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The impact of palliative radiotherapy on health-related quality of life in patients with head and neck cancer – Results of a multicenter prospective cohort study

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ABSTRACT

Purpose: Palliative radiotherapy for patients with head and neck cancer can be used to alleviate symptoms. Only a few studies have investigated its impact on patient-reported outcomes (PRO). Therefore, we conducted a prospective multicenter observational study. The primary objective was to assess changes in health-related quality of life (HrQoL) per PRO.

Methods: Eligibility criteria included i.) head and neck cancer and ii.) palliative radiotherapy indicated ($EQD_{2Gy} < 60$ Gy). The primary follow-up date was eight weeks after radiotherapy (t_{8w}). PRO measures included the EORTC QLQ-C30 and EORTC QLQ-H&N43 and pain per Numeric Rating Scale (NRS). Per protocol, five PRO domains were to be reported in detail as well as PRO domains corresponding to a primary and secondary symptom as determined by the individual patient. We defined a minimal important difference (MID) of 10 points.

Results: From 06/2020 to 06/2022, 61 patients were screened and 21 patients were included. Due to death or decline in health-status, HrQoL data was available for 18 patients at the first fraction and for eight patients at t_{8w}. The MID was not met for the predefined domains in terms of mean values as compared from first fraction to t_{8w}. Individually in those patients with available HrQoL data at t_{8w}, 71% (5/7) improved in their primary and 40% (2/5) in their secondary symptom domain reaching the MID from first fraction to t_{8w}, respectively. There was a significant improvement in pain per NRS in those patients with available data at t_{8w} per Wilcoxon signed rank test ($p = 0.041$). Acute mucositis of grade ≥ 3 per CTCAE v5.0 occurred in 44% (8/18) of the patients. The median overall survival was 11 months.

Conclusion: Despite low patient numbers and risk of selection bias, our study shows some evidence of a benefit from palliative radiotherapy for head and neck cancer as measured by PRO.

German Clinical Trial Registry identifier: DRKS00021197.

1. Introduction

Radical radio(chemo)therapy is an effective treatment for patients with head and neck cancer [1]. It is, however, associated with prolonged treatment courses and significant toxicity. Shorter and less intense radiotherapy regimens exist for patients with head and neck cancer in various clinical situations prompting palliative treatment [2]. Such clinical situations may arise from a combination of patient factors such as advanced age, comorbidity, or frailty as well as tumor characteristics such as recurrent disease or presence of distant metastases [3,4].

Abbreviations: CTCAE, common terminology criteria for adverse events; ECOG, Eastern Cooperative Oncology Group; ePRO, electronic patient-reported outcomes; HrQoL, health-related quality of life; NRS, numeric rating scale; MID, minimal important difference; PRO, patient-reported outcomes; SD, standard deviation.

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Internationally, a variety of palliative radiotherapy regimens have been proposed and have shown to offer varying trade-offs between tumor control and toxicity [5].

Patient-reported outcomes (PRO) are outcomes directly reported by the patient without interpretation by proxy. Questionnaires to measure PRO, patient-reported outcome measures, have been acknowledged as gold standard to capture a patient's health-related quality of life (HrQoL) as essential trial endpoint [6,7]. Accordingly, Howell and colleagues have found an increased use of PRO in radiation oncology trials conducted within the National Clinical Trials Network [8]. As reported by their review, the use of PRO varied across disease sites. The use of PRO was low in trials of thoracic cancer (19%) whereas it was high in trials of head neck cancer (77%). Paradoxically in trials of palliative radiotherapy for head and cancer, however, the use of PRO appears to be less frequent. A systematic review conducted by our group, for example, sought to evaluate the benefit of palliative radiotherapy for head and neck cancer patients on the basis of PRO results from prospective trials [9]. Only four trials met the eligibility criteria and their sample sizes ranged from 17 to 37 patients. One trial used PRO as primary endpoint. These findings were surprising as palliative interventions aim to improve health-related quality of life or symptoms. In addition, to our knowledge, there is no prospective data of palliative radiotherapy for patients with head and neck cancer in Germany.

Therefore, we conducted a longitudinal observational study of patients treated with palliative radiotherapy for head and neck cancer at five radiotherapy departments in Germany. The overarching aims were to describe patterns of care in palliative radiotherapy for head and neck cancer as well as to assess the feasibility of longitudinal evaluation of PRO in this setting. The primary study objective was to describe the longitudinal course of patient-reported HrQoL. Secondary study objectives were to assess changes in pain scores, intake of analgesics, patient satisfaction, performance status, toxicity, unplanned hospital admissions, and overall survival.

2. Materials and Methods

2.1. Study design and setting

We conducted a multicenter, prospective, longitudinal, observational, and exploratory cohort study. Study centers included two academic and three non-academic departments of radiation oncology in Northern Germany. Approval by the local ethics committee was acquired for each center. We planned an overall sample size of 70 patients. The sample size calculations were generated from estimations of patient numbers treated at each participating center over a recruitment period of 24 months. The recruitment period was from June 2020 until June 2022. Inclusion criteria were i) mucosal squamous cell carcinoma of the head and neck, ii) any form of palliative radio(chemo)therapy prescribed for head and neck cancer, iii) ability to complete questionnaires, iv) age $\geq$18 years, and v) written informed consent. Exclusion criteria were i) prescription of radical radiotherapy for the current radiotherapy course (defined as $EQD_{2Gy} \geq 60$ Gy; $\alpha/\beta = 10$) and ii) cutaneous primary. To reduce potential bias, radiation oncologists prescribing a course of palliative radiotherapy for a specific patient were not involved in the conduct of the cohort study. We respected the STROBE guidelines, CONSORT-PRO extension guidelines, and recommendations for graphical display of PRO data as applicable to report the study [10–12].

2.2. Variables and outcomes

We collected data using an electronic case report form. Variables included patient and treatment characteristics, the age-adjusted Charlson Comorbidity Index, toxicity per Common Terminology Criteria for Adverse Events (CTCAE) v5.0, overall survival, patient-reported head and neck cancer pain intensity per Numeric Rating Scale (NRS 0-10), patient satisfaction, and the patient-reported questionnaires EORTC QLQ-C30 as well as EORTC QLQ-H&N43 [13,14]. Furthermore, patients were asked to indicate their two most burdensome symptoms (hereafter termed primary or secondary symptom) related to the head and neck cancer if present [15]. Patients could choose to complete the questionnaires electronically on a personal device or paper-based. Time points of data collection at clinical encounters were baseline, first fraction of radiotherapy, last fraction of radiotherapy, one week after radiotherapy, and eight weeks after radiotherapy (Supplementary Table 1). Subsequent remote PRO data collection was planned. However, results after eight weeks were not analyzed due to a limited number of available questionnaires at various following time points. The follow-up date at one week after radiotherapy was included due to concerns of a delayed onset of acute toxicity in anticipation of the use of hypofractionated radiotherapy regimens. Data for survival was collected until October 2022.

Concerning questionnaire data, we predefined to report in detail the domains "Global health status/quality of life", "Physical functioning", "Pain in the mouth", "Swallowing", and "Fatigue" at eight weeks after radiotherapy in comparison to the first fraction of radiotherapy. We hypothesized that these domains and the time frame should be relevant for the majority of the patients based on previous studies [5]. Primary and secondary symptoms were linked to a coherent questionnaire domain prior to statistical analysis. For two symptoms, the coherent symptom domain was ranked zero (=absence of the symptom) by the respective patient and the analysis was therefore deemed infeasible for those symptoms.

2.3. Statistical analysis

We used descriptive statistics to illustrate patient characteristics and outcomes. HrQoL data from both EORTC questionnaires were processed according to the respective scoring manuals [14,16]. In both EORTC questionnaires, high values in functioning scales represent a high level of functioning, whereas high levels in symptom scales represent a high level of symptom burden. Prior to analysis, we defined the minimal important difference (MID) of change in domain scores over time as 10 points using a distribution-based approach [17]. Although various definitions and perspectives coexist, the MID represents a magnitude of change of a PRO that is clinically relevant in contrast to a mere statistically significant difference [18]. The Wilcoxon signed rank test was used to test for differences in dependent ordinal data. The Kaplan-Meier method using log rank test was employed for overall survival. Overall survival was defined as time from baseline (=patient inclusion in study) until death by any cause. Mean follow-up time for overall survival was calculated from first fraction of radiotherapy per reverse Kaplan-Meier method. We used SPSS v29.0 (IBM Corp. [2020], Armonk, NY, USA) for all analyses and considered p-values <0.05 in two-sided tests statistically significant.

3. Results

3.1. Patient enrollment and characteristics

Of 61 screened patients, 35 did not meet the eligibility criteria and four refused to participate (Fig. 1). Twenty-two patients were included in the study. Of these, one patient transitioned to radical radiotherapy resulting in 21 patients included in the analysis. Three centers did not include patients within one year and were subsequently closed for recruitment. Mean follow-up time was 20.4 months for overall survival.

Characteristics of patients and palliative radiotherapy are shown in Table 1. The median patient age was 73 years and 71% (15/21) were male. The most common radiotherapy regimens were 45 Gy in 15 fractions (48%; 10/21) and 36 Gy in 12 fractions (14%; 3/21), each in five fractions per week. The remaining eight radiotherapy regimens were only prescribed in one case each. The target volume was confined to the macroscopic tumor in 95% (20/21) of the cases. Thirty-four

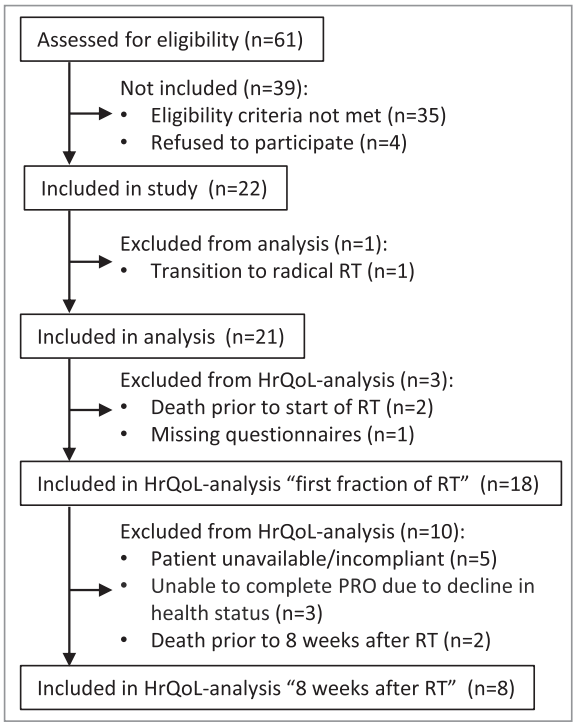

Fig. 1. Study flow chart. Abbreviations: HrQoL, health-related quality of life; RT, radiotherapy.

percent (7/21) had prior radiotherapy for head and neck cancer. Reasons for prescribing palliative radiotherapy instead of radical radiotherapy were advanced age (n = 10), comorbidity (n = 7), local extent (n = 7) and recurrent disease (n = 6) (Supplementary Fig. 1). A combination of multiple reasons was present in 62% (13/21) of the patients.

3.2. Patient-reported outcomes

One patient (5%; 1/21) chose to complete questionnaires electronically instead of paper-based. Concerning the questionnaires EORTC QLQ-C30 and EORTC QLQ-H&N43, 18 questionnaires were available at the first fraction of radiotherapy, 13 at the last fraction of radiotherapy, 10 at one week after radiotherapy, and eight at eight weeks after radiotherapy (Fig. 1). A summary of results of all questionnaire domains is given in Supplementary Table 2. As predefined, we analyzed the domains "Global health status/quality of life", "Physical functioning", "Pain in the mouth", "Swallowing", and "Fatigue" in more detail comparing the date of the first fraction of radiotherapy with eight weeks after radiotherapy in those patients who had data for both time points. The MID of 10 points was not met in any of these domains when analyzed per mean values across patients (Fig. 2).

Among those patients with available questionnaires at the first fraction and at eight weeks after radiotherapy, five reported a primary and secondary symptom, two patients indicated only a primary symptom and one patient could neither indicate a primary nor a secondary symptom. On an individual patient level, the primary symptom improved by more than 10 points in 71% (5/7) and worsened by more than 10 points in none of the patients (Fig. 3). The secondary symptom improved by more than 10 points in 40% (2/5) and worsened by more than 10 points in none of the patients.

The mean NRS score for pain caused by head and neck cancer was 3.2 at baseline (n = 21) and 0.8 at eight weeks after radiotherapy (n = 9) (Supplementary Table 3). There was no increase in the intake of opioid analgesics at eight weeks after radiotherapy (Supplementary Table 3). A Wilcoxon rank test showed that the difference in mean NRS was not statistically significant (p =.065). The difference in mean NRS, however, was statistically significant per Wilcoxon signed rank test when analyzed only in patients with data at eight weeks after radiotherapy (p =.041). The baseline mean pain score for these nine patients was 3.6 (standard deviation (SD) = 3.6). Concerning patient satisfaction, 100% (9/9) of the patients with available data at eight weeks after radiotherapy would have chosen the course of radiotherapy again in retrospect.

Table 1
Characteristics of patients (n = 21) and palliative radiotherapy. Absolute numbers are given and percentages are displayed in brackets unless indicated otherwise. Numbers may not add up to 100% due to rounding error or missing values. Abbreviations: CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; HNC, head and neck cancer; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy; SD, standard deviation.

Patient characteristics		
Total number of patients		21 (100%)
Age		Median: 73; IQR: 17
Sex	Female: male	6: 15
ECOG	1	6 (29%)
	2	11 (52%)
	3	4 (19%)
Age-adjusted CCI		Median: 4; IQR: 4
Smoking status	Current or former smoker	16 (76%)
	Never smoked	5 (24%)
History of risky alcohol use [a]		9 (43%)
Tracheostomy in place		4 (19%)
PEG tube in place		9 (43%)
HNC site	Oral cavity	8 (38%)
	Oropharyngeal	7 (33%)
	Laryngeal	3 (14%)
	Other	3 (14%)
UICC stage (TNM v8)	II	1 (5%)
	III	2 (10%)
	IV	17 (81%)
HPV-positive disease	p16	4 (19%)
Recurrent HNC		7 (33%)
HNC treatment prior to pall. RT	Surgery	7 (33%)
	Radiochemotherapy	5 (24%)
	Radiotherapy	2 (10%)
	Immunotherapy	2 (10%)
HNC treatment after pall. RT	Immunotherapy	3 (14%)
	Re-Radiotherapy	2 (10%)
Global health status/ quality of life	Per EORTC QLQ-C30	Mean: 66.7; SD: 20.3
Radiotherapy characteristics		
Radiotherapy regimen	45 Gy/15fx	10 (48%)
	36 Gy/12fx	3 (14%)
	Other	8 (38%)
Radiotherapy completed as prescribed		13 (62%)
Radiotherapy technique [b]	VMAT or IMRT	17 (81%)
	3DCRT	3 (14%)
GTV volume (ml)		Mean: 95.45 SD: 102.6
Concurrent systemic therapy	Immunotherapy	2 (10%)
	Chemotherapy	1 (5%)

[a] History of risky alcohol use defined as male >2 glasses per day and female >1 glass per day for more than 3 months (1 glass = 0,3l beer, 0,125 l wine, 4 cl liquor); [b] One patient died prior to the completion of radiotherapy planning.

3.3. Additional outcomes

The Eastern Cooperative Oncology Group (ECOG) performance status score remained stable in 56% (5/9) of the patients and declined in 44% (4/9) patients at eight weeks after radiotherapy (Supplementary Table 4). Also, at eight weeks after radiotherapy, body weight remained stable in 78% (7/9) and declined in 22% (2/9) of the patients (Supplementary Table 4). Toxicity per CTCAE v5.0 is shown in Table 2. Mucositis greater than or equal to grade 3 was present in 44% (8/18) of the patients at the last fraction of radiotherapy, in 33% (3/9) one week after radiotherapy and in no patient eight weeks after radiotherapy.

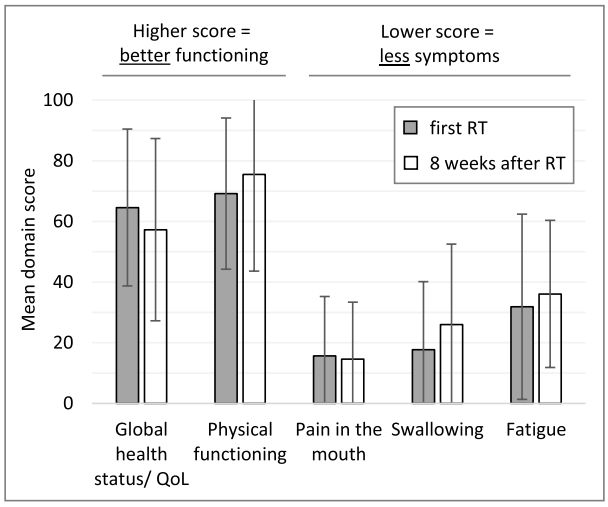

Fig. 2. Predefined health-related quality of life domains from the EORTC QLQ-C30 and EORTC QLQ-H&N43 questionnaires (n = 8). Bars show mean values. Error bars represent standard deviations. Abbreviations: QoL, quality of life; RT, radiotherapy.

There were no unplanned hospital admissions during the course of radiotherapy. Yet one patient was admitted to the hospital between the last fraction and one week after radiotherapy for cachexia, pain, pneumonia, and progressive pulmonary metastases. Another patient was admitted between one and eight weeks after radiotherapy due to a cerebrovascular accident. The median overall survival was 11 months (Fig. 4).

4. Discussion

In this prospective observational study of palliative radiotherapy and its impact on PRO of head and neck cancer patients, we faced low patient accrual and considerable drop-out rates. MIDs in predefined domains of patient-reported HrQoL were not reached across patients after palliative radiotherapy. On an individual level, however, most patients had a relevant improvement in their primary symptom caused by the head and neck cancer.

Concerning patterns of care of palliative radiotherapy for head and neck cancer, 71% of the patients had an ECOG performance status of 2 or higher and 81% of the patients had UICC stage IV disease. Previous cohorts of prospective studies of palliative radiotherapy for head and neck cancer reported an ECOG performance status of 2 or higher in 25% to 71% of the patients [19–23]. UICC stage IV disease was present in 53% to 97% of the patients in these studies [21,23]. Therefore, our study cohort consists of patients with a worse than average performance status while still being representative in the context of previous trials. However, we found that palliative radiotherapy was a surprisingly rare indication for head and neck cancer patients in the participating centers. Reasons for this may be that an individual patient is either considered "too fit" for palliative radiotherapy prompting a radical approach or "too frail" which might call for best supportive care. This was underlined by the fact that one patient transitioned to radical radiotherapy and that two patients died prior to initiation of the prescribed course of palliative radiotherapy. In fact, two more patients died prior to the time point of our primary analysis at eight weeks after radiotherapy. Three patients had a decline in health-status which precluded completion of HrQoL questionnaires. Unfortunately, the limited accrual of our observational study is not unusual at least for trials of palliative radiotherapy for head and neck cancer conducted in Europe. A Dutch randomized controlled trial comparing two regimens of palliative radiotherapy for head and neck cancer, for example, closed early due to poor accrual after 34 enrolled patients [19].

As for the feasibility to employ PRO, an interesting finding was the fact that only one patient chose to complete questionnaires electronically on a personal device. Although most of the patients were elderly at a median age of 73 years, we expected a higher preference for electronic PRO (ePRO). This was based on a previous German study which offered an electronic or paper-based version of PRO to breast cancer patients [24]. In this study even among those 70–80 years of age, 88% of the patients preferred the electronic version. Furthermore, a previous study of ePRO monitoring in head and neck cancer patients treated with radical radiotherapy reported a compliance rate of 94% concerning ePRO [25]. A worse performance status in the palliative setting, however, may have been a barrier to ePROs in our study. Further studies are underway to establish the role of ePROs [26]. Taken together, our observational study sets a note of caution for the implementation of electronic PRO in the setting of head and neck cancer patients undergoing palliative radiotherapy.

Concerning longitudinal HrQoL results, no meaningful improvements were found in predefined domains at eight weeks after radiotherapy across patients. The results remain inconclusive in this regard which may relate to the low patient number. Mean values of PRO have also been reported as inconclusive before by other studies due to low patient numbers [19]. When observed at the individual level as predefined, however, the majority of the patients experienced an improvement above the MID concerning their primary symptom. Among these symptoms were "Swelling in the neck", "Pain in the mouth", or "Swallowing". The latter two have been shown to be potentially improved after palliative radiotherapy for head and neck cancer by previous studies. Fortin and colleagues, for example, reported that pain in the head and neck as measured by the EORTC QLQ-H&N35 questionnaire was improved or stable in 83% out of 32 patients after palliative radiotherapy [20]. Furthermore, Porceddu and colleagues reported that swallowing as measured by the FACT-H&N questionnaire was improved or stable in 81% out of 37 patients after palliative radiotherapy [22]. These previous studies, however, mainly reported symptom improvement by any degree without reporting MID. In fact, reporting of PRO data in trials of palliative radiotherapy in general appears to be suboptimal as evidenced by a recent systematic review of our group [27]. Pain caused by the primary tumor per NRS is another common PRO measure [28]. In our cohort, values of pain per NRS were significantly lower in patients who responded to this question at eight weeks after radiotherapy. This effect is consistent with previous retrospective and prospective studies which also reported a significant improvement in pain per NRS or Visual Analogue Scale [23,29]. Taken together, our study offers evidence on the individual patient level that palliative radiotherapy may have a positive impact on key symptoms of head and neck cancer patients.

The most prevalent toxicities in our cohort were dysphagia and mucositis. Especially mucositis of grade 3 or higher was not present at baseline but in 44% of the patients at the last fraction of radiotherapy. Mucositis already decreased at one week after radiotherapy which was reassuring in the light of hypofractionated radiotherapy regimens. Still, the rate of acute mucositis is considerable in a palliative context but has also been reported by other studies. The most common radiotherapy regimen in our study was 15 fractions of 3 Gy in five fractions per week to a total dose of 45 Gy. The randomized trial mentioned above, for example, used 16 fractions of 3.125 Gy in four fractions per week to a total dose of 50 Gy in one arm and reported acute mucositis of grade 3 or higher in 43% of the patients [19]. Other regimens such as the "Quad Shot", 25 Gy in five daily fractions, or 6 fractions of 6 Gy twice per week are less toxic with mucositis of grade 3 or higher well below 10% [19,20,30]. These regimens may be preferred when toxicity is of special concern. However, a higher dose of radiotherapy might be associated with improved overall survival.

The median overall survival in our cohort was 11 months. Studies of less intense radiotherapy regimens such as the "Quad Shot" or 25 Gy in five daily fractions reported median survival times of roughly 6 months

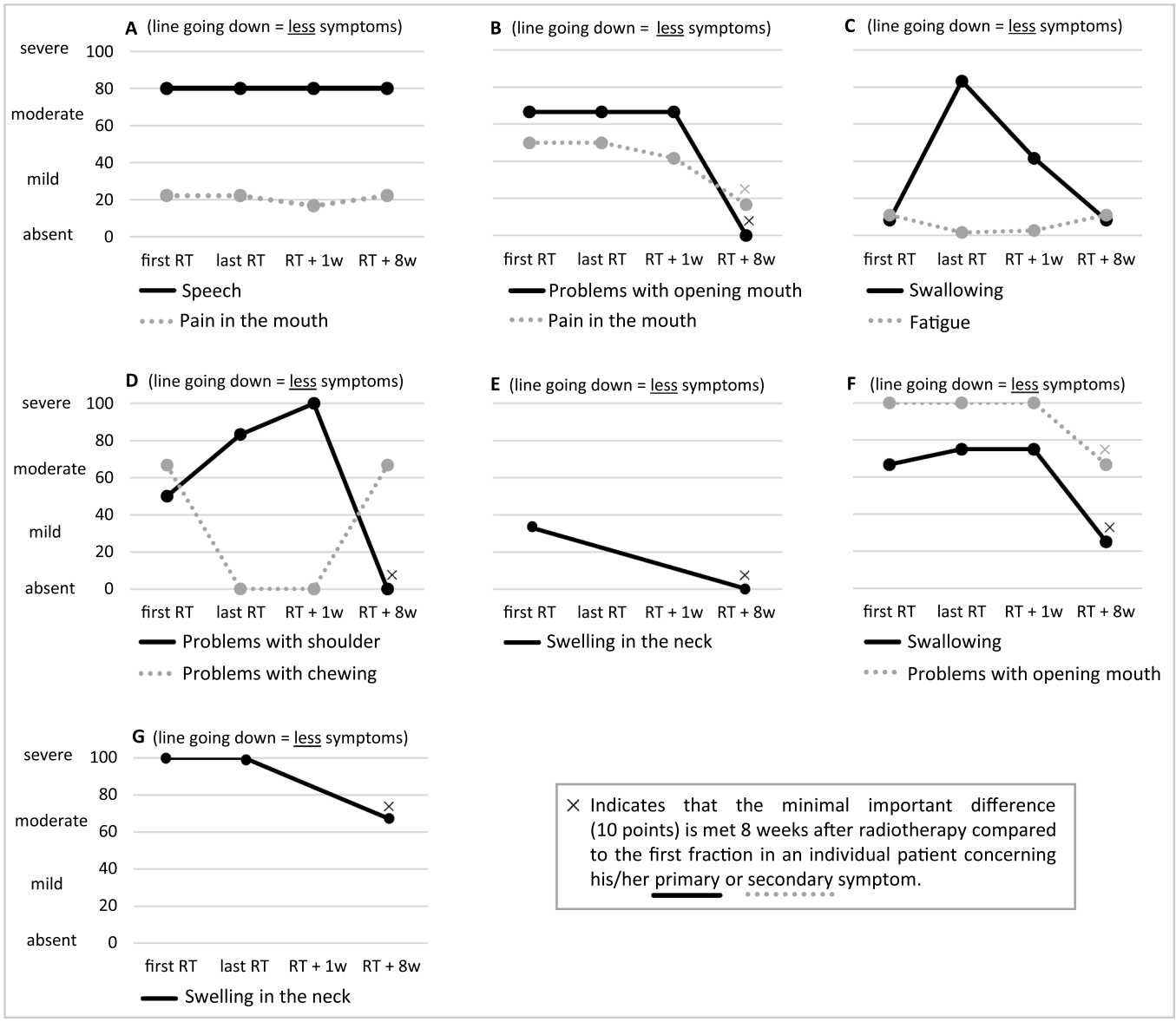

Fig. 3. Health-related quality of life domains corresponding to primary and secondary symptom as reported by each patient individually (n = 7) (A-G). Symptoms were linked to a corresponding domain of the questionnaires EORTC QLQ-C30 or EORTC QLQ-H&N43 prior to analysis. Some patients indicated only a primary symptom. Bullets on lines indicate available data points. Abbreviations: RT, radiotherapy; w, weeks.

Table 2
Toxicity according to the Common Terminology Criteria for Adverse Events v5.0 (related and unrelated to radiotherapy). Absolute numbers are given and percentages are displayed in brackets. Abbreviations: RT, radiotherapy.

	Baseline, n = 20		Last fraction of RT, n = 18		1 week after RT, n = 9		8 weeks after RT, n = 9	
	°2	≥°3	°2	≥°3	°2	≥°3	°2	≥°3
Mucositis	2 (10%)	0 (0)	5 (28%)	8 (44%)	4 (44%)	3 (33%)	1 (11%)	0 (0)
Dermatitis	0 (0)	0 (0)	1 (6%)	0 (0)	1 (11%)	1 (11%)	0 (0)	0 (0)
Dysphagia	3 (15%)	6 (30%)	5 (28%)	9 (50%)	4 (44%)	2 (22%)	2 (22%)	2 (22%)
Xerostomia	1 (5%)	0 (0)	1 (6%)	1 (6%)	3 (33%)	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	2 (2%)	0 (0)	0 (0)	0 (0)

[20,21]. Yet studies of more intense radiotherapy regimes have reported a median overall survival up to 17 months [31]. The Dutch randomized controlled trial showed a higher median overall survival after the more intense radiotherapy regimen of 15 months compared to the less intense regimen with 9 months median survival [19]. This difference was, however, not statistically significant. On the other hand, a systematic review reported an inverse correlation of radiation dose and overall survival in elderly patients treated with palliative radiotherapy for head and neck cancer [32]. Taken together, the relationship of radiotherapy dose and survival remains unclear in this setting, but the overall survival of our cohort fits well within the reported literature.

A limitation of our study is the low patient number and high rate of

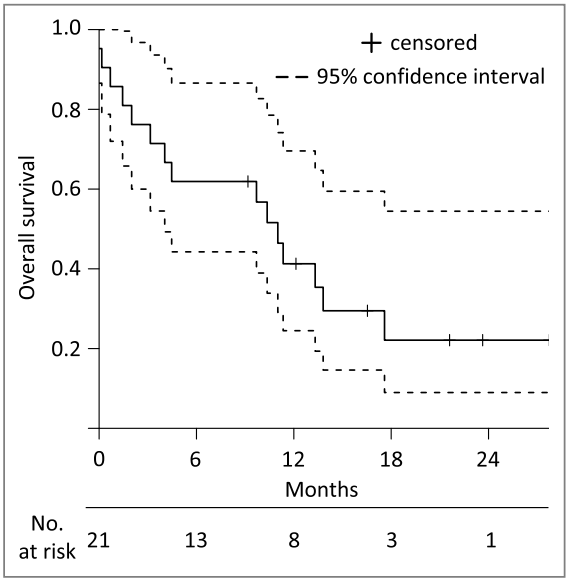

Fig. 4. Overall survival per Kaplan-Meier method. Dotted lines indicate the 95% confidence interval.

drop-out. Although we predefined major aspects of our analyses, their results may be affected by selection bias and reduced representativeness. Moreover, we did not collect data on local control or radiographic response rates precluding analyses of progression-free survival. However, this approach was predefined as PRO data and overall survival are widely considered as patient-centered endpoints in prospective studies [33,34]. Furthermore, a distribution-based MID across symptom domains has been used commonly in previous studies and offers an intuitive starting point [17]. Yet more elaborate approaches to calculate MID have been proposed recently [14,18].

5. Conclusion

Our study shows some evidence of a benefit from palliative radiotherapy for head and neck cancer as measured by PRO. The benefit was present concerning an improvement in pain and on an individual level in HrQoL domains. Further prospective studies should validate these findings, but palliative radiotherapy is an option for carefully selected head and neck cancer patients.

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Data statement

Raw data of this analysis is available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

DK received honoraria from Merck Sharp & Dohme and Pfizer as well as research funding from Merck KGaA, outside of the submitted work.

The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100633.

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