Clinical Pain Research

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Pain management in patients undergoing radiation therapy for head and neck cancer – a descriptive study

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Abstract

Objectives: Patients with head and neck cancer (HNC) experience serious pain related to tumour, surgery, chemotherapy, and radiotherapy treatment (RT). Oral mucositis, a painful complication of RT, may require opioid analgesics to control pain. This longitudinal study, during RT but also four weeks post-RT, examines the relationships between oral mucositis, pain, and opioid doses in HNC patients. The aim was to evaluate the clinical effectiveness of an opioid treatment strategy.

Methods: Sixty-three patients with HNC undergoing radiotherapy answered self-reported questionnaires on pain intensity on a 0–10 numerical rating scale (NRS) three times a week. Oral mucositis signs were evaluated using the WHO mucositis index score, ranging from 0 (normal) to 4 (severe), and pharmacological treatment with opioids was registered prospectively once a week. All data were related to given radiation dose, and all outcome measures at each time point therefore relate to the same radiation dose (i.e., not to when the patient was included in the study).

Results: Opioids were used by 78% of the patients. Most of the patients experienced only mild pain (NRS 0–4), although the majority developed mucositis grade 2–4 according to WHO mucositis index. Function-related pain intensity and opioid doses were highest during the sixth

week of RT, with 3.67 (0–9) in NRS and 84 (0–430) mg oral morphine equivalents per day (median, range). At that same time point, significant positive correlations were found between the grade of mucositis and pain intensities. Patients with mucositis grade 2–4 were investigated further; in this subgroup, we found that opioid doses did not differ between patients with mild pain and patients with moderate to severe pain. Our multivariate data analysis defined a cluster of patients characterized by the presence of mucositis, cancer site in pharynx, concomitant chemotherapy, and the absence of surgery.

Conclusions: In HNC patients who were followed closely by pain care personnel during and after RT, pain was often satisfactorily alleviated with a structured use of opioids, including stepwise increases of fentanyl patches and oral morphine as needed. However, some patients with oral mucositis grade 2–4 experienced severe pain. Strong opioids, i.e. the third step of the WHO pain ladder, remain the mainstay of analgesic therapy in treating moderate to severe cancer-related pain, including patients with HNC. This real-life study indicates that RT-related pain is not a fatality. A proactive stance, monitoring these patients closely and regularly, is probably crucial in order to achieve good treatment results. Further studies are needed to develop better pain treatment strategies for those patients who develop severe oral mucositis-related pain despite intensive opioid treatment.

Keywords: head and neck cancer; mucositis; opioids; pain; radiotherapy.

Introduction

Worldwide, head and neck cancer (HNC) affects more than 500,000 people, representing about 6% of all cancer diagnoses, and causes 350,000 deaths yearly [1, 2]. Head and neck cancer is a heterogeneous group of diseases concerning incidence, treatment, and prognosis [3]. Treatment of HNC may include surgery, chemotherapy, and radiotherapy (RT) in various combinations [1, 4]. A common RT

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regimen is two gray (Gy) per day five days per week for a total cumulative dose of 50–70 Gy [4].

Patients treated for HNC suffer from several psychological and physical symptoms that negatively impact daily life, including depression and a sense of lack of meaning, pain, xerostomia and swallowing disorders [5]. According to the National Comprehensive Cancer Network Task Force, nausea, vomiting and mucositis are the most physical common adverse events in connection with cancer treatment [6]. Oral mucositis is an inflammation of the oral and oropharyngeal mucous membrane resulting from the toxic effects of RT and chemotherapy [7].

The onset of RT-induced mucositis is usually 10–14 days after start of treatment, and concomitant chemotherapy increases the frequency, duration, and severity of mucositis [4, 8]. The grade of mucositis is commonly assessed according to the World Health Organization (WHO) mucositis index scale (0=normal and 4=severe). Initial symptoms are usually mild pain with erythema of the mucous membrane (grade 1), followed by areas of mucosal ulceration (grade 2) that continue to spread and penetrate deeper with gradually increasing pain and an inability to swallow (grades 3 and 4) [8].

Prevalence of pain among patients with HNC is high, with up to 80% of patients reporting pain during their RT treatment [4, 7, 9, 10]. It has been reported that patients with HNC, in early treatment of RT (within 0–20 Gy), mainly describes low pain intensity and in this context the pain is in the first place considered as nociceptive [11]. However, neuropathic pain mechanisms are also thought to be involved [12]. Hence, oral mucositis RT-related pain probably includes both nociceptive and neuropathic pain components [13].

In accordance with the WHO pain ladder, strong opioids are the mainstay of analgesic therapy in treating moderate to severe cancer-related pain, including HNC pain [14–16]. Previous studies have described that adequate pain relief for patients with HNC who suffer from RT-related oral mucositis is difficult to achieve [13, 17–21]. For this group of patients, local guidelines at Pain and Rehabilitation Centre (PRC), University Hospital, Linköping, Sweden, are based on the WHO ladder, i.e., acetaminophen, non-steroid anti-inflammatory drugs (NSAID), and opioid analgesics [15]. As a complement all patients with HNC undergo weekly oral care checks by the hospital dentist and use daily mouthwash with lidocaine hydrochloride and mycostatin. When the pain mechanism is considered to be neuropathic, adjuvant analgesia can be provided with gabapentinoids such as pregabalin [21]. Attention is given to side effects of opioid therapy such as dry mouth, constipation, nausea, and decreased alertness

[19, 22]. Fentanyl patches are usually prescribed when swallowing difficulties are present and/or to minimize side effects such as constipation and nausea [22] and, at PRC, the primary choice of opioid for this group of patients is fentanyl patches.

This longitudinal study evaluated the effects of the above-mentioned local guidelines in clinical practice in a cohort of patients with HNC undergoing RT, examining the relationships between opioid doses, oral mucositis, and pain.

Methods

Participants

This descriptive study was part of a larger longitudinal project about patient education and self-care in order to reduce pain, improve quality of life (QoL), and evaluate psychological aspects during and after RT in patients with HNC. The results showed no statistical difference between the control and intervention group regarding pain, QoL, and psychological aspects. Likewise, no significant difference was seen regarding gender and age between the groups [23]. Thus, in this paper, we could consider these two groups as a unified group to study and analyse the issue of the current study.

During 2016–2017, patients with HNC undergoing RT were recruited by the PRC. Recruitment of patients for the study was based on referred patients from the oncology clinic to the PRC prior to RT. Registration of received referrals to the PRC varied from two weeks before RT and two weeks into the start of RT treatment. The intention was to recruit the patient for the study before pain arose related to RT and mucositis.

Regarding the patients who underwent surgery before RT, all had recovered from wound and postoperative pain at inclusion in the study. That is, according to the local guidelines at the local oncology clinic, 6–8 weeks would pass before the start of radiation therapy. Patients became eligible for PRC after referral from the oncologist as expected pain in connection with RT often requires structured pain treatment.

In connection with the first appointment with the responsible research nurses (RN) at PRC, which took place within 1–2 weeks after start of RT, all eligible patients received written and oral information as well as offer to participate in the study. Eligible patients were 18 years old or older, able to read, write, and understand Swedish, and scheduled to receive curative RT for HNC. Informed consent was obtained from all participants included in the study.

Measurement points

In this longitudinal study, we report data week-by-week. Importantly, all weekly measurement points were defined according to given radiation dose and not according to when patients were included in the study. Hence, all outcome measures at each time point relate to the same radiation dose, a strategy that enables a better assessment of the effects of RT over time: e.g., the measurement 0–10 Gy (abbreviated MP 0–10) is the first week of cumulative dose of RT, MP 11–20 is the second week of cumulative dose of RT, etc.

Outcome measures for the present study

Assessment of oral mucositis: Oral mucositis was diagnosed according to WHO mucositis index score, as evaluated weekly by a specialist dentist at the University Hospital. The WHO mucositis index measures the severity of mucositis on a five-point scale ranging from 0 (normal) to 4 (severe) [8]. The result was documented in the medical record. Once a week, two RN reviewed the degree of mucositis in the medical record.

Pain intensity ratings by short message services: Every Monday, Wednesday, and Friday of the ten-week data collection period, all participants answered a Short Message Services (SMS) questionnaire with seven items on pain intensity and interference with oral activity.

This study focuses on two of the items from the validated Oral Cancer Pain Questionnaire included in the SMS: (1) pain in connection with (function-related pain) and (2) not with (spontaneous pain) speaking, talking, and drinking [24]. The items were scored on a numeric rating scale (NRS) from 0 (no pain) to 10 (the most intense pain sensation imaginable) the previous 24 h. For each subscale and item, the average score of the three weekly scores was calculated, generating a weekly NRS value. Mild pain was defined as NRS 0–4, moderate pain as NRS 5–6, and severe pain as NRS 7–10 [25–27]. In this paper the patients were divided into two groups concerning pain; mild pain group (NRS 0–4), vs. pain group (NRS 5–10).

At baseline, at four weeks, and at 10 weeks, the patients also completed a survey questionnaire about pain, QoL, psychological aspects, and barriers to pain management. These findings have been reported elsewhere [11, 23].

Pharmacological treatment with opioids during radiotherapy: If the patients reported pain (NRS >3) via the SMS survey, the RN phoned the patient the same day (if a weekend no later than three days) and pharmacological treatment was initiated or adjusted.

The pharmacological treatment prescribed by PRC physicians followed the local guidelines; patients with NRS >3 were prescribed acetaminophen in combination with nonsteroidal anti-inflammatory drug treatment with the intention to inhibit the production of substances resulting damage and inflammation. If the pain intensity was NRS >6 and assessed as nociceptive and derived from the oral cavity or pharynx, for example wounds and/or blisters, a strong long-acting opioid was prescribed. For opioid-naïve patients (in this paper all patients) the lowest dose of fentanyl patch was prescribed. If breakthrough pain occurred, short-acting morphine was prescribed. In case of poor response after optimization with opioids and if the pain was evaluated as neuropathic, pregabalin was prescribed.

If the patient continued to report unchanged pain the following day, the pharmacological treatment was evaluated again for possible further adjustments. Opioid doses were registered in a study form for each individual patient, in connection with weekly contact between RN and the patient during RT and as long as the patient was medicated with opioids. However, the study includes 10 weeks of patient reporting.

For each patient, daily doses of short- and long-acting opioids were converted into daily oral morphine equivalents (OME), which were calculated according to standard equianalgesic tables [28–30].

According to the specialist dentist's prescription, during the first week of RT, local anesthetics such as oral lidocaine solution was also prescribed against pain in the oral mucosa.

Statistical methods

Data were analyzed using SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive data are presented as median (minimum–maximum). For inferential statistics, non-parametric tests were used: (1) for comparisons between two independent groups, the Mann Whitney U test or, for categorical data, the Chi-square test; (2) for correlations between two variables, the Spearman's correlation coefficient (r); (3) for changes in pain intensity, grade of mucositis and opioid dose over time, the Friedman test. In order to be able to use the Friedman test, occasional missing values were imputed by calculating the mean of existing nearby variables (i.e., before and after) [31, 32]. For all statistical analyses, a p -value of <0.05 was accepted as significant.

Multivariate data analysis (MVDA) was used to enable an explorative analysis of the whole data material at once at MP 51–60, taking the whole correlation structure of the material into account (i.e. akin to a kind of multivariate correlation analysis instead of multiple tests). Details of this have been published elsewhere [33–36], but in short, we started with principal component analysis (PCA) to identify potential multivariate outliers. The following variables were used in the PCA analysis: age; sex; pain intensities; opioid dose; oral mucositis grade; smoking habits (non-smoker, smoker, ex-smoker); cancer site (oral cavity, pharynx, larynx, other location); cancer treatment (RT with or without chemotherapy, RT with or without surgery (surgery before or after RT)). The PCA analysis was followed by hierarchical cluster analysis (HCA) on the same variables, enabling us to define two groups of patients based on the aforementioned variables. Then, orthogonal partial least square – discriminant analysis (OPLS-DA) enabled us to find the variables most distinctive for discrimination between the two groups. Variables with $p(\text{corr})$ values >0.5 were considered “significant”.

Results

Description of the patients

The analysis included 63 consecutive cases of patients with various HNC (Table 1, see “Total” column). The mean age of the participants was 65 years. Most patients were men (62%) and a majority were smokers or former smokers (60%). The most common cancer site was the pharynx (41%) and the most commonly occurring cancer treatment was a combination of surgery and RT (43%). All participants were scheduled to receive RT for their cancer, with a minimum prescribed radiation dose of 50 Gy and a maximum dose of 68 Gy (10 Gy per week).

Oral mucositis, pain intensity, and opioid doses

The WHO mucositis index score in this study cohort changed over time ($p < 0.001$) and were highest at MP 51–60 and thereafter decreased over time (Figure 1 and Table 2).

Table 1: Socio-demographic, clinical, and treatment data of 63 patients with HNC and comparison between pain- and mucositis groups.

Variables	Total	In-depth analysis at the cumulative dose of RT 51–60 Gray			
		Mild pain group ^a	Moderate-to-severe pain group ^b	Grade of mucositis ^c 0–1	Grade of mucositis ^c 2–4
Participants, n	63	42	21	24	39
Age in years					
Median (min–max)	67 (36–86)	67 (42–86)	66 (57–79)	64 (48–78)	67 (36–86)
Sex, n (%)					
Female	24 (38)	17 (71)	7 (29)	9 (38)	15 (62)
Male	39 (62)	25 (64)	14 (36)	15 (38)	24 (62)
Smoking habits, n (%)					
Non-smokers	25 (40)	19 (76)	6 (24)	8 (32)	17 (68)
Smokers	10 (16)	6 (60)	4 (40)	2 (20)	8 (80)
Ex-smokers	28 (44)	17 (61)	11 (39)	14 (50)	14 (50)
Cancer site, n (%)					
Oral cavity	14 (22)	8 (57)	6 (43)	5 (36)	9 (64)
Pharynx	26 (41)	16 (62)	10 (38)	4 (15)	22 (85)
Larynx	6 (10)	5 (83)	1 (17)	4 (67)	2 (33)
Others	17 (27)	13 (76)	4 (24)	11 (65)	6 (35)
Cancer treatment, n (%)					
RT only	11 (18)	9 (82)	2 (18)	5 (45)	6 (55)
RT with chemotherapy	16 (25)	10 (62)	6 (38)	3 (19)	13 (81)
RT and surgery	27 (43)	17 (63)	10 (37)	14 (52)	13 (48)
RT with chemotherapy and surgery	9 (14)	6 (67)	3 (33)	2 (22)	7 (78)
Cumulative dose of radiotherapy, gray, median, (min–max)	68 (50–68)	68 (50–68)	68 (50–68)	60 (50–68)	68 (50–68)
Opioid use yes/no (%)					
Yes (%)	49 (78)	30 (61)	19 (39)	15 (31)	34 (69)
No (%)	14 (22)	12 (86)	2 (14)	9 (64)	5 (36)
Opioid use (mg/day)^d, median (min–max)	84 (0–430)	60 (0–430)	120 (0–400)	22 (0–149)	120 (0–430)
Concomitant of opioid- and NSAID use					
Yes (%)	26 (41)	16 (62)	10 (38)	8 (31)	18 (69)
No (%)	37 (59)	26 (70)	11 (30)	16 (43)	21 (57)
Acetaminophen use					
Yes (%)	53 (84)	35 (83)	18 (86)	18 (5)	35 (90)
No (%)	10 (16)	7 (17)	3 (14)	6 (25)	4 (10)

n, total number of participants; RT, radiotherapy; Ex-smokers, former smokers; OM, oral mucositis; NSAID, non-steroidal anti-inflammatory drugs. ^aMild pain group=function-related pain (Oral Cancer Pain Questionnaire), numerical rating scale (NRS) ≤ 4 at measurement point (MP) 51–60. ^bModerate-to-severe pain group=function-related pain, NRS ≥ 5 at MP 51–60. ^cGrade of mucositis at MP 51–60. ^dOpioid use at MP 51–60.

Both function-related pain and spontaneous pain changed over time ($p < 0.001$ and $p < 0.001$) and were highest at MP 51–60, i.e., associated with cumulative dose of Gy and thereafter decreased over time (Figure 2 and Table 2).

Opioids were used by 78% of patients (Table 1; Total column). In most cases, treatment with opioids included a fentanyl patch in combination with oral short-acting morphine as needed. The opioid doses changed over time ($p < 0.001$) and were highest at MP 51–60 with a median of

84 (min-max 0–430) mg OME per day (Figure 3 and Table 2).

Other analgesic treatment

Majority of the participants used acetaminophen (84%) and nearly half also used NSAID (48%). Opioids in combination with NSAID were used by 41% of patients (Table 1), and 16% ($n=8$) of the patients undergoing

Figure 1: Oral mucositis in relation to cumulative dose of Gy⁰⁻⁷⁰ and post RT¹⁻⁴=weeks after completed radiation therapy. Median values are represented by horizontal lines and the interquartile ranges by boxes. The ends of the whiskers represent minimum and maximum values. Points represent outliers.

opioid therapy had a supplement of pregabalin with a median of 75 (min-max 50–300) mg/day.

Treatment with NSAIDs and or pregabalin was not found to have a reducing effect on OME. Patients treated with pregabalin had a significantly ($p=0.003$) higher dose of OME than those who did not have pregabalin.

In-depth analysis at MP 51–60

Pain intensities and opioid doses were highest at MP 51–60 (Table 2). At that time point, significant and substantial positive correlations were found between the grade of mucositis and (1) pain intensity in connection with speaking, talking, and drinking (function-related pain) ($r=0.48$, $p<0.001$) and (2) resting pain ($r=0.42$, $p=0.002$), respectively. Patients with mucositis grade 0–1 ($n=20$) had significantly lower pain intensity than patients with mucositis grade 2–4 ($n=31$) at function-related pain ($p=0.004$) and at spontaneous pain ($p=0.001$) (Figure 4).

Patients with mucositis grade 0–1 had significantly lower opioid doses than patients with mucositis grade 2–4 ($p<0.001$, Figure 5). For further comparisons between mucositis 0–1 and mucositis 2–4 groups, see Table 1.

Patients with mucositis grade 2–4 ($n=39$) were investigated further. Importantly, in patients with mucositis grade 2–4, there were no statistically significant differences in opioid doses between the mild pain group and the moderate to severe pain group (this concerns

Table 2: Data of 63 patients with HNC. Distribution of cumulative dose of RT and changes within the groups: differences in pain intensity (NRS=numeric rating scale), grade of mucositis and weekly dose of morphine. Descriptive data are presented with median values (range) and statistical analysis is performed with the Friedman test (imputed data).

	Cumulative dose of radiotherapy											p-Value (effect over time)
	0–10 Gy median (min–max)	11–20 Gy median (min–max)	21–30 Gy Median (min–max)	31–40 Gy median (min–max)	41–50 Gy median (min–max)	51–60 Gy median (min–max)	61–70 Gy median (min–max)	Post RT ¹ median (min–max)	Post RT ² median (min–max)	Post RT ³ median (min–max)	Post RT ⁴ median (min–max)	
Pain intensity ^a	0.67 (0–7)	2.00 (0–8)	2.67 (0–9)	3.00 (0–8)	3.33 (0–9)	3.67 (0–9)	2.33 (0–10)	3.00 (0–7)	2.00 (0–7)	1.33 (0–7)	2.00 (0–9)	0.000
Pain intensity ^b	0.67 (0–4)	1.33 (0–7)	2.00 (0–9)	2.33 (0–8)	2.33 (0–9)	2.33 (0–9)	2.00 (0–10)	2.00 (0–7)	1.17 (0–7)	1.00 (0–6)	2.00 (0–9)	0.000
Mucositis	0 (0–2)	1.00 (0–3)	2.00 (0–3)	2.00 (0–4)	2.00 (0–4)	2.00 (0–4)	2.00 (0–4)	1.00 (0–4)	1.00 (0–4)	1.00 (0–4)	0 (0–3)	0.000
Morphine g/day	0 (0–120)	0 (0–180)	29 (0–340)	58 (0–420)	60 (0–605)	84 (0–430)	80 (0–430)	60 (0–300)	60 (0–420)	60 (0–440)	59 (0–240)	0.000

Gy, gray; post RT, post radiotherapy^{week 1–4}. ^{a,b} Pain intensity= The items on pain intensity included pain in connection with^a and without^b speaking, talking, and drinking (0–10); Morphine=mg/day; Mucositis=0 (normal) to 4 (severe).

Figure 2: Pain intensity (NRS 0–10) in connection with (function-related pain) and not with (spontaneous pain) speaking, talking, and drinking, development of pain in relation to cumulative dose of Gy^{0–70}, post RT^{1–4}=weeks after completed radiation therapy. Median values are represented by horizontal lines and the interquartile ranges by boxes. The ends of the whiskers represent minimum and maximum values. Points represent outliers and asterisks represent extremes.

Figure 3: Opioid dose in oral morphine equivalents (mg/d) in relation to cumulative dose of Gy^{0–70} and post RT^{1–4}=weeks after completed radiation therapy. Median values are represented by horizontal lines and the interquartile ranges by boxes. The ends of the whiskers represent minimum and maximum values. Points represent outliers and asterisks represent extremes.

function-related pain, $p=0.385$; Figure 6). In addition, there was no correlation between opioid dose and function-related pain ($r=0.21$, $p=0.26$). Results were similar for spontaneous pain (data not shown).

Multivariate association at MP 51–60

No patient was an outlier according to the PCA model ($n=63$, two principal components, $R^2=0.23$ and $Q^2=0.07$). The OPLS-DA model (one latent variable, $R^2=0.76$ and $Q^2=0.71$, $p<0.001$ by CV-ANOVA) showed that one of the two groups of patients (called Group 2, $n=34$, in Figure 7) identified by HCA was characterized by its association with chemotherapy, cancer site in pharynx, no surgery, and the presence of mucositis (see Figure 7). The corresponding $p(\text{corr})$ values for chemotherapy, cancer site in pharynx, no surgery, and the presence of mucositis were 0.87, 0.82, 0.58, and 0.54, respectively (i.e., all these were “significant”). The other group (Group 1, $n=29$) was the opposite. Hence, our MVDA analysis showed that, taking the whole correlation structure of the material into consideration, there was a group of patients characterized by cancer site in pharynx and being treated (in addition to RT) with chemotherapy and not with surgery, and that this group tended to have a higher degree of mucositis. This was confirmed by additional inferential statistics – i.e., the proportion of patients with mucositis grade 2–4 was

Figure 4: Pain intensity (NRS 0–10) in connection with (function-related pain) and not with (spontaneous pain) speaking, talking, and drinking at MP 51–60 in relation to mucositis 0–1 and 2–4. Median values are represented by horizontal lines and the interquartile ranges by boxes. The ends of the whiskers represent minimum and maximum values.

Figure 5: Opioid dose in oral morphine equivalents (mg/d) at MP 51–60 in relation to mucositis groups 0–1 and 2–4. Median values are represented by horizontal lines and the interquartile ranges by boxes. The ends of the whiskers represent minimum and maximum values. Points represent outliers.

Figure 6: Opioid dose in oral morphine equivalents (mg/d) at MP 51–60 in patients with mucositis grade 2–4. Patients are divided according to pain intensity (function-related pain): mild pain (NRS 0–4) and moderate to severe pain (NRS 5–10) in function-related pain. The ends of the whiskers represent minimum and maximum values. Points represent outliers.

significantly higher for patients with cancer site in pharynx compared to other sites (22/26 vs. 17/35, $p=0.004$). This was also true for patients receiving chemotherapy compared to not receiving chemotherapy (20/25 vs. 19/36, $p=0.029$). Descriptive data in Table 1 are consistent with this conclusion, as patients with pharynx cancer and patients undergoing chemotherapy had a high frequency of mucositis grade 2–4 (85 and 81%, respectively). As mentioned above, the MVDA analysis also showed that not undergoing surgery was associated with higher degree of mucositis, but this was only apparent in the MVDA model and not by additional inferential statistics (19/26 vs. 20/35, $p=0.2$).

Discussion

This real-life study evaluated the effectiveness of our local guidelines in clinical practice, investigating the

Figure 7: Predictive loadings column plot for clustering-based OPLS-DA model. See Methods. Briefly, variable columns near Group 1 are positively associated with Group 1 (and not with Group 2) and vice versa.

With_chemo, radiotherapy (RT) in combination with chemotherapy; Pharynx, cancer site in pharynx; RT_no_Surg, RT without surgery; Mucositis_Gy6, grade of mucositis at the cumulative dose of RT 51–60 gray=measurement point (MP) 51–60; Q1_Gy6, function-related pain at MP 51–60; Morfin_Gy6, morphine use at MP 51–60; Q2_Gy6, spontaneous pain at MP 51–60; ExSmokers, former smokers; Larynx, cancer site in larynx; RT_Surgery_before, surgery before RT; Other_loc, other types of tumours; nasopharynx, salivary glands, thyroid, lip and cancer of unknown primary location; Oralcav, cancer site in the oral cavity; RT_Surgery_after, surgery after RT; No_chemo, RT without chemotherapy.

relationships between opioid doses, oral mucositis and pain during HNC-related RT. We studied the temporal dynamics involved (longitudinal aspects), but we also focused on MP 51–60, which was the time point of highest opioid doses, highest grade of mucositis and highest pain intensities.

From a pathophysiological point of view, one of the strengths of the present study is that we structured the material from the point of view of accumulated radiation dose (Gy) and not according to the time (weeks) when

patients were included. This strategy allowed us to relate the development of mucositis to actual radiation dose. As expected, this study found that patients diagnosed with HNC developed mucositis and pain during RT and that this was related to the dose of radiation.

Pain treatment according to local guidelines at PRC led to most of the patients (67% at MP51–60) experiencing only mild pain (NRS 0–4). This finding is consistent with one earlier study where mild pain intensities among patients with HNC undergoing RT were also reported [37]; however, that study did not report what pain treatment strategies were used and therefore its findings cannot be used to inform clinical practice from a pharmacological point of view. Thus, it is possible to achieve adequate pain control in a majority of HNC-patients receiving RT. This is not a self-evident finding as many studies have shown that pain in this group of patients is difficult to treat [13, 18, 38, 39].

All patients were referred to the PRC within two weeks before, and up to two weeks into, RT. This early surveillance strategy probably affected outcomes as it made early intervention possible. It has been reported that early pain management, i.e. pre-emptive medications during post-operative period for cancer patients, was associated with increased pain control [40]. In addition, early analgesic treatment might diminish the occurrence of chronic pain as well as reduce the physiological and psychological consequences of severe pain [22, 41, 42].

Based on early and continuous follow-up contacts, opioid doses should be adjusted according to the patient's reported symptoms [22]. On the other hand, side effects can sometimes limit the dose of opioids, leading to unrelieved pain [43]. The interval between dose escalations should be long enough to allow for a steady state; concerning transdermal patches the interval should be between 3 and 6 days [22].

However, even in the present study, there is still a subgroup of patients who had moderate to severe pain despite pain treatment according to local guidelines (PRC). In our material, it seems clear that these treatment-refractive patients are to be found among patients with clinically significant oral mucositis; at MP51–60, only two patients with mucositis grade 0–1 had moderate pain and none had severe pain (Figure 4). Hence, in the absence of significant mucositis, good pain relief can be expected with comparatively low levels of opioids (Figures 4 and 5). These findings are consistent with two previous studies where pain in the oral cavity was found to increase with increased ulceration surface area and more extensive mucositis [44, 45].

We chose to specifically analyse patients with oral mucositis grade 2–4. We found that patients with mild pain did not receive more opioids than the moderate-to-severe pain group; if that had been the case, higher doses of

opioids in the moderate-to-severe pain group would have been the obvious answer to the problem. Of course, it could be argued that the moderate-to-severe pain group should unequivocally have received much *higher* doses than was actually the case, and that one should therefore not be content with ensuring that they, on average, at least did not get less than those whose pain turned out to be well-controlled. However, in our opinion, this simple line of reasoning disregards some important facts. First, it is important not to automatically conflate the categories of “more” and “better”. Second, as can be seen in Figure 6, there is a wide range of dosages (0–400 mg OME/day); while indeed some patients might have been undertreated, it seems too simplistic to argue for higher doses *in general* and for all patients. Third, doses must be related to the speed of escalation. At MP51–60, the median dose in the moderate-to-severe pain group was 120 mg OME/day, a rather substantial dose for patients who have rather recently started their opioid treatment. Our clinical impression is that we have generally increased opioids in a rather proactive fashion, and that substantially increasing the “inclination” of the opioid escalation curve does not seem warranted. Treatment aggressiveness should be counterbalanced by thoughtful consideration of the risk of the troublesome and potentially dangerous side-effects of opioids. In this study, treatment was careful with standardized titration, i.e. at least three days between increases in opioids to avoid opioid related side effects.

So far, there is insufficient evidence from the literature to advise on a specific pharmacological management for pain in HNC patients. The current recommendation for these patients is simply to follow the WHO pain ladder, with some add-ons recommendations to use local drugs (e.g., lidocaine mouthwash) [14–16]. Local guidelines at the PRC are in line with this, and a strength of the present study is that it describes the outcome of such a strategy in clinical practice. Gender, age and smoking habits were generally representative of patients with HNC (which in itself suggests good validity).

There are, however, obvious limitations. The sample size of this uncontrolled study was relatively small ($n=63$) and therefore might be insufficiently representative for populations of patients with HNC, conditions that limit the generalisability of these findings. Detailed subgroup analysis in such a small sample is also fraught with difficulties. In addition, it is possible that the patients who agreed to participate were those who were least ill (i.e., risk of selection bias), which also might affect the external validity. Notably, the patients are also affected by other stressors that the study did not measure, for example nausea and vomiting, conditions which can affect how the

patients report pain [5, 6, 46]. Furthermore only 16% of the patients were treated with pregabalin. Randomized controlled studies of adjuvant pregabalin for this group of patients would be of value.

In conclusion, this real-life study indicates that severe RT-related pain in HNC patients is not a fatality. However, further studies are needed to develop better pain treatment strategies for those patients who do develop severe oral mucositis-related pain despite adequate opioid treatment.

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