0%	0%
Hematological cancer	37%	18%	9%	7%
Number of (types of) treatment[a], %				
No treatment	3%	4%	1%	6%
1 type of treatment	31%	46%	25%	40%
2 types of treatment	36%	28%	31%	30%
>2 types of treatment	29%	22%	43%	24%
Hospital of diagnosis, %				
Academic or cancer-specialized hospital	27%	17%	13%	8%
Top-clinical hospital	45%	48%	48%	51%
General hospital	29%	36%	39%	41%
Hospital of treatment, %				
Academic or cancer-specialized hospital	56%	43%	25%	12%
Top-clinical hospital	30%	37%	45%	51%
General hospital	14%	20%	30%	37%
Diagnosis and treatment in one hospital, %				
Yes	33%	51%	42%	64%
No	67%	49%	59%	36%
Number of hospitals patients were treated in, %				
1	60%	80%	57%	74%
≥2	40%	20%	43%	26%

[a] Types of treatment include surgery, radiation, chemotherapy, hormonal therapy, targeted therapy, stem cell transplantation, active surveillance and wait-and-see.

DISCUSSION

Main findings

The aim of this study was to explore possible differences in health care experiences between patients with RC and patients with CC. Our results indeed showed differences between these two adult patient groups. Patients with RC are more often diagnosed and treated in different hospitals compared to patients with CC. Treatment more often takes place in one hospital for patients with RC, but if treatment takes place in multiple hospitals, they experience this as more negative than patients with CC. Patients with RC are more often advised by their physician about the hospital to go to for a second opinion than patients with CC. In addition, RC patients are more likely to choose a hospital specialized in their cancer type, while CC patients are more likely to choose a hospital close to home. Finally, patients with RC are more often willing to travel as long as necessary to receive care from a specialized hospital in comparison to patients with CC.

Interpretation of findings

Our study showed that diagnosis and treatment of patients with RC mostly take place in different hospitals. This finding is in line with previous literature on rare cancers. Scandinavian registry studies revealed, for example, that nearly all patients, after being diagnosed with bone sarcoma (derived from the Scandinavian Sarcoma Register [22]) or soft-tissue sarcoma (derived from the Swedish Cancer Registry [23]) are referred to a sarcoma expert center for their treatment [22, 23]. This implies that most patients with RC in our survey are referred to another hospital for treatment in case the hospital of diagnosis is lacking expertise for the treatment of the specific rare cancer type. While such a treatment decision may benefit the patient, it also may lead to fragmentation of care [24].

Focusing specifically on treatment, patients with RC more frequently receive this care in a single hospital compared to patients with CC, probably indicating a certain level of centralization of care for those with a rare tumor type. This is in line with the study by Gatta et al. (2017) on patients with RC, diagnosed in 2000-2007, in seven European countries [5]. Although centralization of care was not completely realized at the time of the study, the authors indicated that the highest centralization patterns were found in Slovenia and in the Netherlands. For example, care for patients diagnosed with bone sarcoma was already highly centralized between 2000-2007 in the Netherlands, i.e., 75% of these patients were seen in only five hospitals. Nowadays, care for these patients is even centralized in four bone tumor centers [25]. Still, while in almost every hospital treatment for CC patients is offered, only a few designated CoE exist in which optimal treatment for patients with RC is available [5, 26]. This centralization of care has been shown to improve disease outcomes for rare cancers [27, 28].

With regard to being treated in multiple hospitals, patients with RC had more negative experiences than patients with CC. Although speculative, negative experiences of being treated in multiple hospitals might, among others, be explained by delays in care caused by patient referral from one to another hospital [29, 30]. Studies showed that these delays may result in major psychosocial worries and dissatisfaction with the health care system [31-33]. Moreover, negative experiences may be more prevalent in patients with RC compared to patients with CC, since the former often lack a clear cancer care pathway due to fragmentation of care [16, 34, 35].

Regarding second opinion, patients with RC were more often recommended by their physician about the hospital to go to for such a second opinion than patients with CC. A possible explanation for this may be related to the confidence of physicians with offering specific care for patients with RC. For a limited number of rare cancers, centralization of care is present, because of which these physicians are aware of the hospital that provides the best care for this patient. Previous studies on second opinions in breast cancer patients showed that physicians specifically inform those patients who are highly educated and more involved in the decision-making process, and these patients were also more likely to request a second opinion [36, 37]. Accordingly, patients with RC in our study had a higher level of education than CC patients, and thus might be more inclined to learn about second opinion options, or request such an opinion themselves.

Considering hospital choice, patients with RC were more likely than patients with CC to choose a hospital with expertise regarding their cancer type. However, for patients with RC, it remains often unclear where the expertise for their specific cancer type is available due to fragmentation of care. Moreover, CC patients were more likely to choose a hospital close to home than RC patients, but expertise for those patients is in general more accessible close to home. Consequently, patients with RC experience longer travel distances to receive specialized care, but they also showed greater willingness to travel for this specialized care. Previous studies in head and neck cancer patients found, in line with our findings, that those patients were willing to travel significant distances to ensure access to better cancer care [38, 39]. Regardless of the travel distance to the hospital, patients with RC seem to deliberately search for the best available cancer care, while patients with CC have a lower incentive to search for better care beyond their regional hospital.

Limitations and strengths

A strength of the present study is that, to the best of our knowledge, this is the first explorative study showing differences in health care experiences between patients with RC and CC. Other strengths of this study are the comparison of the survey data with cancer registry data from all Dutch cancer patients, which enabled the researchers to investigate the generalizability of the study results, and the large sample size. Yet,

results should be interpreted with caution, as statistically significant differences in such a large sample size might not always be clinically relevant.

Several limitations of this study need to be addressed as well. First, participants were mainly recruited through cancer patient organizations and might therefore not be representative for all cancer patients. That is, patients with hematological cancers were overrepresented in the survey. Also, patients related to these organizations often have a higher educational level, which was found in our study as well. Second, although we included a broad sample of participants, the number of RC and CC patients who chose not to complete the survey is unknown, which might have resulted in participation bias. Third, in this study, no data was collected on year of diagnosis, relapse status, and whether patients changed hospitals at their own request or through active referral. Not having gathered data on these items may have influenced our interpretation of the experiences patients reported in this study. Fourth, the questionnaire was only available in Dutch and no psychometric properties were tested. Fifth, cancer diagnosis was self-reported, and the classification of a cancer being either rare or common was done in retrospect, which might have led to misclassification of patients. Sixth, it should be emphasized that our cross-sectional study merely established associations, and no causal relations. Finally, regarding generalizability, one should be aware that the Dutch health care system and degree of centralization might differ from other countries. On a global level, centralization of rare cancer care is still suboptimal, with the exception of a country such as France where clear organization of rare cancer care exists [40]. Due to these limitations, findings should be interpreted with caution.

Implications for research and clinical practice

Future research on rare and common cancers should classify the cancer type beforehand, using the list of rare cancers as comprised by RARECARENet [41]. Also, researchers should aim to include a generic group of patients with RC and CC in future studies, i.e., a higher percentage of male and low educated patients in our study sample would have given a more accurate representation of the overall group of cancer patients. Further, longitudinal studies on health care experiences between RC and CC patients should be conducted to enable assessment of causal relationships. Finally, in order to reduce heterogeneity, researchers should further examine differences between patients with RC and CC by site.

With regard to clinical practice, health care providers should be aware of the different health care experiences of patients with RC and CC. They should take into account the experiences of patients with RC when referring them to another hospital for treatment (e.g., if possible, they should refer them to a CoE and/or support a patient's request for a second opinion). Also, they should offer them appropriate guidance and support to reduce their negative experiences when treated in multiple hospitals. In addition, observed differences in health care experiences between patients with RC and CC could be reduced by establishing regional clinical networks and ensuring appropriate care to

all rare cancer patients regardless their point of access. Such a network could, among others, simplify and accelerate referrals, which may diminish challenges patients with RC are facing during their patient journey. Health care providers can play an important role in this by developing a clear patient pathway, giving support during the whole cancer trajectory and, if necessary, proper referral to CoE. Herewith, they support similar access and continuity of health care for both patients with RC and CC.

CONCLUSION

The results of this study showed that differences in health care experiences between adult patients with RC and CC exist. Regional clinical networks should be established to support proper referral of patients with RC to centers of expertise, and to improve their care. Future longitudinal studies are needed to determine the causal relationship between care and health-related outcomes in patients with RC.

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SUPPLEMENTARY

SURVEY 1

1. This questionnaire is intended for people who have (had) cancer. Does this apply to you?
   a. Yes, I have (had) cancer
   b. No

About you

2. What is your sex?
   a. Male
   b. Female
   c. Other

3. What is your year of birth? ...

4. What is your highest level of education?
   a. No education achieved
   b. Primary school (primary education)
   c. Lower vocational secondary education (e.g., LTS, LHNO, huishoudschool, VMBO-basis beroepsgericht, VMBO-kader beroepsgericht, LEAO)
   d. Secondary general education (e.g., ULO, MULO/MAVO, 3 jaars-HBS, VMBO-T)
   e. Secondary vocational education (MBO)
   f. Senior general secondary education/pre-university education (e.g., HAVO, VWO, gymnasium, HBS, MMS)
   g. Higher professional education (HBO, bachelor, post-HBO)
   h. University education (university, master, doctoral degree)
   i. I would rather not say
   j. Otherwise, namely

About your disease and treatment

5. Which type of cancer do/did you have?

If you have (had) more types of cancer, then fill in the most recent type of cancer. Pay attention: the type of cancer you fill in here, will appear during the rest of the questionnaire.

6. Which treatment(s) did you have for [Q5]?

Multiple answers possible.

   a. Surgery
   b. Chemotherapy
   c. Radiation
   d. Hormonal therapy

e. Immunotherapy
f. Targeted therapy
g. Stem cell transplantation
h. Wait and see
i. Active surveillance or watchful waiting
j. Stoma placement
k. Pain-relieving treatment
l. I do not know which treatment I have had
m. I did not have any treatment
n. Otherwise, namely ...

7. In which year did your most recent treatment* for [Q5] take place?
** By treatment we mean: surgery, chemotherapy, radiation, hormonal therapy, immunotherapy, targeted therapy, stem cell transplantation, wait and see, active surveillance or watchful waiting, stoma placement or pain-relieving treatment.*

8. Which of the following descriptions matches your situation (at this moment) the most, regarding [Q5]?
a. I (probably) do not have cancer anymore
b. I will (probably) get better
c. I will (probably) not get better
d. I do not know/not applicable

About your hospital(s)

9. In which hospital was your diagnosis [Q5] made? ...

10. In which hospital were you treated* for [Q5]?
*Have you been treated in several hospitals? Then assume the hospital that was your first point of contact** for your treatment.*
** By treatment we mean: surgery, chemotherapy, radiation, hormonal therapy, immunotherapy, targeted therapy, stem cell transplantation, wait and see, active surveillance or watchful waiting, stoma placement or pain-relieving treatment.*
*** By the hospital that is your first point of contact for your treatments, we mean the hospital where you have the most checks and conversations. The medical specialist, who has an overview of all your treatments as well as treatments in other hospitals, also works in this hospital.*

11. In how many hospitals* in total have you been treated** for [Q5]?
a. One hospital
b. Two hospitals
c. Three or more hospitals

** One hospital can have multiple locations, e.g., VieCuri Medisch Centrum Venlo and VieCuri Medisch Centrum Venray. We regard this as one hospital. Therefore, this question concerns different hospitals and not different locations of the same hospital.*

*** By treatment we mean: surgery, chemotherapy, radiation, hormonal therapy, immunotherapy, targeted therapy, stem cell transplantation, wait and see, active surveillance or watchful waiting, stoma placement or pain-relieving treatment.*

12. How did you experience treatment in multiple hospitals for [Q5]?
    a. I (mostly) experienced this as positive
    b. I have not experienced this as positive nor as negative
    c. I (mostly) experienced this as negative
    d. I do not know/not applicable

13. What have you experienced (mostly) as positive or (mostly) as negative about the fact that you were treated in two or more hospitals for [Q5]?
    ...

14. You have been treated in multiple hospitals for [Q5]. To what extent have you experienced the arguments below (in general)?

Answer possibilities: Always, mostly, sometimes, never, I do not know/not applicable

- I felt supported by my doctor(s) in one hospital, when I was referred to another hospital for (a part of my) treatment
- My file or medical research results in one hospital were on time available in the other hospital
- My health care providers in one hospital were well informed of what happened to me in the other hospital
- I knew in which hospital I had to be with questions or problems

Give an explanation if necessary: ...

Second opinion

15. Have you had a second opinion* for [Q5]?

Multiple answers possible.

    a. Yes, shortly after my diagnosis, but before I started my first treatment
    b. Yes, later in my illness, during or after my treatment(s)
    c. No
    d. I do not know/not applicable

    ** With a second opinion, another doctor (in another hospital) will look at your diagnosis and treatment options again. You can request a second opinion if you want more certainty about your diagnosis or treatment options.*

16. You have had a second opinion for [Q5] once or multiple times. To what extent have you experienced the arguments below (in general)?

Answer possibilities: Always, mostly, sometimes, never, I do not know/not applicable

- I felt supported by my doctor(s) in one hospital, when I went to another hospital for a second opinion
- The doctor in one hospital advised me a hospital to go to for a second opinion
- My file or medical research results in one hospital were on time available in the hospital of the second opinion

Give an explanation if necessary: ...

About the choice for your hospital

17. Have you ever thought about which hospital is most suitable for you for the treatment of [Q5]?
    a. Yes
    b. No
    c. I do not know/not applicable

Give an explanation if necessary: ...

18. Have you searched for information and/or discussed with someone to find out which hospital for you is most suitable for treatment of [Q5]?
    a. Yes
    b. No
    c. I do not know/not applicable

19. Where did you search for information and/or with whom did you discuss to find out which hospital for you is most suitable for treatment of [Q5]?

Multiple answers possible.

    a. Website hospital
    b. Website cancer patient organization
    c. Website health care insurer
    d. Other website(s)
    e. A decision aid* completed on the internet
    f. Flyer hospital
    g. Flyer cancer patient organization
    h. Discussed with my general practitioner
    i. Discussed with hospital
    j. Discussed with cancer patient organization
    k. Discussed with health care insurer
    l. Discussed with fellows/acquaintances
    m. I do not know/not applicable
    n. Otherwise, namely ...

    * *A decision aid is an instrument on the internet that helps you choose a hospital that suits you the most. The decision aid asks you several questions and you indicate what is important to you. Thereafter, you receive an overview of hospitals that suit your wishes the most. You can then compare the hospitals.*

20. What were your reasons for choosing hospital [Q10] for the treatment of [Q5]?

Multiple answers possible.

a. This hospital was close to home
b. The travel and/or parking costs for this hospital were low
c. I was already being treated for another disease in this hospital
d. I already knew this hospital
e. I had a doctor at this hospital with whom I felt comfortable
f. This hospital seemed good to me
g. By information I found on the internet, this hospital seemed most suitable for me
h. My general practitioner recommended this hospital to me
i. My doctor in another hospital recommended this hospital to me
j. The cancer patient organization recommended this hospital to me
k. My health care insurer recommended this hospital to me
l. Fellows/acquaintances recommended this hospital to me
m. This hospital is specialized in [Q5]
n. I have had a second opinion in this hospital
o. In this hospital I could get a specific treatment, which I could not get in the other hospital (e.g., surgery or participating in a trial)
p. My other hospital could not (further) help me and this hospital could
q. There was no specific reason why I chose this hospital
r. I do not know/not applicable
s. Otherwise, namely ...

21. How much trust do you have in the medical expertise of hospital [Q10] when it comes to treatment of [Q5]?

Give a score between 1 and 10 (1=no trust at all – 10=maximum trust, I do not know/not applicable):
...
Give an explanation if necessary: ...

22. Do you know which hospital(s) is/are specialized in [Q5]?

a. Yes
b. No

Give an explanation if necessary: ...

About travelling to your hospital

23. What was your travel time* (one-way) to [Q10], when you were treated for [Q5]?

a. Less than half an hour
b. Between half an hour and 1 hour
c. Between 1 hour and 1,5 hours
d. Between 1,5 and 2 hours
e. Between 2 and 3 hours
f. More than 3 hours

** By travel time we mean: the time you travel from home to hospital (one-way). Without time that you spend in the parking garage or for walking to the outpatient clinic.*

24. How did you experience travelling* to [Q10], when you were treated for [Q5]?
    a. I did not have a problem with travelling
    b. I sometimes had a problem with travelling
    c. I often had a problem with travelling
    d. I always had a problem with travelling

    ** By travelling we mean: the travel distance, the travel time and the comfort of travelling.*

25. Why was travelling to [Q10], when you were treated for [Q5] (to a greater or lesser extent) a problem for you?

Multiple answers possible.

    a. I was (sometimes) too ill or I (sometimes) had too much pain to travel
    b. I often had to go to this hospital for treatment
    c. The travel distance and/or travel time to the hospital was too long
    d. The travel and/or parking costs were too high for me
    e. I had to go to the hospital on my own, nobody could come with me
    f. I do not have my own transportation
    g. I thought it was a burden for my loved ones who came with me
    h. The hospital was too far away for my loved ones, so I received little or no visit in the hospital
    i. I do not know/not applicable
    j. Otherwise, namely ...

26. How long would you be willing to travel (one-way) for care from a hospital that is specialized in [Q5]?

Indicate your maximum travel time.*

    a. Half an hour maximum
    b. 1 hour maximum
    c. 1,5 hours maximum
    d. 2 hours maximum
    e. 3 hours maximum
    f. There is no maximum travel time. I will travel as long as necessary to receive the care of a hospital that is specialized in [Q5]
    g. I do not know/not applicable

Give an explanation if necessary: ...

** By travel time we mean: the time you travel from home to hospital (one-way). Without time that you spend in the parking garage or for walking to the outpatient clinic.*

If you could redo it…

27. In retrospect, would you have done something else if it concerns the choice for [Q10] for the treatment of [Q5]?

Multiple answers possible.

a. Yes, I would have found out (better), which is the right hospital for me
b. Yes, I would have discussed (more) with my general practitioner, which is the right hospital for me
c. Yes, I would have discussed (more) with my doctor in the hospital of diagnosis, which is the right hospital for me
d. Yes, I would have discussed (more) with a cancer patient organization, which is the right hospital for me
e. Yes, I would have discussed (more) with my health care insurer, which is the right hospital for me
f. Yes, I would have discussed (more) with fellows/acquaintances, which is the right hospital for me
g. Yes, I would have done a second opinion (earlier)
h. Yes, I would not have gone to this hospital
i. Yes, I would have chosen a different hospital (earlier), namely a hospital that is specialized in [Q5]
j. Yes, I would have chosen a different hospital (earlier), namely a hospital closer to home
k. Yes, I would have chosen a different hospital (earlier), namely a hospital where I was already being treated for another disease
l. Yes, I would have chosen a different hospital (earlier), namely a hospital that I already know
m. No, I would not have done something else
n. I do not know/not applicable
o. Otherwise, namely …

Finally

28. Finally, is there anything you would like to share?
To protect your privacy, we ask you to not fill in any personal information.
…

29. We would like to improve our Donate Your Experience. It helps us to know how people get into our questionnaires. How did you get into this questionnaire?
Multiple answers possible.

a. I am member of the Donate Your Experience panel
b. Through a cancer patient organization
c. Through a hospital
d. Through the general practitioner
e. Through social media

f. Through Gezondheidsplein.nl or dokterdokter.nl
g. Through Kanker.nl
h. Through KWF (social media/website)
i. Through an online advertisement
j. Through family/friends/acquaintances
k. Other

CHAPTER 7

The solitary versus supported experience: care inequality between rare and common cancer patients

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ABSTRACT

Objective: Patients with a rare cancer often have a more complex disease trajectory than patients with a common cancer. Research involving both patient groups is needed to identify differences and resemblances. In this study, we aimed to explore and compare experiences, needs and quality of life of patients with rare and common cancer throughout the disease trajectory.

Methods: A qualitative focus group study was conducted, including patients with rare and common cancer (n=25). Participants were purposively selected to reflect heterogeneity of cancer types. A semi-structured topic list was used. Focus groups (n=4) were recorded, transcribed verbatim and analysed, using thematic analysis.

Results: Three themes were identified emphasizing care inequality between patients with rare and common cancer: 1) The solitary experience: lack of information and support impact the rare cancer patient, 2) Sudden impact, but recognition reduces the common cancer burden, and 3) Absence of psychosocial care requires being empowered as a cancer patient.

Conclusions: Patients with rare cancer are faced with enormous challenges due to the high impact of their solitary experience on their quality of life, while patients with common cancer generally experience social support and recognition alleviating their burden. Centralisation of care for patients with a rare cancer is needed and tailored psychosocial care should be provided to overcome inequalities.

BACKGROUND

Rare cancers, defined by the RARECARE consortium as those cancers with <6/100,000 people per year [1], comprise 24% of all cancer diagnoses in Europe [2]. Five-year survival rates for patients with a rare cancer (RC) are worse and improvements in survival are lagging behind compared to patients with a common cancer (CC) [2, 3]. Moreover, RC patients are confronted with additional challenges, including a delayed diagnosis and limited therapeutic options [4-6]. This might result in a more complex disease trajectory for RC patients compared to those with a CC type [7].

In general, expertise for CC patients is widely available, while RC patients might need specific referral to centres of expertise for optimal diagnostics and treatment. Previous research has shown that RC patients are more often than CC patients diagnosed and treated in different hospitals, resulting in negative experiences [7]. They reported lower quality of life (QoL) and more unmet supportive care needs [8, 9], with highest unmet needs in the healthcare system and information domain [10].

Despite these differences between CC and RC patients within healthcare, they might also have similar patient experiences and needs. In a systematic review in CC patients, highest unmet needs were reported in the daily living, psychological and information domains [11], comparable to findings in RC patients [10]. Moreover, various experiences and needs of CC patients (e.g., dealing with the effects of treatment) [12-14] were also found in RC patients [15, 16]. However, numerous specific experiences (e.g., uncertainty regarding diagnosis) were reported to be present in patients with a RC only [15].

While gaps in experiences and needs, present in both patient groups, might be minimised via generic intervention programs, gaps within either RC or CC care should be dealt with separately. Therefore, the aim of this study was to explore and compare experiences, needs and QoL of RC and CC patients throughout the disease trajectory.

METHODS

Design

A qualitative study design was employed, in which focus group interviews with RC and CC patients were conducted in April and May 2022. Methods and results are described using the Consolidated Criteria for Reporting Qualitative Research (COREQ) [17] (Appendix 1). The Medical Ethics Review Committee of VU University Medical Centre confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply and that an official approval was not required (2021.0722).

Participant recruitment and procedure

Participants were purposively selected to reflect heterogeneity of cancer types (i.e., both within RC and CC groups and within focus groups) [18]. Patients with cancer were eligible for participation if they were: (1) diagnosed with cancer (i.e., RC [19] or CC); (2) of adult age (>18 years) at time of diagnosis; and (3) able to understand and speak Dutch. Patients were excluded if they were suffering from severe psychological problems.

Recruitment of patients took place via healthcare professionals (HCPs) (e.g., medical specialists), relevant stakeholders (e.g., representatives of the Dutch Federation of Cancer Patient Organisations), and social media. Recruitment of participants stopped when data saturation was reached.

Patients could express their interest in participation to their medical specialist or directly via mail to the researcher (EdH). In case a patient was interested, an information letter, informed consent form and short questionnaire (including sociodemographic, diagnosis- and treatment-related questions) were provided. Upon return of the completed documents, inclusion criteria were checked, and eligible patients were contacted to check availability for the focus group.

Data collection

Focus groups were semi-structured, and a predetermined topic list was used (Appendix 2). Through a guided discussion, the participants explored their experiences, needs, and QoL during the different phases of the disease trajectory (i.e., diagnostic, treatment, and posttreatment phase). The focus groups were moderated by a senior researcher (SD) and a PhD candidate (EdH). There were two observers (ED and KvdC/JMvdZ) present during each focus group session, who took field notes and audiotaped the sessions. All focus groups were audio recorded, transcribed verbatim, and pseudonymized before analysis. Focus groups lasted about 2.5 hours each and were hosted at the office of the Netherlands Comprehensive Cancer Organisation. Participants were compensated for travel expenses.

Data analysis

Sociodemographic characteristics were retrieved from the questionnaire and reported by descriptive statistical analysis. In the analysis, data transcripts were the primary data source, complemented by field notes taken during the focus groups. Data were analysed using a thematic analysis approach, as described by Braun and Clarke [20].

Two researchers (EdH and ED) independently coded and discussed one transcript until consensus on the initial coding tree was reached. The three remaining focus groups were coded by one researcher (EdH). Preliminary themes were derived from the coded data (EdH and ED), based on the different phases of the disease trajectory. The final data analysis findings were discussed with two other researchers (SD, KvdC),

not involved in the coding of the transcripts, to reach ultimate themes. Quotes were selected for the manuscript to illustrate the themes. ATLAS.ti 22.0 software (Scientific Software Development ATLAS.ti 2022) was used to manage the data [21].

RESULTS

Participant characteristics

Four focus groups were conducted with, in total, 25 patients with cancer (12 RC patients, 10 CC patients, and 3 patients with both a RC and a CC). Mean age of RC patients was 62 years (range 47-74), 9 patients were female (75%), and 6 patients were 0-5 years from diagnosis (50%). Mean age of CC patients was 63 (range 50-75), 5 patients were female (50%), and most participants were 0-5 years from diagnosis (80%). All characteristics, including those of patients with both a RC and a CC, can be found in Table 1.

Table 1. Patient characteristics

Characteristics	Rare cancer (N = 12)	Common cancer (N = 10)	Rare and common cancer (N = 3)
	n (%)	n (%)	n (%)
Age at time of focus group (years) (mean (SD); range)	62 (6.9); 47-74	63 (7.7); 50-75	58 (2.9); 54-61
Sex			
Male	3 (25%)	5 (50%)	0 (0%)
Female	9 (75%)	5 (50%)	3 (100%)
Education level			
General secondary education	2 (17%)	2 (20%)	0 (0%)
Secondary vocational education	1 (8%)	2 (20%)	1 (33%)
Higher professional education	5 (42%)	5 (50%)	1 (33%)
University	4 (33%)	1 (10%)	1 (33%)
Marital status			
Married	10 (83%)	8 (80%)	2 (67%)
Cohabiting	1 (8%)	1 (10%)	0 (0%)
Widow	1 (8%)	1 (10%)	1 (33%)

Table 1. Patient characteristics *(continued)*

Characteristics	Rare cancer (N = 12)	Common cancer (N = 10)	Rare and common cancer (N = 3)
	n (%)	n (%)	n (%)
Type of cancer †			
Anal cancer	1 (8%)	0 (0%)	0 (0%)
Brain tumour	1 (8%)	0 (0%)	0 (0%)
Breast cancer	0 (0%)	2 (20%)	2 (33%)
Colorectal cancer	0 (0%)	1 (10%)	0 (0%)
Endometrial clear cell cancer	1 (8%)	0 (0%)	0 (0%)
Esophageal cancer	0 (0%)	1 (10%)	0 (0%)
Haematological cancer	1 (8%)	2 (20%)	0 (0%)
Lung cancer	0 (0%)	3 (30%)	1 (17%)
Ovarian carcinoma	1 (8%)	0 (0%)	0 (0%)
Prostate cancer	0 (0%)	1 (10%)	0 (0%)
Sarcoma	2 (17%)	0 (0%)	1 (17%)
Skin lymphoma	4 (33%)	0 (0%)	0 (0%)
Thyroid cancer	1 (8%)	0 (0%)	2 (33%)
Years since diagnosis (at time of focus group) †			
0-5	6 (50%)	8 (80%)	3 (75%)
5-10	3 (25%)	1 (10%)	1 (25%)
>10	3 (25%)	1 (10%)	0 (0%)
Metastases			
Distant	2 (17%)	2 (20%)	0 (0%)
Lymph nodes	5 (42%)	5 (50%)	3 (100%)
None	5 (42%)	3 (30%)	0 (0%)
Completed treatment types			
Single treatment	4 (33%)	3 (30%)	1 (33%)
Multimodal treatment	8 (67%)	5 (50%)	2 (67%)
None	0 (0%)	2 (20%)	0 (0%)

† Some numbers add up to >3 within the rare and common cancer group because of dual cancer diagnoses.

Themes

Three themes emerged from the data, of which one specifically relates to RC, one to CC and one to both patient groups. Per theme, experiences, needs and impact on QoL have been described.

The solitary experience: lack of information and support impact the rare cancer patient

Most patients with a RC experienced a lack of information throughout their disease trajectory, causing insecurity about how best to move forward. They reported to have experienced a long period of uncertainty prior to and around time of the definite diagnosis, due to missing or incorrect information, and to have felt helpless in their information search. As a result, some patients actively searched for information about their diagnosis (e.g., scrutinizing their own medical dossiers to ensure the right cancer diagnosis was made) or possible treatment options (e.g., seeking international scientific evidence) themselves.

In contrast to RC patients, most CC patients received adequate and complete information. For example, patients with breast cancer received, at time of diagnosis, a ring binder with information, which was continuously filled with new material. Herewith, these patients were supported in their information needs and could gradually process the information tailored to each phase of their disease trajectory.

> "*The lack of information was killing. You know that something is really wrong, but you cannot come to grips with it and you do not know how to start solving it.*" – Patient with a RC

> "*When I was diagnosed with breast cancer, they proactively presented me with a lot of useful information in the form of a huge binder. (…) A huge contrast with sarcoma* [i.e., second cancer]. *I had to search information on the Internet myself and I only found a little."* – Patient with a CC and a RC

The lack of information about RCs was mentioned to negatively affect the level of support throughout the disease trajectory. Patients with a RC felt that the unfamiliarity of their diagnosis unintentionally impacted support from both family/friends and HCPs. Consequently, from diagnosis onwards, RC patients reported feelings of loneliness due to limited understanding and empathy. Moreover, RC patients indicated that they do not feel heard or taken seriously by their general practitioner (GP) and treating physician (due to misinterpretation or trivialisation of their symptoms). CC patients did not recognize this unawareness and related lack of support during the diagnostic and treatment phase, but instead felt understood by and received sympathy, compassion and understanding from their surroundings and HCPs.

> *"They* [i.e., HCPs] *did not care what I was going through. I felt like a package being passed through the hospital. They only looked at the package, not being interested in the feelings of that package at all."* – Patient with a RC

Some RC patients experienced their diagnostic and treatment trajectory as a 'search' within the healthcare system due to fragmentation of care including multiple hospitals and/or physicians. As a result, they felt obliged to take the lead and become an 'expert patient' themselves, for example, with regard to healthcare system navigation, finding expert care, and obtaining specific information about their diagnosis and treatment. Some even reported to feel more knowledgeable than their own treating physician, which adversely affected the patient-physician trust.

> "*I gave up on asking them* [i.e., HCPs] *a lot of questions* [i.e., about providing information]. *It is just all so disappointing. And (…) I am my own director now. I just do it all by myself.*" – Patient with a RC

Patients with a RC expressed the need for tailored information and a more empathic approach from their treating physician. Specifically, they desired information provision adapted to their needs within each phase of the disease trajectory, transparency about best treatment options and expertise regarding their RC type, and psychosocial support for themselves and their family. In CC patients, the specific informational needs and related support were not prevalent.

Regarding the impact on QoL, patients with a RC stated that while their physical functioning was mainly negatively impacted during the treatment phase (i.e., due to physical deterioration), the decline in mental functioning was predominant throughout their disease trajectory. Patients explained that specifically their uncertain and complex diagnostic trajectory negatively affects their QoL, for example, due to a delayed diagnosis, misdiagnosis, and uncertainty about prognosis.

> "*For me, the impact on QoL was really high, because every day I was concerned about whether I would still be alive in three months and how it would impact my children. And I did not have any information, so that was a dramatic experience.*" – Patient with a RC (no advanced disease stage at time of the focus group)

Sudden impact, but recognition reduces the common cancer burden

Most patients with a CC experienced suddenly 'being a cancer patient' as difficult. They required time to process and overthink treatment options. Whereas CC patients faced difficulties in coping with the rapid cancer diagnosis, patients with a RC experienced tough times with their long, uncertain diagnostic trajectory and felt relieved when the correct diagnosis was finally made.

> *"And then, from one day to another, you have to say that you are ill. And that feels very strange. (…) Because you are still able to do everything."* – Patient with a CC

Despite the challenges associated with the rapid cancer diagnosis, patients with a CC shared the experience of feeling understood and supported by their social environment during this stage. The recognition among family, friends, and fellow patients, as well as the received support from HCPs and their surroundings, was experienced as easing the burden. Most patients also indicated that, during the diagnostic and treatment phase, a transparent, standardized patient pathway was present in terms of comprehensible and tailored information about their diagnosis and prognosis, and treatment options. On the contrary, RC patients indicated that care paths during the diagnostic and treatment phase are missing.

> *"There was a short period of restlessness when I received the breast cancer diagnosis. I had the feeling that something was not right. The week after I had quite some panic. But once the diagnosis is there, those* [care] *paths are very clear."* – Patient with a CC

While CC patients explained to feel in control due to shared decision making, based on the information they were given, RC patients were not, due to the lack of treatment options and accompanying information. Patients with a CC did not feel the need to manage their own disease trajectory (i.e., investigating best treatment options and most experienced physician). Many patients with a CC indicated that they had a strong personal belief in getting better due to the provision of reassurance and trust provided by their HCP during treatment. Patients with a RC, on the other hand, explained that they often did not fully trust their physician due to the absence of expertise.

> *"But the physician also immediately said: 'We are going to cure you.' So, I completely relied on that and (…) I really trusted that I would get better."* – Patient with a CC

Despite the sudden cancer diagnosis, many patients with a CC indicated that the cancer diagnosis had modest impact on their QoL, as the received support, presence of clear care pathways, and recognition among fellow patients alleviated their burden. Some patients even stated that, in the end, their cancer diagnosis might have had a positive impact, because of changes they, for example, made regarding lifestyle.

> *"I am convinced that my breast cancer gave me a loving kick in the pants like: 'now you have the choice (…), to approach life differently.'"* – Patient with a CC

Absence of psychosocial care requires being empowered as a cancer patient

Both patients with a RC and a CC stated the lack of psychosocial support, either throughout the disease trajectory (RC patients) or during the transition from treatment to posttreatment (CC patients). They shared the impression that some HCPs mainly focus on the technical outcomes (i.e., obtaining diagnostic results and managing treatment procedures), rather than showing empathy and paying personal attention to the patient's emotional and psychosocial functioning when needed. Some patients explained that this might be due to time constraints or a lack of experience with psychosocial care with their specific cancer type.

> "*They have asked about my skin conditions, but they have never asked how I was really doing. And they never offered me any support.*" – Patient with a RC

At time of transition to the posttreatment phase, most RC and CC patients were not satisfied with the information provision and psychosocial support they received. Some (mainly CC) patients called this phase a 'black hole', that is, the struggle to return to 'normal' life again. They felt like they were not properly prepared for this transition by their HCPS and stated the absence of suitable information and communication.

Both patients with a RC and CC type stated that the absence of psychosocial care forced them to become empowered. They indicated that assertive behaviour is required, e.g., asking for psychosocial care, searching for information, and taking control of their own disease trajectory. One patient with a brain tumour explained that after complete surgical removal of the tumour, HCPs focused on the successful treatment only, and completely ignored her psychosocial problems.

> *"I notice that you really have to ask for it. The physical care in* [name hospital] *is good. (...) But even though I have been going there for years, no doctor knows who I am. They ask: 'How is your illness?' I feel like I am a disease. (...) So yes, if I need something, I have to ask for it myself."* – Patient with a CC

Regarding needs, both patients with a RC and a CC expressed the need for a fixed point of contact. Those who had been appointed one indicated that support and personal attention from their fixed point of contact (e.g., nurse practitioner, physician, or GP) throughout the disease trajectory had been useful in terms of care navigation, information provision, and reduction of stress and anxiety. However, the majority of the patients stated they lacked such a fixed point of contact.

Furthermore, patients with a RC and a CC wished for better communication with and collaboration between HCPs throughout the disease trajectory. This need was even more prevalent in (mainly RC) patients who were diagnosed and/or treated in multiple hospitals, thus involving multiple physicians. Patients mentioned difficulties regarding bonding with a new HCP and repeatedly having to explain their disease trajectory.

DISCUSSION

Patients with a RC recognized the lack of information and support, from both their social environment and HCPs, as an additional burden on top of having to deal with the diagnosis of a life-threatening disease, leaving them feeling isolated and alone during their disease trajectory. This dearth of information and support has been confirmed in previous research [10, 22, 23]. In our systematic review on unmet needs of RC patients, we demonstrated that the information provision throughout the disease trajectory was insufficient [10]. Moreover, Martins et al. [23] showed that patients with soft tissue sarcoma, who felt unsupported by their HCPs and lacked a social supportive network, reported worse healthcare experiences. In concordance with findings from Bergerot et al. [8], RC patients rated the impact of their disease on their QoL higher than patients with a CC. This might be due to the high extent of illness uncertainty [24] for patients with a RC, including ambiguity, complexity, and unpredictability during their disease trajectory, which might negatively influence their QoL.

Patients with a CC acknowledged that their cancer diagnosis was a sudden and life-changing event, but indicated that the general awareness and recognition of their CC diagnosis made it easier to cope with their disease. The awareness difference between both patient groups has also been described by Robinson et al. [25]. They found that the recognition and widespread general awareness for male breast cancer, by both the general public and HCPs, is lagging behind compared to female breast cancer. Previous research in patients with a CC has shown that social support leads to better health outcomes and lower levels of psychological distress [26-30]. This sense of security and reassurance offered by the social support system of CC patients enhances their coping with the cancer diagnosis, while this is less applicable to RC patients.

Both patient groups stressed the absence of psychosocial care and support. Yet, RC patients experienced this especially throughout the disease trajectory while CC patients experienced a change in support mainly during the transition to and in the posttreatment phase. In line with previous research of Duijts et al. [31], experiencing such a change in offered support might considerably impact CC patients, potentially even more than the continuous struggle regarding information and support RC patients are confronted with. Both groups also indicated the necessity to become empowered and assertive in order to receive this support, as it is not fully integrated into the healthcare system. This might be caused by specific barriers for the delivery of psychosocial care within the oncology setting, experienced by both patients and HCPs [32]. Patients with a CC reported difficulties asking for supportive care, and the perception that they do not need psychosocial care to address unmet needs [32-35]. Barriers experienced by HCPs are mainly related to the care system, for example, a lack of time, heavy workload, and inexperience [32, 36, 37]. Specifically for RC patients, HCPs might not have the experience with psychosocial care for a specific RC and they might lack time to provide this care, due to the complex process of unravelling the diagnosis and employing adequate treatment. Furthermore, when psychosocial screening and

assessment are not part of the continuum of care, both RC and CC might be unaware of their own (unmet) needs and the availability and value of psychosocial support services to address these needs.

Study limitations

Based on the findings of this study, no statements on the experiences, needs, and QoL can be made on behalf of patients with a specific RC or CC type. Also, findings are based on a relatively small sample size, which may not fully represent the diverse experiences and needs of all rare and common cancer patients. Further, possible selection bias (due to majority of participants being female, highly educated and articulated), could have occurred, and the consequences of the COVID-19 pandemic on patients' experiences need to be acknowledged.

Clinical implications

For patients with a RC, tailored guidance with navigation through the healthcare system should be offered from diagnosis onwards by, for example, specialized nurse practitioners. In the Netherlands, according to the quality standards of the Foundation for Oncological Cooperation, every patient with cancer should have access to at least one fixed point of contact and be seen by, for example, an oncology nurse for further information and support before treatment [38]. However, the feasibility of those quality standards for RC patients is uncertain due to low patient volumes and limited expertise of oncology nurses with the heterogeneous group of RCs. This, together with the difficulty of obtaining an early and correct diagnosis, indicates that centralisation of RC care by the development of RC pathways is crucial. For patients with a CC, support in coping with the rapid cancer diagnosis should be provided. Due to the relatively quick diagnosis and the existing care pathways for CC patients, the prehabilitation period represents a window of opportunity. Within this period, patients not only have time to process their diagnosis, but they also benefit from preparation (for treatment) in terms of physical training, mental support, and lifestyle improvements. This should ideally also be implemented for RC patients, stressing the importance of improving rapid RC diagnostics**.** Support should also be intensified during the transition from treatment to posttreatment, which – specifically in CC patients – might be considered a 'phase of change' in support, potentially increasing their vulnerability. For both patient groups, stakeholders (e.g., HCPs, policy makers, and cancer patient organisations) should pay attention to the integration of psychosocial support into the healthcare system. They should be aware that some patients have inadequate capacity to be empowered and demonstrate a high level of assertiveness, due to low socioeconomic status and limited health literacy. Nevertheless, in line with the current and future healthcare challenges (i.e., increasing incidence trends and prevalence burden), the focus should shift from being solely dependent on the clinicians' expertise towards patient empowerment and

self-management. To enhance this autonomy and patient empowerment, psychosocial or patient education programmes aimed at stimulating self-management for patients diagnosed with cancer should be developed. Additional support could be provided by primary healthcare (e.g., GP or nurse practitioners) or drop-in cancer centres to relieve the increasing burden on clinicians, although this requires optimal communication, collaboration, and time dedication. Finally, one could say that there is an unequal distribution of care between patients with a RC and a CC. Patients with a RC are forced to show a high level of empowerment in order to progress through their disease trajectory (e.g., actively searching for information, asking for a second opinion), while CC patients stated to feel supported by the healthcare system**,** at least until the posttreatment phase. An urgent need for a more equitable distribution exists, which could be established by providing (also unsolicited) tailored support for patients with a RC.

CONCLUSION

Patients with a RC report their disease trajectory to be a solitary experience, impacting their QoL. CC patients generally experience that support and recognition, throughout most of their trajectory, alleviate their burden. HCPs should be aware of existing differences and provide tailored psychosocial care. Still, due to the increasing cancer burden, patient empowerment should be enhanced in both patient groups, and centralisation of especially RC care, including the development of cancer pathways and access to a fixed point of contact, is needed to specifically ease the RC patients' trajectory.

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SUPPLEMENTARY

Table S1. COREQ criteria

Item	Guide questions/description	Report
Personal characteristics		
Interviewer/ facilitator	Which author/s conducted the interview or focus group?	Focus groups were conducted by SFAD and EdH (Methods; Data collection).
Credentials	What were the researcher's credentials?	SFAD: PhD. EdH: MSc.
Occupation	What was their occupation at the time of the study?	SFAD: Senior researcher. EdH: PhD student.
Gender	Was the researcher male or female?	Both researchers were female.
Experience and training	What experience or training did the researcher have?	SFAD: Experienced senior researcher in psycho oncology, and qualitative research methods. EdH: Basic training in qualitative research and experience with one-on-one interviews, and supervised by SFAD.
Relationship with participants		
Relationship established	Was a relationship established prior to study commencement?	There was no relationship established between the researchers and participants prior to study commencement.
Participant knowledge of the interviewer	What did the participants know about the researcher?	Participants were informed about the personal goals of the researchers and the reasons for doing the research.
Interviewer characteristics	What characteristics were reported about the interviewer/facilitator?	Both interviewers introduced themselves as researchers.
Theoretical framework		
Methodological orientation and theory	What methodological orientation was stated to underpin the study?	Thematic analysis (Methods; Data analysis).
Participant selection		
Sampling	How were participants selected?	A purposive sampling approach was used (Methods; Participant recruitment and procedure).

Table S1. COREQ criteria *(continued)*

Item	Guide questions/description	Report
Method of approach	How were participants approached?	Participants were approached in person by their medical specialist, or they approached the research team by mail via social media or independent cancer organisations (Methods; Participant recruitment and procedure).
Sample size	How many participants were in the study?	Twenty-five patients were included in the study (Results).
Non-participation	How many people refused to participate or dropped out? Reasons?	Two participants dropped out due to illness. Eight potential participants were excluded.
Setting		
Setting of data collection	Where was the data collected?	Focus groups were hosted at the office of the Netherlands Comprehensive Cancer Organisation in Utrecht (Methods; Data collection).
Presence of non-participants	Was anyone else present besides participants and researchers?	No others were present besides participants and researchers (moderator and observers).
Description of sample	What are the important characteristics of the sample?	Results; Table 2, Characteristics of focus group participants.
Data collection		
Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	The researchers used interview guides (Methods; Data collection, Supplementary Table S2).
Repeat interviews	Were repeat interviews carried out? If yes, how many?	No repeat interviews were carried out.
Audio/visual recording	Did the research use audio or visual recording to collect the data?	The interviews were audio recorded (Methods; Data collection).
Field notes	Were field notes made during and/or after the interview or focus group?	Field notes were made during the interview (Methods; Data collection).
Duration	What was the duration of the interview or focus group?	The average length of focus groups was 2,5 hours (Methods; Data collection).
Data saturation	Was data saturation discussed?	Yes. Recruitment of participants stopped when data saturation was reached (Methods; Participant recruitment and procedure).

Table S1. COREQ criteria *(continued)*

Item	Guide questions/description	Report
Transcripts returned	Were transcripts returned to participants for comment and/or correction?	The transcripts were not returned to participants.
Data analysis		
Number of data coders	How many data coders coded the data?	There were two data coders (Methods; Data analysis).
Description of the coding tree	Did authors provide a description of the coding tree?	No.
Derivation of themes	Were themes identified in advance or derived from the data?	Themes were derived from the data. (Methods; Data analysis).
Software	What software, if applicable was used to manage the data?	Atlas.ti was used to manage the data (Methods; Data analysis).
Participant checking	Did participants provide feedback on the findings?	No.
Reporting		
Quotations presented	Were participant quotations presented to illustrate the themes/ findings? Was each quotation identified?	Participant quotations were presented, and each quotation was identified for patients with rare and common cancer (Results).
Data and findings consistent	Was there consistency between the data presented and the findings?	Yes.
Clarity of major themes	Were major themes clearly presented in the findings?	Major themes are presented in the findings (Results; Themes).
Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Minor themes are not explicitly indicated, but the sections of the major themes (Results; Themes) do feature minor themes.

Table S2. Semi-structured interview guide

Category	Subcategories	Questions
Introduction		Could you please briefly introduce yourself? (Name, cancer diagnosis)
Diagnosis	Diagnostic phase Obtaining the correct diagnosis Information provision regarding diagnosis Needs Quality of life	How would you describe your diagnostic phase in one word? How did you obtain your cancer diagnosis? How did you experience the period up to the cancer diagnosis? What information did you receive about your cancer diagnosis and are you satisfied with it? What were your (unmet) needs during the diagnostic phase? What would you like to change or see differently? How would you rate the impact of the diagnostic phase on your quality of life? (Range from 0, no impact, to 10, a lot of impact).
Treatment	Treatment phase Information provision regarding treatment Needs Quality of life	How would you describe your treatment phase in one word? Would you, in retrospect, have chosen the same treatment route? If yes, why? If not, why not? Are you referred to another hospital or did you consciously choose for treatment in another (specialised) hospital? How did you experience this? How did you experience the information provision regarding treatment and possible side effects? Are you satisfied about the received information regarding treatment and possible side effects? What were your (unmet) needs during the treatment phase? What would you like to change or see differently? How would you rate the impact of the treatment phase on your quality of life? (Range from 0, no impact, to 10, a lot of impact).
Posttreatment	Posttreatment phase Psychosocial care Needs Quality of life	How would you describe your posttreatment phase in one word? Did you receive during the posttreatment phase psychosocial support? If yes, how did you experience this support? What were your (unmet) needs during the posttreatment phase? What would you like to change or see differently? How would you rate the impact of the posttreatment phase on your quality of life? Range from 0 (no impact) to 10 (a lot of impact).

Table S2. Semi-structured interview guide *(continued)*

Category	Subcategories	Questions
Throughout the disease trajectory	Support from healthcare professionals and main point of contact	How satisfied are you with the support and/or guidance from healthcare professionals (physician and/or nurse practitioner) throughout the disease trajectory? Did you have a main point of contact throughout the disease trajectory? If yes, how did you experience this? If not, would you have needed it? How could healthcare professionals contribute to improving quality of life throughout the different phases of the disease trajectory?
Closing		Are there any topics that have not yet been given a chance, but are still important to discuss?

CHAPTER 8

General discussion

GENERAL DISCUSSION

As highlighted in the chapters of this thesis, rare cancers, defined as those with an annual incidence of less than 6 per 100,000 people per year [1], pose unique challenges to patients and healthcare professionals. The findings in this thesis demonstrated the distinct epidemiological and psycho-oncological differences between rare and common cancers. These will be further elaborated within this General Discussion, addressing organisation of care, policymaking, supportive care, and research, whereby every paragraph starts with an important statement to give direction and encourage action. Furthermore, methodological issues within research into rare cancers will be addressed, and future perspectives will be provided.

Overcome existing inequalities between rare and common cancers by providing funding and targeted policies

The inequalities between rare and common cancers are diverse and complex, affecting both epidemiological and psycho-oncological outcomes. We showed that 5-year survival is worse and improvement in survival over a 25-year period is less for rare cancers compared with common cancers (**Chapter 2**). Moreover, we found that patients with a rare cancer report lower quality of life (QoL) than patients with a common cancer (**Chapter 4**) and have more unmet needs within the 'healthcare system and information' domain (**Chapter 5**). These disparities can be explained by the various challenges posed by rare cancers in terms of diagnostics, treatment, clinical expertise, and research [1-3]. These should be overcome by providing funding to advance research and by establishing targeted policies to improve outcomes for patients with a rare cancer worldwide.

Rare cancers have long been a neglected area of research, and yet, the majority of cancer research investments is directed towards common cancers [4]. Nevertheless, steps have been taken to raise attention and funding opportunities for this specific group worldwide. For example, the European Commission funded epidemiological research into rare cancers [5], and Rare Cancers Australia provided research funding to develop supportive care for patients with a rare cancer [6, 7]. Within the Netherlands, the Dutch Cancer Society has declared 'rare cancers and difficult-to-treat cancers' as one of their focal points [8], and allocated about one-fifth of their research funding to rare cancers in the period 2016–2022 [9]. Subsequent funding initiatives should be aimed at improving diagnostics and developing novel therapies and, where possible, making use of the achievements made in common cancers. For example, the introduction of whole-genome sequencing has improved diagnostics for patients with Cancer of Unknown Primary (CUP) (i.e., metastatic disease without an identifiable primary cancer site) [10], and treatment initially used for patients with prostate cancer has shown to be effective for patients with salivary gland cancer [11]. These efforts have been successful due to investments in research and intensive collaboration among multiple stakeholders. Furthermore, since rare cancers belong to both groups of cancers and rare diseases,

we can learn from the progress made within the field of rare diseases [12]. That is, the establishment and adoption of policies for rare diseases has led to global coalition among a wide range of (inter)national stakeholders and significant advances in research. For example, the International Rare Diseases Research Consortium has set three 10-year goals for 2017–2027 focused on fast and accurate diagnosis, treatment, and care for rare diseases (including rare cancers) [13]. Moreover, after a successful campaign by multiple stakeholders [14], the United Nations Resolution for rare diseases was adopted in 2021 [15]. These important milestones have led to a shift in the global policy landscape in favour of rare diseases. Yet, rare cancers necessitate a tailored policy approach due to the existing differences between rare diseases and rare cancers (e.g., definition, organisation of care) [16]. Therefore, to make rare cancers a global public health priority as well, similar steps within international politics should be taken. The recommendations given within both the Rare Cancer Agenda (published in 2019) [17] and the Rare Cancers Europe Call to Action (published in 2021) [18] as well as the adoption of rare cancers within the Beating Cancer Plan (adopted in 2022) [19] are important first steps. In the Netherlands, addressing rare cancers has become one of the highlighted goals outlined in the Dutch Cancer Agenda [20], established by the Dutch Cancer Collective (a partnership initiated by The Netherlands Comprehensive Cancer Organisation, the Dutch Cancer Society, and the Dutch Federation of Cancer Patient Organisations). Particularly, these initiatives emphasised the need for (inter) national policymakers to prioritise research, allocate funds, and stimulate equal access to treatment and care for all cancer patients. In the Netherlands, the Ministry of Health, Welfare and Sport plays an important role in this process.

The negative impact of challenges faced by patients with a rare cancer demands support to navigate the healthcare system

All patients with cancer are confronted with uncertainty due to the diagnosis of a life-threatening disease. However, patients with a rare cancer might be impacted even more due to the unique challenges they face throughout their disease trajectory. We found that the uncertainty experienced during the diagnostic trajectory as well as the lack of a clear cancer pathway, limited information, and insufficient support in healthcare navigation can lead to emotional distress, feelings of isolation, and poorer QoL in patients with a rare cancer (**Chapter 4, 5 and 7**). Furthermore, due to fragmentation of care, these patients feel less supported by and experience more communication problems with their healthcare professionals compared with patients with a common cancer (**Chapter 6**). Whereas treatment plans, care pathways, and evidence-based guidelines are available for common cancers, they are often lacking for rare cancers. Previous research in patients with CUP showed that the relationship between a patient's understanding of their cancer diagnosis and psychological stress is mediated by illness uncertainty [21]. Reducing uncertainty among patients with a rare cancer therefore seems crucial and can be addressed by centres of expertise delivering tailored support

on management of and coping with illness uncertainty. For example, in a systematic review, it was shown that interventions on illness uncertainty management that target informational, emotional, appraisal, and instrumental support have positive effects on uncertainty outcomes in patients with cancer and their caregivers [22].

Specifically for patients with a rare cancer who must coordinate multiple hospitals and/or clinicians, support in healthcare system navigation is needed. In another previous systematic review, it was shown that interventions to coordinate cancer care improved patient health outcomes, including healthcare utilisation, patient experiences with care, and QoL [23]. This support and coordination could be provided by a fixed point of contact. The importance of having such a fixed point of contact has been widely recognised and received more attention in the past years in the Netherlands [24, 25]. According to the quality standards of the Foundation for Oncological Cooperation, every cancer patient should have access to at least one fixed point of contact and receive additional information and support from an oncology nurse prior to treatment [26]. Furthermore, the Dutch Taskforce Cancer Survivorship Care is committed to ensuring that 'every patient with cancer has a fixed point of contact' during a three-year implementation period (May 2023–May 2026) [25]. Specifically for patients with a rare cancer, the allocation of a fixed point of contact might take away the uncertainty they have to deal with, thereby enhancing their psychosocial functioning and QoL. Centres of expertise should take a leadership role in offering patient navigation support by appointing oncology nurse navigators: the support provided by centres of expertise is essential for the continuity of care – even in an advanced cancer stage [27] – and well-being of patients with a rare cancer.

Patients with a rare cancer should not feel urged to become experts themselves due to a lack of information and complex disease trajectory

The persisting lack of information for patients with a rare cancer has a widespread impact: for some rare cancers, e.g., ultra-rare cancers, hardly any reliable information is available. Consequently, healthcare professionals might not have access to resources for providing sufficient information on best treatment options and possible short- and long-term sequalae. This places a significant burden on patients with a rare cancer (**Chapter 4 and 5**), as well as their caregivers. Moreover, the absence of practical support for managing their disease forces patients with a rare cancer to become an 'expert patient' themselves (**Chapter 7**). Actions they take to get more knowledge about their disease and to ensure the best possible care are seeking disease-specific information, advocating for additional medical testing, and finding expert care. Whereas taking an active role in their own health seems necessary for these patients, such actions should not be attributed to the patient's responsibilities. Moreover, this proactive behaviour might be a coping strategy to restore a sense of perceived control, both pre-and post-diagnosis. Previous research has shown that individuals facing diagnostic uncertainty would rather know that they – or their loved ones – have a serious illness such as cancer

than continue struggling without a diagnosis [28, 29]. Finally having a complete and understandable medical explanation not only provides certainty on prognosis and start of treatment, but can also lead to a sense of relief. Nevertheless, simultaneously encountering a delayed diagnosis or a misdiagnosis and experiencing difficulties with healthcare system navigation, can lead to feelings of dissatisfaction with healthcare professionals and even a loss of confidence in the healthcare system [30]. In line with our findings reported in **Chapter 7** in the perspective of rare cancers, patients with rare diseases and their caregivers reported feeling abandoned and more knowledgeable than their healthcare providers [31, 32]. This lack of expertise among healthcare professionals might have a negative impact on the patient-physician relationship [33], and may create an urgent feeling among these patients to become an 'expert patient' themselves [34]. Consequently, healthcare professionals should acknowledge the active role of the patient as an informed and involved partner in care and within the shared decision-making process [35]. Nevertheless, since not every patient is able to become empowered, e.g., seriously ill patients or those with a low socioeconomic status or health literacy [36, 37], there is a need for appropriate communication skills for healthcare providers and additional support for patients. Healthcare professionals can provide this support if they stay up to date with the latest treatment options and psychosocial support needs for specific rare cancer types and share this knowledge with other healthcare professionals. In addition, they should actively engage patients with a rare cancer in the process of unravelling the diagnosis, finding the best treatment options, and assessing prognosis to give them a sense of control in times of uncertainty. Moreover, ideally, each patient with a rare cancer should be referred to the centre of expertise for their specific cancer type.

Recognition and understanding for patients with a rare cancer starts with awareness and education

The lacking recognition for rare cancers results in patients not being adequately acknowledged, understood, or addressed within the healthcare system, research, and society. Alongside the adverse effects on health outcomes, we have found that patients with a rare cancer feel less understood by their healthcare professionals and their surroundings (**Chapter 6 and 7**). Therefore, raising awareness of rare cancers, both among healthcare professionals and the general population, is key to decreasing possible delayed or wrong diagnosis and treatment. Nevertheless, within clinical practice, recognition of rare cancers is complicated by their rarity and heterogeneity, and the relatively small number of patients. This also applies to general practitioners: as the first point of contact for patients, they have a pivotal role in identifying potential cancer cases and facilitating timely referrals to hospital. While some vague symptoms of rare cancers might be hard to distinguish, certain 'red flag' symptoms should raise suspicion for the presence of a rare cancer. For example, the 'On The Ball' public awareness campaign in the United Kingdom aimed to increase awareness among general

practitioners about sarcoma's 'red flag' symptoms and prompt referrals of suspected cases to sarcoma specialists [38]. Several similar campaigns aiming to raise awareness among the general population have been launched, e.g., the 'Make Sense Campaign' for head and neck cancers [39] and the yearly Dutch national awareness week on rare cancers organised by the Patient Platform for Rare Cancers [40]. Furthermore, medical education and training for rare cancers is a key aspect in increasing its recognition and understanding. A previous study among European healthcare providers showed that education and training in rare cancers is insufficient [41]. To improve this, the European Union of Medical Specialists (UEMS) has published a syllabus covering all rare adult solid cancers [42], the European Society for Medical Oncology (ESMO) has initiated the annual Sarcoma and Rare Cancers congress [43], and the European Commission is currently working on a European Reference Network (ERN) Academy for rare disease training and education [44]. These educational resources may establish a basis for rare cancer education on a national level and may contribute to the harmonisation of training purposes across Europe. Nevertheless, the educational efforts in this area, e.g., by the ERNs, are not adequately communicated, officially regulated, or incorporated into the continuous medical education by important stakeholders [35, 42]. In order to have a successful knowledge implementation of rare cancers in Europe and beyond, Tumiene et al. have proposed a rare disease education and training continuum following the pyramid principle: at the bottom, students and primary care professionals should establish a general knowledge base, while at the top, experts and leaders should be the ones with highly-specialised knowledge and knowledge generation [35]. Still, to improve the recognition and understanding of rare cancers, (inter)national policies should promote awareness of rare cancers and stimulate building and implementing a comprehensive continuum on education of rare cancers.

Methodological issues

Research into rare cancers faces several methodological challenges. One prominent challenge is related to the sample size: both the relatively small number of cases and heterogeneity within the rare cancers group reduce statistical power and generalisability. Whereas randomised controlled phase III trials are often considered as the 'gold standard' for establishing treatment efficacy, reaching a sufficient accrual in rare cancers research is difficult and sometimes unfeasible. Moreover, heterogeneity within the rare cancer group adds complexity to comparisons both within this group and between rare and common cancers. Nevertheless, in some settings it remains necessary to consider rare cancers collectively as a 'group': rare cancers face similar challenges including a lack of expertise, quality of care concerns, and disparities in medical and psychosocial outcomes [45]. Another challenge relates to study design: rare cancers demand innovative study designs to deal with the small and heterogeneous populations. Innovative approaches have previously been applied in rare cancers research, including Bayesian methods, uncontrolled n-of-1 trials, and umbrella and basket trials [46].

For example, the Bayesian approach generates robust estimates in small areas or populations by taking into account previously obtained information, while simultaneously preserving data confidentiality [47]. Previous studies in Europe [48] and Australia [49] have successfully predicted incidence and prevalence estimates in rare cancer populations through Bayesian statistical models. Moreover, basket trials assess a single drug or a combination of drugs within cohorts of cancer patients defined by shared histological, molecular or demographic characteristics [50]. Within the Netherlands, the Drug Rediscovery Protocol (DRUP), a multi-centre basket trial, has demonstrated that patients with a rare cancer have a similar clinical benefit from off-label targeted agents as patients with a common cancer [51]. Finally, selection of appropriate outcome measures and data collection are challenging factors within rare cancers research. Within cancer trials, overall survival, progression-free survival, or disease-free survival are considered as the most meaningful outcomes. However, for rare cancers, the European Medicines Agency and the Food and Drug Administration acknowledge the challenge of trials, and suggests that the outcome measures should be tailored to the cancer frequency and its clinical and biological behaviours (e.g., surrogate clinical end-points) [46]. Moreover, whereas cancer data within population-based registries are – in contrast to rare diseases – fairly complete and widespread, data collection on patient-reported outcomes and QoL among cancer patients has not been fully standardised yet, and are hereby lacking [52]. Furthermore, the questionnaires used within clinical research are often generic measures and might not capture the unmet needs of patients with a specific rare cancer type [53]. Collection of patient-reported outcomes, e.g., unmet needs and QoL, as part of standard care of rare cancers can provide valuable information on experiences of patients with a rare cancer and can aid in the treatment decision-making to preserve optimal QoL and enhance HLE.

FUTURE PERSPECTIVES

Patient narrative

February 29th, 2032

Linda (56 years), dentist, married to Job, mother of two children – diagnosed with pseudomyxoma peritonei (PMP)

"It has only been four weeks since I encountered my general practitioner upon first complaints. I had been tired for a long time, but it suddenly got much worse in the last weeks. Also, my belly got way bigger lately. It even reminded me of my pregnancies. This surprised me, because I focus on maintaining a healthy lifestyle and I quit alcohol consumption five years ago after seeing a major public campaign. When I felt a small lump at the bottom right of my belly, it was the final straw to seek out my general practitioner. He carefully listened to my complaints, recorded them in the general practitioner information system, and performed a number of physical examinations.

He did not trust it and assessed my symptoms using Artificial Intelligence (AI) support techniques. By entering my described complaints, the system provided him the tools to assess the complaints with a 'red flag' percentage. Based on this, he concluded that I might be suffering from a serious disease, and referred me directly to the hospital for further examinations. This, of course, concerned me but, fortunately, I was able to have a consultation in the hospital the next day. I could barely sleep that night, fretting that obtaining an accurate diagnosis would take ages, since I had heard a similar story from a client in my dental practice several years ago. The next day, they performed a fine needle aspiration biopsy. Luckily, through the use of digital pathology and computational image analysis, results were available within a mere hour. The doctors at the hospital then told me and my husband that they had bad news and that it was cancer. They had looked into the information in my electronic health record, which is continuously shared between primary, secondary, and tertiary care, and already suspected from the AI data that it was a rare cancer. Therefore, with my consent, they shared the diagnostic results within an international rare cancer network. Within this network, an online platform has been set up where pathology reports of all 'suspect' rare cancers are collected. Based on the available evidence and algorithms, they concluded that it was pseudomyxoma peritonei (PMP). PMP is a rare cancer that causes a build-up of mucin in the abdomen and pelvis. That explained my growing 'jelly belly'. I was immediately referred to the centre of expertise for PMP. Here, all details regarding the diagnosis were clearly explained to us by the multidisciplinary team. Still, my husband and I were quite shocked by this diagnosis. My treating physician in this centre of expertise explained that we would meet each other later that week to discuss the treatment plan. In the meantime, we received psychosocial support, and were assigned a 'nurse navigator'. We were well taken care of by Annemiek. From the first moment, she has been my fixed point of contact for all my questions. Annemiek reassured us that we are in the safe hands of a multidisciplinary team with the right expertise for my rare cancer. She also showed us the online portal with more information about PMP, what to expect during the cancer pathway, how to manage my disease with self-management tools, and possibilities to contact her if necessary. She showed me the website of the rare cancer platform and specifically their international portal 'Rare2Meet'. That way, if I felt the need, I could get in touch with fellow sufferers of PMP. The information and support provided by Annemiek gave me confidence in the healthcare professionals and their specialised care.

That same week, my treating physician discussed treatment options with me. He indicated that they work according to international clinical-based guidelines and, as the only centre of expertise for PMP in the Netherlands, closely collaborate with experts worldwide. He also provided a transparent insight into the clinician's acquired knowledge and expertise on PMP, and how many times the surgery has been performed in the last couple of years. It was very pleasant that he clearly informed me about all treatment options and that I did not have to search for information online. He also told me that participation in a multinational study for PMP would be an option for

me. Through shared funding, involving multiple stakeholders worldwide, a study was set up to improve treatment for PMP and outcomes for patients. It felt good to be engaged within the shared decision-making process, and I immediately jumped at this opportunity. In this way, I also hope to be valuable for future patients with PMP. After the treatment planning conversation with my treating physician, I spoke to Annemiek in person. She paid a lot of attention to my wellbeing. She also showed me in the online portal how to complete the questionnaire on my daily functioning, my symptoms, and my perceived QoL, and pointed out various psychosocial care resources for me and my family.

Prior to the treatment, I tried to prepare myself as much as possible with the available self-management tools in the online portal. Nevertheless, I found the treatment and its' aftermath tough. Nowadays, the surgery takes about 1.5 hours, which is much faster than before due to developments in robotic techniques, and was followed by half an hour of chemo irrigation. Rehabilitation went quite well due to adequate cooperation between my general practitioner and the doctors at the hospital. Currently, I am in the follow-up phase. My prognosis looks good. I have had one follow-up consultation online, and, based upon my completed questionnaires, Annemiek responded very well to my needs. I feel very supported in picking up my life again. The provided list on paramedic services and the availability of the online tools within the portal makes me feel more empowered. I hope to be able to participate fully in society and resume my work as a dentist soon. Altogether, my PMP diagnosis has been a real rollercoaster, but I have been so lucky to have experienced a rapid referral to the centre of expertise, continuity of care, collaboration among my general practitioner and the multidisciplinary team at the hospital, and optimal support for me and my family."

The narrative of Linda, taking place in the near future in 2032, outlines the ideal patient pathway for a patient with a rare cancer. It is my dream that every future patient with a rare cancer is entitled to the right expertise, experiences continuity of care, and has similar access to optimal diagnostic approaches, treatment, and medical and psycho-oncological care as patients with a common cancer. No cancer patient, regardless of their diagnosis, should fall between the cracks. By framing the future perspectives within a patient narrative, a spot on the horizon is set and it becomes evident what still needs to be done in the upcoming years to improve the care and experiences of patients with a rare cancer.

CONCLUSION

In this thesis, the epidemiological and psycho-oncological differences between rare and common cancers have been described. Rare cancer survival improvements are still lagging behind those of common cancers, and this inequality demands further improvement in diagnosis, treatment, and management of rare cancers. Moreover, patients with a rare cancer report a lower QoL compared to patients with a common

cancer. They also report high unmet supportive care needs throughout the disease trajectory, with the highest reported needs regarding information provision and healthcare system navigation. The complex disease trajectory of patients with a rare cancer leads to different healthcare experiences than patients with a common cancer. Also, patients with a rare cancer report their disease trajectory to be a solitary experience due to the faced challenges, including a lack of information and support. In order to improve rare cancer care and well-being of patients with a rare cancer, targeted policies are needed to promote rare cancer awareness, stimulate equal access to care, and ensure proper referral to centres of expertise. Those centres of expertise should in particular take a leadership role in building expertise, disseminating and sharing knowledge, performing innovative research, and offering tailored psychosocial care and patient navigation support within networks. Altogether, if these steps can be accomplished, future patients with a rare cancer will hopefully have a better prognosis, enhanced psychosocial and QoL outcomes, and improved access to expert care and the newest developments in the field of rare cancers.

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SUMMARY / SAMENVATTING

SUMMARY

Rare cancers, defined as those with an incidence of <6 per 100,000 per year, are a heterogeneous group of cancers. Although they are considered 'rare' and not as widely recognised as common cancers, they make up a large proportion of the cancer burden: one out of five new patients with cancer has a diagnosis of a rare cancer. Epidemiological discrepancies exist between rare and common cancers, and patients with a rare cancer face unique challenges during their disease trajectory. The objective of this thesis was to provide insights into the differences and resemblances between rare cancers and common cancers, both from an epidemiological perspective as well as a psycho-oncological perspective.

PART I: EPIDEMIOLOGICAL FOCUS

In **Chapter 2**, a population-based study is described in which a comparison was made between rare and common adult solid (non-haematological) cancers in the Netherlands, by providing incidence, prevalence, and survival rates during 2010-2019, and evaluating trends in survival from 1995-1999 to 2015-2019. Individual rare cancer entities within EURACAN domains and 'Joint Action on Rare Cancers' (JARC) families were compared as well. Patient, tumour, and treatment data from all adult patients with malignant solid cancers in the Netherlands between 1995 and 2019 were obtained from the Netherlands Cancer Registry (NCR). Rare cancers accounted for 18% of the total cancer incidence, and 15% of the total ten-year prevalence during 2010-2019. Overall 5-year survival was worse for rare cancers (52.0%) than for common cancers (68.7%) and increased to a lesser extent for rare cancers (6.4%) than for common cancers (13.2%) over a 25-year period (1995-1999 to 2015-2019). The majority of rare cancer entities did not show an improvement in 5-year survival, and differences were found with regard to the partitioning of individual rare cancer entities between domains and families. The found differences in survival indicate major challenges for rare cancer care and emphasise that improvement is highly needed. Observed inequalities need to be overcome by investing in early diagnosis, novel therapies, scientific research and in establishing centres of expertise.

In **Chapter 3**, the life expectancy and proportion of remaining life that survivors with a subset of rare and common cancers spend in good health through the use of healthy life expectancy (HLE) estimates is highlighted, as well as the determinants of poor perceived health in rare cancer survivors. To calculate HLE, survival data from the NCR of survivors with a subset of rare cancers (i.e., ovarian cancer, thyroid cancer, Hodgkin lymphoma, non-Hodgkin lymphoma) and a common cancer (i.e., colorectal cancer (CRC)) were combined with quality of life (QoL) data from the PROFILES registry. Patients previously diagnosed with a rare cancer (of the included subset) had an average

life expectancy of 8 to 36 years and spent ≥67% of their remaining life in good health. CRC survivors had an average life expectancy of 10 years with approximately 65% of their remaining life spent in good health. For all cancer types, those aged ≥65 years or with stage IV had the lowest HLE. Low socioeconomic status, advanced stage, and having received radiotherapy were important predictors of poor perceived health among rare cancer survivors. HLE can provide meaningful perspective for patients and clinical practice for all cancer types, including rare cancers. Yet, data on QoL for rare cancers should be routinely collected, as such will serve as an indicator for monitoring and improving cancer care, QoL, and HLE in cancer survivors.

The results of a cross-sectional study are presented in **Chapter 4**, in which the difference in QoL between patients with a rare cancer and patients with a common cancer (i.e., CRC) was assessed, and the association between disease trajectory-related factors and QoL in patients with a rare cancer was examined. Data was collected among adult patients with a rare cancer by a nationwide online survey in the Netherlands. Data on CRC patients was obtained from the Prospective Dutch Colorectal Cancer cohort (PLCRC). Patients with a rare cancer were found to have a significantly lower self-reported QoL than patients with CRC. Several disease trajectory-related factors were significantly associated with QoL in patients with rare cancer, namely: time until diagnosis, misdiagnoses, information on best treatment options, information on late and/or long-term effects, and both satisfaction with physician and specialised nurse care. In order to improve QoL of patients with a rare cancer, appropriate guidance, and support throughout the disease trajectory by healthcare professionals is needed, as well as early diagnosis and proper referral to centres of expertise.

PART II: PSYCHO-ONCOLOGICAL FOCUS

In **Chapter 5**, a systematic review is presented on the unmet supportive care needs of patients with a rare cancer throughout the disease trajectory, for each rare cancer subdomain, and the predictive factors for these unmet needs. Patients with a rare cancer most frequently reported unmet needs in the healthcare system and information domain, followed by the psychological domain and the physical and daily living domain. Specific unmet needs were present in patients with rare female genital organ cancer, namely, in the sexual domain; in patients with rare male genital and urogenital cancer, namely, in the economic domain, and in patients with rare head and neck cancer, namely, in the disease-specific domain. Unmet needs were mainly reported in the posttreatment phase. The most frequently identified predictors were higher anxiety, younger age, and higher neuroticism. Healthcare professionals should be aware of the different unmet needs per rare cancer subdomain and phase of the disease, and these unmet needs should be recognised and individually addressed starting from diagnosis onwards.

In **Chapter 6**, the results from a national cross-sectional survey on the differences in healthcare experiences between patients with a rare and common cancer are described. Data on the experiences of diagnosis and treatment, hospital (choice), second opinion, and traveling to the hospital was collected among (former) adult patients with cancer through a national online survey in the Netherlands. Patients with a rare cancer were more often diagnosed and treated in different hospitals compared to patient with a common cancer. Patients with a rare cancer also received treatment more often in one hospital, but reported more negative experiences when treated in multiple hospitals than patients with a common cancer. Furthermore, they more often received advise from their physician about the hospital to go to for a second opinion, were more likely to choose a hospital specialised in their cancer type and were more often willing to travel as long as necessary to receive specialised care compared to patients with a common cancer. Thus, patients with a rare cancer and patients with a common cancer differ in their healthcare experiences. To improve healthcare for patients with a rare cancer, regional clinical networks for rare cancers should be established to enable proper referral to centres of expertise.

In **Chapter 7**, the results from a qualitative focus group study on the experiences, needs, and QoL of patients with rare and common cancer throughout the disease trajectory are described. Participants were purposively selected to reflect heterogeneity of cancer types. Four focus groups were conducted with, in total, twenty-five patients with cancer (i.e., twelve patients with a rare cancer, ten patients with a common cancer, and three patients with both a rare and a common cancer). Patients with a rare cancer reported their disease trajectory to be a solitary experience, due to the lack of information and support, impacting their QoL. Patients with a common cancer acknowledged that their cancer diagnosis was a sudden and life-changing event, but indicated that the recognition and social support alleviated their burden. Both patient groups stressed the absence of psychosocial support: whereas patients with a rare cancer experienced this especially throughout their disease trajectory, patients with a common cancer experienced this during the transition to and in the posttreatment phase. Healthcare professionals should be aware of the existing differences between patients with a rare and common cancer and provide tailored psychosocial support. Yet, in line with the increasing cancer burden, patient empowerment should be enhanced for both patient groups. Moreover, centralisation of care for patients with a rare cancer, including the presence of clear cancer pathways and access to a fixed point of contact, is needed to overcome the care inequalities between rare and common cancers.

In **Chapter 8**, the main findings of this thesis are summarised, the methodological issues within rare cancer research are addressed, and the future perspectives for research and clinical practice are given. Existing inequalities between rare and common cancers should be overcome by funding to advance research and by establishing targeted policies to improve outcomes of patients with a rare cancer. Furthermore, to reduce

the negative impact of challenges patients with a rare cancer are faced with, support in healthcare system navigation by, e.g., a fixed point of contact, should be provided. In addition, despite the fact that patients with a rare cancer might feel urged to become experts themselves due to the lack of information and a possible complex disease trajectory, healthcare professionals should stay updated on the latest findings, and maintain a supportive and engaged approach towards the patient. Moreover, raising awareness of rare cancers and improving rare cancer medical training are key aspects in increasing its' recognition and understanding, both among society and healthcare professionals. Finally, methodological issues within rare cancer research include the relatively small sample sizes, present heterogeneity within the rare cancer group, need for innovative study designs, and selection of appropriate outcome measures and data collection.

SAMENVATTING

Zeldzame kankers, gedefinieerd als kankers met een incidentie van <6 per 100.000 per jaar, vormen een heterogene groep van kankers. Hoewel ze als 'zeldzaam' worden beschouwd en niet zo algemeen erkend zijn als veelvoorkomende kankers, vormen ze een groot deel van de totale kankerlast: één op de vijf patiënten met kanker heeft een zeldzame vorm van kanker. Er zijn epidemiologische verschillen tussen zeldzame en veelvoorkomende kankers en patiënten met een zeldzame vorm van kanker staan voor unieke uitdagingen tijdens hun ziekteproces. Het doel van dit proefschrift was om inzicht te geven in de verschillen en overeenkomsten tussen zeldzame en veelvoorkomende kankers, zowel vanuit epidemiologisch perspectief als vanuit psycho-oncologisch perspectief.

DEEL I: EPIDEMIOLOGISCHE FOCUS

In **hoofdstuk 2** wordt een populatie-gebaseerd onderzoek beschreven waarin een vergelijking is gemaakt tussen zeldzame en veelvoorkomende solide (niet-hematologische) kankers bij volwassenen in Nederland, op basis van incidentie, prevalentie en overleving van 2010 tot en met 2019 en overlevingstrends van 1995-1999 tot 2015-2019. Ook zijn individuele zeldzame kankerentiteiten (kankersoorten) binnen de EURACAN-domeinen en de 'Joint Action on Rare Cancers' (JARC) families met elkaar vergeleken. Patiënt-, tumor- en behandelingsgegevens van alle volwassen patiënten met kwaadaardige solide kankers in Nederland tussen 1995 en 2019 werden verkregen uit de Nederlandse Kankerregistratie (NKR). Zeldzame kankers vormden 18% van alle solide kankerdiagnoses (incidentie) en 15% van de totale tienjaarsprevalentie in de periode 2010-2019. De totale vijfjaarsoverleving in 2010-2019 was slechter voor zeldzame kankers (52,0%) dan voor veelvoorkomende kankers (68,7%) en nam in mindere mate toe voor zeldzame kankers (6,4%) dan voor veelvoorkomende kankers (13,2%) over een periode van 25 jaar (tussen de periode 1995-1999 en de periode 2015-2019). De meerderheid van de zeldzame kankerentiteiten vertoonde geen verbetering in vijfjaarsoverleving en er werden verschillen gevonden met betrekking tot de verdeling van individuele zeldzame kankerentiteiten tussen EURACAN-domeinen en JARC-families. De gevonden verschillen in overleving duiden op grote uitdagingen voor de zorg voor zeldzame kankers en benadrukken dat verbetering hard nodig is. De geconstateerde ongelijkheden moeten aangepakt worden door te investeren in vroegtijdige diagnose, nieuwe behandelingen, wetenschappelijk onderzoek en het aanwijzen van expertisecentra.

In **hoofdstuk 3** wordt de levensverwachting en het deel van het resterende leven dat overlevenden van een zeldzame en veelvoorkomende vorm van kanker in goede gezondheid doorbrengen (gezonde levensverwachting) belicht, evenals de

determinanten van een slechte gezondheid bij overlevenden van een zeldzame vorm van kanker. Om de gezonde levensverwachting te berekenen werden overlevingsgegevens uit de NKR van overlevenden van een zeldzame vorm van kanker (namelijk: eierstokkanker, schildklierkanker, Hodgkin lymfoom, non-Hodgkin lymfoom) en een veelvoorkomende vorm van kanker (namelijk: darmkanker) gecombineerd met gegevens over de kwaliteit van leven uit de PROFIEL studie. Overlevenden van de zeldzame vormen van kanker hadden gemiddelde levensverwachtingen van 8 tot 36 jaar en brachten ≥67% van hun resterende leven in goede gezondheid door. Overlevenden van een veelvoorkomende vorm van kanker hadden een gemiddelde levensverwachting van 10 jaar en spendeerden ongeveer 65% van hun resterende leven in goede gezondheid. Voor alle kankersoorten hadden mensen ouder dan 65 jaar of met stadium IV de laagste gezonde levensverwachting. Een lage sociaaleconomische status, een vergevorderd stadium en het ondergaan van bestraling waren belangrijke voorspellers van een slechte gezondheid bij overlevenden van een zeldzame vorm van kanker. Het in kaart brengen van de gezonde levensverwachting kan een zinvol perspectief bieden voor zowel patiënten met kanker als clinici. Toch moeten gegevens over kwaliteit van leven voor zeldzame kankersoorten routinematig verzameld worden, omdat dit kan dienen als indicator voor het monitoren en verbeteren van de kankerzorg, kwaliteit van leven en gezonde levensverwachting bij overlevenden van kanker.

De resultaten van een cross-sectionele studie worden in **hoofdstuk 4** gepresenteerd. Het verschil in kwaliteit van leven tussen patiënten met een zeldzame vorm van kanker en patiënten met een veelvoorkomende vorm van kanker (namelijk: darmkanker) is beoordeeld en de associatie tussen ziektetraject-gerelateerde factoren en kwaliteit van leven bij patiënten met een zeldzame vorm van kanker is onderzocht. De gegevens werden verzameld onder volwassen patiënten met een zeldzame vorm van kanker door middel van een landelijke online vragenlijst in Nederland. Gegevens over patiënten met darmkanker werden verkregen van het Prospectief Landelijk CRC cohort (PLCRC). Patiënten met een zeldzame vorm van kanker ervaarden een significant lagere kwaliteit van leven dan patiënten met darmkanker. Van alle fasen van het ziektetraject waren bepaalde factoren significant geassocieerd met kwaliteit van leven bij patiënten met een zeldzame vorm van kanker, namelijk: tijd tot diagnose, verkeerde diagnoses, informatie over de beste behandelopties, informatie over late en/of langetermijneffecten en zowel tevredenheid over de zorg van de arts als die van gespecialiseerd verpleegkundigen. Om de kwaliteit van leven van patiënten met een zeldzame vorm van kanker te verbeteren, is passende begeleiding en ondersteuning van zorgverleners nodig gedurende het hele ziektetraject, evenals een vroegtijdige diagnose en een juiste doorverwijzing naar een expertisecentrum.

DEEL II: PSYCHO-ONCOLOGISCHE FOCUS

In **hoofdstuk 5** wordt een systematische review gepresenteerd van de onvervulde ondersteunende zorgbehoeften van patiënten met een zeldzame vorm van kanker gedurende het hele ziektetraject en de voorspellende factoren voor deze onvervulde behoeften. Patiënten met een zeldzame vorm van kanker rapporteerden het vaakst onvervulde behoeften in het domein 'verkrijgen van informatie en de weg vinden in het zorgsysteem', gevolgd door het domein 'psychologisch functioneren' en het domein 'fysiek en dagelijks leven'. Patiënten met een zeldzame kanker van de vrouwelijke geslachtsorganen ervaarden specifieke onvervulde behoeften in het seksuele domein, patiënten met een zeldzame kanker van de mannelijke geslachtsorganen en urogenitale kanker in het economische domein en patiënten met hoofdhalskanker in het ziekte-specifieke domein. Patiënten rapporteerden onvervulde behoeften voornamelijk in de fase na de behandeling. In alle fasen van de ziekte werden een jongere leeftijd, een hogere angstscore, en een hoger neuroticisme geïdentificeerd als voorspellende factoren voor onvervulde behoeften. Zorgverleners moeten zich bewust zijn van de verschillende onvervulde behoeften per zeldzame kankersoort en per fase van de ziekte, en deze onvervulde behoeften moeten tijdig worden geïdentificeerd en doelgericht worden aangepakt vanaf de diagnose.

In **hoofdstuk 6** worden de resultaten beschreven van een landelijk cross-sectionele studie naar de verschillen in zorgervaringen tussen patiënten met een zeldzame en veelvoorkomende vorm van kanker. Via een nationale online vragenlijst in Nederland werden gegevens verzameld over de ervaringen met diagnose en behandeling, ziekenhuis(keuze), second opinion en reizen naar het ziekenhuis onder volwassen (ex-)kankerpatiënten. Patiënten met een zeldzame vorm van kanker werden vaker gediagnosticeerd en behandeld in verschillende ziekenhuizen dan patiënten met een veelvoorkomende vorm van kanker. Patiënten met een zeldzame vorm van kanker werden ook vaker in één ziekenhuis behandeld, maar indien de behandeling in meerdere ziekenhuis plaats vond, ervaarden zij dit als negatiever dan patiënten met een veelvoorkomende vorm van kanker. Ze werden ook vaker door hun arts geadviseerd over naar welk ziekenhuis ze moesten gaan voor een second opinion dan patiënten met een veelvoorkomende vorm van kanker. Bovendien kozen patiënten met een zeldzame vorm van kanker vaker voor een gespecialiseerd ziekenhuis en waren ze vaker bereid om zo lang te reizen als nodig was om gespecialiseerde zorg te ontvangen in vergelijking met patiënten met een veelvoorkomende vorm van kanker. Patiënten met een zeldzame vorm van kanker en patiënten met een veelvoorkomende vorm van kanker verschillen hiermee in hun zorgervaringen. Om de zorg voor patiënten met een zeldzame vorm van kanker te verbeteren, moeten er regionale, klinische netwerken voor zeldzame kankers worden opgezet om doorverwijzingen naar een expertisecentra te ondersteunen.

In **hoofdstuk 7** worden de resultaten van een kwalitatief onderzoek naar de ervaringen, behoeften en kwaliteit van leven van patiënten met zeldzame en veelvoorkomende vorm van kanker gedurende het hele ziektetraject beschreven. De deelnemers werden doelgericht geselecteerd om de heterogeniteit van kankertypes te vertegenwoordigen. Er werden vier focusgroepen gehouden met in totaal vijfentwintig patiënten met kanker. In totaal waren er twaalf patiënten met een zeldzame vorm van kanker, tien patiënten met een veelvoorkomende vorm van kanker en drie patiënten met zowel een zeldzame als een veelvoorkomende vorm van kanker. Patiënten met een zeldzame vorm van kanker gaven aan dat zij hun ziektetraject als eenzaam hebben ervaren door het gebrek aan informatie en ondersteuning. De diagnose zeldzame kanker had een grote impact op hun kwaliteit van leven. Patiënten met een veelvoorkomende vorm van kanker erkenden dat hun kankerdiagnose een plotselinge en levensveranderende gebeurtenis was, maar gaven aan dat de erkenning en sociale steun hun last verlichtten. Beide patiëntengroepen benadrukten het gebrek aan psychosociale ondersteuning: terwijl patiënten met een zeldzame vorm van kanker dit vooral ervaarden tijdens het hele ziektetraject, ervaarden patiënten met een veelvoorkomende vorm van kanker dit tijdens de overgang naar en in de fase na de behandeling. Zorgverleners moeten zich bewust zijn van de bestaande verschillen tussen patiënten met een zeldzame en een veelvoorkomende vorm van kanker en psychosociale ondersteuning op maat bieden. Toch moet, in lijn met de toenemende kankerlast, de zelfredzaamheid van patiënten voor beide patiëntengroepen worden vergroot. Bovendien is centralisatie van zorg voor patiënten met een zeldzame vorm van kanker, waaronder de aanwezigheid van duidelijke zorgpaden en een vast aanspreekpunt, nodig om de ongelijkheden in de zorg tussen zeldzame en veelvoorkomende vormen van kanker weg te nemen.

In **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift samengevat, de methodologische kwesties binnen het zeldzame kankeronderzoek uitgelicht en de toekomstperspectieven voor onderzoek en klinische praktijk beschreven. Bestaande ongelijkheden tussen zeldzame en veelvoorkomende vormen van kanker moeten aangepakt worden door financiering (voor de bevordering van onderzoek naar zeldzame kankers) en door gericht beleid op te stellen (voor de verbetering van de uitkomsten van patiënten met een zeldzame vorm van kanker). Om de negatieve gevolgen van de uitdagingen waarmee patiënten met een zeldzame vorm van kanker worden geconfronteerd te verminderen, moet bovendien ondersteuning worden geboden bij het navigeren door het zorgstelsel, bijvoorbeeld door middel van de toewijzing van een vast aanspreekpunt. Ondanks het feit dat patiënten met een zeldzame vorm van kanker zich, door het gebrek aan informatie en een mogelijk complex ziektetraject, gedwongen kunnen voelen om zelf ‘expert’ te worden, moeten zorgverleners zoveel mogelijk op de hoogte blijven van de nieuwste bevindingen en een ondersteunende en betrokken houding ten opzichte van de patiënt behouden. Daarnaast zijn het vergroten van de bekendheid van zeldzame kankers en het verbeteren van de medische opleiding op het gebied van zeldzame kanker belangrijke aspecten voor het vergroten van de

bekendheid en het begrip ervan, zowel in de samenleving als bij zorgverleners. Tot slot omvatten methodologische kwesties binnen het onderzoek naar zeldzame kankers de relatief kleine steekproefgroottes, de aanwezige heterogeniteit binnen de groep zeldzame kankers, de noodzaak van innovatieve onderzoeksopzetten en de selectie van geschikte uitkomstmaten en gegevensverzameling.

APPENDICES

RESEARCH DATA MANAGEMENT

Ethics and privacy

This thesis is based on epidemiological and psycho-oncological data of patients with cancer. Each study containing epidemiological data in this thesis was approved by the Netherlands Cancer Registry's Supervisory Committee. For Chapter 3, involving several cohorts from the 'Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship' (PROFILES) registry, ethical approval was obtained for each cohort separately from local certified Medical Ethics Committees [1]. The studies described in Chapter 4, 6 and 7 were not subject to the Medical Research Involving Human Subjects Act (WMO). The Medical Ethics Review Committee of the VU University Medical Centre confirmed that the WMO does not apply, and that ethical approval was not required (2021.0722 for Chapter 4 and 7; 2020.257 for Chapter 6). For Chapter 4, informed consent was obtained from all participants within the Prospective Dutch Colorectal Cancer (PLCRC) cohort, and data from the PLCRC cohort was registered at Clinicaltrials.gov (NCT02070146) and approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht (NL47888.041.14) [2]. For the study described in Chapter 6, all research participants provided consent, and were informed about privacy policies, in accordance with the General Data Protection Regulation (EU) 2016/679 [3]. For the study described in Chapter 7, informed consent was obtained from all research participants. Technical and organisational measures were followed to safeguard the availability, integrity, and confidentiality of the data. These measures include the use of pseudonymization, access authorization and secure data storage. All data used in this thesis were handled according to the privacy statement of IKNL [4].

Data collection and storage

Clinical data for Chapter 2, 3, 4 and 6 were collected by well-trained data managers of the Netherlands Cancer Registry (NCR) by consulting the electronic patient files. The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). The data is registered, maintained, and saved within the 'Registratie Applicatie van de Nederlandse Kankerregistratie' (RANK) and exported to Stata (StataCorp LLC). The data in the NCR will be stored for as long as the NCR exists. The data is used securely and in accordance with policy, laws, and regulations in the Netherlands. IKNL is certified according to NEN7510 (i.e., the Dutch standard for information security in healthcare), and ISO 27001. Requesting data from the NCR is done under strict privacy conditions.

IKNL approved studies with pseudonymized data were analysed in Stata and saved on the IKNL secured network (G-desk) with access limited to involved members of the research team. Pseudonymized data from the PROFILES registry and PLCRC cohort were analysed in Stata, stored on the IKNL network and only accessible by involved project members working at IKNL. Data for Chapter 4 and 6 were collected through the

questionnaires developed by the Dutch Federation of Cancer Patients Organizations (NFK). Restrictions applied to the availability of these data, whereby analyses were performed in SPSS by the NFK team only and output was provided to the IKNL research team. Paper (hardcopy) data are stored in cabinets at IKNL for 15 years.

Availability of data

The studies described in Chapter 6 and 7 are published open access. Data from all chapters within this thesis will be stored for up to 15 years after completion of the study. Anonymous data can be requested from the NCR [5]. Reusing the data for future research is only possible after renewed permission from NCR, PROFILES, PLCRC, or NFK. Statistical code used for the studies in this thesis can be made available post publication from the corresponding author upon reasonable request.

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Other publications

van Dongen J, **de Heus E**, Eickholt L, Schrieks M, Zantingh I, Brouwer OR, Oonk MHM, Grotenhuis BA, Ezendam NPM, Duijts SFA. Challenges and controversies patients and (health care) professionals experience in managing vaginal, vulvar, penile or anal cancer: The SILENCE study. *European journal of cancer care*. 2022; 31(6), e13676. doi: https://doi.org/10.1111/ecc.13676.

Olischläger DLT, den Boer LXY, **de Heus E**, Brom L, Dona DJS, Klümpen HJ, Stapelfeldt CM, Duijts SFA. Rare cancer and return to work: experiences and needs of patients and (health care) professionals. *Disability and Rehabilitation*. 2023; 45:16, 2585-2596. doi: 10.1080/09638288.2022.2099589.

Simons BCR, Hillen MA, Aarts JWM, Tromp JM, **de Heus E**, Duijts SFA. Disentangling trust of patients with rare cancer in their healthcare professionals and the healthcare system: a qualitative interview study. *Under review*.

PHD PORTFOLIO

PhD portfolio of Eline de Heus

Department: Medical Oncology
PhD period: 01/08/2020 – 29/02/2024
PhD Supervisor(s): Prof. dr. M.A.W. Merkx, Prof. dr. C.M.L. van Herpen
PhD Co-supervisor(s): Dr. S.F.A. Duijts, Dr. J.M. van der Zwan

Training activities	Hours
Courses	
Radboudumc – Introduction day (2020)	6
RIHS – Introduction course for PhD candidates (2020)	15
Radboud University – Scientific Writing for PhD candidates (2021)	84
Radboud University – Project Management for PhD candidates (2021)	56
Radboudumc – Scientific integrity (2021)	20
Radboudumc – Poster presentation course (2021)	12
Radboud University – BMS08 Qualitative research (2021)	84
Nederlandse Vereniging voor Oncologie (NVvO) – Basiscursus Oncologie (2022)	70
Radboudumc – Department of Health Evidence: 'Junior refereren Epidemiologie' (2022)	42
Radboudumc – eBROK course (for researchers working with human subjects) (2022)	26
Radboud University – Workshop: 'Zelfinzicht: de sleutel voor je loopbaan' (2022)	8
Netherlands Comprehensive Cancer Organisation (IKNL) – Media training (2022)	2
International Agency for Research on Cancer (IARC) – Workshops Networking for results, Personal Brand, Leadership practical skills, and Managing your early career (2023)	14
Radboud University – BMS56 Health Outcome Measurement (2023)	84
Radboud University – BMS84 Longitudinal and multilevel analysis (2024)	84
Seminars	
KWF – Psychosocial Oncology meetings (2020-2022)	11
Netherlands Comprehensive Cancer Organisation (IKNL) – 'Refereerbijeenkomsten' (2020-2023)	15
RIHS – Webinar Science Communication (2020)	1
Netherlands Comprehensive Cancer Organisation (IKNL) – Webinars Personal Health Train, What editors want, Behind the scenes of RANK, Unlocking PRO-data, report 'Kanker bij jongvolwassenen' and 'Oncologiezorgnetwerken' (2020-2022)	7
Netherlands Comprehensive Cancer Organisation (IKNL) – Workshops Quality Control and Datawarehouse NKR (2020, 2021)	3

Joint Action on Rare Cancers (JARC) – Webinar Rare cancers (2021)	1
Radboudumc – Research integrity rounds (2021-2022)	9
PROFILES/Antoni van Leeuwenhoek – Webinar PROMs, PREMs and wearables (2021)	4
Nederlandse Vereniging Psychosociale Oncologie (NVPO) – Early Career Research Network Research Days and 'Praktijkdag' (2021, 2022, 2023)	19
Netherlands Comprehensive Cancer Organisation (IKNL) – BlueBerry kick-off meeting (2022)	8
MEDTalks – Webinars Rare cancers (2022)	8
Nature – Webinars Research communication, writing, impact, and submission (2022)	14
International Psycho-Oncology Society (IPOS) – Webinar Cancer self-management (2023)	4
Vereniging voor Epidemiologie (VvE) – Syndemics: Integrating health and social context (2023)	**2**
International Agency for Research on Cancer (IARC) – Diet and its impact on the risk of developing cancers: latest evidence (2023)	1

Conferences

Netherlands Cancer Registry (NCR) symposium (2020)	11
Dutch Rare Cancer Platform (DRCP) symposium (2021)	8
Nederlandse Vereniging Psychosociale Oncologie (NVPO) congress (2021)	8
Dutch Thyroid Cancer Group (DTCG) symposium (2021)	8
International Association of Cancer Registries (IACR) congress (2021)	6
Netherlands Cancer Registry (NCR) symposium (2 poster presentations) (2021)	12
Dutch Rare Cancer Platform (DRCP) symposium (oral presentation) (2022)	16
Nederlandse Vereniging Psychosociale Oncologie (NVPO) congress (poster pitch) (2022)	12
V&VN Oncologiedagen (oral and poster presentation) (2022)	28
Vereniging voor Epidemiologie (VvE) WEON congress (poster presentation) (2022)	28
European Cancer Survivorship and Rehabilitation Symposium (ECRS) symposium (oral presentation) (2022)	28
Netherlands Cancer Registry (NCR) symposium (poster presentation) (2022)	8
International Association of Cancer Registries (IACR) congress (2022)	8
Netherlands Comprehensive Cancer Organisation (IKNL) PhD retreat (2023)	16
Dutch Rare Cancer Platform (DRCP) symposium (oral presentation) (2023)	16
Nederlandse Vereniging Psychosociale Oncologie (NVPO) congress (poster presentation) (2023)	12
International Psycho-Oncology Society (IPOS) symposium (2 oral presentations) (2023)	32
RIHS PhD retreat (2023)	16

Other	
Co-organizing Netherlands Cancer Registry (NCR) symposium (2020)	56
Co-organizing Dutch Rare Cancer Platform (DRCP) symposium (2022-2023)	44
Committee member Dutch Rare Cancer Platform (DRCP) Working Group 'Communicatie, Symposia en Nascholingen' (2021-2024)	56
Committee member Dutch Thyroid Cancer Group (DTCG) (2021-2024)	24
Committee member Dutch Adrenal Network (DAN) Scientific Committee (2022-2024)	8
Advisory member IKNL Young (2022-2023)	8
Reviewer for scientific publications (2021-2022)	12
Writing a blog about a KWF Psychosocial Oncology meeting (2021)	1
Netherlands Comprehensive Cancer Organisation (IKNL) – PhD Journal club (2021-2023)	120
Netherlands Comprehensive Cancer Organisation (IKNL) – Theme meetings team Rare Cancer (2021-2023)	20
Netherlands Comprehensive Cancer Organisation (IKNL), KWF, Patiëntenplatform Zeldzame Kankers (PZK) – 'Kwartaalbijeenkomsten' (2021-2022)	8
Dutch Federation of Cancer Patients Organisations (NFK) – Meeting research agenda rare cancers (2021, 2022)	5
Netherlands Comprehensive Cancer Organisation (IKNL) – Co-author of report 'Zeldzame kanker: Organisatie van expertise' (2023)	84
Teaching activities	
Lecturing	
Vrije Universiteit Amsterdam – Oncology & Public Health: Mentoring student work groups (2020-2023)	200
Vrije Universiteit Amsterdam – Oncology & Public Health: lecture rare cancers (2023)	10
Supervision of internships / other	
Netherlands Comprehensive Cancer Organisation (IKNL) – Generating and presenting regional hospital reports about thyroid cancer (2020-2023)	150
Supervision Bachelor/Master students for research internship (2021-2023)	175
Netherlands Comprehensive Cancer Organisation (IKNL) – Presentation data managers (2021-2023)	19
Total	**1,987**

DANKWOORD

It's a wrap! Na 3,5 jaar is mijn proefschrift af en kan ik met trots terugkijken op een ontzettend leuke en leerzame tijd. Dit heb ik echter niet alleen gedaan en daarom wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. Zonder jullie hulp, begeleiding en steun was het mij niet gelukt. Een aantal mensen wil ik graag in het bijzonder bedanken.

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ABOUT THE AUTHOR

Hilletje Elisabeth (Eline) de Heus was born on November 21, 1994 in Beusichem, the Netherlands. After graduating from secondary school at Koningin Wilhelmina College in Culemborg in 2013, she started her Bachelor's degree in Nutrition and Health at Wageningen University & Research (WUR) and graduated in 2016. Thereafter, she continued with the Master Nutrition and Health (specialisation Nutritional Physiology and Health Status) at WUR. During her Master's degree, her interest in nutrition, healthcare, and diseases grew. She performed an internship within the department of Value-Based Healthcare at the St. Antonius hospital in Nieuwegein, and obtained her Master's degree in 2018. During and after her study, she worked as a student assistant (2018) and research assistant (2019) at WUR.

In 2019, she started working as a junior researcher within the team 'Rare cancers' at the Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht. In 2020, she officially started her PhD research project at IKNL, in collaboration with Radboud University Medical Center (Radboudumc), Nijmegen. Her research focused on the epidemiology and psycho-oncology of rare cancers and the results are presented in this thesis. She presented her work at several national and international conferences, supervised several students, performed educational activities, and helped organising the Netherlands Cancer Registry symposium (2020) as well as the Dutch Rare Cancer Symposium (2022, 2023). During her PhD, she received a travel grant from IKNL, enabling her to work for three months as an Early Career and Visiting Scientist at the International Agency on Research for Cancer (IARC) in Lyon, France. With completing her PhD, she will obtain her Epidemiologist Researcher degree at PhD level (Epidemiologist B). Currently, she works as a researcher at IKNL.

integraal kankercentrum Nederland

Radboudumc university medical center

Radboud University