Clinical and Translational Radiation Oncology 20 (2020) 13–18

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

# The association between oral candidiasis and severity of chemoradiotherapy-induced dysphagia in head and neck cancer patients: A retrospective cohort study

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ARTICLE INFO

*Article history:*
Received 27 June 2019
Revised 21 October 2019
Accepted 26 October 2019
Available online 31 October 2019

*Keywords:*
Head and neck cancer
Dysphagia
Candidiasis

ABSTRACT

*Background and purpose:* Concurrent chemoradiotherapy (CCRT) for head and neck cancer (HNC) is a risk factor for oral candidiasis (OC). As *Candida* spp. are highly virulent, we conducted a retrospective study to determine whether OC increases the severity of dysphagia related to mucositis in HNC patients.
*Patients and methods:* We retrospectively analyzed the cases of consecutive patients with carcinomas of the oral cavity, pharynx, and larynx who underwent CCRT containing cisplatin (CDDP) at our hospital. The diagnosis of OC was based on gross mucosal appearance. We performed a multivariate analysis to determine whether OC was associated with the development of grade 3 dysphagia in the Radiation Therapy Oncology Group (RTOG) Acute Toxicity Criteria. The maximum of the daily opioid doses was compared between the patients with and without OC.
*Results:* We identified 138 HNC patients. OC was observed in 51 patients (37%). By the time of their OC diagnosis, 19 (37%) had already developed grade 3 dysphagia. Among the 30 patients receiving antifungal therapy, 12 (40%) showed clinical deterioration. In the multivariate analysis, OC was independently associated with grade 3 dysphagia (OR 2.75; 95%CI 1.22–6.23; p = 0.015). The patients with OC required significantly higher morphine-equivalent doses of opioids (45 vs. 30 mg/day; p = 0.029).
*Conclusion: Candida* infection causes refractory dysphagia. It is worth investigating whether antifungal prophylaxis reduces severe dysphagia related to candidiasis.


## 1. Introduction

The standard curative approach for locally advanced head and neck cancer (HNC) is concomitant chemotherapy containing cisplatin (CDDP) and radiotherapy (RT) (CCRT; concurrent chemoradiotherapy) [1,2]. One of the most frequent adverse events in CCRT for HNC is severe dysphagia related to mucositis [3,4]. CCRT-associated dysphagia is detrimental to the patients' quality of life and increases the need for nutritional support, and >50% of the HNC patients undergoing CCRT require either enteral or parenteral nutrition (PN) [5,6]. Several approaches to the prevention of dysphagia have been explored, including intensity-modulated RT (IMRT) to reduce the dose to the pharyngeal constrictors, and de-escalated CCRT regimens [7–9]. However, these approaches are not recognized as standard treatments. It is crucial to elucidate the pathophysiology of CCRT-associated dysphagia and to establish an effective prophylactic approach [10].

*Candida* spp. colonize the upper aerodigestive tract in 70% of HNC patients [11,12]. Under physiological conditions, the virulence

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https://doi.org/10.1016/j.ctro.2019.10.006
2405-6308/

of *Candida* spp. is suppressed by mucosal epithelium and T cells [13], whereas the breakdown of the mucosal barrier leads to opportunistic candidiasis. Invasive candidiasis is associated with high morbidity and mortality rates [14]. It has thus been speculated that mucosal candidiasis causes oropharyngeal dysfunction in HNC patients undergoing CCRT. Busetto et al. conducted a prospective cohort study (MIR; Mycosis in Radiotherapy) and analyzed the relationship between the development of oral candidiasis (OC) and various toxicity outcomes in HNC patients undergoing curative RT [15]. They reported that among the patients with OC, the incidences of high-grade mucositis and dysphagia were significantly increased compared to the patients without OC.

Several studies have investigated OC in HNC patients undergoing RT [11,15–17]. These reports, which were written before CDDP-based CCRT had become a common practice, suffer from the heterogeneity of concomitant chemotherapy. The concomitant administration of RT and CDDP synergistically causes severe mucosal damage [18] and is thought to aggravate the symptoms of OC. We conducted the present study to elucidate (1) the severity of dysphagia associated with OC, (2) the impact of OC on the magnitude of dysphagia and the pain caused by mucositis, and (3) the response to antifungal agents among HNC patients undergoing CDDP-based CCRT.

## 2. Patients and methods

### 2.1. Eligible patients

Consecutive patients with carcinomas of the oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx who were treated at our radiation oncology department during the 7+-year period between January 2011 and May 2018 were identified through an institutional cancer registry. The inclusion criteria were: (1) undergoing curative CCRT containing CDDP, and (2) being capable of oral intake at the start of the CCRT. Staging was done according to the 7th version of the American Joint Committee on Cancer (AJCC) TNM Classification. The patients' concurrent chemotherapy regimen was either (*a*) 5-fluorouracil (5FU) 700 mg/m$^2$ on days 1–5 and 29–33, plus CDDP 70 mg/m$^2$ on days 1 and 29, or (*b*) CDDP 80 mg/m$^2$ on days 1, 22, and 43. In general, we administered the CDDP + 5FU regimen from 2011 to 2014, and we administered the CDDP regimen in 2015 or later as concomitant chemotherapy.

All patients underwent CT simulation and 70 Gy in 35 once-daily fractions of RT delivered with 4–10 MV linear accelerators. The details of the dose prescription were 44–46 Gy to the elective regional nodes and 70 Gy to the gross tumor volume. The nasopharyngeal cancer patients treated in 2013 or later underwent IMRT, and the other patients underwent 3D conformal RT. The maximal dose to the spinal cord was kept at <50 Gy. In the IMRT planning, the mean dose to the parotid glands was kept at $\leq$25 Gy. No thresholds were set for the dose to the pharyngeal constrictors.

We used an opt-out approach in which eligible HNC patients and their family members were advised to contact the researchers only if they declined to be included in the study [19]. The study was approved by the institutional review board of our hospital (no. 2018–0127).

### 2.2. Data collection

All patients were hospitalized for the entire period from the start of their CCRT until their recovery of oral intake. Otolaryngologists examined the oropharyngeal mucosa with a fiberoptic scope 2×/week. Specialist dentists or dental hygienists provided oral care 1×/week. Acetaminophen and long-acting and short-acting opioids were prescribed based on the severity of the pain caused by mucositis [20]. The diagnosis of OC was based on the gross mucosal appearance, and mycological confirmation was not mandatory [15,21]. It was left to each physician's judgement whether to initiate antifungal treatment. Both topical and systemic antifungal agents were used [22].

A radiation oncologist (SH) reviewed all of the patients' medical charts. The severity of dysphagia was graded according to the Radiation Therapy Oncology Group (RTOG) Acute Toxicity Criteria [23]. At our institution, the use of a specific mucositis severity scale is not mandatory; we used the opioid dose as a surrogate for the severity of the pain caused by mucositis. The maximal daily dose of long-acting opioids was converted into the intravenous morphine-equivalent dose [24,25]. In the patients who developed OC, the RTOG grade of dysphagia was recorded at the time of OC diagnosis. The patients' responses to antifungal agents was judged retrospectively: "deterioration" corresponded to the worsening of mucosal lesions, the increase in opioid doses, or the initiation of nutritional therapy within 14 days of antifungal treatment [26], and "improvement" corresponded to the complete or partial resolution of symptoms without deterioration. The other responses were classified as "indistinguishable".

### 2.3. Statistical analyses

We first used Fisher's exact test to investigate the relationships between the development of OC and various clinical factors including age, gender, chemotherapy, performance status (PS), primary site, presence of diabetes mellitus (DM), and stage. We tested the

**Table 1**
Baseline characteristics of the HNC patients (n = 138).

| | CDDP + RT n = 88 | CDDP + 5FU + RT n = 50 | *p* |
|---|---|---|---|
| Age (median, range) | 65 (37–78) | 66 (32–78) | 0.635 |
| Gender | | | |
| Male | 77 (88%) | 46 (92%) | 0.572 |
| Female | 11 (12%) | 4 (8%) | |
| Histology | | | |
| SqCC | 88 (100%) | 49 (98%) | 0.362 |
| AC | 0 | 1 (2%) | |
| Primary site | | | |
| Hypopharynx | 35 (40%) | 17 (34%) | 0.9 |
| Larynx | 8 (9%) | 4 (8%) | |
| Nasopharynx | 17 (19%) | 13 (26%) | |
| Oral cavity | 3 (3%) | 2 (4%) | |
| Oropharynx | 25 (28%) | 14 (28%) | |
| Stage | | | |
| II | 11 (12%) | 13 (26%) | 0.033 |
| III | 29 (33%) | 8 (16%) | |
| IV | 48 (55%) | 29 (58%) | |
| ECOG PS | | | |
| 0 | 7 (8%) | 2 (4%) | 0.771 |
| 1 | 79 (90%) | 47 (94%) | |
| 2 | 2 (2%) | 1 (2%) | |
| RT techniques | | | |
| 3DCRT | 71 (81%) | 44 (88%) | 0.345 |
| IMRT | 17 (19%) | 6 (12%) | |
| Dose (Gy; median, range) | 70 (66–70) | 70 (60–70) | 0.653 |
| YOT | | | |
| 2011 | 0 | 14 (28%) | NA |
| 2012 | 0 | 7 (14%) | |
| 2013 | 6 (7%) | 8 (16%) | |
| 2014 | 3 (3%) | 11 (22%) | |
| 2015 | 13 (15%) | 7 (14%) | |
| 2017 | 29 (33%) | 1 (2%) | |
| 2018 | 7 (8%) | 0 | |

Abbreviations; HNC = head and neck cancer, CDDP = cisplatin, RT = radiotherapy, 5FU = 5-fluorouracil, SqCC = squamous cell carcinoma, AC = adenocarcinoma, ECOG = Eastern Cooperative Oncology Group, PS = Performance Status, 3DCRT = 3D conformal radiotherapy, IMRT = intensity-modulated radiotherapy, YOT = year of treatment.

**Table 2**
Univariate analysis of the association between OC and clinical factors.

| | Development of OC | | |
|---|---|---|---|
| | No | Yes | *p* |
| Chemotherapy | | | 0.587 |
| CDDP | 57 | 31 | |
| CDDP + 5FU | 30 | 20 | |
| Gender | | | 0.411 |
| Male | 79 | 44 | |
| Female | 8 | 7 | |
| Age | | | 0.161 |
| ≤65 | 47 | 21 | |
| ≥66 | 40 | 30 | |
| Primary site | | | 0.275 |
| Hypopharynx | 35 | 17 | |
| Larynx | 9 | 3 | |
| Nasopharynx | 21 | 9 | |
| Oral cavity | 3 | 2 | |
| Oropharynx | 19 | 20 | |
| ECOG PS | | | 0.545 |
| 0 | 5 | 4 | |
| 1 | 81 | 45 | |
| 2 | 1 | 2 | |
| RT techniques | | | 1 |
| 3DCRT | 72 | 43 | |
| IMRT | 15 | 8 | |
| Stage | | | 0.697 |
| II | 17 | 7 | |
| III | 22 | 15 | |
| IV | 48 | 29 | |
| YOT | | | 1 |
| 2011–2015 | 43 | 26 | |
| 2016–2018 | 44 | 25 | |
| DM | | | |
| No | 72 | 45 | 0.47 |
| Yes | 15 | 6 | |

Abbreviations; OC = oral candidiasis, CDDP = cisplatin, RT = radiotherapy, 5FU = 5-fluorouracil, ECOG = Eastern Cooperative Oncology Group, PS = Performance Status, 3DCRT = 3D conformal radiotherapy, IMRT = intensity-modulated radiotherapy, YOT = year of treatment, DM = diabetes mellitus.

**Table 3**
Univariate analysis of the association between grade 3 dysphagia and clinical factors.

| | Dysphagia grade | | |
|---|---|---|---|
| | 1–2 | 3 | *p* |
| Chemotherapy | | | 0.352 |
| CDDP | 32 | 56 | |
| CDDP + 5FU | 14 | 36 | |
| Gender | | | 0.385 |
| Male | 43 | 80 | |
| Female | 3 | 12 | |
| Age | | | 0.37 |
| ≤65 | 20 | 48 | |
| ≥66 | 26 | 44 | |
| OC | | | 0.0264 |
| No | 35 | 52 | |
| Yes | 11 | 40 | |
| Primary site | | | 0.349 |
| Hypopharynx | 14 | 38 | |
| Larynx | 6 | 6 | |
| Nasopharynx | 11 | 19 | |
| Oral cavity | 3 | 2 | |
| Oropharynx | 12 | 27 | |
| ECOG PS | | | 0.673 |
| 0 | 3 | 6 | |
| 1 | 43 | 83 | |
| 2 | 0 | 3 | |
| RT techniques | | | 1 |
| 3DCRT | 38 | 77 | |
| IMRT | 8 | 15 | |
| Stage | | | 0.061 |
| II | 4 | 20 | |
| III | 17 | 20 | |
| IV | 25 | 52 | |
| YOT | | | 1 |
| 2011–2015 | 23 | 46 | |
| 2016–2018 | 23 | 46 | |

Abbreviations; CDDP = cisplatin, RT = radiotherapy, 5FU = 5-fluorouracil, OC = oral candidiasis, ECOG = Eastern Cooperative Oncology Group, PS = Performance Status, 3DCRT = 3D conformal radiotherapy, IMRT = intensity-modulated radiotherapy, YOT = year of treatment.

hypothesis that OC is associated with grade 3 dysphagia by performing both univariate and multivariate analyses. The associations of grade 3 dysphagia with clinical factors including the development of OC were tested with Fisher's exact test. The variables that showed relative significance ($p < 0.10$) in the univariate analysis were included in the binary logistic regression model [27]. The morphine-equivalent doses of opioids were compared between the patients with and without OC (Mann-Whitney U test). P-values < 0.05 were considered significant. All analyses were performed with EZR ver. 1.35, a graphical user interface for R statistical software [28].

## 3. Results

We identified 471 consecutive HNC patients, and 138 met the inclusion criteria (Fig. A1). There were no significant differences in the baseline patient demographics between the group of patients treated with RT + 5FU + CDDP (n = 50) and the group of patients treated with RT + CDDP (n = 88) (Table 1). The median follow-up period for all patients, which was calculated from the first day of CCRT, was 26.1 months. All eligible patients were hospitalized throughout their CCRT, and the complete medical chart was available for all patients. Ninety-two patients (67%) required either PN or tube feeding and were judged as having developed grade 3 dysphagia.

OC was observed in 51 patients (37%). Fifty patients were diagnosed with pseudomembranous OC, and one patient was diagnosed with hyperplastic OC. No patients were diagnosed with erythematous OC. Mycological culture tests using oral swabs were performed in eight patients, and *C. albicans* was recovered from all specimens. The median cumulative dose at the time of OC diagnosis was 38 Gy (range 6–70 Gy). These patients were diagnosed with OC at a median of CCRT day 29 (range 5–83). There were no significant differences in the incidence of OC by the primary site, stage, age, or chemotherapy (Table 2).

The RTOG grade of dysphagia at the time of OC diagnosis was grade 0–1 in 11 patients (22%), grade 2 in 21 patients (41%), and grade 3 in 19 patients (37%). Among the 32 patients whose dysphagia grade was 0–2 at the time of OC diagnosis, 21 patients (66%) developed grade 3 dysphagia. Topical antifungal agents were administered in 28 patients. Two patients underwent systemic azole therapy; one patient received 200 mg/day of itraconazole syrup for 7 days, and the other received 200 mg/day of intravenous fluconazole for 13 days. The topical agents failed to improve the symptoms of OC in 10 patients (36%), and the systemic azoles failed in both patients (100%). Five of the 28 patients receiving topical agents showed an improvement of symptoms.

The patients with OC developed grade 3 dysphagia significantly more frequently compared to the patients without OC (78% vs. 60%, p = 0.026) (Table 3). Similarly, the stage II patients tended to have a higher incidence of grade 3 dysphagia compared to the stage III patients (83% vs. 54%, Bonferroni-adjusted p = 0.081). In the multivariate analysis, OC alone was independently associated with grade 3 dysphagia (OR 2.75, 95%CI 1.22–6.23, p = 0.015) (Table 4).

We drew the histogram of the maximum of daily morphine-equivalent doses of opioids for the OC group and the non-OC group, respectively. The opioid dose peak was observed in the 40–60 mg interval in the OC group, whereas the peak was observed in the

**Table 4**
Multivariate logistic regression analysis of grade 3 dysphagia.

| Variable | OR (95%CI) | *p* |
|---|---|---|
| OC | 2.75 (1.22–6.23) | 0.015 |
| Stage | | |
| IV | Reference | |
| II | 2.68 (0.81–8.83) | 0.11 |
| III | 0.53 (0.23–1.22) | 0.14 |

Abbreviations; OC = oral candidiasis.

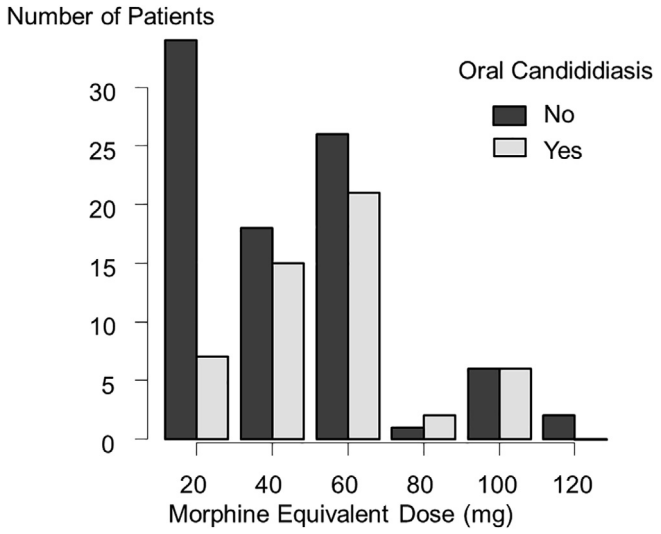


**Fig. 1.** Histogram of morphine-equivalent of the maximum of daily opioid doses in the OC and non-OC groups.

0–20 mg and 40–60 mg intervals in the non-OC group (Fig. 1). Thirty-five patients in the non-OC group required ≥40 mg morphine-equivalent dose of opioids. The patients with OC required significantly higher morphine-equivalent doses of opioids (45 vs. 30 mg/day; p = 0.029). One patient developed sepsis and OC, but the association between sepsis and OC is unclear.

## 4. Discussion

The results of the present study demonstrated that the development of oral candidiasis (OC) during CDDP-based CCRT aggravates the pain and dysphagia related to mucositis. These findings are consistent with the results of the prospective MIR Study by Busetto et al. [15]. It thus appears that *Candida* infection is not only the consequence of chemoradiation-induced mucositis; rather, it is also one of the aggravating factors of mucositis and dysphagia. Based on the findings of the latest high-quality molecular biological study of the peptide toxin of *C. albicans* [29], it is obvious that *Candida* spp. vigorously destroy the mucosa and aggravate dysphagia secondary to radiation-induced mucositis.

We also observed that by the time of the recognition of mucosal lesions of OC, more than one-third of the patients had developed high-grade dysphagia, which makes the early diagnosis of OC difficult. Another obstacle to the early detection of OC may be the presence of erythematous candidiasis. Formerly called "antibiotic sore tongue," erythematous candidiasis is characterized by localized mucosal hyperemia and associated pain [30]. These lesions are generally more difficult to recognize compared to pseudomembranous OC [31,32]. In our present patient cohort, the incidence of OC was 37%, which was disproportionately lower compared to the *Candida* colonization rate of 70% [11,12]. The histogram analysis revealed that 35 patients (25% of the entire cohort) experienced severe pain without typical pseudomembranous lesions of OC. We suspect that some of these patients might have developed "undiagnosed" erythematous candidiasis.

OC associated with cytotoxic chemotherapy or RT is refractory to antifungal treatment. In the guidelines provided by the Infectious Diseases Society of America, topical antifungal agents including miconazole gel are recommended for mild OC, whereas systemic fluconazole or itraconazole is recommended for moderate to severe OC [22]. In the OC associated with HIV infection, systemic fluconazole or itraconazole provides the complete cure of symptoms in 80%–90% of the cases [26,33–35]. In the OC associated with cytotoxic chemotherapy or RT, the clinical cure rate falls to 45%–75% [36,37] (Table 5).

We propose a biological hypothesis to explain how CCRT-associated OC causes refractory dysphagia in HNC patients. Combined RT and CDDP disrupt the mucosal barrier, thus facilitating *Candida* infection [13]. The aspartyl proteinases and cytotoxic peptides secreted by *C. albicans* destroy the desmosomes and plasma membranes of the mucosal epithelium and aggravate mucositis [29,38,39]. The inflammatory processes involve the submucosal pharyngeal constrictors and lead to severe dysphagia [40]. It is difficult to restore the function of the mucosa and pharyngeal constrictors with antifungal treatment initiated upon the onset of OC, because the physiological wound healing capacities are severely impaired during and after CCRT.

For these reasons, CCRT-associated OC is difficult to detect at the early stage of infection, and antifungal prophylaxis seems to be efficacious. In a nonrandomized prospective trial by Nicolatou-Galitis et al., the prophylactic administration of fluconazole during RT for various head and neck malignancies reduced the incidence of severe mucositis compared to the control group [41]. Rao et al. published a similar report about their retrospective anal-

**Table 5**
Treatment outcomes of OC in precedent clinical trials.

| Patients | Drug | Daily dose (mg) | Duration (days) | Clinical cure rate (%) | Author and publication year | Reference No. |
|---|---|---|---|---|---|---|
| AIDS | Fluconazole | 100 | 14 | 82.5 | Vazquez et al. 2006 | [26] |
| AIDS | Fluconazole | 100 | 14 | 87 | Graybill et al. 1998 | [33] |
| | Itraconazole | 200 | 14 | 97 | | |
| | Itraconazole | 200 | 7 | 86 | | |
| AIDS | Fluconazole | 150 | 14 | 95.5 | Hamza et al. 2008 | [34] |
| AIDS | Fluconazole | 100 | 14 | 87 | Pons et al. 1997 | [35] |
| RT for HNC | Miconazole MAT | 50 | 14 | 52.5 | Bensadoun et al. 2008 | [36] |
| | Miconazole gel | 500 | 14 | 45.4 | | |
| Malignant tumor | Fluconazole | 100 | 10 | 74 | Oude Lashof et al. 2004 | [37] |
| | Itraconazole | 200 | 15 | 62 | | |
| CCRT for HNC | Fluconazole | 200 | 13 | 0 | Present study | |
| | Itraconazole | 200 | 7 | 0 | | |

Abbreviations; AIDS = acquired immunodeficiency syndrome, RT = radiotherapy, HNC = head and neck cancer, OC = oral candidiasis, MAT = mucoadhesive tablet, CCRT = concurrent chemoradiotherapy.

ysis [17]. However, mucositis-associated dysphagia and pain were not evaluated in these studies. A prospective trial is necessary to determine whether antifungal prophylaxis reduces the severity of pain and dysphagia related to mucositis in HNC patients.

The present study has several limitations. First, the study dealt with a small cohort with heterogenous characteristics and treatment details (different primary tumor sites, IMRT vs. 3DCRT, differing doses to pharyngeal constrictors, etc.) We performed a multivariate analysis to reduce these biases. Second, the patients' daily medical charts generally lack microbiological data. Third, the response to antifungal treatment was not mentioned in the medical charts and was judged retrospectively. Nevertheless, it was clear that both two patients treated with systemic azole therapy showed clinical failure, which implies the refractoriness of chemoradiation-associated OC. Despite these limitations, we consider that our study revealed clinically relevant information, and our findings pose an important question that should be addressed in a prospective trial; i.e., whether antifungal prophylaxis reduces the severity of pain and dysphagia related to mucositis in HNC patients.

## 5. Conclusions

*Candida* infection aggravated the severity of pain and dysphagia related to mucositis during CCRT for head and neck cancer. One-third of the patients with OC in our cohort had already developed high-grade dysphagia by the time of their diagnosis of OC. CCRT-associated OC was refractory to antifungal treatment. As the early diagnosis of OC is difficult, it is worth investigating whether antifungal prophylaxis reduces the severity of dysphagia related to candidiasis.

## Funding support

The present work was supported by a grant from the Japanese Society for Promotion of Science KAKENHI, grant #19K17262.

## Declaration of Competing Interest

The 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.

## Appendix

Fig. A1.

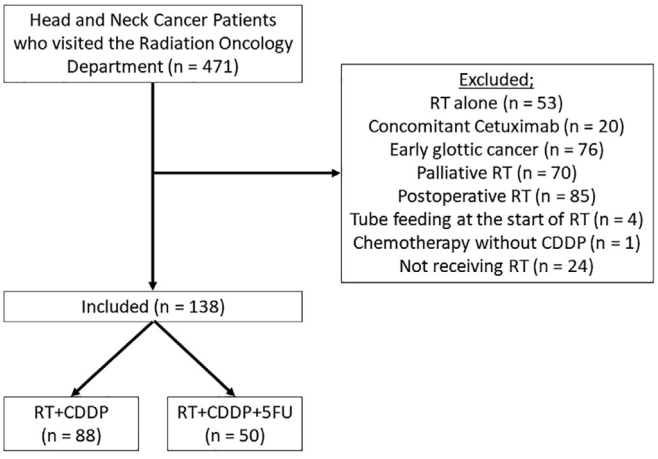


**Fig. A1.** CONSORT diagram. Abbreviations; RT = radiotherapy, CDDP = cisplatin, 5FU = 5-fluorouracil.

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