Influence of travel burden on tumor classification and survival of head and neck cancer patients

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Abstract

Purpose Cancer patients have to overcome various barriers to obtain diagnostics and treatment at head and neck cancer centers. Travel distance to a specialized hospital may result in psychosocial and financial distress, thus interfering with diagnostics, treatment, and follow-up care. In this study, we have aimed to analyze the association of travel distance with cTNM status, UICC stage at primary diagnosis, and survival outcomes of head and neck cancer (HNC) patients.

Methods We have analyzed data of 1921 consecutive HNC patients diagnosed between 2014 and 2019 at the head and neck cancer center of the Comprehensive Cancer Center Ulm (CCCU), Germany. Postal code-based travel distance calculation in kilometers, TNM status, and UICC stage were recorded at initial diagnosis. The assembly of travel distance-related groups (short, intermediate, long-distance) has been investigated. Moreover, group-related survival and recurrence analysis have been performed.

Results In contrast to observations from overseas, no association of travel distance and higher cTNM status or UICC stage at primary diagnosis has been observed. Furthermore, no significant differences for recurrence-free survival and overall survival by travel distance were detected.

Conclusion In southern Germany, travel distance to head and neck cancer centers seems to be tolerable. Travel burden is not synonymous with travel distance alone but also involves sociodemographic, monetary, and disease-specific aspects as well as accessibility to proper infrastructure of transport and health care system.

Keywords Travel distance · Cancer · Tumor · Infrastructure · Telemedicine

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Introduction

Cancer patients have to overcome several barriers before obtaining individualized diagnostics and treatment [1]. Psychological, social, and economic aspects play an important role even before seeking council of experts for an examination of their symptoms [2, 3]. Once patients have decided to travel to a medical institution, distance to a specialized center may represent a relevant hurdle [1, 4]. Financial concerns regarding the journey and the travel time seem to be substantial [1, 3, 5, 6]. Such considerations and the planning of the trip to a medical institution may cost precious time, especially if the patient's mobility is impaired or support from a social network is missing [2, 7]. On account of this, access to the healthcare system and its specialized facilities is supposed to be limited for patients who are not living close to an urban center [7, 8]. Conjoined with this consideration, it has to be noticed that in particular, treatment at large volume cancer centers may be associated with shorter hospitalization and favorable outcome [2, 4, 9, 10]. Centralization of the healthcare system supports the formation of such high-volume centers, but which also implicates that the mean travel distance of associated patients is inevitably rising [11, 12]. Older and sicker patients, when living in rural areas, are consequently affected to a greater extent [12, 13]. These circumstances may result in more advanced disease status at diagnosis and may interfere with optimal treatment, compliance, and follow-up care [2, 14]. In this manner, several retrospective studies have underpinned a possible distance-related, negative association with cancer stage or treatment compliance among various cancer entities in different countries, predominantly in the United States of America [2, 7]. To assess the potential impact of travel burden on disease stage at initial diagnosis and survival outcomes, we analyzed a large cross-sectional cohort from a central European head and neck cancer (HNC) center in southern Germany.

Methods

Patient cohort and data acquisition

We analyzed data of 1921 HNC patients diagnosed between 2014 and 2019 at the head and neck cancer center of the Comprehensive Cancer Center Ulm (CCCU), Germany. Data were acquired from the Clinical Cancer Registry of the Comprehensive Cancer Center Ulm and analyzed in an anonymized format. Patient registration to Clinical Cancer Registries is required by German Federal Law. Patients signed informed consent for data analysis at hospital admission. All newly diagnosed cases within the timeframe have been registered into this database. The final, study-related follow-up was performed in August 2020. The sample may be considered as representative for southern Germany contributing to Slovin's formula with an error tolerance $< 5\%$. Patients' travel distance [km] drivable by car to the CCCU was based on postal codes. Patients with missing data and outliers, defined as patients living abroad, have been excluded beforehand ($n = 771$). Geographical area measuring has been executed with Image J (Madison, Wisconsin, USA).

Assessment of heterogeneity and statistical analysis

Statistical analysis and visualization were performed using MS Office 2019 (Redmond, Washington, USA), IBM SPSS Statistics 26 (Armonk, New York, USA) and GraphPad Prism 9.0.2 (San Diego, California, USA). Before testing for significant differences among calculated means of different variables, data sets have been checked for normality and homogeneity by Shapiro–Wilk and Levene's Test. The data were not normally distributed, but a homogeneity of variances was given. Therefore Mann–Whitney U Test was used to compare distributions of two independent samples and Kruskal–Wallis Test was used for more than two independent samples. Furthermore, to compare observed with expected frequencies of defined categorial variables, Chi-Square Test was computed, requirements for minimal frequency of each cell have been fulfilled. Survival and recurrence analysis was performed using the Kaplan–Meier method and pairwise comparisons utilizing Log-Rank Tests. Overall survival time was measured in days and displayed in months (1 month $\triangleq$ 30 days) from primary diagnosis to the time of death or latest follow-up. Recurrence-free survival was as well measured in days and displayed in months (1 month $\triangleq$ 30 days) from primary diagnosis to the time of recurrence, death, or latest follow-up.

Results

Patient cohort

The analyzed study population ($n = 1921$) consists of 80% male participants. The mean age was 62.5 years. The majority of patients had been diagnosed with advanced UICC stage (UICC IV: 56%) at initial presentation. Analysis of tumor subsites showed a high fraction of oropharyngeal cancer (31%). Primary surgery was performed on 49.7%. Patient characteristics are summarized in Table 1.

Table 1 HNC patients characteristics including age, sex, stage, tumor subsites and treatment.

HNC patients characteristics (n = 1921)		
Age	Mean: 62.5 years (min= 18 years, max= 94 years, SD= 11.1)	
Sex	Male: n = 1536 (80.0%)	Female: n = 385 (20.0%)
Stage	UICC I	n = 287 (14.9 %)
	UICC II	n = 237 (12.3 %)
	UICC III	n = 312 (16.2 %)
	UICC IV	n = 108 (56.5 %)
Localisation	Oropharynx	n = 598 (31.1 %)
	Larynx	n = 446 (23.2 %)
	Hypopharynx	n = 334 (17.4 %)
	Oral cavity	n = 288 (15.0 %)
	Nose and paranasal sinus	n = 140 (7.3 %)
	Salivary glands	n = 54 (2.8 %)
	Nasopharynx	n = 48 (2.5 %)
	Lips	n = 7 (0.4 %)
	Multiple sites	n = 6 (0.3 %)
Treatment with surgery	Yes: n = 955 (49.7 %)	No: n = 966 (50.3 %)

Overall travel distance and distribution pattern regarding cTNM status and UICC stage

First, the geographical distribution of all HNC patients included in the analysis was visualized to portray the catchment area and travel distance. Figure 1a demonstrates the allocation of all involved HNC patients to their domestic zone in Germany and the location of Ulm. In Fig. 1b, the particular travel distances are displayed in a histogram with a logarithmic scale. The main catchment area of the CCCU is located along and across the southern border of Baden-Wuerttemberg and Bavaria. Its total dimension based on postal codes, calculated with Image J consists of close to 20.000 km^2 (5.6% of Germany). This catchment area incorporates 5.23 Mio people (6% of the German population) according to the German census bureau [15]. In general, the

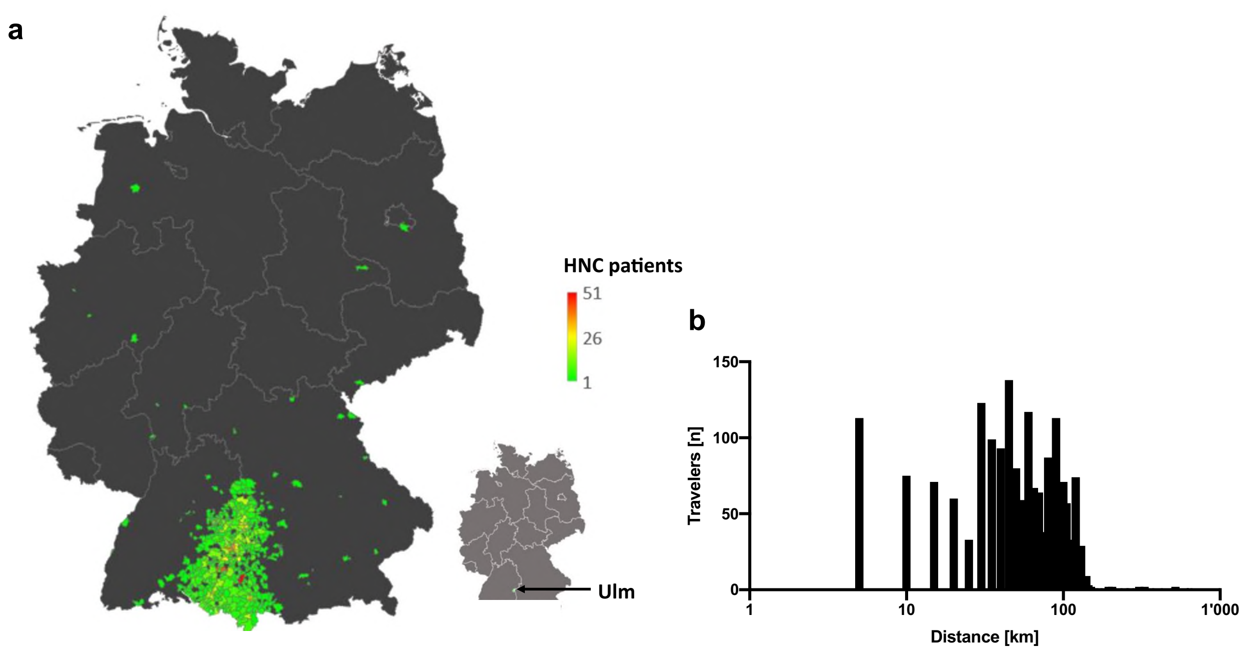

Fig. 1 Geographical distribution of HNC patients treated at the head and neck center of the Comprehensive Cancer Center Ulm (CCCU), Germany: **a** number and distribution of HNC patients based on postal codes during the years 2014–2019 (n = 1921) and localisation of the city Ulm, **b** histogram of patients travel distances to the CCCU

incidence of HNC in Germany is estimated at 50/100.000 according to data of the German Cancer Society [16].

The mean travel distance of patients diagnosed at the CCCU was 62.6 km. Moreover, differences among travel distances to the CCCU have been calculated and compared with regard to cTNM status and UICC stage (*Fig. 2*).

Median travel distance was compared by cT status and visualized in Fig. 2a. Median travel distances for patients did not differ significantly by cT status ($p = 0.60$). For cN status (Fig. 2b), no significant differences among distributions have been identified too ($p = 0.91$). Subsequently, cM status has been analyzed (Fig. 2c). Here as well, no differences among distributions have been identified between cM status and travel distance ($p = 0.16$).

We have carried on testing for differences among UICC stage-related travel distances (Fig. 2d). Anyhow, no differences among variances have been identified between the UICC stage and travel distance ($p = 0.62$).

We can summarize that calculated mean travel distances CCCU based on postal codes related to cTNM status and UICC stage are not significantly different among groups. Furthermore, examinations of the geographical distribution pattern of patients sorted by cTNM status (Supplementary Fig. 1a–h) and UICC stage (Supplementary Fig. 1i–l) were performed. Hereby no relevant agglomeration zones were noted. Such zones could have indicated the existence of unequal, specific factors of influence, which might not have been detected by analysis of average distances alone.

Analysis of distance-related groups concerning cTNM status and UICC stage fraction

Patients travel distances were grouped into three distance groups: short (group 1: ≤ 40.6 km), intermediate (group 2: > 40.6 to and < 70.6 km) and long-distance (group 3: ≥ 70.6 km) containing almost equal patient numbers (group 1: n = 639, group 2: n = 639, group 3: $n = 643$). Relative patient numbers have been compared between the groups concerning TNM classification and the UICC stage (Fig. 3).

Starting with cT status (Fig. 3a), we have observed that among the three groups cT1, cT2, cT3, and cT4 fractions ranged from 20 to 33%. But no differences among T status-related grouped travel distances have been identified ($p = 0.44$). Looking at cN status (Fig. 3b), cN0 fractions and cN1-3 fractions have ranged from 42 to 58%.

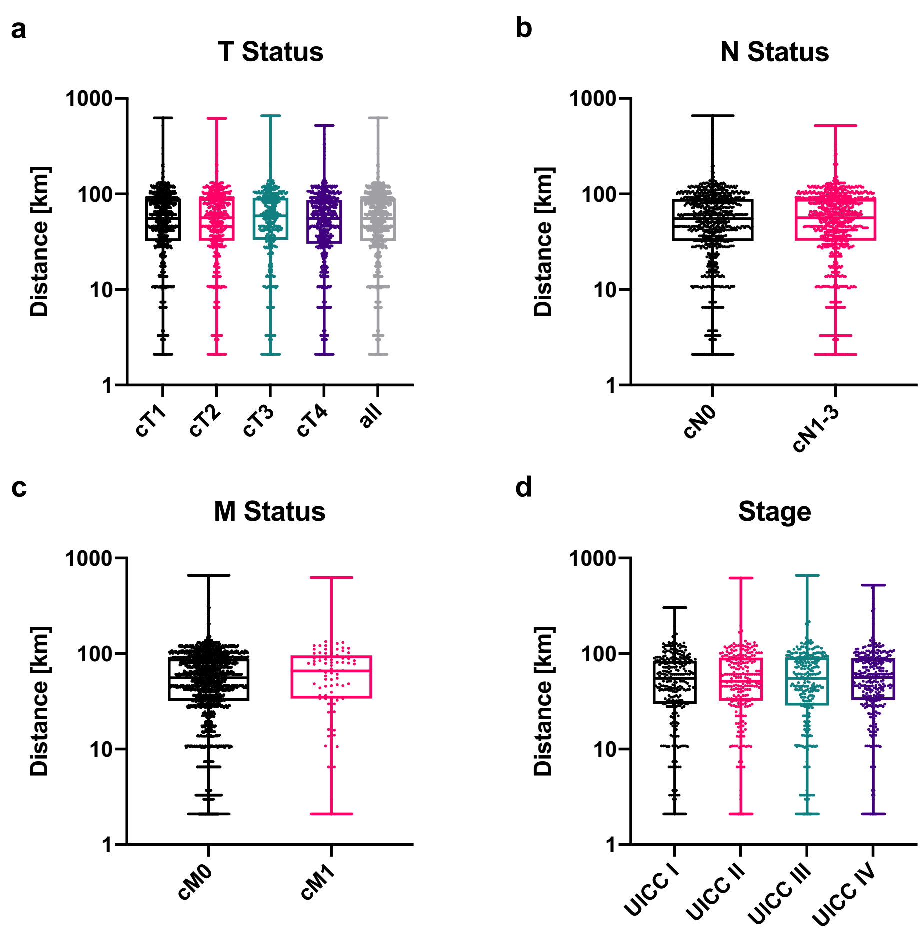

Fig. 2 HNC patients travel distance to head and neck cancer center of the Comprehensive Cancer Center Ulm (CCCU) related to cTNM status and UICC stage, displayed in box plots with median (midline), quartiles (Q1: bottom line, Q3: top line), whiskers (related to 1,5 times interquartile range) and single readings (points): **a** travel distance related to T classification [km], **b** travel distance related to cN classification [km], **c** travel distance related to cM classification [km], **d** travel distance related to UICC classification [km]

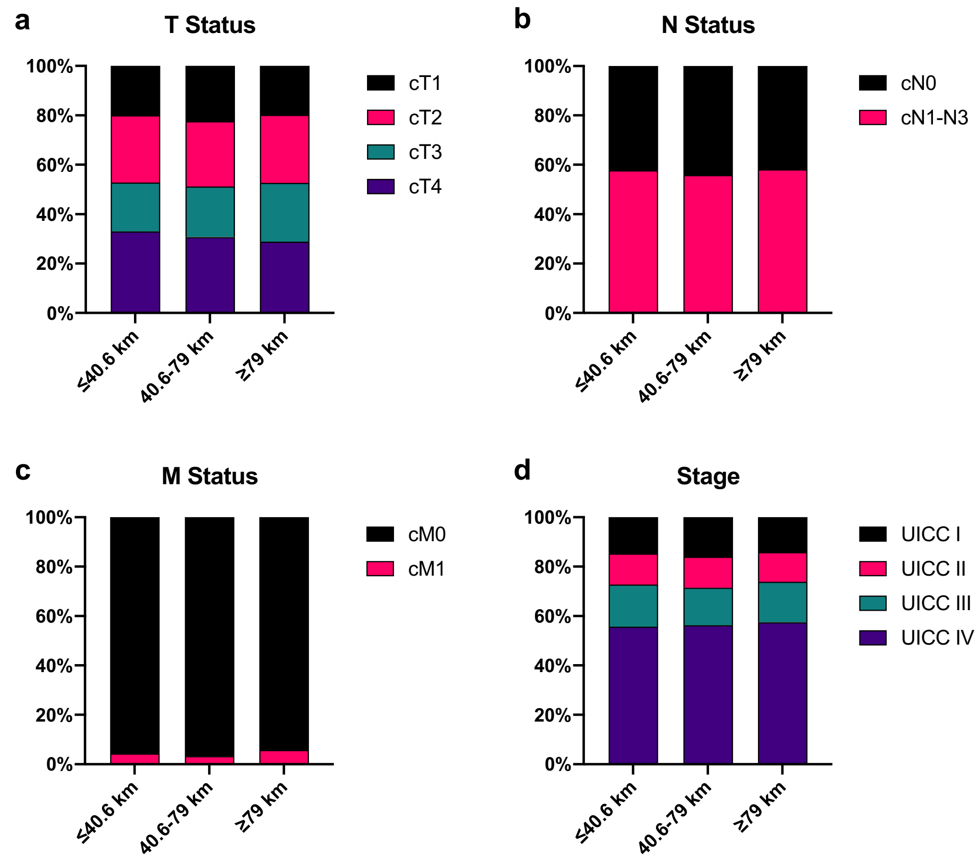

Fig. 3 HNC patients travel distance to head and neck cancer center of the Comprehensive Cancer Center Ulm (CCCU) sorted in groups (short distance: ≤ 40,6 km, intermediate distance: > 40,6 km & < 79 km, long distance: ≥ 79 km) concerning their cTNM status and UICC stage fraction [%]: **a** regarding cT classification, **b** referring to cN classification, **c** concerning cM classification, **d** corresponding to UICC stage

Anyhow, no differences among cN status-related grouped travel distances have been identified ($p = 0.68$). By cM status (Fig. 3c), we detected that cM0 factions have ranged from 94 to 97% and cM1 fractions from 3 to 6%, and no significant differences for grouped travel distance were identified ($p = 0.10$). Finally, no differences among UICC stage-related grouped travel distances were identified ($p = 0.93$). We can hereby state that by dividing the HNC population into three groups (short, intermediate, long distances), depending on travel distance to CCCU, no further insights concerning a possible association with their cTNM status and UICC stage fraction [%] could have been observed.

Selection of surgical treatment among distance-related groups

The mean values of primary surgery performance among distance-related groups (Table 1), classified by short (group 1), intermediate (group 2), and long (group 3) travel distance, were not significantly different (mean: 48.31%; SD = 3.6).

Cumulative and recurrence-free survival in dependence on travel distance

Finally, we have examined overall survival (Fig. 4a) and recurrence-free survival (Fig. 4b) in the cohort in relation to travel distance grouped as described above. Group 1 has contained 336 (47.4%), group 2 of 314 (50.8%) and group 3 of 301 (53.3%) events (deaths) in total during the observation time until the year 2020. The mean survival time was 79.6 months (6.5 years) in group 1, 86,0 months (7.1 years) in group 2 and 86.2 months (7.1 years) in group 3 (group 1: SD = 3.5; group 2: SD = 3.9; group 3: SD = 4.2). Pairwise comparison did not show any significant differences among groups (group 1/2: $p = 0.27$; group 1/3: $p = 0.48$; group 2/3: $p = 0.67$). Referring to recurrence-free survival, time has been measured between primary diagnosis and recurrence or latest follow-up or rather death. In group 1, 135 (21.1%), group 2, 131 (20.5%) and group 3, 99 (15.4%) events (recurrences) were registered. The mean recurrence-free survival time has been 72.21 months (6.0 years) in group 1, 74.65 months (6.2 years) in group 2, 75.8 months (6.3 years) in group 3

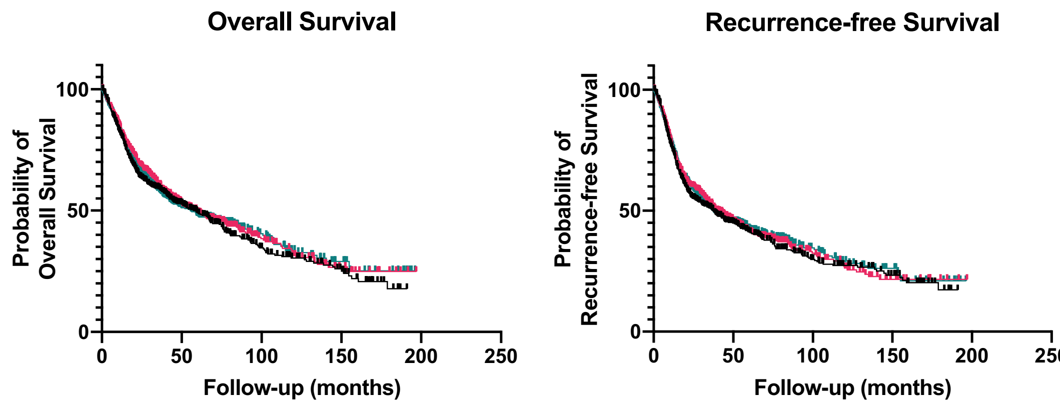

Fig. 4 Overall survival (**a**) and recurrence-free survival (**b**) after primary diagnosis of HNSCC [%] related to travel distance (short, intermediate, long distance); group 1: distance to head and neck cancer center of the Comprehensive Cancer Center Ulm (CCCU) ≤ 40,6 km, group 2: distance > 40,6 km & < 79 km, group 3: distance ≥ 79 km

(group 1: SD = 3.2; group 2 SD = 3.4; group 3 SD = 3.7). Pairwise comparison has not shown any significant differences between groups (group 1/2: $p = 0.41$; group 1/3: $p = 0.69$; group 2/3: $p = 0.62$). In conclusion, long travel distance was not associated with shorter recurrence-free survival than short travel distance.

Discussion

Travel burden may complicate immediate diagnostics and treatment of cancers [2, 3, 17]. Thus, travel distance itself is supposed to be a major hurdle [4]. In this pioneering study, we focused on the association of travel distance with cTNM status, UICC stage, and survival outcomes of 1921 HNC patients treated by the head and neck cancer center of the CCCU in Germany. We discovered that in contrast to published data from the USA [2, 7, 8, 17–20], there were no significant differences between travel distances of patients grouped by cTNM status and UICC stage. Also, travel distance seemed not to affect treatment decisions. Furthermore, no significant differences for overall survival or recurrence-free survival among patients by travel distance were detected. Anyhow our retrospective monocentric study has some limitations due to its structure and because of the fact, that the calculation of distances by postal codes cannot be as accurate as using the exact postal addresses.

At first glance, it may appeal that high travel distance is negligible. But interestingly, several international studies are illuminating the impact of travel burden by having a sophisticated look at different checkpoints of decision-making, cancer diagnostics, treatment, and follow-up care. In this context, researchers reviewed studies comprising a total of 401,755 cancer patients with different cancer types. In 10 out of 12 of these cited studies (nine in the USA, one in Australia, one in Scotland, and one in South Africa), patients who traveled 50 miles (80 km) or more than one hour in driving time were linked with a more advanced cancer stage at diagnosis [2]. Furthermore, patients with limited geographical access or living in the countryside were nearly twice as likely to not have a proper cancer staging (18.3%) than were urban inhabitants (9.6%) [2]. Similarly, another study among 808 HNC patients in the USA detected a significant association of travel distance with advanced T status with an odds ratio of 1.97 for each hour driven [7]. Intriguingly, they, and other authors, also correlated distance with income and demonstrated that patients with low income tend to live farther away from a clinical center [7, 8]. In this context, ethnic aspects were considered as well, meaning that some ethnic groups like Hispanics or patients with black race seemed to be more susceptible to travel distance than others [10, 14, 20]. This could be as well partly explained by the association of several ethnic groups with low socioeconomic status [21]. Even when looking at cancer entities, which usually underlie frequently performed screening examinations, like breast cancer or prostate cancer, authors found that the odds for advanced breast [19] and prostate cancer [18] were higher for patients living farther away from a specialist. Besides, even if cancer patients have been properly diagnosed, travel distance may still be relevant for treatment decisions [2, 22, 23], supportive therapy [24], and follow-up care [14]. For instance, the impact on treatment is reflected by the observation that a significant decrease in the likelihood of receiving adjuvant radiotherapy after breast-conserving surgery among women with early-stage breast cancer living 15–20 miles (24–32 km) or more from a hospital was monitored in eight retrospective studies with 165.435 included patients [2]. In the same way, patients with colon cancer (n = 34′694) were more likely to not receive adjuvant chemotherapy after colectomy if patients had to travel more than 50 miles (80 km) or more compared to < 12.5 miles (20 km) [22]. Finally, in line with the suggested influence of travel distance on protraction of visiting a medical specialist, decision-making and decreased likelihood to sticking to adjuvant therapy or the follow-up care, the distance may also lead to the poorer overall survival of cancer patients like it is described in trials with lymphoma, breast, stomach, rectal and extrahepatic biliary cancer patients [2, 25, 26].

Accordingly, it was surprising that our results concerning HNC patients in southern Germany are suggesting no influence of travel distance on the cancer stage at diagnosis or survival. There might be various reasons for that. Numerous studies supporting a negative impact of travel distance on cancer progression and treatment have been performed in the USA [1, 2, 7, 8, 17–20]. It has to be noticed that about 231 inhabitants/km^2 are living in Germany, whereas there are only 33 inhabitants/km^2 in the USA and 3 inhabitants/km^2 in Australia [27]. Therefore, it seems conceivable that in connection with the lower population density in the USA, infrastructure of the transport sector and maybe even social support may not be as easily accessible and as well developed as in Germany [1]. Routes to comparable health care facilities may be longer and more demanding in the USA than in Germany [1]. Furthermore, there is (still) a widespread network of well-educated ENT physicians in private practice in Germany who can help to guide the admission of patients to head and neck tumor centers [28]. Besides, a different policy of health care insurance is existing. Every German inhabitant is compulsorily health insured and has a free choice of doctor and hospital [29]. In the USA, currently, about 10.7% of employed and 26.3% of unemployed inhabitants lack health insurance [30]. Therefore, people with low income in the USA, who are prone to live further away from an urban center [7, 26], may consider additional reasons like missing health insurance as a greater obstacle than urban inhabitants. Furthermore in the USA, the choice of doctor and hospital, as well as the extent of insurers' coverage, is often restricted [31].

Nevertheless, there are reports from US authors who are suggesting, that precisely taking the burden of long-distance traveling by HNC or esophageal cancer patients is associated with treatment in high-volume hospitals and therefore affiliated with better overall survival [10, 32]. But this need not contradict the previous results if these special study groups are seen as an exception to the standard behavior compared to the overall population of cancer patients. As a possible limitation in this respect, it should be noted that long travel distances usually correlate with younger patient age (not with, e.g., old and frail patients) [20]. However, other authors claim that traveling in a progressive, industrialized world, in general, becomes increasingly affordable and uncomplicated; therefore, the aspect of cancer-related travel burden may be slowly vanishing [33]. For instance, medical tourists from Europe and North America even travel to developing countries like India, Thailand, and Brazil to skip long waits and high costs (with at least debatable treatment success) [34].

Meanwhile, to counterbalance the eventually occurring travel burden, telemedicine with the establishment of remote-monitored satellite facilities with self-delivery formats seems to be a useful approach to improve local health care and quality of life even in cancer patients [1, 28, 35–37]. This concept may be supplemented by a country-specific improvement of infrastructure of the transport and health care sector and the orientation on patients' needs [1].

At the moment, it seems that the effect of travel distance on cancer patients' care and outcome moreover depends on additional local infrastructural conditions and its effect must be evaluated individually, although studies suggesting a negative impact of travel distance on cancer progression appear to predominate [38]. The concept of travel burden includes many other factors than distance alone like age, comorbidity, social support, fortune, and local infrastructure [2, 7, 20]. Future studies may be constructed as multicenter, prospective trials also considering possible amplification effects of travel distance with comorbidity, frailty, as well as socio-economic aspects contributing to the whole shape of travel burden.

Conclusion

The analysis of the impact of travel distance on cancer stage at primary diagnosis of HNC patients in southern Germany (CCCU) implied a tolerable local travel distance. In addition to travel distance, travel burden involves sociodemographic, monetary, and disease-specific aspects as well as accessibility to proper infrastructure of transport and health care system. Reducing travel burden represents an important objective for nearly every necessary treatment, especially for disadvantaged patients.

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Availability of data and material Source data underlies restrictions of data privacy and cannot be shared unencrypted upon request.

Code availability Not applicable.

Declarations

Conflict of interest Simon Laban: Advisory Boards: Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Astra Zeneca (AZ), Sanofi Genzyme. Honoraria: MSD, BMS, AZ, Merck Serono. Patrick

Schuler: Advisory Boards: BMS, MSD. Thomas K. Hoffmann: Advisory Boards: MSD, BMS. Honoraria: MSD, BMS, Merck Serono. All other authors declared no conflict of interests, which could have influenced this work.

Informed consent and ethical approval Explicit informed consent and ethical approval were not required as long as this work was based on anonymized secondary data and did not influence the treatment of patients in any kind.

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