Original Article

Feasibility and patient reported tolerance of cryotherapy with Cooral mouth cooling device in patients undergoing radiation therapy (CooRay): a pilot study

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Background: Radiation-induced oral mucositis (RIOM) is a major side-effect of (chemo)radiation (CRT) of patients with head and neck cancer (HNC). This study tries to establish a novel cryotherapy (CyT) method using a mouth care device (MCD; Cooral®, BrainCool AB, Lund, Sweden) to prevent RIOM.

Methods: Patients were non-randomly assigned to use the MCD after every radiotherapy session for 30–60 minutes. Subjects were asked to answer daily questionnaires assessing tolerability of the intervention. Mucositis was assessed at baseline, once weekly and at weeks 1/3/6 after CRT. The primary endpoint was patient tolerance, defined by the time the MCD was used and the patients' perception. Secondary outcomes were the degree (CTCAE v5.0) and duration of RIOM.

Results: Ten patients were eligible with a mean age of 62 years. Four patients received concurrent platinum-based CRT, whereas the others received radiotherapy alone. Overall, 214 CyT sessions were performed (73% of planned CyT sessions). The mean daily CyT duration was 48 minutes (range, 30–60 minutes). All patients reported cooling as comfortable. Nine completed the intervention, one terminated it early due to hypersalivation. No Grade 4 RIOM was observed. Grade 3 mucositis was observed in 4 and Grade 2 in 3 cases.

Conclusions: The Cooral System was well tolerated, with a duration of application that was acceptable for most patients. We concluded that the MCD can be safely used in patients undergoing CRT. A prospective phase II trial, assessing the efficacy in preventing RIOM, is planned.

Keywords: Cryotherapy (CyT); oral mucositis (OM); head and neck cancer (HNC)

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Introduction

Worldwide 900,000 patients are diagnosed with head and neck cancer (HNC) every year, including 250,000 in Europe, accounting for four percent of all cancer cases (1,2). The major curative treatment options are surgery and (chemo)radiation (CRT), or a combination thereof (3). One of the major side effects of CRT or radiotherapy (RT) in the head and neck area is oral mucositis (OM) (4,5).

Patients receiving RT for HNC have a risk of 30–80% to develop radiation-induced oral mucositis (RIOM) (5-7), and in some cases the incidence is as high as 80–90% (8). The severity of RIOM increases in case of CRT (7-9). OM can be extremely painful and causes reduction of oral intake due to oral pain leading to dehydration or malnutrition. Additionally, it can be a route of systemic infections. Those effects can compromise the course of treatment, hence affecting treatment outcome and impairing the patient's quality of life (6). Moreover, OM is linked to requirement of opioid drugs, extended hospital visits, and potential socio-economic impact (10,11). Several guidelines for the prevention or treatment of OM have been proposed with differences between etiologies of OM (12-15). However, the management remains challenging as there is no gold standard treatment. Management of OM mainly focuses on pain relief (16). Apart from recommendations such as general oral care in mucositis management, there is evidence for the use of anti-inflammatory agents such as benzydamine, photobiomodulation with low-level laser (light) therapy, coating agents such as sucralfate, growth-factors and cytokines such as palifermin or the use of natural agents such as glutamine or honey (11,12). More recently, there is growing evidence for the use of probiotics in preventing and treating RIOM (17-19). Another modality that has previously been described is cryotherapy (CyT), which is widely recommended in high dose chemotherapy prior to stem cell transplantation (16,20). One common application of CyT is the use of ice cubes. However, these have downsides such as chills, numbness, taste disturbance, headache or teeth sensations. In addition, it remains uncertain if all regions of the oral cavity are cooled equally. Moreover, a continuous supply of ice chips is necessary during treatments. Previous studies have also investigated the effect of CyT in preventing RIOM, with two randomized trials having shown promising effects (21,22). However, due to insufficient evidence, no recommendations have been made on CyT using ice chips (20). Walladbegi *et al.* have successfully investigated an alternative CyT method with an intraoral cooling device in patients receiving chemotherapy for multiple myeloma (10,23,24). Although Walladbegi *et al.* have shown the positive effects of CyT with an intraoral cooling device on chemotherapy OM side effect, this is the first study investigating the effect of an alternate CyT method other than ice chips in patients with HNC receiving RT. The aim of this pilot study was to test the feasibility of the method employed by Walladbegi *et al.* in patients receiving RT or CRT for HNC. We present this article in accordance with the TREND reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1313/rc).

Highlight box

Key findings

- Patients found cooling tolerable and acceptable.

What is known and what is new?

- Oral mucositis is a side effect of radiation therapy of head and neck region. Oral mucositis affects treatment outcomes and diminishes quality of life.
- Cryotherapy shows promising in alleviating symptoms of oral mucositis. Feasibility and tolerability of a cooling device in radiation therapy was tested.

What is the implication, and what should change now?

- Patients found the cooling device tolerable and acceptable.
- Future studies on the effectiveness of the cooling device on treatment and prevention of oral mucositis will be performed.

Methods

Eligibility and ethical considerations

Patients who were admitted to the Department of Radiotherapy and Radiation Oncology at University Hospital, Basel were eligible. All patients had been diagnosed with HNC and were scheduled to initiate RT or CRT as part of their standard treatment. Recruitment was performed as voluntary self-selection. Inclusion and exclusion criteria are listed in *Table 1*. All patients signed an informed consent before entry into the study. The study was approved by the local Institutional Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz, approval number: 2021-00887) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The trial was registered at clinicaltrials.gov (identifier: NCT04915599).

Cooral oral cooling device

In the present study CyT was delivered using the Cooral System. The Cooral System consists of an energy control unit (ECU) with a computerized control system (ECU 200-refrigeration and control unit), to which an intraoral cooling device is connected (Cooral Mouth device; *Figure 1*). Sterile water is circulated from the tank through the plastic tubes of the intraoral device, designed to specifically cool

the areas where the major arteries enter the oral cavity. The Cooral System pushes temperature-controlled coolant into the Cooral Mouth device. This results in heat exchange between the Cooral Mouth device and the patient's oral mucosa. The coolant temperature is controlled by a thermostat and its temperature probe. The temperature is controlled independently and the device generates alarms if the thermostat malfunctions and the temperature becomes hazardous. The Cooral System maintains a controlled coolant temperature at 8 ℃ during the entire treatment period. Any deviations from the default temperature are automatically adjusted by the system.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria
Age ≥18 years
KPS ≥60%
Histologically proven malignancy of the head-and-neck
Indication for definitive or adjuvant radiotherapy or (chemo)radiation
IMRT Radiotherapy of the head-and-neck tumor
Dmin oral mucosa ≥30 Gy (EQD2, α/β=10)
Simultaneous use of oral mouth washes in accordance with the treating physician
Life expectancy >9 months
Exclusion criteria
Preexisting chemotherapy associated oral mucositis within last 3 months
Previous radiotherapy to the head-and-neck
Chemotherapy within last 6 weeks
Dmin oral mucosa ≤30 Gy (EQD2, α/β=10)
Oral cryotherapy within last 6 weeks
Simultaneous use of any other form of oral cryotherapy
Ethylen-Vinyl-Acetat-Allergy
Macroscopic tumor of the oral cavity or known close margin resection of oral cavity tumors

KPS, Karnofsky Performance Status; IMRT, intensity-modulated radiation therapy; EQD, equivalent dose.

Method of CyT

Patients were treated at the Department of Radiotherapy and Radiation Oncology at University Hospital, Basel. Participation in the study was entirely voluntary, and no financial or other incentives were provided. Note that this was a feasibility study and thus, no calculation of sample size was performed. All interventions were administered by trained nursing staff under the supervision and guidance of the treating physician. All patients included in the study were provided standard education about the importance of maintaining standard oral hygiene (brush teeth 2–3 times a day using a soft bristle toothbrush with nonabrasive toothpaste and floss gently 1–2 times a day) before initiating the study. Patients received an individual plastic mouthpiece weekly. After every RT fraction a 60-minute oral cooling period was started using the Cooral System. Patients remained under the visual surveillance of trained staff over the whole period. In case of discomfort, three breaks of maximum 10 minutes each were accepted. Any longer break led to interruption of the procedure on that specific day. CyT of less than 30 minutes was not considered for further evaluation. Patients were allowed to choose a total

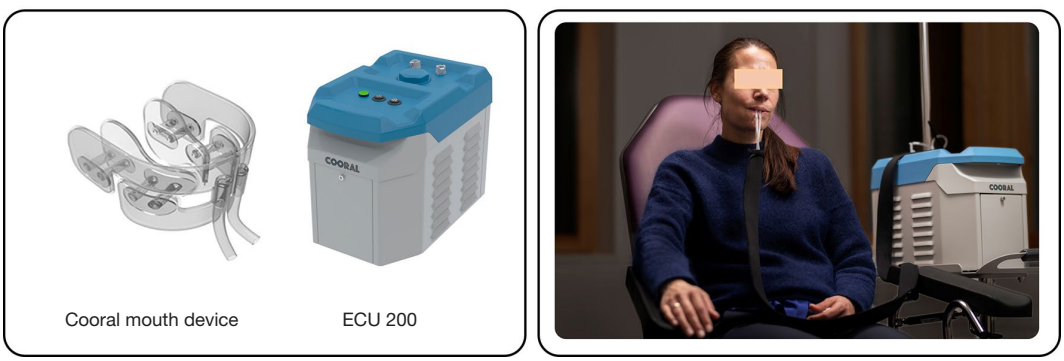

Figure 1 Cooral System (BrainCool AB, Lund, Sweden) consisting of ECU 200 cooling unit to which the mouth device is connected through a hosing system (left panel). Cooral System cooling device operation (right panel). This image is published with the participant's consent. ECU, energy control unit.

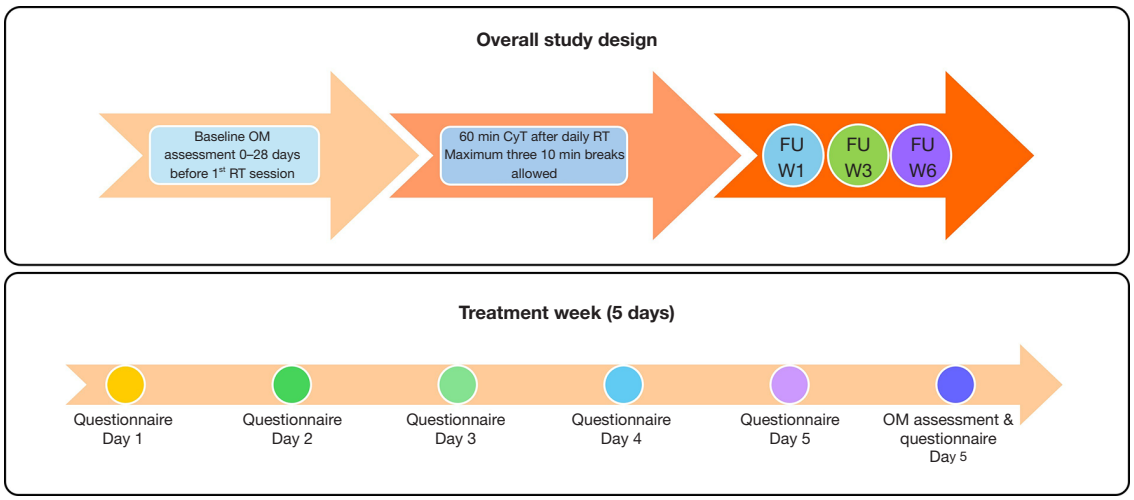

Figure 2 Overall study design (top panel): baseline OM assessed at day 0 (before the start of RT). Maximum 60 minutes of CyT after each RT session. Assessment of OM at one, three and six weeks following completion of RT. Treatment week (bottom panel): regular daily questionnaire with addition of clinical assessment on 5th therapy session. CyT, cryotherapy; FU, follow-up; OM, oral mucositis; RT, radiotherapy.

treatment period of 30 minutes before start of the individual CyT session. In this case no breaks were allowed. Patients were allowed to skip CyT procedures. If patients elected to skip CyT procedures, this was accepted and documented by the study team. The number of RT and CRT sessions for each patient varied based on several factors, including the stage of the cancer, its location, and the patient's overall health. Overall, treatments were delivered in daily fractions (sessions) over a course of several [5–7] weeks leading to 25–35 sessions in total (*Figure 2*).

Patient report

As the primary outcome measure, patients were asked to complete a self-reported questionnaire [see supplementary file (Appendix 1)] at the end of every CyT session. Questions comprised of comfort of wearing and handling the intraoral device, estimation of CyT duration, possible discomforts such as hypersalivation, choking, dyspnea, toothache, headache, numbness or nausea. Answers were graded from comfortable to highest level of discomfort. Additionally, patients were asked for their overall subjective sensation of oral cooling on oral pain.

Mucositis assessment

Once a week a mucositis assessment was performed by a trained physician to obtain a mucositis score (Common Terminology Criteria for Adverse Events; CTCAE version 5.0) (25). Eleven Regions of the oral mucosa were investigated for pain, erythema und ulceration: lower and upper lip, right and left buccal mucosa, right and left lateral tongue, back of the tongue, hard palate, soft palate. CyT ended with the last RT fraction. Follow up with mucositis assessment was continued at weeks one, three and six after termination of treatment, to assess how RIOM further developed. CTCAE v5.0 is widely used in oncology to standardize the reporting of side effects from treatments. The inter-rater reliability of CTCAE v5.0 has been evaluated in a previous study (26). While the CTCAE has shown good agreement in some areas, the reliability may vary depending on the nature of the adverse event (e.g., physical symptoms like rash *vs.* subjective symptoms like fatigue). The inter-rater reliability was reported as 0.6 denoting moderate level of reliability (26). The content validity of CTCAE v5.0 is supported by the fact that it covers a comprehensive range of adverse events relevant to cancer therapy ensuring its coverage of clinically meaningful toxicities (25). In summary, the psychometric evaluations (particularly inter-rater reliability) of CTCAE v5.0 have been found to be acceptable. The mucositis assessment score and duration of RIOM were considered as secondary outcome measures.

Radiotherapy

RT planning was computed tomography (CT) and magnetic

Table 2 Patient characteristics

Patient characteristics	Values
Tumor localisation	
Oral cavity	2
Oropharynx	4
Hypopharynx	1
Larynx	1
Thyroid	1
Parotid	1
Age (years)	62 [47–76]
Sex	
F	2
M	8
Tumor directed therapy	
Chemoradiation	4
Radiotherapy	6
Percentage of CyT sessions performed (total/planned)	73% (214/293)
CyT session duration in minutes	48 [30–60]
Oral cavity Dmean/EQD2 (α/β=10, Gy)	35.2 [12–58]
Oral cavity Dmax/EQD2 (α/β=10, Gy)	60.4 [47.1–72.6]
Patients' perception	
Comfortable	9
Reducing pain	6
Degree of mucositis (CTCAE v5.0)	
1	3
2	3
3	4
4	0

Values are presented as n or mean [range] unless otherwise specified. EQD, equivalent dose; SD, standard deviation.

resonance imaging (MRI) based. A simulation CT with an immobilization mask was performed approximately one week before treatment started. Contouring and planning were performed using the Monaco® (version 5.51.10; Elekta Inc., Stockholm, Sweden) treatment planning software. Auto-contouring of organs at risk was performed using Limbus Contour (version 1.4.0; Limbus AI Inc., Regina, Canada), with manual correction as needed by the planning physician. RT was delivered using volumetric modulated arc therapy (VMAT) technique on Elekta Synergy® (Elekta Inc., Stockholm, Sweden) linear accelerators. Patients undergoing RT or CRT in curative intent were treated using a simultaneous integrated boost (SIB) approach based on clinical target volumes (CTVs) as advised by the Danish Head and Neck Cancer Group (DAHANCA) guidelines (27). For definitive CRT, our standard approach was to deliver 35 fractions of RT to a total dose of 52.5 Gy (CTV1; elective nodal regions), 61.25 Gy (CTV2; macroscopic disease with a CTV-margin of 10 mm), and 70 Gy (CTV3; macroscopic disease with a CTV-margin of 5 mm), equating to single doses of 1.5, 1.75 and 2 Gy, respectively. For adjuvant CRT, our standard approach was to deliver 33 fractions to a total dose of 51.15 Gy (CTV1; elective nodal regions) and 61.05 Gy (CTV2; primary and nodal tumor bed with 10 mm CTV-margin), equating to single doses of 1.55 and 1.85 Gy, respectively.

Chemotherapy

Concurrent CRT was given in case of definitive CRT approaches or in the adjuvant setting in the presence of risk factors such as extranodal extension (ENE) or positive resection margins (28). Chemotherapy of choice was cisplatin, either given in weeks one, three and seven as intravenous infusion at 100 mg/m^2 body surface or weekly at 40 mg/m^2 body surface (29). For CRT with curative intent, a cumulative cisplatin dose of 200 mg/m^2 body surface was the objective (30).

Statistical analysis

For the purpose of this feasibility trial only descriptive statistical analyses were performed. These analyses were performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

Results

Patients

Out of 13 eligible patients, ten (two females and eight males) patients with a mean age of 62 years (range, 47–76 years) consented to participation in the study between June, 2021 to April, 2022. Descriptive data from all ten patients are presented in *Table 2*. Primary tumor locations were oral cavity [2], oropharynx [4], hypopharynx [1], larynx [1],

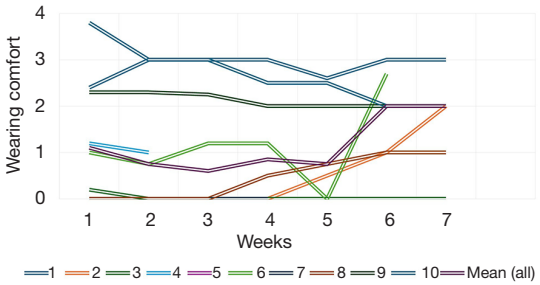

Figure 3 Wearability of the Cooral device for 10 patients represented as colored lines at the basis of the graph. On x-axis are treatment weeks. Patient number 4 (blue line) interrupted radiotherapy after eight sessions.

thyroid gland [1]. Tumors were predominantly squamous cell carcinomas (SCC; n=8). One patient had anaplastic thyroid carcinoma, and one patient had a parotid gland metastasis of an adenocarcinoma of the lung. All patients with SCC received RT in the adjuvant setting. Nine patients were treated with curative intent; four receiving CRT and five RT alone. Only the patient with the parotid gland metastasis was treated with palliative intent. Even though one patient had Grade 3 chronic obstructive pulmonary disease (COPD) the therapy sessions were completed without complications.

Duration

Nine out of ten patients completed CyT treatments. One male patient abandoned treatment due to hypersalivation but continued with adjuvant CRT. Out of the 293 planned CyT sessions, 214 sessions (73%) were performed. Sessions were missed due to: chemotherapy-induced nausea or pain after implantation of a percutaneous endoscopic gastrostomy (PEG)-tube (25), conflicting appointments (21), general tiredness/fatigue (14), respiratory syncytial virus (RSV)-related isolation (7), hypersalivation, coughing and choking (5) and temporary malfunction of the device (water spillage) (5). The mean daily CyT duration was 48 minutes (range, 30–60 minutes). Five patients completed at least 57 minutes of the daily 60-minute sessions, and one patient out of the five completed the entire 60-minute CyT every day without interruptions. Two patients opted for mainly 30-minute therapy sessions. The patient who abandoned treatment due to hypersalivation completed only 8 out of 33 sessions.

Comfort

Overall, at the end of the therapy, no Grade 4 discomfort of using the Cooral device was reported. One patient rated the Cooral device as “uncomfortable” (Grade 4) in the first week of treatment. After the mouthpiece was replaced with a new one from the manufacturer the same patient reported Grade 3 comfort for the following weeks and even a comfort grade of 2 in the last week. The other patients gave mainly constant ratings on the tolerability of the device with sporadic variation of the grade of discomfort. The reported tolerability varied by no more than one point on the grading scale. There was no significant increase of discomfort reported by the end of the treatment (*Figure 3*).

Sensation of cold

None of the patients perceived the cold sensation in the mouth as painful. There was a clear preference for the cold sensation in the mouth during the treatment as almost all patients perceived it as pleasant (93% of the sessions were perceived as pleasant). Three of the patients consistently reported the cold sensation as being pain relieving (100% of the reports from those patients). One of them inconsistently reported the unpleasant feeling (31.6% of the sessions) of cold in the mouth across the sessions. Two additional patients perceived the cold as pain relieving as the treatment was approaching the end.

Hypersalivation

In regards to hypersalivation, seven out of ten patients reported a reduction of the salivation during the cooling sessions as the treatment progressed. One of the seven patients reported a reduction from Grade 3 hypersalivation at the beginning to Grade 0 at the end of the treatment. The discomfort caused by the hypersalivation for those patients mostly ameliorated from the initial maximum grade of 3 to a maximum end grade of 1. More than half of the patients (60%) reported a discomfort grade of 0 by the end of the treatment.

One patient submitted a hypersalivation grade of 2 in the first week with an increase to Grade 3 in the following weeks. The grade for the sensation of discomfort caused by the saliva was equal to the grade of hypersalivation. One patient reported inconsistently between Grade 0, 1 and 2. For this patient the discomfort level of hypersalivation also

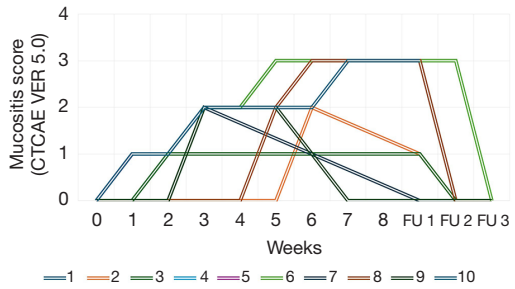

Figure 4 Development of radiation-induced oral mucositis during treatment and FUs at 1, 3 and 6 weeks post radiotherapy. Patients depicted as colored lines at the basis of the graph. Baseline is week 0. Treatment weeks are represented on the x-axis (1 to 8). FU, follow-up.

varied between 0, 1 and 2. One tracheotomized patient described severe hypersalivation leading to coughing attacks, finally leading to discontinuation of the trial treatment after eight CyT sessions.

Mucositis

The RIOM score increased as the RT progressed to the maximum grade of 3 for four patients. For two patients there was an increase of the RIOM score to a maximum grade of 2 with a subsequent amelioration by the end of the treatment to no evidence of RIOM. One patient had an increase of the RIOM grade to 1 with a normalization by the end of the treatment. No Grade 4 RIOM was observed. None of the patients showed remaining signs of RIOM at the last follow-up (*Figure 4*).

Discussion

To the best of our knowledge, we present the first study investigating the use of a novel oral cooling device in patients undergoing CRT for HNC. OM is a severe side effect of RT or CRT of head and neck malignancies, often compromising the course of treatment. Despite OM's frequency, impact on patients, and health and economic costs, there are currently limited evidence-based options for the prevention of OM.

Since the treatment of HNC is already very expensive, the treatment of complications caused by the therapy, such as OM, is an added economic burden on patients. As per a study by Elting *et al.* performed in 2007, the presence of OM in patients with HNC having RT was associated with increased use of costly resources, such as hospital days and emergency department visits (31). The increased use of resources among patients with OM led to a corresponding increase in cost, averaging approximately USD 1,700 among patients who experienced Grade 1–2 OM and USD 3,600 among those who developed Grade 3–4 OM. After adjustment for differences in site and stage of disease, lymph node involvement, fractionation, age, and comorbidities, the mean cost of RT alone was USD 14,646 (95% CI: USD 11,801–USD 18,178) among patients without OM and USD 20,624 (95% CI: USD 19,227–USD 22,122) among those with OM (P=0.006). Follow-up costs were minimal among patients who received RT alone, although they were higher among patients who had experienced OM (31).

Improvements in radiation techniques such as the use of IMRT or VMAT have previously had an impact on the rate and degree of RIOM (5,32). Besides, mucositis prevention with general oral care is recommended by the Multinational Association of Supportive Care in Cancer (MASCC) guidelines (12). Other modalities to prevent mucositis such as palifermin or amifostine have been investigated in studies and showed symptom relief (15,33,34). However, both showed side effects up to Grade 5 toxicities so that no overall recommendations can be made (33,35). Oral CyT, mostly done with ice chips, has been established as a standard method to prevent mucositis during high dose or 5-fluorouracil (5-FU) based chemotherapies for hematologic diseases (20). The effect is caused by vasoconstriction of mucosal capillaries that reduces the perfusion of basal cells with the cytotoxic substance (4). RIOM, however, has a different pathogenesis, with radiation-induced lysis of epidermal cells resulting in reduced proliferation of basal cells (21). Cooling itself does not prevent this process but effects the nociception. By ameliorating the symptoms, RIOM may be better tolerated. Hence the use of analgesics, tube dependency or hospitalizations could be reduced. Two prior prospective trials have investigated the effect of oral cooling on RIOM (21,22). Both studies used ice chips in the interventional group, while the control group did not receive any specific RIOM prevention measure, besides general oral care. Soliman *et al.* described a benefit especially in middle and at the end of RT compared to the control group (22). Kakoei *et al.* described a trend towards pain reduction (21). In both studies, ice chips were used for only five minutes before and after RT. Both were able to show some effects, however without statistical significance. Besides, both had methodological limitations so that no recommendations could be drawn (16,20). Walladbegi *et al.* addressed this issue by adopting a novel CyT modality.

Sterile water cooled by a thermostat to 8 ℃ circulates into a mouthpiece that provides cooling to the intraoral mucosa. It was possible to show in a prospective trial with 182 patients who received chemotherapy for multiple myeloma or lymphoma that OM can be significantly reduced using the oral cooling device compared to ice chips (24).

The aim of our study was to adopt this method for patients undergoing RT for HNC. We used a cooling system to avoid contact of the mucosa with water. This is an advantage compared to the use of ice chips, as ice chips can be contaminated and hence open pathways for infections in patients with a weakened immune system (36,37). We also reduced the risk of contamination by disinfecting the mouthpiece after every session of CyT and changing the mouthpiece weekly.

There were apprehensions that a mouthpiece situated between the inner part of the lips and gingiva will lead to discomfort, making the used system unsuitable in patients under CRT. Even though the mouthpiece was made out of a soft plastic material it had some rigidity. Out of 13 eligible patients, ten completed the trial. However, some cooling sessions were missed either due to conflicting appointments or due to discomfort caused by nausea or hypersalivation. Based on previous data we performed daily cooling of at least 30 minutes up to 60 minutes with three optional breaks of maximum 10 minutes each (23,24,36). This was feasible in most cases. Two patients preferred to undergo only 30 minutes of CyT every day. Our experience was that half an hour of CyT had an ameliorating effect upon RIOM. Most patients described cooling as comfortable, whilst three reported a decrease in oral pain. We chose to slowly reduce the temperature from 19 to 8 ℃ instead of immediately starting at a low temperature to avoid uncomfortable sensation at the teeth and gums. Walladbegi *et al.* described in their study with healthy volunteers that higher temperature is far better tolerated, however we did not experience less tolerability whilst temperature decreased (10,37). Studies investigating this CyT method in combination with chemotherapy alone, are proceeding with oral cooling during chemotherapy infusion (36). We opted against CyT during radiation, since vasoconstriction might impact the treatment efficacy.

The present study was a feasibility trial with a small patient number, not designed to investigate the effect of oral cooling on RIOM. Patients with HNC, regardless of type or treatment, were included. Most patients underwent postoperative radiotherapy alone, which may be more tolerable than definitive CRT. However, patients did not only express comfort due to the cooling, but also amelioration of RIOM-associated pain during the procedures. Most patients tolerated more than 45 minutes of CyT, while only one patient accepted the scheduled 60 minutes every day. This and the observed amelioration of RIOM suggests that a shorter cooling period may be sufficient, which was also shown in earlier trials (21,22). Wearing comfort scores were mostly consistent showing sporadic variations. This suggests that the feeling of discomfort was mainly attributed to the mouthpiece, which can be adjusted, and to the subjective perception of the patient. One patient discontinued the trial after eight cooling sessions due to hypersalivation and tracheotomy-caused dysphagia. The timing of CyT remains unclear. In other words, is one long cooling session more beneficial or whether multiple short cooling periods provide better RIOM prevention. Since two patients perceived the cooling as pain relieving towards the end of treatment, this might suggest a more noticeable effect of the cooling during later treatment phases. However, it remains unclear if oral cooling should start at the beginning of CRT, or after two to three weeks of treatment, when the onset of RIOM may typically be expected.

Conclusions

Oral CyT with the Cooral System is feasible and well tolerated by patients undergoing CRT. Although signs of pain relief were observed, no statistical analysis was performed due to limitations of the study design. Further investigation is needed to statistically evaluate the effect of oral cooling on RIOM, and to define its optimal application during the treatment period. Additionally, future studies are planned to include comparisons between patients receiving cooling and a control group.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1313/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1313/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1313/coif). S.D.J. is an employee of BrainCool AB which produced the cooling device for current study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients signed an informed consent before entry into the study. The study was approved by the local Institutional Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz, approval number: 2021-00887) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The trial was registered at clinicaltrials.gov (identifier: NCT04915599).

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