Nationality as an influencing factor on early concomitant symptoms and side effects in radiooncological therapy

Doctoral thesis

to obtain a doctorate

from the Faculty of Medicine

of the University of Bonn

Romy Julia Streppel, M.Sc.

from Bonn

2024

Written with authorization of

the Faculty of Medicine of the University of Bonn

First reviewer: Univ.-Prof. Dr. med. Eleni Gkika, MBA

Second reviewer: Prof. Dr. Maria Wittmann

Day of oral examination: 29.08.2024

From the Clinic for Radiotherapy and Radiooncology

Director: Univ.-Prof. Dr. med. Eleni Gkika, MBA

Meiner Familie gewidmet.

Table of contents

List of abbreviations

CCI	Charlson Comorbidity Index
CNS	Central Nervous System
CT	Chemotherapy
CUP	Cancer of Unknown Primary
CTCAE	Common Criteria of Adverse Events
GWAS	Genome-wide association studies
Gy	Gray
HT	Hormone therapy
ICD-O3	International Classification of Diseases for Oncology, 3. Edition
ICD-10	International Classification of Diseases, 10. Revision German Modification Version 2022
ImT	Immune therapy
KI	Karnofsky Index
NK Cells	Natural Killer Cells
NOS	Not otherwise specified
RT	Radiotherapy
SNV	Single-nucleotide variation
SOC	System Organ Class
SPC	Second primary cancer
ST	Stem cell transplantation

1. Introduction

1.1 Background

1.1.1 Population and cancer incidence in Germany: Present and future

The population of Germany is heterogeneous and dynamic: Through the years, it has increasingly become a popular destination, primarily for immigrants from Europe but also other continents (Rudiger et al., 2021). Immigration to Germany has occurred throughout the nation's history; today it represents one of the most popular destinations for immigrants in the world. According to data from the German Federal Statistical Office, well over 1 million people moving to Germany each year since 2013 and over the past 10 years, the number of foreign citizens living there increased from 14.9 million to 22.3 million, representing ~27.3% of the total population (Destatis Statistisches Bundesamt, 2022; Organisation for Economic Co-operation and Development, 2023). Around 10.9 million (52.4%) have already obtained German citizenship (Federal Office for Migration and Refugees, 2018). Apart from the continuous flow of immigrants into Germany since the 1960s, current events such as the humanitarian crisis in Ukraine also contribute to a changing population. Indeed, Eurostat forecasts a constant increase in net migration to Germany from 891,000 in 2015 to a peak of 1.37 million people by 2036 (Eurostat, 2019).

Simultaneously, an ongoing transition in health care takes place (Schmerler, 2018): the proportion of foreign medical patients in Germany increased from 2.7% in 2008 to 11.7% in 2020 (Radkte, 2022). In addition to the steady influx of immigrants, the concept of medical tourism leads to an increase in the number of non-German patients receiving treatment in Germany. Medical tourism is defined as the process of leaving home for treatment and care abroad or elsewhere domestically (Oltean et al., 2020). For this group of patients, literature and data are scarce (Schmerler, 2018), consistently describing medical tourists as demanding and require high levels of care. Usually, they come from the upper income brackets. Primarily, they travel to Germany in order to receive care in the areas of oncology, neurology, orthopedics and several invasive disciplines such as bariatric and thoracic surgery.

As the proportion of foreign patients in Germany increased, the incidence of oncological diseases has followed a similar trend. Considering the aging population, greater cancer risk with age, and improving cancer survival rate, the global incidence of cancer is expected to rise from ~9 million in 2017 to ~26 million by 2030 (Carlotto et al., 2013; De Ruysscher et al., 2019; Hayes et al., 2018). Commonly combined with surgery, chemotherapy, and immunotherapy, radiotherapy is part of first-line cancer treatment in approximately 50% of cancer patients (Barton et al., 2014; Begg et al., 2011; Delaney et al., 2005; Lapierre et al., 2022), contributing to around 40% of cures (Baskar et al., 2012). Thus, given that foreign patients living in Germany or foreign patients traveling to Germany for treatment are equally affected by this development, their use on radiotherapy as a component of their cancer treatment regimen is expected to increase in the future.

1.1.2 Radiotherapy and toxicity

Radiotherapy comprises the treatment of benign and malignant diseases. As stated, it is an essential component of oncological treatment and is part of cancer treatment in about half of all cancer patients (Barton et al., 2014; Begg et al., 2011; Delaney et al., 2005; Lapierre et al., 2022). Along with surgery and chemotherapy, it represents one of three important pillars of curative, but also palliative intended oncological therapy. Curative and palliative intended radiotherapy uses ionizing radiation and aims to eliminate cancer stem cells by producing DNA damage leading to tumor death while limiting damage to normal tissues (Barazzuol et al., 2020; Wang and Tepper, 2021).

In recent decades, radiation oncologists' ability to personalize radiotherapy parameters based on specific tumor and patient characteristics has dramatically improved due to clinical research (Baumann et al., 2016; Bernier et al., 2004; Verellen et al., 2007). Technological advances have evenly contributed to this development by decreasing toxicity whilst improving the ability to deliver radiotherapy maximizing tumor dose and minimizing organ dose. In addition, image-guidance methods make treatments more accurate (Lemanska et al., 2017). However, despite the use of optimized and state-of-the-art techniques, approaching the physical limits of shaping high doses to the target volume, co-irradiation of peritumoral tissues is inevitable (Baumann et al., 2016).

The pathophysiology of co-irradiation, or radiation injury to normal tissue, underlies following, briefly depicted mechanism: Ionizing radiation initiates its effect by directly or indirectly via reactive oxygen species damaging DNA, prompting a cascade of events potentially leading to cell death. The degree of cell killing and resistance, and with that, clinical representation of radiation injury, varies, depending on the localization and cumulative and fractionated dose of the ionizing radiation as well as affected organ sensitivity. An organ's sensitivity is primarily determined by cell properties such as degree of differentiation and mitotic rate (Bentzen, 2006). Organs anatomy and physiology also express influence on how the effect of ionizing radiation on normal tissue is manifested: organs can be considered to consist of functional units arranged either in parallel (e.g., liver and lung) or in series (e.g., esophagus and nerve), each with characteristic pathways to toxicity (Wang and Tepper, 2021).

A myriad of undesirable and extensive side effects can occur both early (≤3 months) and late (>3 months) after treatment (De Ruysscher et al., 2019; Lapierre et al., 2022; Welzel and Tanner, 2018). Acute effects usually manifest in inflammation or reflect epithelial depopulation of rapidly growing epithelial cells. Among acute toxicities, dermatitis, mucositis, xerostomia or nausea are commonly-encountered side effects. Late effects often present as fibrosis, vascular injury, or gradual parenchymal injury, which may decrease global organ function, probably manifesting years after treatment. Recovery or repopulation of damaged tissue is substantially influenced by turnover and transit time for normal tissue stem cells, determining timing of symptoms. Therefore, patients completing radiotherapy are counseled that acute side effects may continue to worsen before recovery (Wang and Tepper, 2021).
Usually, a direct relationship between radiation dose, normal tissue dose and risk of toxicity can be identified, resulting in guidelines and recommended dose limits for most tissues. Yet, the risk of occurrence of side effects underlies multifactorial reasons. It becomes apparent, that the study of radiotherapy related side effect is complex and represents a legitimate core component of the profession of radiation oncology, continuing to evolve alongside advances in cancer management. An understanding of acute and late effects in different organ systems is clinically pertinent to both oncologists and nononcologists (Wang and Tepper, 2021).

Not all patients are equally vulnerable to radiotherapy-related side effects, some display more severe side effects than others (Sonis, 2015). Response to treatment and severity of side effect is, to some degree, associated with multiple factors such as regimen selection, drug or radiation dose, and route of administration, yet, patient-centric variables are thought to be major contributors, too (Sonis, 2015). Hence, predicting which patients are most susceptible to severe side effects of radiotherapy is important in order to personalize treatment planning, allow treatment modification, prevent toxicity and improve quality of life of cancer survivors (Lapierre et al., 2022). Given the heterogeneous and dynamic population in Germany, striving for migration-adapted patient care in radiotherapy is an important goal.

1.2 Empiricism to date

Appropriate selection of patients for treatments, maximising efficacy and minimising toxicities, has long been a fundamental part of clinical practice, but limited tools determining which patients will benefit and which may suffer toxicities were available (Jackson and Chester, 2015). The primary focus of recent research is directed towards identification of genetic markers and cancer predisposition genes (Chin et al., 2011; Dzau et al., 2015; Ginsburg and Phillips, 2018; Golubnitschaja et al., 2016; McCarthy et al., 2013) as well as further development of molecularly targeted therapies (Jackson and Chester, 2015). Nevertheless, selecting the treatment regimen that is most beneficial to each patient while reducing toxicity requires consideration of patient's characteristics in a multifaceted way, including sociodemographic characteristics and clinical features next to genetic markers (Conti et al., 2010; Di Sanzo et al., 2017; Tremblay and Hamet, 2013). However, given this primary focus, limited information is available on the influence of sociodemographic characteristics on therapeutic outcomes.

Studies focusing on foreign cancer patients have evaluated disease risk diversity and incidence, treatment response, progression, and survival (Andreeva et al., 2007; Arnold et al., 2010; Budde et al., 2019; Budde, 2020; Hemminki et al., 2013; Hjerkind et al., 2017; Latif et al., 2015; Mousavi et al., 2012; Rudiger et al., 2021; Simberg-Danell et al., 2016; Spix et al., 2008; Thøgersen et al., 2018). For example, studies show that risk of prostate cancer underlies remarkable international variations, with an extreme near tenfold

between high-risk Austrians and low-risk Serbians and Romanians (Hemminki et al., 2013). There is similar evidence that foreign patients undergo changes in breast cancer' risk after relocation, accompanied by an increased overall breast cancer incidence (Andreeva et al., 2007). Hjerkind et al. (2017) found differences in incidence patterns between immigrants and Norwegian-born, depending on country of origin and cancer type. One study investigated age- and time-dependent changes in cancer incidence among immigrants: In their study, age at immigration was associated with the risk trend of cancer (Mousavi et al., 2012). Additionally, it was shown, that non-western patients had a more favourable all-cancer morbidity and mortality compared with native populations of European host countries, yet, they showed considerable site-specific risk diversity: non-western patients were more prone to cancers that are related to infections experienced in early life, such as liver, cervical and stomach cancer (Arnold et al., 2010). Budde et al. (2019) compared German to foreign patients and found differences in progression-free survival, i.e. a subgroup analysis of patients with head and neck cancer showed significantly longer progression-free survival for German patients. In line with this, a study conducted by the German Cancer Childhood Registry showed significantly lower survival for children of Turkish descent with lymphoid leukemia (Spix et al., 2008). Furthermore, a nationwide registry-based study comprising subjects diagnosed with cancer between 1990 and 2014 have also reported worse survival in foreign patients from sub-Saharan Africa, Eastern Europe and Balkan with breast cancer, prostate cancer and melanoma relative to the host populations (Latif et al., 2015; Simberg-Danell et al., 2016; Thøgersen et al., 2018).
Contrary to those findings, Rudiger et al. (2021) found no evidence that response rates to treatment or overall cancer survival were significantly affected by migration background of cancer patients, reporting several limitations in the study.

The vast majority of studies mentioned above indicate that differences between groups of patients from different nationalities in terms of risk diversity and incidence, treatment response, progression, and survival exist (Arnold et al., 2010; Budde et al., 2019; Budde, 2020; Hemminki et al., 2013; Hjerkind et al., 2017; Latif et al., 2015; Simberg-Danell et al., 2016; Spix et al., 2008; Thøgersen et al., 2018). Yet, those studies have not sought to identify unique patient characteristics that predict beneficial or unwanted outcomes of

therapy. Thus, a deeper understanding of the impact of sociodemographic characteristics on therapeutic outcomes, including unfavorable side effects, is needed to further personalize healthcare and ensure migration-adapted patient care in radiotherapy (National Health System England, 2016).

1.3 Research question and hypotheses

The objective of this retrospective matched-pair control study was to investigate differences in the severity of early side effects of radiotherapy depending on patients' nationality and other sociodemographic and clinical characteristics. The increasing number of foreign patients in an aging population with increasing cancer incidence makes the comparison of therapeutic side effects between foreign patients and the host population relevant and essential, undermining the relevance of the present study (Thøgersen et al., 2018). A priori, we formulated following hypotheses:

- H_{a1}: There is a significant association between side effect severity and patient nationality.

- $H_{a2:}$ There is a significant association between side effect severity and tumor entity.

- H_{a3}: There is a significant association between side effect severity and concomitant therapy.

- H_{a4}: There is a significant association between foreign patients' side effect severity and BMI.

- H_{a5}: There is a significant association between side effect severity and age in the Turkish cohort.

Our findings show that foreign patients are at higher risk for severe side effects, suggesting that patients' nationality needs to be considered when planning treatment regimens for cancer patients to minimize unwanted side effects and improve their quality of life.

2. Materials and methods

2.1 Data collection

A total of 9,187 patients were documented in our university medical center records between January 2017 and December 2021 having received radiotherapy. The nationality of the patients was determined using the information stored on the electronic health card (eHealth Card). The eHealth Card is read into ORBIS®, transferred into the radiology information system MEDOS® (Version 8.42., MEDOS AG, Langenselbold, 2006) and finally transferred into ARIA® (Version 15.1, Varian Medical Systems, Palo Alto, CA, U.S.A.). A description of the information systems follows in the course. Based on this information, 8,651 patients had German nationality and 536 patients had non-German (i.e., foreign) nationality. Two patients were incorrectly identified as German on their eHealth Cards as evidenced by having addresses at the embassy of the United Arab Emirates. After reclassifying these patients, 8,649 and 538 patients had German and foreign nationality, respectively. A total of 289 foreign patients were excluded due to having no diagnosis recorded in our medical records, 43 foreign patients were excluded for receiving radiotherapy at other institutions, and 7 foreign patients were excluded because their nationality was unclearly filed (Figure 1).

2.1.1 Hospital information systems

2.1.1.1 ARIA®

ARIA® has been developed by Varian Medical Systems (Version 15.1, Palo Alto, CA, U.S.A, 2018) and is a unified information system for radiology and radiation therapy, medical and surgical oncology. We used ARIA® to complement our data collection.

2.1.1.2 MEDOS®

MEDOS® (Radiologieinformationssystem (RIS) Version 8.42, MEDOS AG, Langensebold, 2006) is a radiology and hospital information system that enables data federation from several separate departmental computers (MEDOS AG, 2010).

2.1.1.3 ORBIS®

We used ORBIS® (Krankenhausinformationssystem (KIS), Version 08043901.02000, DEDALUS Healthcare Group AG, Bonn, 2022) to collect our data (ORBIS, 2022). It represents the entirety of all data-processing units for organizing medical and administrative data in the hospital. It integrates medicine, nursing, patient management and accounting information.

2.2 Matched-pair analysis

Matched-pair analysis, adjusting for baseline differences, was conducted to match each included foreign patient with a German patient at a 1:1 ratio based on the agreement of the following relevant patient characteristics: age (±15 years), sex, and ICD-10 diagnosis code (ICD-10-GM, International Classification of Disease) (WHO, 2021).

In ICD-10, neoplasms are categorized using four-digit codes according to the origin of the tumor, allowing primarily topographic determination of neoplasms (Bundesinstitut für Arzneimittel und Medizinprodukte, 2022). The fourth digit describes an even more detailed localization of the pathology as a respective subcategory. For our purposes, a match of three of the four digits of the code was sufficient.

If all matching criteria besides ICD-10 code corresponded between patients, ICD-O-3 classification (International Classification of Diseases for Oncology) was used for matching (WHO, 2019). The ICD-O-3 classification adds information about the morphology of the neoplasia to the ICD-10, Chapter II (Neoplasms) and consists of five digits, with the first four indicating the histologic designation (Bundesinstitut für Arzneimittel und Medizinprodukte, 2019). This ICD-O-3 matching approach was used for 10 matched pairs (i.e., 20 patients). Out of these, eight matched pairs shared the same ICD-O-3 code of M8070/3 [squamous cell carcinoma, not otherwise specified (NOS)]. Of the 16 patients included in these eight matched pairs, 14 were assigned an ICD-10 subchapter code of C00-C14 (malignant neoplasms of lip, oral cavity, and pharynx), 1 was assigned a subchapter code of C76 (malignant neoplasm of other and ill-defined sites; localized cervically), and 1 was assigned a chapter code of C80 (malignant neoplasm without specification of site; localized cervically). Regarding the remaining two ICD-O-3-matched pairs, one pair had divergent ICD-10 codes of C18 and C21 (malignant neoplasm of colon/anus and anal canal) but the same subchapter code (malignant neoplasm of

digestive organs) and radiation site (rectum and pelvic lymphatic drainage area) as well as corresponding ICD-O-3 code M8140/3 (adenocarcinoma, NOS). In the other matched pair, both patients presented with leukemia [lymphoid (C91) and myeloid (C92) leukemia, respectively], corresponding to the ICD-O-3 code M9801/3 (acute leukemia, NOS). We considered these discrepancies to be minor, so we proceeded with analysis.

A VBA program (Visual Basic for Applications, programming language for Excel, enables automation workflows) was developed, which compared the data of one foreign patient with the data of all German patients regarding sex, age and diagnosis. Possible matching pairs were identified and matched using information stored in documentation tools and information systems introduced above, i.e. ARIA®, MEDOS® and ORBIS®.

After excluding 21 foreign patients for whom no suitable matched German partner was found, a total of 178 matched pairs were included in the analysis. Strategy of data collection is depicted in Figure 1.

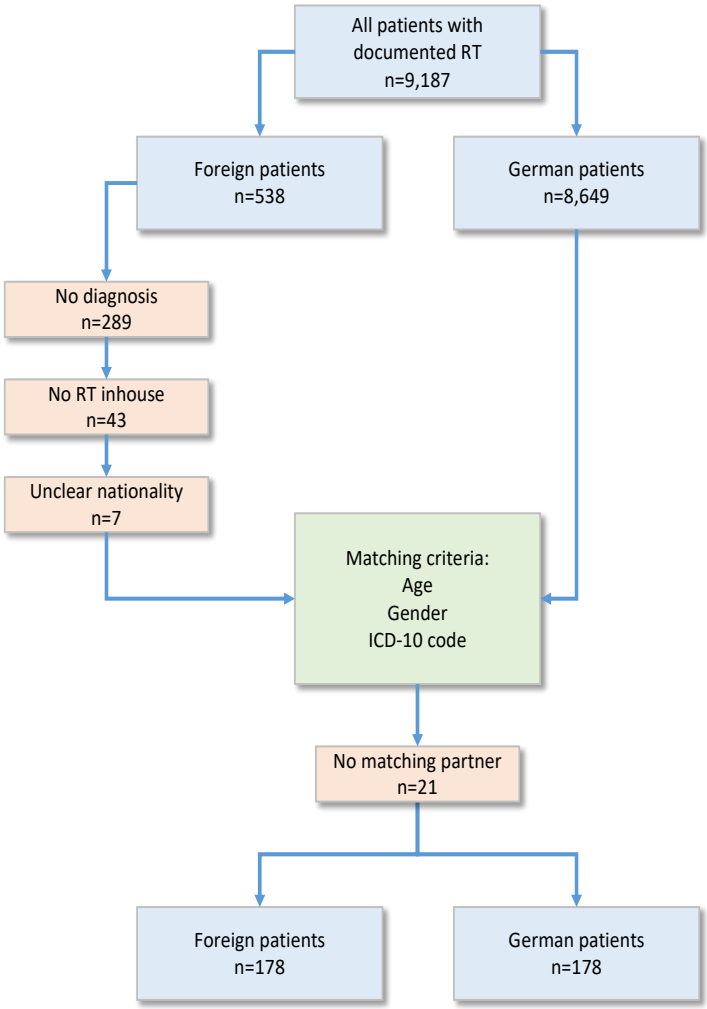

Fig. 1 Strategy of data collection and matching process

Annotation. N = number of patients, RT = Radiotherapy, Age = Match in the range ± 15 years, ICD-10 Code = Match of first three digits

Thus, the total cohort consisted of 356 patients. An overview of all collected parameters is shown in Table 1. The parameters were collected from the electronic patient records, described in the following.

Table 1 Overview of collected parameters

Display of all information obtained on the descriptive level about the patients

	Parameters
Demographic variables	Name, patient ID
Patient characteristics	Body mass index (BMI), smoking, alcohol, supportive therapy, medication, Charlson Comorbidity Index (CCI), Karnofsky Index (KI)
Therapy	Duration of radiotherapy (RT), concomitant therapy [RT alone, RT with chemotherapy (CT), RT with immune/hormone therapy (ImT/HT)], pre/post therapy administered [RT, CT, ImT, HT, surgery, stem cell transplantation (ST), radionucleid therapy], therapy goal (definitive, adjuvant, palliative, pre-ST), dose in Gray (Gy), irradiation site, break RT, termination RT
Diagnosis	Date of first diagnosis, tumor entity, tumor status (primary, secondary, relapse), and tumor grading
Others	Informed consent (alone/with relatives/with interpreter), language of informed consent, treatment setting (outpatient/inpatient), follow-up received, number of patient rounds
Side effects	Number, and severity of side effects (Common Criteria of Adverse Events, CTCAE v5.0)

2.3 Collected parameter

2.3.1 CTCAE

Internationally, the Common Criteria for Adverse Events (CTCAE, Version 5.0) of the National Cancer Institute represent the standard tool for recording acute side effects occurring up to 90 days after radiation. They are defined as “any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure” (U.S. Department of Health and Human Services, 2017). Early side effects (≤3 months after ending radiotherapy) experienced by patients were identified by CTCAE terms grouped into 26 System Organ Classes (SOC) according to Medical

Dictionary for Regulatory Activities hierarchy (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2022). Example SOC included cardiac disorders, general disorders and administration site conditions, immune system disorders, and nervous system disorders. In our data collection, 18 out of 26 SOC could be recorded at least once (Table 4). The grading scale for side effect severity ranged from 1 for asymptomatic or mild symptoms to 5 for death related to side effects. Not all severity grades are appropriate for all side effects, therefore some side effects are listed with fewer than five grades. In the present cohort, severity grades 4 or 5 did not occur. Data on side effects was obtained via systematic search of patients' medical records and collection of clinically relevant entries in the oncology information system Varian ARIA®. Those relevant entries include documentation of patient rounds, correspondence by email or telephone, physician letters, final and follow-up reports. The interval between follow-up appointments is defined for each entity in the national radio-oncology guidelines: The first follow-up is scheduled up to 8 weeks after the end of the first radiation treatment. In the following five years, it is supposed to take place at least four times. Follow-up appointments can be delegated and conducted in close cooperation with the referring physicians and an out-patient oncologist. These appointments can be carried out in person or during Corona period by telephone. The patient's well-being, possible side effects and treatment success data are collected and documented by a specialist and an assistant physician. Side effects are classified according to CTCAE version 5 into four severity categories by specialist or assistant physicians and are recorded in the designated area of the oncology information system Varian ARIA®.

2.3.2 Charlson Comorbidity Index

Comorbidities were assessed using the Charlson Comorbidity Index (CCI), a method of predicting mortality by classifying and balancing comorbid conditions and age of the patient. The index has widely been utilized by health researchers to measure burden of disease and case mix and has been validated for its ability to predict mortality in various disease subgroups, including cancer, demonstrating its value as a prognostic indicator for mortality (Quan et al., 2011). Scores were based on the number of comorbidities, each given a weighted integer from 1 to 6 depending on its severity (Austin et al., 2015). Comorbidities include any history of or present condition of Myocardial infarction,

Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Hemiplegia or paraplegia, Dementia, Chronic pulmonary disease, Rheumatologic disease, Peptic ulcer disease, Diabetes with/without chronic complications, Renal disease, Any malignancy, including leukemia and lymphoma, Metastatic solid tumor, Mild liver disease, Moderate or severe liver disease and AIDS/HIV.

2.3.3 Karnofsky Index

The Karnofsky Index (KI) is a widely used method to assess the functional status of a patient. For years, it has been an important tool in clinical practice. It describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death). In cancer medicine, KI holds a prevalent role being an excellent prognostic factor in a variety of tumor entities (Péus et al., 2013).

2.3.4 Body Mass Index

A patient's height and weight were recorded by means of Body mass index or BMI, a statistical index providing an estimate of body fat in males and females of any age. It is calculated by taking a person's weight, in kilograms, divided by their height, in meters squared, or BMI = weight (in kg)/ height^2 (in m^2). The number generated from this equation is then the individual's BMI number. BMI is known to be an individual risk factor of survival. BMI categories were formed according to the guidelines of German Obesity Society: category 1:<18.5 = underweight, category 2: 18.5 - 24.9 = normal weight, category 3: >24.9 = overweight, category 4: >30 = obesity (Deutsche Adipositas-Gesellschaft e.V., 2014).

2.4 Statistical Analysis

IBM SPSS® (Chicago, IL) for Mac (Version 28.0.1.1) was used for statistical analyses. Collected data were documented in an Excel file (Microsoft® Excel for Mac, Version 16.63.1), structured, and imported into SPSS®.

2.4.1 Statistical tests

Descriptive statistics and frequency tables were used to summarize patient characteristics. Variables were stratified by nationality. Pearson's Chi-square tests were used to evaluate associations among nationality, other patient characteristics, and side effect severity. Observed cases were compared to expected cases: The expected count is generated by default, all categories have equal values, and presents the predicted frequency for a cell under the assumption that the null hypothesis, stating there is no association between the variables, is true. If > 20% of expected cell counts were less than 5, possibly causing erroneous results, Fisher's exact test for smaller contingency tables (4*2) and Monte Carlo method for bigger tables (17*2) were additionally calculated for clarification.

Following a significant Kolmogorov-Smirnov test ($p < 0.01$), a Mann-Whitney U test was used to determine whether the number of side effects differed between German and foreign patients. All tests were two-sided, with $p < 0.05$ indicating statistical significance. Since there is no adjustment for multiple tests, p-values should be interpreted as exploratory only.

2.5 Graphical representation

The programs Excel, PowerPoint (Microsoft® Office for Mac, Version 16.63.1), and SPSS (Version 28.0.1.1. (14) for Mac; Chicago, IL) were used for graphical representation.

2.6 Literature search

In parallel, the literature search was conducted primarily on PubMed, a text-based meta-database with references to medical articles, ScienceDirect, and Wiley Online Library. Keywords of the search were migration, medical tourism, radiation toxicity, cancer survival, cancer therapy, matched-pair analysis, adverse reaction.

3. Results

3.1 Patient characteristics

Possible significant differences for all matching parameters age, gender and diagnosis code between the two patient cohorts could be excluded using statistical tests (t-test, χ^2). Both the German and foreign patient groups included 87 males and 91 females (Table 2).

Table 2 Patient characteristics

Results of statistical procedures used to test for differences between groups: Chi Square Test, Mann-Whitney U Test, Independent Samples Median Test

All patients (n = 356)	**Foreign (n = 178)**		**German (n = 178)**					
	n	**%**	**n**	**%**	**Chi-square**	**Mann-Whitney U**	**Independent Samples Median Test**	**p-value**
Age (years)								
<60	93	52.2	98	55.1				
≥60	85	47.8	80	44.9	0.595			0.282
Mean	56.1		55.9			15686.5		0.873
Median	58.5		58.0				0.101	0.750
Range	Min. = 3, Max. = 89		Min. = 2, Max. = 85					
Gender								
Male	87	48.9	87	48.9				
Female	91	51.1	91	51.1				
Tumor status					0.801			0.444
Primary	66	37.1	72	40.4				
Secondary	89	50.0	85	47.8				
Relapse	23	12.9	21	11.8				
Concomitant therapy					0.856			0.774
RT	111	62.5	105	59.0				

Table 2, continued on page 23

Chemoradiotherapy	55	30.9	57	32.0				
Immunotherapy	9	5.1	12	6.7				
Hormone therapy	3	1.7	4	2.2				
RT goal					0.834			0.866
Definitive	32	18.0	38	21.3				
Adjuvant	85	47.8	80	44.9				
Palliative	58	32.6	58	32.6				
Pre- stem cell transplantation	3	1.7	2	1.1				
Treatment setting					1.071			0.585
Outpatient	112	62.9	114	64.0				
Inpatient	66	37.1	64	36.0				
Treatment termination					1.544			0.214
No	167	93.8	172	96.6				
Yes	11	6.2	6	3.4				
Informed consent					55.348			<0.001
No information	34	19.1	66	37.1				
With relatives	100	56.2	108	60.7				
With relatives and interpreter	23	12.9	0	0				
Without relatives	1	0.6	4	2.2				
With interpreter	20	11.2	0	0				
Follow-up					6.813			0.078
Did not take place	57	32.0	37	20.8				
Took place in person	73	41.0	88	49.4				
Took place via phone	48	27.0	52	29.2				
Took place via mail	0	0.0	1	0.01				

Annotation. P-value significance level <0.05

Mean age was 56.1 years (range, 2–85 years) among German patients and 55.9 years (range, 3–89 years) among foreign patients. A total of 138 patients (38.8%) had a primary tumor, 174 (48.9%) had secondary manifestations (i.e., metastases), and 44 (12.4%) had disease relapse. Most patients received radiotherapy alone (n = 216; 60.7%) or combined

chemoradiotherapy (n = 112; 31.5%). The presence or absence of relatives and/ or interpreters during informed consent differed between the groups: interpreters (alone or with relatives) were only present with foreign patients (n = 43; German patients n = 0), whereas German patients were more often accompanied solely by relatives (n = 108; foreign patients n = 100) (Table 2).

3.2 Tumor entity

Across both patient groups, significantly more patients had solid tumors (n = 326; 91.5%) than malignant hematologic diseases (n = 30; 8.5%) (p<.001) (Figure 2).

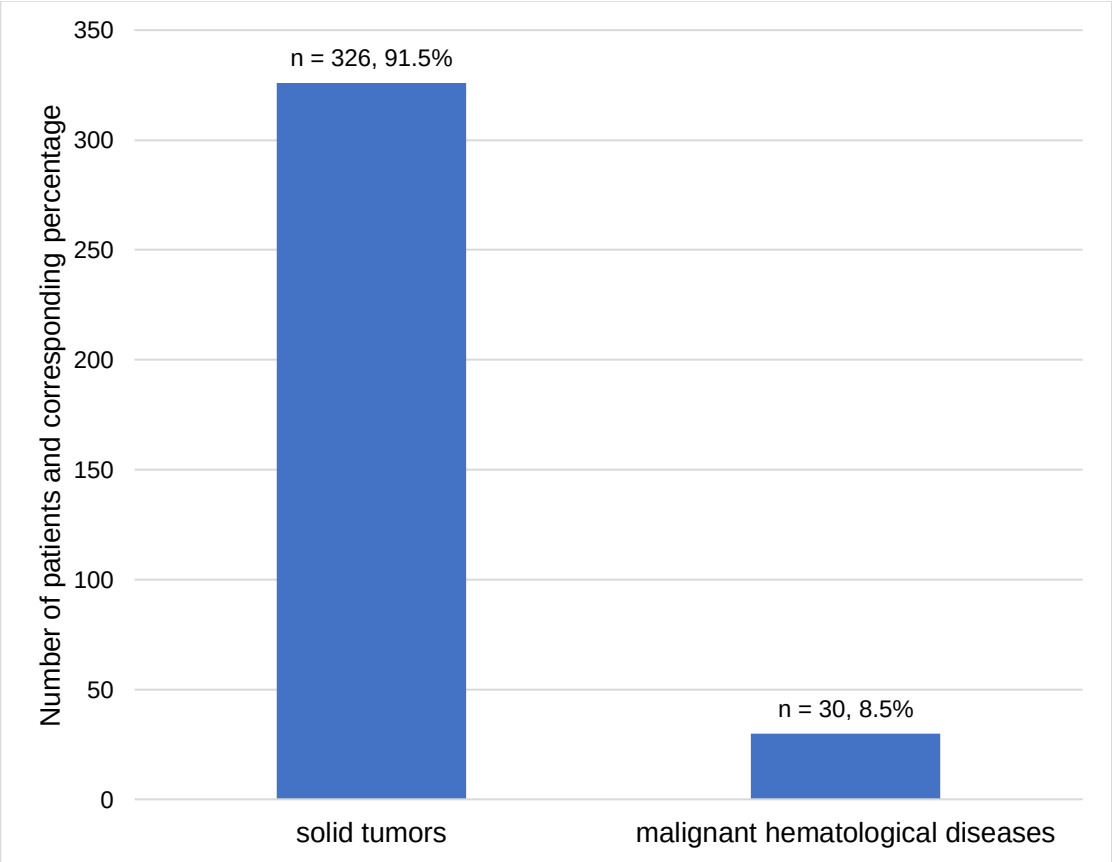

Fig. 2 Frequencies of solid tumors and malignant hematological diseases among sample

Solid tumors were categorized in 14 superordinate groups: Brain tumor, Brain metastases, Head and neck cancer, Bronchus and lung cancer, Breast cancer, Rectal and anal cancer, Gynecological cancer, Prostate cancer, Urinary tract cancer, Bone metastases, Melanoma, Secondary unspecified neoplasms of Lymph node, Cancer of unknown

primary (CUP) and Others. Malignant hematological diseases were categorized into three groups: Lymphoma, Leukemia and Multiple myeloma.

Brain tumors were the most common group of tumor entities (n = 68; 19.1%), followed by breast carcinomas (n = 62; 17.4%) and head and neck tumors (n = 44; 12.4%). Gynecological caner and urinary tract cancer formed the second smallest group of tumor entities: Each group included 4 patients, respectively (1.1%). Cancer of unknown primary (CUP) formed the smallest group (n = 2; 0.6%). Concerning malignant hematological diseases, Lymphomas were the most common group tumor entity (n = 18; 5.1%) (Figure 3).

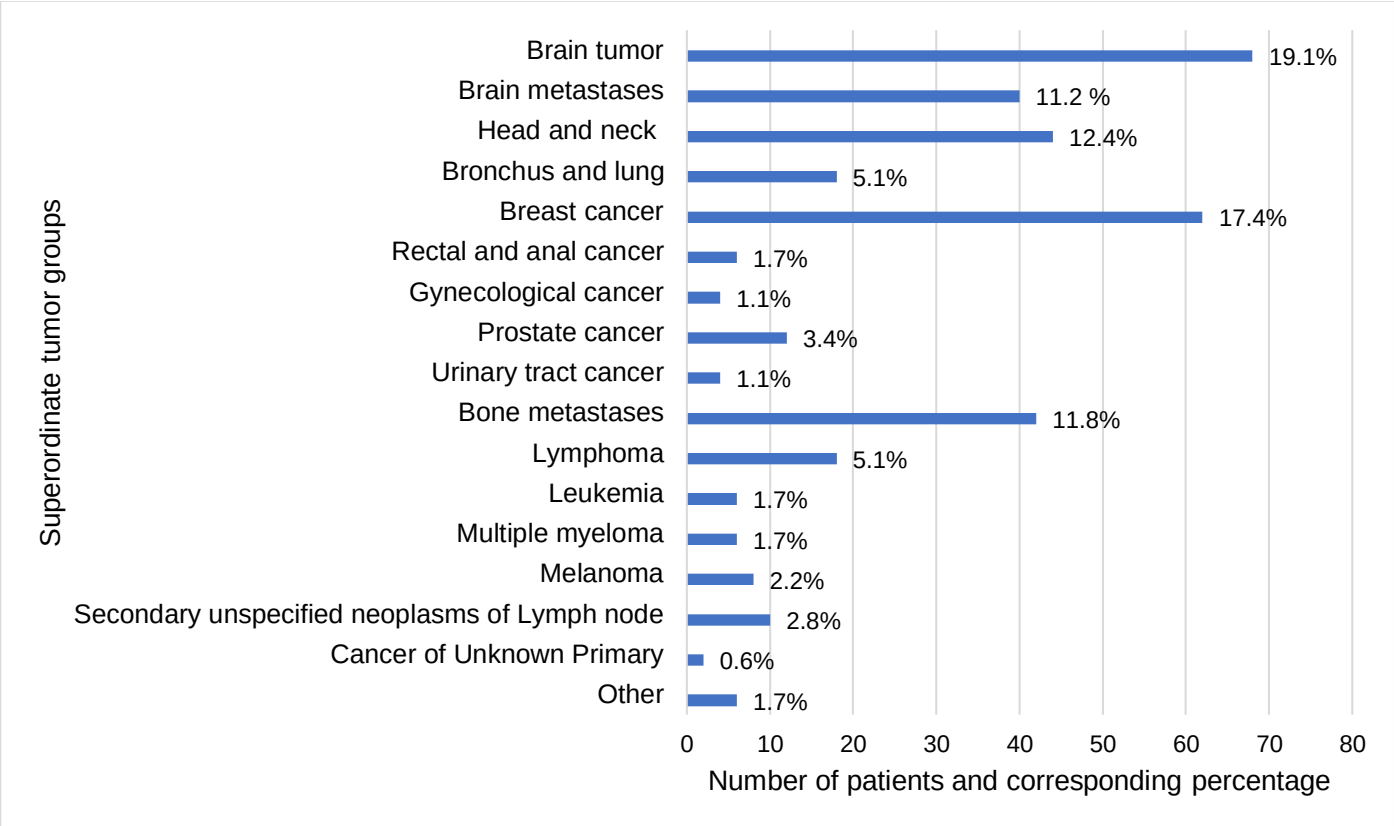

Fig. 3 Frequencies of tumor entities by categorization into 17 superordinate groups

The 17 superordinate tumor groups comprised 43 different tumor entities. The following table (Table 3) gives a more detailed overview of the frequencies and distribution of entities according to ICD-10 classification and superordinate groups.

Table 3 Frequencies of different tumor entities across both patient groups (n = 356)

Frequencies of different tumor entities calculated for both subgroups and total, stated in relative and absolute quantity

Tumor entity		**n**	**% of subgroup**	**% of total**
Brain tumors				
	C71 Malignant neoplasms of the brain	60	88.2	16.8
	D32 Benign neoplasm, meninges unspecified	4	5.9	1.1
	D33 Benign neoplasm of brain and other parts central nervous system (CNS)	4	5.9	1.1
Total		**68**	**100.0**	**19.1**
Brain metastases				
	C79.3 Secondary malignant neoplasm of brain and cerebral meninges	40	100.0	11.2
Total		**40**	**100.0**	**11.2**
Head and neck tumors				
	C01 Malignant neoplasm of base of tongue	2	4.5	0.6
	C02 Malignant neoplasm of other and unspecified parts of tongue	3	6.8	0.9
	C03 Malignant neoplasm of gum	4	9.1	1.2
	C04 Malignant neoplasm of floor of mouth	3	6.8	0.9
	C05 Malignant neoplasm of palate	1	2.3	0.3
	C06 Malignant neoplasm of other and unspecified parts of mouth	2	4.5	0.6
	C09 Malignant neoplasm of tonsil	6	13.6	1.7
	C10 Malignant neoplasm of oropharynx	6	13.6	1.7
	C11 Malignant neoplasm of nasopharynx	3	6.8	0.9
	C13 Malignant neoplasm of hypopharynx	2	4.5	0.6
	C15 Malignant neoplasm of esophagus	4	9.1	1.2
	C32 Malignant neoplasm of larynx	6	13.6	1.7
	C76.0 Malignant neoplasm of other and ill-defined sites: head, face, neck	1	2.3	0.3
	C80 Malignant neoplasm, without specification of site	1	2.3	0.3
Total		**44**	**100.0**	**12.4**

Table 3, continued on page 27

Bronchial carcinomas			
C34 Malignant neoplasm of bronchus and lung	16	88.9	4.5
C78 Secondary malignant neoplasm of respiratory and digestive organs	2	11.1	0.6
Total	**18**	**100.0**	**5.1**
Breast carcinomas			
C50 Malignant neoplasm of breast	62	100.0	17.4
Total	**62**	**100.0**	**17.4**
Colorectal and anal cancer			
C18 Malignant neoplasm of colon	1	16.7	0.3
C20 Malignant neoplasm of rectum	4	66.7	1.2
C21 Malignant neoplasm of anus and anal canal	1	16.7	0.3
Total	**6**	**100.0**	**1.7**
Gynecological cancer			
C52 Malignant neoplasm of vagina	2	50.0	0.6
C53 Malignant neoplasm of cervix uteri	2	50.0	0.6
Total	**4**	**100.0**	**1.1**
Prostate cancer			
C61 Malignant neoplasm of prostate	12	100.0	3.4
Total	**12**	**100.0**	**3.4**
Urinary tract cancer			
C64 Malignant neoplasm of kidney, except renal pelvis	2	50.0	0.6
C67 Malignant neoplasm of bladder	2	50.0	0.6
Total	**4**	**100.0**	**1.1**
Bone metastases			
C79.5 Secondary malignant neoplasm of bone and bone marrow	42	100.0	11.8
Total	**42**	**100.0**	**11.8**
Lymphomas			
C81 Hodgkin lymphoma	6	33.3	1.7
C83 Non-follicular lymphoma	6	33.3	1.7
C84 Mature T/Natural Killer-cell lymphomas	2	13.3	0.6
C85 Other and unspecified types of non-Hodgkin lymphoma	4	22.2	1.2
Total	**18**	**100.0**	**5.1**

Table 3, continued on page 28

Leukemia				
	C91 Lymphoid leukemia	5	83.3	1.4
	C92 Myeloid leukemia	1	16.7	0.3
Total		**6**	**100.0**	**1.7**
Multiple myeloma				
	C90 Multiple myeloma and malignant plasma cell neoplasms	6	100.0	1.7
Total		**6**	**100.0**	**1.7**
Melanomas				
	C43 Malignant melanoma of skin	4	50.0	1.1
	C44 Other malignant neoplasms of skin	4	50.0	1.1
Total		**8**	**100.0**	**2.2**
Secondary, unspecified neoplasms of lymph node				
	C77 Secondary and unspecified malignant neoplasm of lymph nodes	10	100.0	2.8
Total		**10**	**100.0**	**2.8**
Carcinoma of unknown primary				
	C80 Malignant neoplasm, without specification of site	2	100.0	0.6
Total		**2**	**100.0**	**0.6**
Others				
	C37 Malignant neoplasm of thymus	2	33.3	0.6
	D35 Benign neoplasm of other and unspecified endocrine glands	4	66.7	1.2
Total		**6**	**100**	**1.7**
Total		**356**		**100**

Annotation. CNS = Central Nervous System, NK – cells = Natural killer cells

Regarding a more specified categorization of diagnoses, Malignant neoplasm of breast (C50) formed the most common tumor entity (n = 62; 17.4%), followed by Malignant neoplasms of the brain (C71) (n = 60; 16.8%) and Secondary malignant neoplasm of bone and bone marrow (C79.5) (n = 42; 11.8%). Concerning Malignant hematological diseases, Hodgkin lymphomas (C81), Non-follicular lymphomas (C83), and Multiple myeloma and Malignant plasma cell neoplasms (C90) were equally frequently represented (n = 6; 1.7%, respectively) (Table 3).

3.3 Nationalities of foreign patients

Foreign patients had a total of 53 different nationalities, which were grouped into seven superordinate regions (Figure 4).

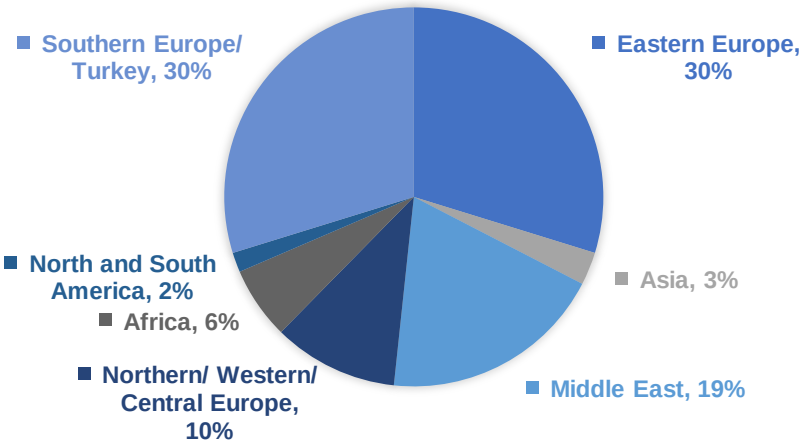

Fig. 4 Frequencies of origin of foreign patients by superordinate geographic region

Patients originated from 53 different nationalities (Table 4), classified into seven superordinate regions

Most patients were Eastern European (n = 53), Southern European/Turkish (n = 53), or Middle Eastern (n = 34). North and South America formed the smallest group (n = 3). Table 4 gives a more detailed overview of the frequencies of 53 represented nationalities in the sample. Regarding those specific countries of origin, foreign patients were most frequently from Turkey (n = 28; 15.7%), Russia (n = 13; 7.3%), Italy (n = 12; 6.7%), or Saudi Arabia (n = 10; 2.8%).

Table 4 Distribution of foreign patients' nationalities

Frequencies of nationality, calculated for both subgroups and total, stated in relative and absolute quantity

	n	% of subpopulation	% of total
Eastern Europe			
Russian	13	24.5	7.3
Hungarian	6	11.3	3.4
Romanian	6	11.3	3.4
Polish	5	9.4	2.8
Bulgarian	4	7.5	2.2
Bosnian	3	5.7	1.7
Georgien	3	5.7	1.7
Ukrainian	3	5.7	1.7
Serbian	2	3.8	1.1
Belarusian	1	1.9	0.6
Czech	1	1.9	0.6
Kazakh	1	1.9	0.6
Kosovo	1	1.9	0.6
Macedonian	1	1.9	0.6
Moldavian	1	1.9	0.6
Slovenien	1	1.9	0.6
Yugoslavian	1	1.9	0.6
Total	**53**	**100.0**	**29.8**
Southern Europe/Turkey			
Turkish	28	52.8	15.7
Italian	12	22.6	6.7
Armenian	3	5.7	1.7
Portuguese	2	3.8	1.1
Greek	4	4.5	2.2
Spanish	4	4.5	2.2
Total	**53**	**100.0**	**29.8**
Middle East			
Saudi-Arabian	10	29.4	5.6
Syrian	8	23.5	4.5
United Arab Emirates	8	23.5	4.5
Iranian	3	8.8	1.7
Iraqi	3	8.8	1.7
Afghan	1	2.9	0.6
Kuwait	1	2.9	0.6
Total	**34**	**100.0**	**19.1**

Table 4, continued on page 31

North, Western, and Central Europe			
French	5	26.3	2.8
Belgian	3	15.8	1.7
Dutch	3	15.8	1.7
British	2	10.5	1.1
Danish	1	5.3	0.6
Finnish	1	5.3	0.6
Lettland	1	5.3	0.6
Luxembourg	1	5.3	0.6
Swedish	1	5.3	0.6
Swiss	1	5.3	0.6
Total	**19**	**100.0**	**10.7**
Africa			
Lybian	3	27.3	1.7
Moroccan	2	18.2	1.1
Congolese	1	9.1	0.6
Namibian	1	9.1	0.6
Somalian	2	18.2	1.1
Togo	1	9.1	0.6
Tunesian	1	9.1	0.6
Total	**11**	**100.0**	**6.2**
North and South America			
American	2	66.7	1.1
Canadian	1	33.3	0.6
Total	**3**	**100.0**	**1.7**
Asia			
Filipino	2	40.0	1.1
Thai	2	40.0	1.1
Pakistani	1	20.0	0.6
Total	**5**	**100.0**	**2.8**
Total	**178**		**100.0**

3.4 Frequency and severity of side effects

For an overview of frequencies of side effects displayed by patients in the sample, i.e. CTCAE terms and corresponding SOC see Table 5. Side effects are listed independent of diagnosis (i.e. administration site) and severity of symptom. “General disorders or administration site condition” describes the class of side effects, which were experienced most common by patients (n = 433). In this class, as well as overall, “Pain (at

administration site)" was the most frequent side effect patients reported (n = 169). "Skin and subcutaneous tissue disorders" were displayed second most common (n = 356), in particular "Erythema multiforme" was reported most frequent in this class (n = 133) (U.S. Department of Health and Human Services 2017).

Table 5 Frequencies of side effects displayed by patients

Side effect classification independent of severity and diagnosis of patient, categorized into System Organ Class (SOC)

CTCAE System Organ Class (SOC)	**CTCAE Term**	**n total**
General disorders or administration site conditions		**433**
	Pain	169
	Fatigue	162
	Localized Edema	68
	Flu like symptoms	15
	Fever	9
	Chills	6
	Gait disturbance	4
Skin and subcutaneous tissue disorders		**356**
	Erythema multiforme	133
	Skin hyperpigmentation	70
	Alopecia (≤ 2)	57
	Rash Maculo Papular: Pruritus, Burning	50
	Skin induration	19
	Dry skin	18
	Hyperhidrosis	2
	Skin ulceration	2
	Telangiectasia	2
	Wound dehiscence	2
	Bullous dermatitis	1
Gastrointestinal disorders		**302**
	Nausea	82
	Dysphagia	61
	Mucositis oral	48
	Dry mouth	27
	Vomitting	21
	Diarrhea	20

Table 5, continued on page 33

	Obstipation	15
	Stomach pain	15
	Flatulence	10
	Esophagitis	2
	Colitis	1
Nervous system disorders		**97**
	Dysgeusia (≤ 2)	28
	Dysesthesia	26
	Headache	17
	Muscle weakness left-sided	7
	Concentration impairment	6
	Seizures	3
	Anosmia	2
	Aphonia (= 3)	2
	Other, specify	2
	Dysarthria	1
	Muscle weakness right-sided	1
	Neuralgia	1
	Peripheral sensory neuropathy	1
Respiratory, thoracic and mediastinal disorders		**94**
	Oropharyngeal pain	33
	Dyspnea	21
	Cough	16
	Hoarseness	7
	Sore throat	7
	Penumonitis	6
	Epistaxis	3
	Wheezing	1
Psychiatric disorders		**86**
	Anxiety	47
	Insomnia	18
	Depression	15
	Confusion	4
	Psychosis	2
Injury, poisoning and procedural complications		**54**
	Dermatitis radiation	54
Ear and labyrinth disorders		**41**
	Vertigo	30
	Hearing impaired	6
	Ear pain	3

Table 5, continued on page 34

	Tinnitus	2
Investigations		**40**
	Weight loss	36
	Creatinine increased	2
	Weight gain	1
	Other, specify	1
Musculoskeletal and connective tissue disorders		**30**
	Joint range of motion decreased	13
	Muscle weakness lower limp	5
	Myalgia	4
	Back pain	3
	Muscle cramp	3
	Athralgia	1
	Osteoporosis	1
Renal and urinary disorders		**28**
	Urinary frequency (incl. Nycturia)	11
	Dysuria (= 1)	9
	Urinary incontinence	5
	Urinary tract obstruction	2
	Urinary retention	1
Infections and infestations		**27**
	Other, specify	11
	Urinary tract infection (≥ 2)	11
	Bronchial infection	2
	Conjunctivitis	2
	Enterocolitis infectious	1
Blood and lymphatic system disorders		**20**
	Anemia	12
	Other, specify	7
	Bone marrow hypocellular	1
Eye disorder		**13**
	Vision decreased	8
	Blurred Vision	2
	Other - Specify	2
	Photophobia	1
Cardiac disorder		**7**
	Palpitations	3
	Atrial fibrillation	2

Table 5, continued on page 35

	Sinus bradycardia	1
	Ventricular arrythmia	1
Metabolism and nutrition disorders		**5**
	Hypokalemia	4
	Hyponatremia	1
Vascular disoders		**5**
	Hypotension	4
	Hypertension	1
Reproductive system and breast disorders		**3**
	Erectile dysfunction (♂)	2
	Ejaculation disorder	1

German patients experienced a total of 776 side effects, whereas foreign patients experienced a total of 865 side effects (Table 6).

Patients were categorized into mild-to-moderate or severe side effect groups based on the maximum severity of all side effects experienced. The mild-to-moderate group had a maximum severity of 0 or 1 for at least one side effect, whereas the severe group had a maximum severity of 2 or 3 for at least one side effect. Less than half of German patients (n = 75, 41.2%) and more than half of foreign patients (n = 98, 55.1%) were categorized into the severe side effect group. After calculating weighted score sums (i.e., mean severity across all indicated side effects), German and foreign patients had mean severity scores of 1.18 and 1.25, respectively.

Table 6 Frequencies of side effects among German and foreign patients

Frequencies of side effects independent of severity and diagnosis of patient

Severity	**German patients (n = 178)**	**Foreign patients (n = 178)**
1	650	683
2	111	150
3	15	32
Total	**776**	**865**

3.5 Results of Chi-square tests of independence

3.5.1 H_{a1}: Side effect severity and patient nationality

Side effect severity was significantly associated with patient nationality [$\chi^2(1) = 5.949$; $p < 0.05$; $\varphi = 0.129$] (Figure 5). More foreign patients experienced severe side effects than expected (98 vs. 86.5), whereas German patients experienced mild-to-moderate side effects more frequently than expected (103 vs. 91.5). However, there was no significant difference in the number of side effects experienced by German and foreign patients (U = 14609.50; Z = -1.277; p = 0.202).

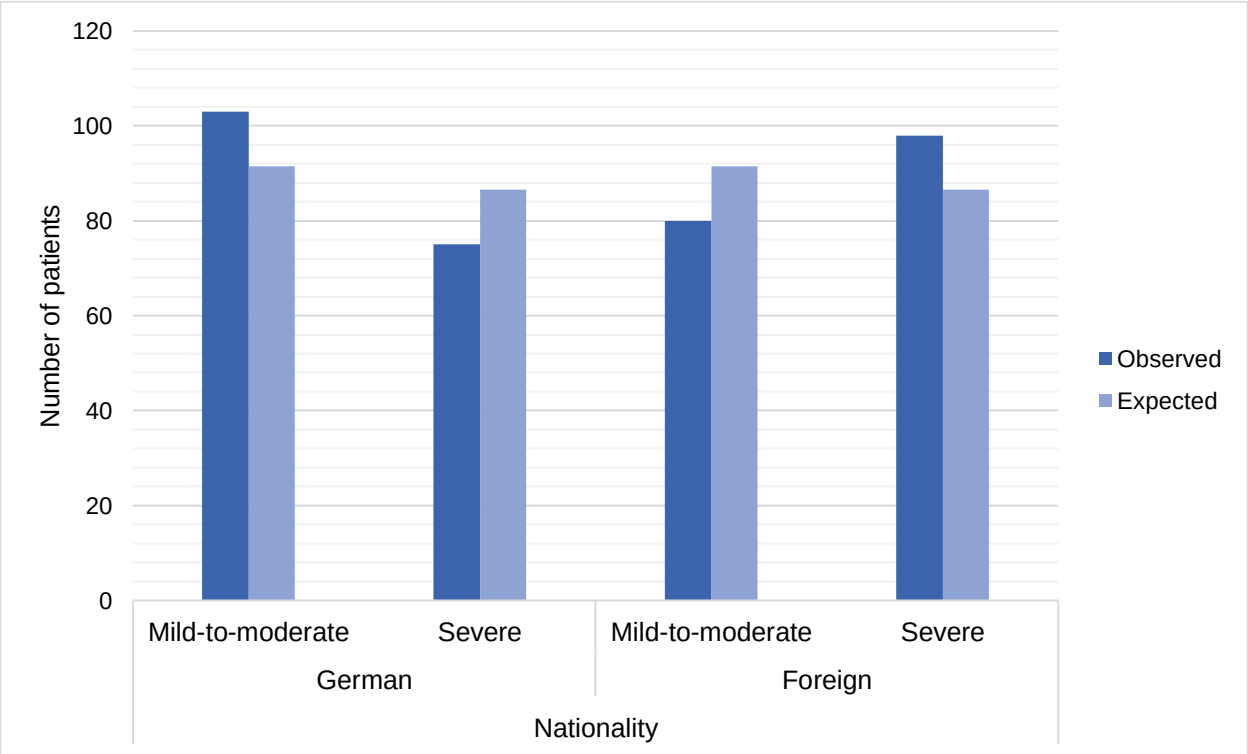

Fig. 5 Expected and observed severity of side effects stratified by nationality

Graphical representation of results of Chi-square (χ2) tests of independence

3.5.2 H_{a2}: Side effect severity and tumor entity

For both groups, German and foreign patients, side effect severity was also significantly associated with tumor entity [$\chi^2(16) = 66.964$; $p < 0.01$; $\varphi = 0.434$]. Regarding tumor entity, more patients with head and neck tumors, regardless of nationality, experienced severe side effects than expected (42 vs. 21.4), whereas less patients with head and neck tumors experienced mild-to-moderate side effects than expected (2 vs. 22.6). The opposite was

true for patients with bone metastases: In this group, more patients experienced mild-to-moderate side effects than expected (27 vs. 21.6) and less patients than expected showed severe side effects (15 vs. 20.4) (Figure 6). In this analysis, 17 out of 34 cells had a frequency of <5 cases, which potentially causes erroneous results. Therefore, implementation of Fisher's exact test is recommended. However, this test is only applicable for small contingency tables. For contingency tables of the present size (17*2), the Monte Carlo method leads to more precise probability estimates. Here, by repeated (e.g. 10000-fold) sampling, the test distribution under the null hypothesis is estimated by the resulting empirical distribution. The Monte Carlo method is indicated when exact tests cannot be calculated for capacity reasons, but the requirements of an approximate method are not fulfilled (e.g. due to weakly populated rows/columns), like in the present case (Mehta Cyrus and Patel Nitin, 2013). Results of this test did not differ from original results ($p<0.001$).

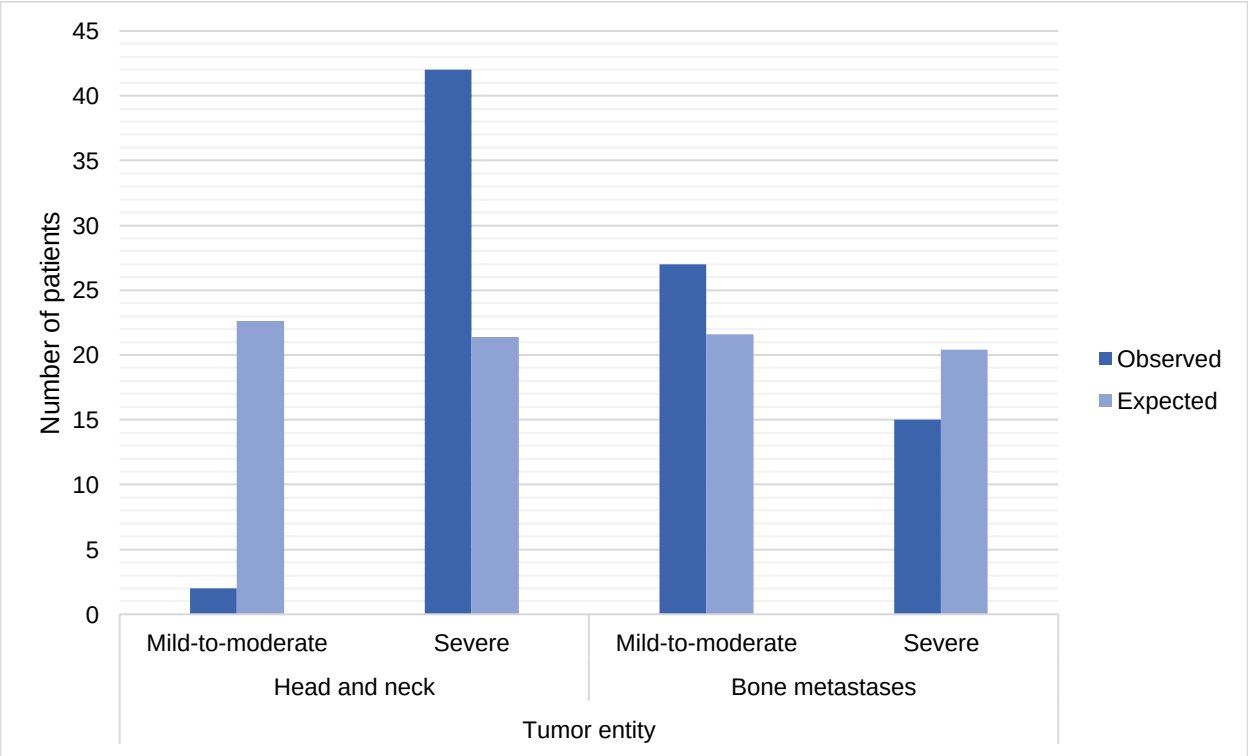

Fig. 6 Expected and observed severity of side effects stratified by tumor entity

Graphical representation of results of Chi-square ($\chi 2$) tests of independence

3.5.3 H_{a3}: Side effect severity and concomitant therapy

In addition, regardless of nationality, severity of side effects was significantly associated with concomitant therapy, [$\chi^2(3) = 15.469$; $p < 0.01$; $\varphi = 0.208$]. More patients receiving combined chemoradiotherapy experienced severe side effects than expected (70 vs. 54.4). Patients receiving no concomitant therapy next to radiation therapy experienced more mild-to-moderate (129 vs. 111) and less severe side effects (87 vs. 105) than expected (Figure 7). The number of patients receiving Immunotherapy or Hormone therapy concomitant to radiation therapy (n = 21; n = 7, respectively) was vanishingly small, therefore, interpretation of the results for those subgroups most likely expresses small external validity.

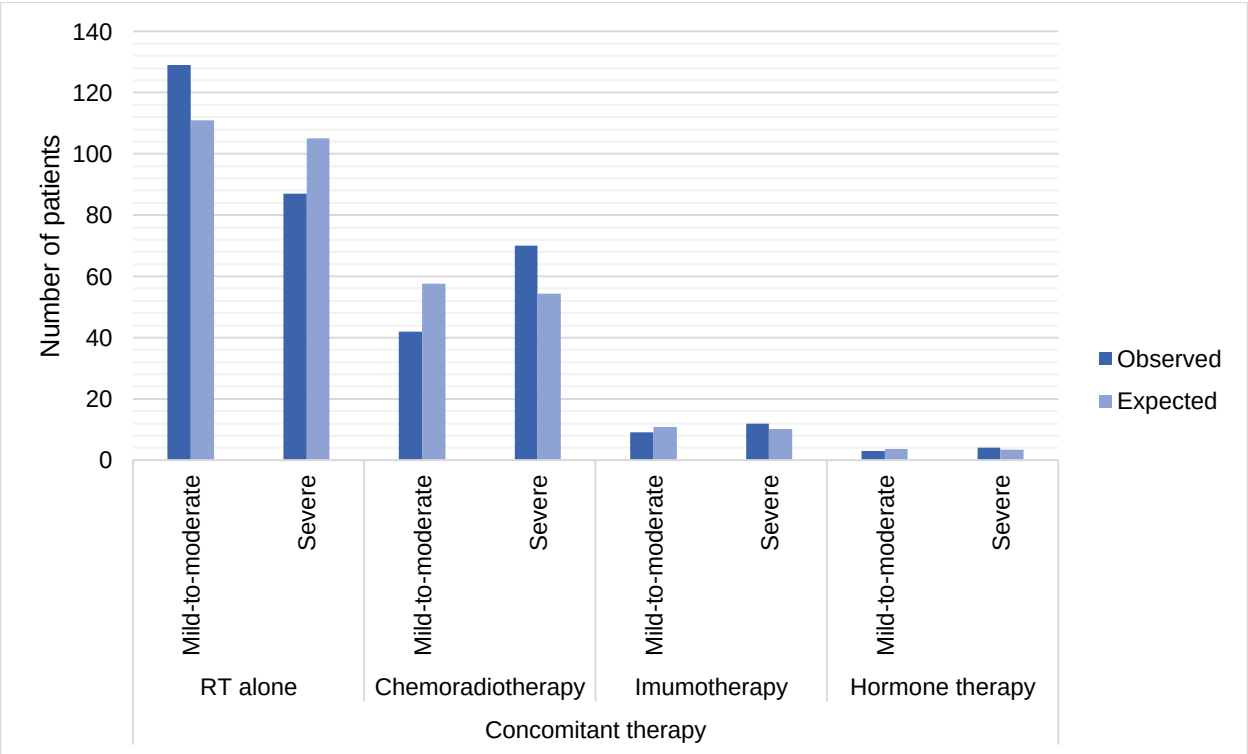

Fig. 7 Expected and observed severity of side effects stratified by concomitant therapy

Graphical representation of results of Chi-square (χ2) tests of independence

To verify results, as 2 out of 8 cells had a frequency of <5 cases, possibly causing erroneous results again, Fisher's exact test was calculated. If > 20% of expected cell counts are less than 5 and for contingency tables of this size, i.e. 4*2, Fisher's exact test

represents the analysis of choice. In accordance with former results, it resulted in significance (p<.001).

3.5.4 H_{a4}: Foreign patients' side effect severity and BMI

Among foreign patients, side effect severity was additionally significantly associated with body mass index (BMI) [$\chi^2(3) = 7.917$; $p < 0.05$; $\varphi = 0.211$]. More patients with a BMI category of 3 or 4 experienced severe side effects than expected (BMI 3 = 37 vs. 29.7, BMI 4 = 15 vs. 13.8), whereas more patients with a BMI category of 1 or 2 experienced mild-to-moderate side effects than expected (BMI 1 = 9 vs. 6.3; BMI 2 = 44 vs. 38.2) (Figure 8).

There were no associations between side effect severity and KI, CCI, smoking, or alcohol consumption.

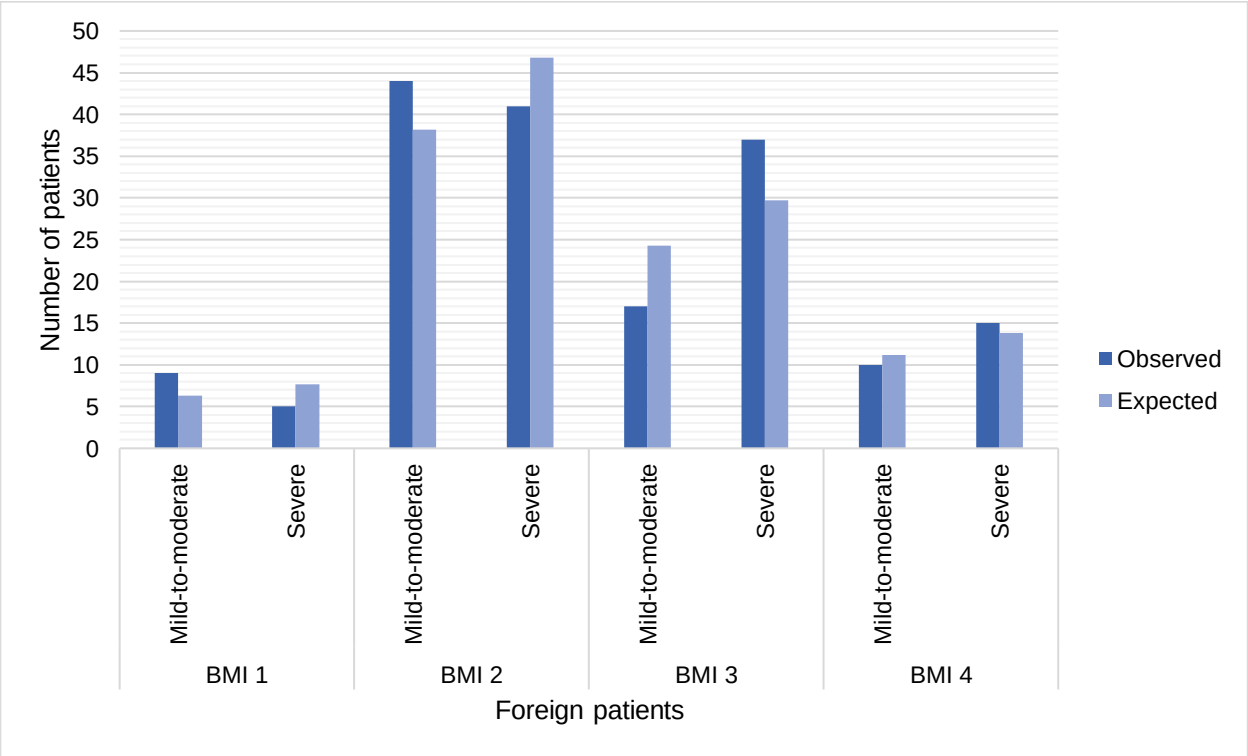

Fig. 8 Expected and observed severity of side effects stratified by Body mass index category (BMI) for foreign patients.

Graphical representation of results of Chi-square (χ2) tests of independence.
BMI 1:<18.5 = underweight, BMI 2: 18.5 - 24.9 = normal weight, BMI 3: >24.9 = overweight, BMI 4: >30 = obesity

3.5.5 H_{a5}: Side effect severity and age in the Turkish cohort

Finally, among Turkish patients (n = 28), side effect severity was significantly associated with age (<60 vs. ≥60 years) [$\chi^2(1) = 7.337$; $p < 0.01$; $\varphi = 0.512$]. Patients older than 60 years suffered from more severe side effects than expected (12 vs. 8.5). Younger patients (<60 years) experienced mild-to-moderate side effects more often than expected (9 vs. 5.5) (Figure 9).

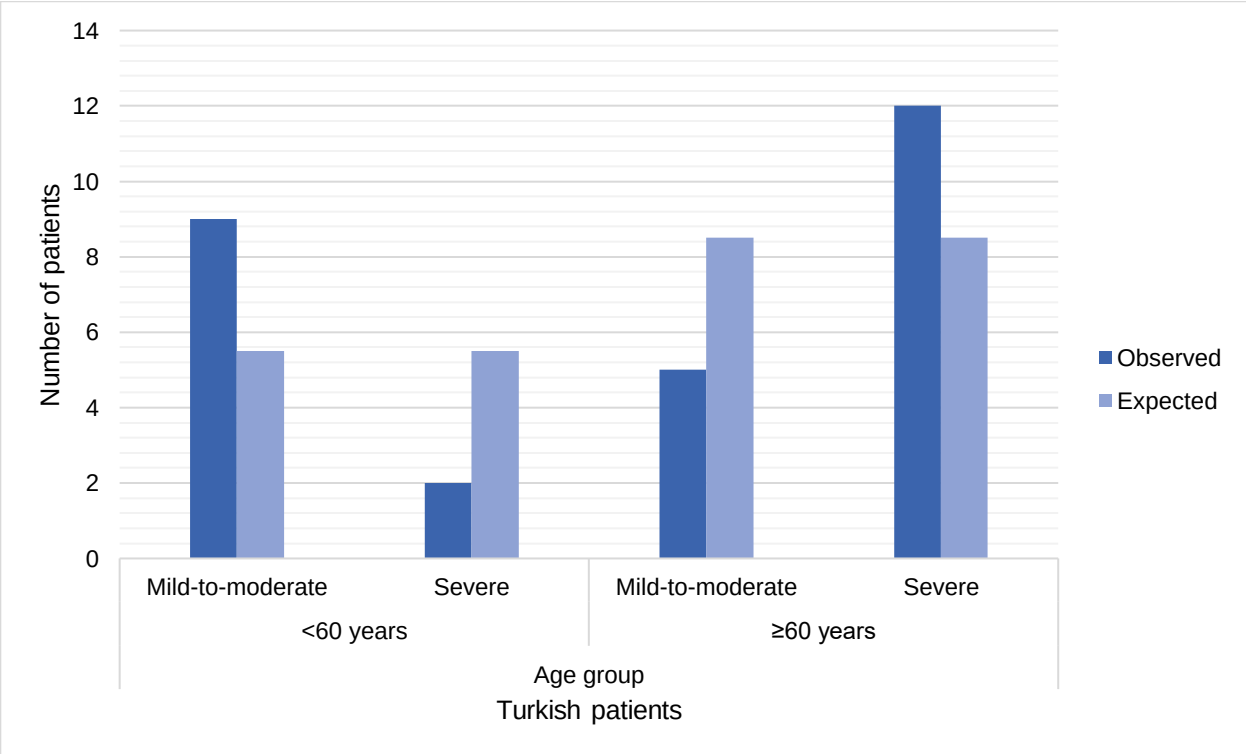

Fig. 9 Expected and observed values for Turkish cohort, stratified by <60 and ≥60 years of age.

Graphical representation of results of Chi-square (χ2) tests of independence

Similar associations were not observed within other regional or country patient subgroups.

4. Discussion

4.1 Summary of results

We investigated whether German and foreign cancer patients differed in the quantity and severity of early side effects experienced following radiotherapy. Although we found no difference in the number of side effects, we found that foreign patients were more likely to experience severe side effects than German patients. Side effect severity was also associated with tumor entity and concomitant therapy, with patients who had head and neck tumors or received combined chemoradiotherapy being more likely to experience severe side effects. Among foreign patients, a higher BMI was associated with a greater risk of severe side effects. KI, CCI, smoking, or alcohol consumption did not show to be associated with severity of side effect. Furthermore, among Turkish patients, older patients (≥60 years) were more likely to experience severe side effects than younger patients (<60 years).

4.2 Empirical context

Previous studies suggest that multiple factors are associated with poorer therapeutic outcomes among foreign patients than among national patients. For instance, foreign people struggle with structural access barriers to health services such as fees, waiting times or travel distances. Those barriers could be partially addressed by providing newcomers with easy-to-understand information on the availability and accessibility of healthcare services available in Germany or developing healthcare apps that promote adherence to therapy and allow the identification of new or worsening side effects (Academy of Medical Sciences, 2007; Klein and von dem Knesebeck, 2018; Starker et al., 2021).

A major factor of cultural competence in health care service includes dealing with language barriers. Those language barriers represent a problem that undermines the accessibility and quality of healthcare services provided to foreign patients and are associated with limited access to health information and patient education, thereby exaggerating social inequities in knowledge regarding health issues (Mosdøl et al., 2018; Rechel et al., 2013). Encouraging patient involvement in treatment choices, which

enhances compliance, requires providing patients with useful information about therapy options and their risks of side effects (Sonis, 2015). In our study, all foreign patients received a German version of a patient education brochure titled “Thieme Compliance for Radiotherapy”; however, only 43 of 178 foreign patients (24.2%) had a personal interpreter with or without relatives present during discussions with a healthcare provider about treatment plans. To address this problem, patient education should be provided in the patient’s native language or healthcare providers should make use of pictures and diagrams to facilitate understanding (Rechel et al., 2013). Also, trained interpreters provided by the healthcare institution should be used to ensure adequate communication and clarification of questions and uncertainties (Thornton et al., 2009). Even though doctors or personnel possess a high language proficiency, trained interpreters may offer additional emotional benefit beyond their interpretation services, having a favorable effect on the patient’s condition (Schmerler, 2018).

In line with previous findings that foreign patients have inherently poorer health behaviors and inaccurate perceptions about the impact of health behaviors (Liu et al., 2019), we found an association between BMI and side effect severity among foreign patients. This result suggests that targeted outreach to foreign patients could be used to provide education on healthy nutrition and the benefits of moderate exercise, which may be particularly effective when performed by “ethnic health educators” in patients’ native languages (Singels, 2009).

Earlier studies illustrated less willingness among foreign patients to participate in screening and prevention programs and poorer compliance with follow-up examinations (Brzoska and Abdul-Rida, 2016; Klein and von dem Knesebeck, 2018). For example, foreign patients have been shown to have lower attendance rates to both cervical and mammography screening and, possibly as a result of this, non-western patients had higher risk of being diagnosed with a more advanced stage of breast cancer (Bhargava et al., 2018; Leinonen et al., 2017). In this situation, delayed diagnosis and subsequent poor prognosis are of great concern. Consistently, we also found that foreign patients had a higher rate of treatment termination and lower rate of attendance at follow-up appointments compared to German patients, although these differences were not

statistically significant (Table 2). In this context, the importance of follow-up appointments needs to be stressed: Its primary goal is to detect tumor relapses at an early stage and initiate treatment as early as possible. Second, it aims at detecting therapy-associated secondary diseases at an earliest possible date, both based on the assumption that early detection, compared with late diagnosis, preferably in the asymptomatic stage, leads to improved outcomes (Szturz et al., 2020). Another goal of follow-up appointments is to maintain or sustainably improve the quality of life of tumor patients. This includes, in particular, addressing the psychosocial components associated with cancer together with colleagues in psychooncology. Practical help and a supportive network can be provided by self-help groups in the respective language (Szturz et al., 2020). Therefore, ensuring patients attendance at follow-up appointments is essential.

To improve patients' attendance at follow-up appointments as well as participation in their own healthcare, active, patient-centered follow-up programs should be established to improve therapeutic outcomes and allow better evaluation of the effectiveness and safety of radiotherapy at the population level (Andreyev, 2007; De Ruysscher et al., 2019).

4.3 Health economics

Acting upon these findings is important not only for improving clinical care and patient outcomes but also for the field of health economics, which plays an increasing role in healthcare decision-making (Sonis, 2015). The economic burden of acute toxicities associated with cancer treatment has long been recognized (Carlotto et al., 2013), with mounting direct costs of managing side effects such as medication, hospitalization, and use of physiotherapists or psycho-oncologists. Furthermore, as side effects carry the risk of eventually becoming chronic, thereby prolonging rehabilitation and incapacity for work (Diz Dios and Diniz Freitas, 2020; Schmielau et al., 2017), indirect costs such as loss of opportunity, work time, and productivity and increased need for caregiver support add to the already heavy economic burden on society. Therefore, preventing side effects of radiotherapy is economically advantageous to treating side effects after they occur (Carlotto et al., 2013). By identifying patients in which severe side effects are most likely to occur, unwanted outcomes of cancer therapy can be prevented, leading to better symptom control and quality of life (De Ruysscher et al., 2019).

4.4. Cultural and religious aspects

Besides economic aspects, cultural and religious peculiarities should be included in the therapy guidance: Such peculiarities can be the separation into male and female spheres or the restriction of certain auxiliary substances or drugs (blood products or narcotics). Due to large individual, regional, cultural and confessional differences in Germany, no systematic catalogue of guidance can be established (Fischer et al., 2019). However, knowledge of such differences, sensitive handling of the cultural-religious particularities of patients and relatives by the medical and nursing staff and cooperation with hospital pastors can strengthen the relationship of trust between doctor and patient and thus improve the conditions for successful oncological therapy (Fischer et al., 2019).

4.5 Tumor entity

In addition to patient nationality, an association between tumor entity and side effect severity was found, such that patients with head and neck cancer were more likely to experience severe side effects. These patients are especially prone to developing side effects given that they are at high risk for malnutrition due to their cancer site, disease process, and intensified treatment approach. Severe mucositis, a common side effect on those sites of irritation associated with head and neck cancers, is accompanied by feeding difficulties compounded by cancer cachexia, impairs healing, and response to stress, affecting general condition leading to more severe experience of side effects. Detrimental lifestyle factors associated with the development of head and neck cancers, such as alcohol misuse, also increase patients' risk for severe side effects (Talwar et al., 2016). Therefore, the prevention and treatment of side effects in patients with head and neck cancers remains a challenge (Nigro et al., 2017). Nursing interventions and patient education play an essential role in reducing the side effects of radiotherapy in head and neck cancers (Majeed and Gupta, 2021). Those include administration of oral hygiene as well as dietary modifications instructions for all patients receiving head and neck irradiation. In addition, consultation with a dentist and treatment of periodontal disease before radiotherapy minimizes the risk of side effects in this area. Use of bland rinses, cryotherapy, mucosal protective agents, antiseptic mouthwashes, topical analgesics, and anti-inflammatory agents or growth factors as necessary may also contribute to the alleviation of symptoms. Literature states, regular assessment and monitoring of high-risk

patients may reduce long-term sequela in these patients and improve the overall quality of life (Majeed and Gupta, 2021). A necessary step for both administration of preventive and curative measures as well as benefitting of its effect is ensuring of patient education in appropriate communication, with the consideration of mother tongue and level of education of foreign patients.

However, as our subgroup analysis included only 44 patients, further evaluation of the risk of early side effects among head and neck cancer patients requires studies with larger sample sizes and more detailed analyses of different types of side effects and potentially predictive characteristics.

4.6 Concomitant therapy

Even though sequential plus concurrent chemoradiotherapy improves survival compared with chemotherapy alone, it is known to increase some serious acute toxicity (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration, 2010; Nieder et al., 2020; Strøm et al., 2013). Consistent with this, in the present study, patients receiving combined chemoradiotherapy developed more severe side effects as expected in contrast to patients receiving neoadjuvant chemotherapy or radiotherapy alone. Two reasons for these findings must be considered: concurrent chemotherapy increases tissue sensitivity to radiation damage, and the total radiation dose to nearby organs is higher, as the effect of neoadjuvant chemotherapy, to minimize the primary tumor, remains off (Yao et al., 2017). In one study, unrevealing a severe effect of acute toxicity whilst receiving concurrent chemoradiotherapy, the majority of patients received platinum-containing regimens (Nieder et al., 2020). Future studies should investigate differences in profile of side effects following neo- or adjuvant chemotherapy, chemoradiotherapy, or radiotherapy alone depending on the administered regimens (especially platinum-containing vs. platinum-free regimen).

4.7 Further parameters

In our study, no effect of KI, CCI, smoking, or alcohol consumption on severity of side effects was found. Those findings are not consistent with previous empirical evidence. For example, studies have found an effect of performance status and comorbidities on therapy

outcome and side effects: According to the current literature, lower performance status was identified as a significant predictor of tube feeding or hospitalization during radiotherapy as well as poorer tolerance in general to radiotherapy (Sommat et al., 2018; Sze et al., 2012). Patients with higher score on the comorbidity index are at a higher risk to develop side effects of radiotherapy and comorbidity was found to be associated with a decrease in overall survival (Correa et al., 2020; Lemanska et al., 2017). Regarding the association between the factor smoking and radiotherapy outcome, a narrative review reports that numerous of the analyzed studies demonstrated a detrimental effect of smoking on overall survival, tumor control, quality of life, treatment toxicity, and the incidence of second primary malignancies (Perdyan and Jassem, 2022). They argue, tobacco smoking may probably be the strongest modifiable factor affecting the outcome of cancer treatment.

In contrast to present results, some studies report an association between alcohol consumption and side effects of radiotherapy, yet, results are inconsistent.

Whereas some studies found a radioprotective effect of moderate or occasional alcohol consumption on occurrence of severe acute side effects radiotherapy (Morganti et al., 2009) other studies state an opposing effect: It is suggested that alcohol may modify the risk of radiotherapy-associated second primary cancer (SPC) occurrence and total mortality (DiMarzio et al., 2018). Alcohol consumption (next to smoking) is a known risk factor for several types of cancer and mortality, and, in combination with radiotherapy, it is thought to further increase these risks (DiMarzio et al., 2018). In line with this, Frowen et al. (2010) found ex-heavy alcohol consumption was associated with worse therapy outcome after radiotherapy in head and neck cancers (here, swallowing).

There may be several reasons why no effect for those parameters was found in our investigation. Due to the observational and retrospective nature of our study, some potentially relevant data might have been missed. Performance status and comorbidities need to be assessed and translated into standardized scales in a consistent fashion by clinicians. In our study, the self-reported smoking status was not validated biochemically. Additionally, the number of patients who quit or continued smoking during treatment, as well as quantitative tobacco exposure (PY), was not recorded. Concerning alcohol consumption, data was not well quantified, either. No uniform survey material was

available, therefore, if no information on alcohol consumption was on the record, cases were recorded as “no alcohol consumption”. Those factors might have distorted results and should be subject of future studies.

4.8 Generation effect

Given that Germany is home to ~ 4 million people with Turkish roots, subgroup analysis of Turkish nationality is of particular importance. Among patients from Turkey, a generation effect was found such that older patients (≥60 years), many of whom may have been first-generation foreigners who migrated to Germany in the 1960s, were more likely to experience severe side effects than younger patients (<60 years). Consistent with our findings, previous studies report differences in treatment outcomes and side effects within migrant populations depending on whether they are first-generation migrants who immigrated to the host country themselves or second-generation migrants who were born in the host country (Starker et al., 2021). However, other studies found no effect of migrant status on health (Wengler, 2011). These discrepant findings may be due to the existence of confounding factors, such as socioeconomic status and education, environmental exposure, language skills, social status, lifestyle, work status, and participation in society, which greatly impact overall health and therapeutic outcomes, including side effects (Weber and Hörmann, 2011). Other studies stress a limited effect for environmental exposures, but emphasize the factor of age at immigration, regardless of migration status, to be associated with the risk trend of cancer: In a cross-national study, Spallek et al. (2009) found that cancer of the respiratory organs is diagnosed less frequently in Turkish men in older birth cohorts, whereas it is more frequent in younger birth. At a structural level, one reason might be, that the healthcare system might provide better services for immigrant groups that has been present for a long period.

Importantly, our finding that foreign patients were more likely to experience severe side effects than German patients was no longer observed when restricting the analysis to patients <60 years of age [$\chi^2(1) = 2.687$; $p = 0.101$; $\varphi = 0.119$]. This finding is in line with studies demonstrating an unchanged trend of breast cancer among those who immigrated at younger ages and an increasing trend for those who migrated at older ages (Mousavi et al., 2012).

One reason for these findings could be that first-generation immigrants are less informed about the German healthcare system and less fluent in the German language compared with second-generation immigrants, thus leading to less active participation in the healthcare system (Glaesmer et al., 2011). It definitely underlines the need to focus on preventing side effects among first-generation immigrants receiving radiotherapy.

4.9. Role of genetics and genomics in radiotherapy toxicity

One factor we were unable to investigate due to the retrospective nature of the study is the impact of genetic variation of patients on side effects of radiotherapy. There is substantial literature implicating patient genetic variations to be an influencing factor in the large patient-to-patient variability in peritumoral tissue reactions after radiotherapy (e.g. Andreassen et al., 2016a, Deichaite et al., 2022, Schack et al., 2022). This scientific field called radiogenomics is growing and aims to identify genetic markers that help to recognize patients at risk of developing radiation-induced adverse effects (Aguado-Barrera et al., 2023, Brothwell et al., 2019, Kerns et al., 2014). Empiricism estimates a contribution of patients' heritability on radiosensitivity generally in the range of 60–80% (Andreassen et al., 2016b). Whereas targeted systemic therapies and immunotherapy are routinely guided by molecular markers, radiotherapy to date is applied based on clinicopathologic features (Earland et al., 2023). Several radiogenomic studies have already demonstrated the potential of molecular biomarkers in form of single nucleotid variations' (SNV) to predict radiosensitivity, radioresistance and treatment-associated toxicities in genome-wide association studies (GWAS) (e.g. Deichaite et al., 2022, Kerns et al., 2020, Naderi et al., 2022). More specific, Schack et al. (2022) conducted an exploratory GWAS in European cohorts of head and neck cancer patients and identified a risk locus for mucositis. Naderi et al. (2023) performed a larger scaled GWAS meta-analysis using 19 cohorts totaling 12042 patients and identified common susceptibility SNVs for radiation induced toxicities across and within individual cancer sites, such as the association of the gene set natural killer cell lectin-like receptor binding to radiation-induced toxicity in breast cancer patients.

Applying these findings to the present results, the study of SNVs of german and foreign patients in form of a GWAS could have explained additional variance in severity of side effects after radiotherapy. The revealed differences in the expression of adverse effects

after RT could partly be due to a common SNV-based heritability of certain national groups predisposing to increased radiosensitivity, and are not explained by nationality itself. Future meta–GWAS among large radiation therapy patient cohorts, carefully clinical designed, that have statistical power to identify new genes associated with toxicity and validate previous findings are needed (Naderi et al., 2023).

4.10 Strengths

Our work contributes to efforts to prevent disease and negative health outcomes among patients who are at higher risk due to personal characteristics, which has generated global policy interest (Dzau et al., 2015). In general, we are confident to rate the present study as robust against selection and information bias. Usually, unmeasured confounding is of particular concern in such studies. In contrast to other studies on this topic, the present study obtained and analyzed a large number of potentially confounding variables, such as performance status, comorbidity, alcohol use, smoking, and BMI.

4.11 Limitations

Despite these strengths, however, our study also has several limitations. Due to the retrospective nature of our study, causal relationships cannot be determined. In addition, two major confounders have to be faced: We were not able to define baseline overall health at time of radiotherapy and the matching process did not take tumor grading into consideration.

All aspects could not be assessed retrospectively but may have a crucial influence on the differences in outcome of radiotherapy related side effect of German national and foreign national patients and thus gives the misleading impression that being a foreign national is a major risk factor in itself.

Also, the number of patients in the present sample (n = 356) is not overly large, especially with regard to even smaller subgroups of nations: Analyses included 17 groups of patients with different tumor entities, some groups being quite small, leading to heterogeneity in the data and limiting statistical power. The biggest group with the only absolute higher number formed by Turkish patients, did show modest but statistically significant findings of increased severity of side effects, which might therefore be misleading, misguiding over-simplification. Furthermore, the number of comparisons conducted makes it likely

that some of the observed differences are due to random error. As such, studies with larger sample sizes are warranted. The statistical error of multiple testing should be mentioned in this context: The more statistical tests are performed for related results, the greater the risk that some of the significant results are significant by chance, resulting in type I errors. This means that one or more results in our study may have turned out to be significant at the p-level, not because they are truly significant in the population, but due to chance. To correct for this error, future studies can apply the Bonferroni or Hochberg correction (Andrade, 2019).

As emphasized at the outset, the population in Germany is heterogenous and dynamic: Future foreign patients treated in Germany will be different from patients that arrived in the past receiving treatment ibid. Therefore, it is of particular importance to carefully consider the generalizability of the results in this study.

In our study, a possible bias with regard to underestimation of side effects is represented by the fact, that foreign patients showed lower rate of attendance at follow-up. Potentially, side effects were failed to be reported by foreign patients.

A further limitation of our study is how patient nationality was determined. We categorized patients based on information stored on their eHealth Cards and grouped all patients with foreign passports into a single category. Due to the retrospective nature of the study, we did not have information about whether patients were economic migrants, students, return migrants, refugees, retirement migrants, or medical tourists, the latter of which show large variations in tacit knowledge about medical treatment and healthcare systems (Ormond, 2016). However, the status of patients may be associated with therapy outcome: e.g., medical tourists bear different consequences and risks compared to foreigners living in Germany; of insufficient verified services, to the improbability of pursuing treatment and supervision after return (Badulescu and Badulescu, 2014). We also could not determine whether migrants were born and raised in Germany, as second- and third-generation foreigners often do not have German citizenship owing to various reasons (Fick, 2016). In addition, we did not assess foreign patients' language skills, length of stay in Germany, or legal status, which are, as mentioned above, associated with use of preventative care and healthcare services as well as overall health (Acevedo-Garcia et al., 2010; Dias et al., 2008; Lebrun, 2012; Starker et al., 2021). Therefore, more detailed assessment of patients' migration background would enable future research to consider the extensive

diversity in socioeconomic, political, and legal statuses of people pursuing and receiving medical treatment abroad (Ormond, 2014; Starker et al., 2021).

Finally, we faced a known challenge for radiotoxicity studies, namely to obtain good quality toxicity data, that is, complete, longitudinal, including pre-treatment, and comprehensive along with other data on possible influencing risk factors (West and Barnett, 2011). The entire data in the present cohort was collected from the patients' file, generated by treating physicians. The quality of the data depends on the accuracy of the documentation, which may be incorrect or incomplete, and could not be controlled for. Especially information on side effects was collected in a subjective manner by clinicians or generated by the researchers based on information contained in medical center records. This approach is prone to error and can underestimate the incidence and severity of symptomatic side effects, thus reducing sensitivity and specificity (Fromme et al., 2004).

The information may be incomplete as there was no targeted survey of side effects and no standardized follow-up procedure has been established. Therefore, employing a standardized follow up procedure including a patient-centered survey of side effects, such as the Patient-Reported Outcomes Version of the CTCAE, may provide a more accurate picture of patients' experiences of side effects as well as subjective burden and health-related quality of life (Fromme et al., 2004, Greimel et al., 2011) and thereby enable better prediction of unfavorable clinical events (Basch et al., 2009).

Taking all those considerations into account, the results of the present study may have questionable clinical significance. Even though side effects are statistically significant more severe in foreign nationals, the absolute differences are quite modest. Further research investigating factors predicting the occurrence of radiotherapy side effects, including other sociodemographic characteristics or the genetic heritage, is needed to better personalize therapy regimens for cancer.

5. Summary

Modern cancer treatment regimens should aim at providing the most suitable treatment for each individual group of patients, ensuring the best possible outcomes for each patient undergoing radiotherapy by identifying disparities between patient's groups predicting unfavorable side effects, and addressing them by means of preventive measures. Given that recent research has primarily focused on disparities in terms of genetic markers, less is known regarding sociodemographic predictors of therapeutic outcomes, such as patient nationality. Here, we investigated whether the severity of early side effects after radiotherapy are associated with patient nationality and other sociodemographic and clinical characteristics. We set out to reveal disparities between foreign and German patients and to identify potential health care barriers. The understanding of acute side effects is pertinent to oncologists, primary care physicians, and other clinicians engaged in cancer treatment, supportive management, and survivorship care, because side effects occur after nearly all types of non-surgical cancer interventions, are dose-limiting, reduce patients' quality of life, and contribute to the economic burden of disease and healthcare costs.

Seeking to improve the prevention of acute side effects, we investigated 356 patients, 178 German and 178 non-German patients, treated at the university institution between 2017 and 2021 and selected for matched-pair analysis based on diagnostic and demographic criteria. Data on side effects from follow-up care after radiotherapy were collected.

We identified side effect severity to be associated with nationality, tumor entity as well as concomitant therapy. In this study, foreign patients appeared to be more vulnerable to severe side effects of radiotherapy than German patients. Furthermore, among foreign patients, a higher BMI was associated with a greater risk of severe side effects. In addition, among Turkish patients, older patients (≥60 years) were more likely to experience severe side effects than younger patients (<60 years). Acknowledging disparities between these groups, our finding suggests that systematic and supportive measures should be incentivized for foreign patients to enhance their therapeutic outcomes and improve their quality of life. This includes the strengthening of cultural competence in health care

services. Measures offered must not necessarily be innovative considering that the simple adaption and improvement of existing clinical processes and treatment approaches can have great value. In addition, existing healthcare information and patient education programs should be tailored for foreign patients considering differences in their needs and preferences.

6. List of figures

7. List of tables

8. References

Academy of Medical Sciences, 2017: Optimizing stratified medicines R&D: addressing scientific and economic issues. https://acmedsci.ac.uk/viewFile/publicationDownloads/120151486883.pdf (Retrieved:15.06.2022)

Acevedo-Garcia, D, Bates, LM, Osypuk, TL, McArdle, N. The effect of immigrant generation and duration on self-rated health among US adults 2003-2007. Soc Sci Med 2010; 71: 1161-1172

Aguado-Barrera, ME, Sosa-Fajardo, P, Gómez-Caamaño, A, Taboada-Valladares, B, Couñago, F, López-Guerra, JL, Vega, A. Radiogenomics in lung cancer: Where are we?. Lung Cancer 2023; 176: 56-74

Andrade, C. Multiple testing and protection against a type 1 (false positive) error using the Bonferroni and Hochberg corrections. Indian J Psychol Medicine 2019; 41: 99-100

Andreassen, CN, Rosenstein, BS, Kerns, SL, Ostrer, H, De Ruysscher, D, Cesaretti, JA. Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. Radiother Oncol 2016a;121:431–9

Andreassen, CN, Schack, LMH, Laursen, LV, Alsner, J. Radiogenomics–current status, challenges and future directions. Cancer Lett 2016b; 382, 127-136

Andreeva, VA, Unger, JB, Pentz, MA. Breast cancer among immigrants: a systematic review and new research directions. J Immigr Minor Health 2007; 9: 307-322

Andreyev, J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol 2007; 8: 1007-1017

Arnold, M, Razum, O, Coebergh, JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. Eur J Cancer 2010; 46: 2647-2659

Austin, SR, Wong, YN, Uzzo, RG, Beck, JR, Egleston, BL. Why Summary Comorbidity Measures Such As the Charlson Comorbidity Index and Elixhauser Score Work. Med Care 2015; 53: e65-72

Badulescu, D, Badulescu, A. Medical tourism: between entrepreneurship opportunities and bioethics boundaries: narrative review article. Iran J public health, 2014; 43, 406

Barazzuol, L, Coppes, RP, van Luijk, P. Prevention and treatment of radiotherapy-induced side effects. Mol Oncol 2020; 14: 1538-1554

Barton, MB, Jacob, S, Shafiq, J, Wong, K, Thompson, SR, Hanna, TP, Delaney, GP. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiother Oncol 2014; 112: 140-144

Basch, E, Jia, X, Heller, G, Barz, A, Sit, L, Fruscione, M, Appawu, M, Iasonos, A, Atkinson, T, Goldfarb S. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009; 101: 1624-1632

Baskar, R, Lee, KA, Yeo, R, Yeoh, K.-W. Cancer and radiation therapy: current advances and future directions. Int J Medical Sci 2012: 9: 193

Baumann, M, Krause, M, Overgaard, J, Debus, J, Bentzen, SM, Daartz, J, Richter, C, Zips, D, Bortfeld, T. Radiation oncology in the era of precision medicine. Nat Rev Cancer 2016; 16: 234-249

Begg, AC, Stewart, FA, Vens, C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011: 11: 239-253

Bentzen, SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 2006: 6: 702-713

Bernier, J, Hall, EJ, Giaccia, A. Radiation oncology: a century of achievements. Nat Rev Cancer 2004: 4: 737-747

Bhargava, S, Tsuruda, KM, Moen, K, Bukholm, IRK, Hofvind S. Lower attendance rates in immigrant versus non-immigrant women in the Norwegian Breast Cancer Screening Programme. J Med Screen 2018: 25: 155-161

Brothwell, MRS, West, CM, Dunning, AM, Burnet, NG, Barnett, GC. Radiogenomics in the era of advanced radiotherapy. Clin Oncol 2019: 31: 319-325

Brzoska, P, Abdul-Rida, C. Participation in cancer screening among female migrants and non-migrants in Germany: A cross-sectional study on the role of demographic and socioeconomic factors. Medicine 2016: 95: e4242

Budde, MK. Outcome von Krebspatienten ausländischer und deutscher Nationalität am Centrum für Integrierte Onkologie Bonn from the faculty of the University Bonn, (2020)

Budde, MK, Kuhn, W, Keyver-Paik, MD, Bootz, F, Kalff, JC, Müller, SC, Bieber, T, Brossart, P, Vatter, H, Herrlinger, U, Wirtz, DC, Schild, HH, Kristiansen, G, Pietsch, T, Aretz, S, Geiser, F, Radbruch, L, Reich, LH, Strassburg, CP, Skowasch, D, Essler, M, Ernstmann, N, Landsberg, J, Funke B, Schmidt-Wolf IGH. A matched-pair analysis on survival and response rates between German and non-German cancer patients treated at a Comprehensive Cancer Center. BMC Cancer 2019; 19: 1024

Bundesinstitut für Arzneimittel und Medizinprodukte, 2019: ICD-O-3 Internationale Klassifikation der Krankheiten für die Onkologie, Dritte Ausgabe. https://www.bfarm.de/DE/Kodiersysteme/Klassifikationen/ICD/ICD-O-3/_node.html. (Retrieved 23.07.2022)

Bundesinstitut für Arzneimittel und Medizinprodukte, 2022: ICD-10-GM Version 2022. https://www.bfarm.de/DE/Kodiersysteme/Klassifikationen/ICD/ICD-10-GM/_node.html. (Retrieved: 15.06.2022)

Carlotto, A, Hogsett, VL, Maiorini, EM, Razulis, JG, Sonis, ST. The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. Pharmacoeconomics 2013: 31: 753-766

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev 2010; 2010: Cd008285

Chin, L, Andersen, JN, Futreal, PA. Cancer genomics: from discovery science to personalized medicine. Nat Med 2011: 17: 297-303

Conti, R, Veenstra, DL, Armstrong, K, Lesko, LJ, Grosse, SD. Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Making 2010; 30: 328-340

Correa, R, Navarro, I, Lobato, M, Otero, A, Jerez, I, Rico, JM, Zapata, I, Lupiañez, Y, Medina, JA, Olmos D, Gómez-Millán J. Influence of the technique and comorbidities in hypofractionated radiotherapy for prostate cancer. Clin Transl Oncol 2020: 22: 311-318

De Ruysscher, D, Niedermann, G, Burnet, NG, Siva, S, Lee, AW, Hegi-Johnson, F. Radiotherapy toxicity. Nat Rev Dis Primers 2019: 5: 1-20

Deichaite, I, Hopper, A, Krockenberger, L, Sears, TJ, Sutton, L, Ray, X, Sharabi, A, Navon, A, Sanghvi, P, Carter, H, Moiseenko, V. Germline genetic biomarkers to stratify patients for personalized radiation treatment. J Transl Med 2022; 20, 360

Delaney, G, Jacob, S, Featherstone, C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005: 104: 1129-1137

Destatis Statistisches Bundesamt, 2022: Migration und Integration. Ausländische Bevölkerung, Ergebnisse des Ausländerzentralregisters. https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Migration-Integration/_inhalt.html#sprg228898. (Retrieved: 01.07.2022)

Deutsche Adipositas-Gesellschaft e.V., 2014: S3-Leitlinie zur Prävention und Therapie der Adipositas aktualisiert. https://register.awmf.org/assets/guidelines/050-001l_S3_Adipositas_Pr%C3%A4vention_Therapie_2014-11-abgelaufen.pdf (Retrieved: 15.07.2022)

DiMarzio, P, Peila, R, Dowling, O, Timony, DM, Balgobind, A, Lee, LN, Ho, GY. Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients. Cancer Epidemiol 2018; 57, 97-103

Di Sanzo, M, Cipolloni, L, Borro, M, La Russa, R, Santurro, A, Scopetti, M, Simmaco, M, Frati, P. Clinical Applications of Personalized Medicine: A New Paradigm and Challenge. Curr Pharm Biotechnol 2017; 18: 194-203

Dias, SF, Severo, M, Barros, H. Determinants of health care utilization by immigrants in Portugal. BMC Health Serv Res 2008; 8: 207

Diz Dios, P, Diniz Freitas, M. Supportive and Palliative Care for Patients with Oral Cancer. In: Warnakulasuriya, S, Greenspan, JS, eds., Textbook of Oral Cancer, London: Springer, 2020: 343-358

Dzau, VJ, Ginsburg, GS, Van Nuys, K, Agus, D, Goldman D. Aligning incentives to fulfill the promise of Personalized Medicine. Lancet 2015; 385: 2118

Earland, N, Chen, K, Semenkovich, NP, Chauhan, PS, Zevallos, JP, Chaudhuri, AA. Emerging roles of circulating tumor DNA for increased precision and personalization in radiation oncology. Semin Radiat Oncol 2023; 33: 262-278

Eurostat, 2019: Statistik über regionale Bevölkerungsprognosen. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Archive:Statistics_on_regional_population_projections/de&oldid=458916. (Retrieved: 01.07.2022)

Federal Office for Migration and Refugees, 2018: The 2018 Migration Report. https://www.bamf.de/SharedDocs/Anlagen/EN/Forschung/Migrationsberichte/migrationsbericht-2018.html?nn=447268. (Retrieved: 08.01.2020)

Fick, P. Warum verzichten zweite und dritte Generation auf den deutschen Pass? Die Bedeutung transnationaler Bindungen im Kontext des deutschen Staatsangehörigkeitsrechts. Soziale Welt 2019; 407-430

Fischer, J, Stope, MB, Gümbel, D, Hakenberg, O, Burchardt, M, Dräger, DL. Influence of culture and religion on the treatment of cancer patients. Urologe A 2019; 58: 1179-1184

Fromme, EK, Eilers, KM, Mori, M, Hsieh, YC, Beer, TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004; 22: 3485-3490

Frowen, J, Cotton, S, Corry, J, Perry, A. Impact of demographics, tumor characteristics, and treatment factors on swallowing after (chemo)radiotherapy for head and neck cancer. Head Neck 2009; 32: 513-528

Ginsburg, GS, Phillips, KA. Precision Medicine: From Science To Value. Health Aff (Millwood) 2018; 37: 694-701

Glaesmer, H, Wittig, U, Braehler, E, Martin, A, Mewes, R, Rief, W. Health care utilization among first and second generation immigrants and native-born Germans: a population-based study in Germany. Int J Public Health 2011; 56: 541-548

Golubnitschaja, O, Baban, B, Boniolo, G, Wang, W, Bubnov, R, Kapalla, M, Krapfenbauer, K, Mozaffari, MS, Costigliola V. Medicine in the early twenty-first century: paradigm and anticipation-EPMA position paper 2016. EPMA Journal 2016; 7: 1-13

Greimel, ER, Bjelic-Radisic, V, Pfisterer, J, Hilpert, F, Daghofer, F, Pujade-Lauraine, E, du Bois A. Toxicity and quality of life outcomes in ovarian cancer patients participating in randomized controlled trials. Support Care Cancer 2011; 19: 1421-1427

Hayes, NS, Hohman, K, Vinson, C, Pratt-Chapman, M. Comprehensive cancer control in the U.S.: summarizing twenty years of progress and looking ahead. Cancer Causes Control 2018; 29: 1305-1309

Hemminki, K, Ankerst, DP, Sundquist, J, Mousavi, SM. Prostate cancer incidence and survival in immigrants to Sweden. World J Urol 2013; 31: 1483-1488

Hjerkind, KV, Qureshi, SA, Møller, B, Weiderpass, E, Deapen, D, Kumar B, Ursin, G. Ethnic differences in the incidence of cancer in Norway. Int J Cancer 2017; 140: 1770-1780

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human, 2022: Medical Dictionary for Regulatory Activities. https://www.meddra.org/. (Retrieved: 01.08.2022)

Jackson, SE, Chester, JD. Personalised cancer medicine. Int J Cancer 2015; 137: 262-266

Kerns, SL, Ostrer, H, Rosenstein, BS. Radiogenomics: using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. Cancer Discov 2014; 4: 155-165

Kerns, SL, Fachal, L, Dorling, L, Barnett, GC, Baran, A, Peterson, DR , Hollenberg, M, Hao, K, Di Narzo, A, Ahsen, ME, Pandey, G, Bentzen, SE, Janelsins, M, Elliott, RM, Pharoah, PDP, Burnet, NG, Dearnaley, DP, Gulliford, SL, Hall, E, Sydes, MR, Aguado-Barrera, ME, Gómez-Caamaño, A, Carballo, AM, Peleteiro, P, Lobato-Busto, R, Stock, R, Stone, NN, Ostrer, H, Usmani, N, Singhal, D, Tsuji, H, Imai, T, Saito, S, Eeles, R, DeRuyck, K, Parliament, M, Dunning, AM, Vega, A, Rosenstein, BS, West, CML. Radiogenomics consortium genome-wide association study meta-analysis of late toxicity after prostate cancer radiotherapy. J Natl Cancer Inst 2020; 112, 179-190

Klein, J, von dem Knesebeck, O. Inequalities in health care utilization among migrants and non-migrants in Germany: a systematic review. Int J Equity Health 2018; 17: 160

Koenig, IR, Fuchs, O, Hansen, G, von Mutius, E, Kopp, MV. What is precision medicine? Eur Respir J 2017; 50

Lapierre, A, Bourillon, L, Larroque, M, Gouveia, T, Bourgier, C, Ozsahin, M, Pèlegrin, A, Azria, D, Brengues, M. Improving Patients' Life Quality after Radiotherapy Treatment by Predicting Late Toxicities. Cancers 2022; 14

Latif, F, Helgeland, J, Bukholm G, Bukholm, IR. Ethnicity differences in breast cancer stage at the time of diagnosis in Norway. Scand J Surg 2015; 104: 248-253

Lebrun, LA. Effects of length of stay and language proficiency on health care experiences among immigrants in Canada and the United States. Soc Sci Med 2012; 74: 1062-1072

Leinonen, MK, Campbell, S, Klungsøyr, O, Lönnberg, S, Hansen, BT, Nygård, M. Personal and provider level factors influence participation to cervical cancer screening: A retrospective register-based study of 1.3 million women in Norway. Prev Med 2017; 94: 31-39

Lemanska, A, Byford, RC, Correa, A, Cruickshank, C, Dearnaley, DP, Griffin, C, Hall, E, de Lusignan, S, Faithfull S. Linking CHHiP prostate cancer RCT with GP records: A study proposal to investigate the effect of co-morbidities and medications on long-term symptoms and radiotherapy-related toxicity. Tech Innov Patient Support Radiat Oncol 2017; 2: 5-12

Liu, SY, Lu, L, Pringle, D, Mahler, M, Niu, C, Charow, R, Tiessen, K, Lam, C, Halytskyy, O, Naik, H, Hon, H, Irwin, M, Pat, V, Gonos, C, Chan, WT, Villeneuve, J, Shani, RM, Chaudhry, M, Brown, MC, Selby, P, Howell, C, Xu, W, Alibhai, SMH, Jones, JM, Liu, G, Eng, L. Impact of immigration status on health behaviors and perceptions in cancer survivors." Cancer Med 2019; 8: 2623-2635

Majeed H, Gupta V. Adverse Effects Of Radiation Therapy. Treasure Island (FL): StatPearls Publishing, 2021

McCarthy, JJ, McLeod, HL, Ginsburg, GS, Genomic medicine: a decade of successes, challenges, and opportunities. Sci Transl Med 2013; 5: 189-184

MEDOS AG, 2010: NEXUS / DIS: MEDOS RIS. Frankfurt, MEDOS AG: Seit 2021 wird MEDOS RIS von der Firma NEXUS/CHILI, Dossenheim vetrieben und betreut

Mehta Cyrus, R, Patel Nitin, R. IBM SPSS Exact Test. Massachusetts: Cytel Software Corporation and Harvard School of Public Health, 2013

Morganti, AG, Digesù, C, Panunzi, S, De Gaetano, A, Macchia, G, Deodato, F, Cece, MG, Cirocco, M, Di Castelnuovo, A, Iacoviello, L, Valentini, V, Cellini, N, de Gaetano, G. Radioprotective effect of moderate wine consumption in patients with breast carcinoma. Int J Radiat Oncol Biol Phys 2009; 74: 1501-1505

Mosdøl, A, Vist, GE, Straumann, GSH, Spilker, RACS, Austvoll-Dahlgren, A. Adapted health information and patient education for persons with immigrant or minority ethnic background – Report. Oslo: Norwegian Institute of Public Health, 2018

Mousavi, SM, Fallah, M, Sundquist, K, Hemminki, K. Age- and time-dependent changes in cancer incidence among immigrants to Sweden: colorectal, lung, breast and prostate cancers. Int J Cancer 2012; 131: E122-128

Naderi, E, Schack, LM, Welsh, C, Sim, AY, Aguado-Barrera, ME, Dudding, T, Summersgill, H, Martínez-Calvoi, L, Ong, EHW, Odding, Y, Varela-Pazos, N, Steenbakkers, RJH, Crijns, APG, Jena, R, Pring , M, Dennis, J, Lobato-Busto , R, Alsner, J, Ness, A, Nutting, C, Thomson, DJ. Meta-GWAS identifies the heritability of acute radiation-induced toxicities in head and neck cancer. Radiother Oncol 2022; 176, 138-148

Naderi, E, Aguado-Barrera, ME, Schack, LMH, Dorling, L, Rattay, T, Fachal, L, Summersgill, H, Martínez-Calvo, L, Welsh, C, Dudding, T, Odding, Y, Varela-Pazos, A, Jena, R, Thomson, DJ, Steenbakkers, RJHM, Dennis, J, Lobato-Busto, R, Alsner, J, Ness, A, Nutting, C, Gómez-Caamaño, A, Eriksen, JG, Thomas, SJ, Bates, AM, Webb, AJ, Choudhury, A, Rosenstein, BS, Taboada-Valladares, B, Herskind, C, Azria, D, Dearnaley, DP, de Ruysscher, D, Sperk, E, Hall, E, Stobart, H, Chang-Claude, J, De Ruyck, K, Veldeman, L, Altabas, M, De Santis, MC, Farcy-Jacquet, MP, Veldwijk, MR, Sydes, MR, Parliament, M, Usmani, N, Burnet, NG, Seibold, P, Symonds, RP, Elliott, RM, Bultijnck, R, Gutiérrez-Enríquez, S, Mollà, M, Gulliford, SL, Green, S, Rancati, T, Reyes, V, Carballo, A, Peleteiro, P, Sosa-Fajardo, P, Parker, C, Fonteyne, V, Johnson, K, Lambrecht, M, Vanneste, B, Valdagni, R, Giraldo, A, Ramos, M, Diergaarde, B, Liu, G, Leal, SM, Chua, MLK, Pring, M, Overgaard, J, Cascallar-Caneda, LM, Duprez, F, Talbot, CJ, Barnett, GC, Dunning, AM, Vega, A, Andreassen, CN, Langendijk, JA, West, CML, Alizadeh, BZ, Kerns, SL. Large-scale meta–genome-wide association study reveals common genetic factors linked to radiation-induced acute toxicities across cancer types. JNCI Cancer Spectr 2023; 7: pkad088

National Health System England, 2016: Improving outcomes through personalised medicine. https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf (Retrieved: 01.07.2022)

Nieder, C, Imingen, KS, Mannsåker, B, Yobuta, R, Haukland, E. Risk factors for esophagitis after hypofractionated palliative (chemo) radiotherapy for non-small cell lung cancer. Radiat Oncol 2020; 15: 91

Nigro, CL, Denaro, N, Merlotti, A, Merlano, M. Head and neck cancer: improving outcomes with a multidisciplinary approach. Cancer Manag Res 2017; 9: 363

ORBIS, 2022. ORBIS KIS. Bonn, DEDALUS Healthcare Group AG

Organisation for Economic Co-operation and Development, 2023: International Migration Database. https://stats.oecd.org/viewhtml.aspx?datasetcode=MIG&lang=en. (Retrieved: 27.04.2022)

Oltean, FD, Gabor, MR, Stăncioiu, AF, Kardos, M, Kiss, M, Marinescu, RC. Aspects of marketing in dental tourism - factor of sustainable development in Romania. Sustainability 2020; 12, 4320

Ormond, M. Medical tourism. In: Lew, AA, Michael Hall, C, Williams, AM, eds., The Wiley Blackwell Companion to Tourism. London: John Wiley & Sons, 2014: 425-434

Ormond, M. Knowledge transfer in the ‘medical tourism’ industry: The role of transnational migrant patients and health workers. In: Thomas, F, ed., Handbook of migration and health. Massachusetts: Edward Elgar Publishing Limited, 2016; 498-514

Perdyan, A, Jassem, J. Impact of Tobacco Smoking on Outcomes of Radiotherapy: A Narrative Review. Curr Oncol 2022; 29: 2284-2300

Péus, D, Newcomb, N, Hofer, S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Medical Inform Decis Mak 2013; 13: 1-7

Quan, H, Li, B, Couris, CM, Fushimi, K, Graham, P, Hider, P, Januel, JM, Sundararajan, V. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol 2011; 173: 676-682

Radkte, R., 2022: Anteil ausländischer Patienten in ausgewählten Ländern 2020. https://de.statista.com/statistik/daten/studie/940844/umfrage/anteil-auslaendischer-patienten-in-ausgewaehlten-laendern/. (Retrieved 08.08.2022)

Rechel, B, Mladovsky, P, Ingleby, D, Mackenbach, JP, McKee, M. Migration and health in an increasingly diverse Europe. Lancet 2013; 381: 1235-1245

Rudiger, R, Geiser, F, Ritter, M, Brossart, P, Keyver-Paik, MD, Faridi, A, Vatter, H, Bootz, F, Landsberg, J, Kalff, JC, Herrlinger, U, Kristiansen, G, Pietsch, T, Aretz, S, Thomas, D, Radbruch, L, Kramer, FJ, Strassburg, CP, Gonzalez-Carmona, M, Skowasch, D, Essler, M, Schmid, M, Nadal, J, Ernstmann, N, Sharma, A, Funke, B, Schmidt-Wolf, IGH. No evidence to support the impact of migration background on treatment response rates and cancer survival: a retrospective matched-pair analysis in Germany. BMC Cancer 2021; 21: 526

Schack, LMH, Naderi, E, Fachal, L, Dorling, L, Luccarini, C, Dunning, AM, The Head and Neck Group of the Radiogenomics Consortium, The Danish Head and Neck Cancer Group, Ong, EHW, Chua, MLK, Langendijk, JA, Alizadeh, BZ, Overgaard, J, Eriksen, JE, Andreassen, CN, Alsner, J. A genome-wide association study of radiotherapy induced toxicity in head and neck cancer patients identifies a susceptibility locus associated with mucositis. Br J Cancer 2022;126:1082–90

Schmerler, K. Medical tourism in Germany. Halle (Saale): Springer International Publishing, 2018

Schmielau, J, Rick, O, Reuss-Borst, M, Kalusche-Bontemps, EM Steimann, M. Rehabilitation of cancer survivors with long-term toxicities. Oncol Res Treat 2017; 40: 764-771

Simberg-Danell, C, Lyth, J, Månsson-Brahme, E, Frohm-Nilsson, M, Carstensen, J, Hansson, J, Eriksson, H. Prognostic factors and disease-specific survival among immigrants diagnosed with cutaneous malignant melanoma in Sweden. Int J Cancer 2016; 139: 543-553

Singels, S. Ethnic Health Educators/Care Consultants in the Netherlands. In: Fernandes, A, Pereira Miguel, J, eds., Health and migration in European Union: better health for all in an inclusive society, Lisboa: Instituto Nacional de Saúde Doutor Ricardo Jorge, 2009: 179-182

Sommat, K, Yit, NLF, Wang, F, Lim, JHC. Impact of comorbidity on tolerability and survival following curative intent intensity modulated radiotherapy in older patients with nasopharyngeal cancer. J Geriatr Oncol 2018; 9: 352-358

Sonis, ST. Genomics, personalized medicine, and supportive cancer care. In: Dizon, DS, ed., American Society of Clinical Oncology Educational Book, Chicago: American Society of Clinical Oncology, 2015: 9-16

Spallek, J, Arnold, M, Hentschel, S, Razum, O. Cancer incidence rate ratios of Turkish immigrants in Hamburg, Germany: a registry based study. Cancer Epidemiol 2009; 33: 413-418

Spix, C, Spallek, J, Kaatsch, P, Razum, O, Zeeb, H. Cancer survival among children of Turkish descent in Germany 1980-2005: a registry-based analysis. BMC Cancer 2008; 8: 355

Starker, A, Hövener, C, Rommel, A. Utilization of preventive care among migrants and non-migrants in Germany: results from the representative cross-sectional study ‘German health interview and examination survey for adults (DEGS1)’. Arch Public Health 2021; 79: 1-13

Strøm, HH, Bremnes, RS, Sundstrøm, SH, Helbekkmo, N, Fløtten, O, Aasebø, U. Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group. Br J Cancer 2013; 109: 1467-1475

Sze, HC, Ng, WT, Chan, OS, Shum, TC, Chan, LL, Lee, AW. Radical radiotherapy for nasopharyngeal carcinoma in elderly patients: the importance of co-morbidity assessment. Oral Oncol 2012; 48: 162-167

Szturz, P, Van Laer, C, Simon, C, Van Gestel, D, Bourhis J, Vermorken, JB. Follow-up of head and neck cancer survivors: tipping the balance of intensity. Front Oncol 2020; 10: 688

Talwar, B, Donnelly, R, Skelly, R, Donaldson, M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016; 130: S32-S40

Thøgersen, H, Møller, B, Robsahm, TE, Babigumira, R, Aaserud, S, Larsen, IK. Differences in cancer survival between immigrants in Norway and the host population. Int J Cancer 2018; 143: 3097-3105

Thornton, JD, Pham, K, Engelberg, RA, Jackson, JC, Curtis, JR. Families with limited English proficiency receive less information and support in interpreted intensive care unit family conferences. Crit Care Med 2009; 37: 89-95

Tremblay, J, Hamet, P. Role of genomics on the path to personalized medicine. Metabolism 2013; 62 Suppl 1: S2-5

U.S. Department of Health and Human Services, 2017: Common Terminology Criteria for Adverse Events (CTCAE). https://academy.myeloma.org.uk/wp-content/uploads/2015/04/CTCAE_v5.pdf. (Retrieved 16.03.2022)

Verellen, D, De Ridder, M, Linthout, N, Tournel, K, Soete G, Storme, G. Innovations in image-guided radiotherapy. Nat Rev Cancer 2007; 7: 949-960

Wang, K, Tepper, JE. Radiation therapy-associated toxicity: Etiology, management, and prevention. CA Cancer J Clin 2021; 71: 437-454

Weber, A Hörmann, G. Migration and health - from deficiency analysis to diversity vision? Gesundheitswesen 2011; 73: 298-307

Welzel, T, Tanner, JM. Imaging of side effects after radiation therapy Radiologe 2018; 58: 754-761

Wengler, A. The health status of first- and second-generation Turkish immigrants in Germany. Int J Public Health 2011; 56: 493-501

WHO, 2019. ICD-O-3 Systematisches Verzeichnis, Internationale Klassifikation der Krankheiten für die Onkologie, Dritte Ausgabe. Cologne, Germany, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) im Auftrag des Bundesministeriums für Gesundheit (BMG) unter Beteiligung der Arbeitsgruppe ICD des Kuratoriums für Fragen der Klassifikation im Gesundheitswesen (KKG)

WHO, 2021. ICD-10-GM Version 2022, Systematisches Verzeichnis, Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme. Cologne, Germany, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) im Auftrag des Bundesministeriums für Gesundheit (BMG) unter Beteiligung der Arbeitsgruppe ICD des Kuratoriums für Fragen der Klassifikation im Gesundheitswesen (KKG)

Yao, JJ, Yu, XL, Zhang, F, Zhang, WJ, Zhou, GQ, Tang, LL, Mao, YP, Chen, L, Ma, J, Sun, Y. Radiotherapy with neoadjuvant chemotherapy versus concurrent chemoradiotherapy for ascending-type nasopharyngeal carcinoma: a retrospective comparison of toxicity and prognosis. Chin J Cancer 2017; 36: 1-8