Two elderly patients with advanced maxillary gingival carcinoma with complete response to concurrent radiotherapy and S-1 chemotherapy

メタデータ	言語: eng 出版者: 公開日: 2017-10-05 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/25205

Two elderly patients with advanced maxillary gingival carcinoma with complete response to concurrent radiotherapy and S-1 chemotherapy

Running title: Concurrent radiotherapy and S-1 chemotherapy

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Abbreviations: OSCC, oral squamous cell carcinoma; CR, complete response; BSA, body

surface area; RECIST, response evaluation criteria in solid tumors; CTCAE v3.0, common terminology criteria for Adverse Events version 3.0; ADL, activities of daily living.

Abstract: The use of the novel oral fluoropyrimidine anticancer drug S-1 as a single-agent or in combined chemotherapy has been reported to be useful for the treatment of advanced oral cancer. We report two elderly patients with advanced oral cancer who achieved complete response (CR) after concurrent radiotherapy and S-1 chemotherapy. Patient 1 was an 81-year-old woman who had a 50 × 40 mm tumor erosion in the right upper gingival region. At 2.5 years after the end of concurrent radiotherapy and S-1 chemotherapy, tumor relapse was observed, although CR continued temporarily. The patient died 3 years after the end of concurrent radiotherapy and S-1 chemotherapy due to tumor relapse and high blood pressure resulting in deterioration of patient condition. Patient 2 was an 89-year-old woman who had a 40 × 30 mm tumor ulcer in the right gingiva. Neither relapse nor metastasis was seen, and patient condition remained good for the 3 years after concurrent radiotherapy and S-1 chemotherapy. In both patients, MRI showed that the tumor had deeply invaded the palatal bone, almost reaching the nasal cavity, with metastasis

to the right upper superior internal jugular nodes. In both patients, biopsy showed a well-differentiated squamous cell carcinoma. Concurrent radiotherapy and S-1 chemotherapy induced CR without severe adverse effects.

Key words: Concurrent chemoradiotherapy, S-1, Squamous cell carcinoma, Gingiva.

Introduction

S-1 is a novel oral fluorouracil antitumor drug that combines three pharmacological agents: tegafur (FT), which is a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihy-droxypryidine (CDHP), which inhibits dihydropyrimidine dehydrogenase (DPD) activity; and potassium oxonate (Oxo), which reduces gastrointestinal toxicity.[1-6] In a late phase II clinical trial involving patients with head and neck cancer, the overall success rate for oral cavity lesions was 36.4%; for those with a primary focus, it was 46.9%, while for those with metastasis to neck lymph nodes, it was 21.7%. This rate was high compared to other anti-cancer agents.[7,8] In addition, S-1 appears to induce radiosensitivity.[9,10]

The two patients presented refused surgical resection, as they were in their eighties and did not have a long life expectancy and to avoid postoperative severe adverse effects. However, elderly patients with advanced oral cancer and related complications are often unable to tolerate

effective chemoradiotherapy dosages, as the side effects are currently very severe. Therefore, concurrent radiotherapy and S-1 chemotherapy is thought to be a suitable treatment for elderly patients with advanced oral cancer and related complications, as there is a potent enhancement of radiosensitivity and comparatively high antitumor effect, while digestive organ toxicity is reduced.

Case reports

The two patients presented refused surgical resection, as they were in their eighties and did not have a long life expectancy. Thus, they chose to have concurrent radiotherapy and S-1 chemotherapy because this approach offered the possibility of a radical cure with less severe side effects.

Patient 1: An 81-year-old female (body surface area (BSA), 1.2 m^2/body; Eastern Cooperative Oncology Group scale performance status, 1) was seen due to right upper gingival pain and erosion. Her past history included hypertension treated with medication.

On examination, erosion in the palate, about 50 × 40 mm, was seen. On pathology of the biopsy specimen, a well-differentiated squamous cell carcinoma was diagnosed. Microscopic findings indicated atypia squamous cell infiltrate under the epithelial membrane with abundant pearls of keratinization (Fig. 1A).

MRI showed that the tumor was adjacent to the nasal cavity, and that there was bone infiltration. On measurement based on MRI data at baseline, the longest diameter was 46 mm and the shortest diameter was 22 mm. Furthermore, the right upper superior internal jugular nodes showed rim enhancement, and the long axis was 16 mm. A diagnosis of advanced oral cancer was made; the tumor was classified as cT3N1M0, according to the classification of the Japan Society for Head and Neck Cancer.

The results of blood tests at the first medical examination were as follows: WBC, 6.0×10^3 /μl; RBC, 4.4×10^6 /μl; and Hb, 12.7 g/dl. At 22 days after the initial examination, concurrent radiotherapy and S-1 chemotherapy was started. The patient was given S-1 orally (S-1 40 mg twice daily; total, 80 mg/day) for 2 weeks, followed by a 1-week, drug-free period, which constituted one cycle. The patient was given concurrent radiation to a total of 66 Gy in increments of 2 Gy /day to the primary and right neck regions. Because oral stomatitis

deterioration (CTC Grade 2-3) had progressed, treatment was temporarily stopped for 6 days at day 43 after concurrent radiotherapy and S-1 chemotherapy was started at a total irradiation dose of 56 Gy. Subsequently, because stomatitis improved, concurrent radiotherapy and S-1 chemotherapy were restarted. Including the days treatment was stopped, total treatment period was 54 days. The patient received four cycles in hospital.

TS-1 continued to be administered until day 227 using a similar regimen. No adverse reactions were observed. Lesions had disappeared on MRI at 5 and 15 months after the concurrent radiotherapy and S-1 chemotherapy had ended. A right upper superior internal jugular node that was judged as showing metastasis at baseline had a reduced long diameter of 6 mm, and typical findings of metastasis were not noted. Thus, complete response (CR) was confirmed. The primary lesion and the lymph node metastasis disappeared (Fig. 2A-F). The strongest hematological toxicity was Grade 2, and this was seen almost immediately after

concurrent radiotherapy and S-1 chemotherapy was started.

At 2.5 years after the end of concurrent radiotherapy and S-1 chemotherapy, recurrence was observed, with slight ulceration. The patient died at 3 years after the end of concurrent radiotherapy and S-1 chemotherapy with recurrent oral cancer, and high blood pressure contributed to rapid deterioration of general status. Based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, the patient achieved CR.[11] Side effects were classified according to the Common Terminology Criteria for Adverse Events version3.0 (CTCAE v3.0).

Patient 2: An 89-year-old female (BSA, 1.0 m^2/body; performance status, 2) was examined due to right upper gingival pain. She had a history of hypertension and a subarachnoid hemorrhage. On examination, a 30 × 30 mm ulcer was seen in the palate. On pathology of the biopsy, a well-differentiated squamous cell carcinoma was diagnosed. On MRI, the tumor was adjacent to the nasal cavity with bone infiltration. On measurement by MRI at baseline, the

longest diameter was 28 mm and the shortest diameter was 25 mm. Furthermore, the right upper superior internal jugular nodes showed rim enhancement, and the long axis was 10 mm. A diagnosis of advanced oral cancer was confirmed, and the tumor was classified as cT3N1M0 according to the classification of the Japan Society for Head and Neck Cancer.

Microscopic findings indicated atypia squamous cell infiltrate under the epithelial membrane, with abundant pearls of keratinization. Inflammatory granulation tissue was also seen in the tumor surroundings (Fig. 1B). The results of blood tests at the first medical examination were as follows: WBC, 3.1×10^3/μl; RBC, 4.2×10^6/μl; and Hb, 11.7 g/dl.

At 27 days after the initial medical examination, concurrent radiotherapy and S-1 chemotherapy was started. Patient 2 had concurrent radiation therapy (60 Gy) and S-1 chemotherapy for a total of four cycles while in hospital. The patient was given S-1 orally (S-1 40 mg twice a daily; total, 80 mg/day) for 2 weeks, followed by a 1-week drug-free period,

which constituted one cycle. The patient was given concurrent radiation at a total of 66 Gy in increments of 2 Gy /day to the primary and right neck regions. Because oral stomatitis deterioration (CTC Grade 2 to 3) had progressed, concurrent radiotherapy and S-1 chemotherapy were temporarily stopped for 13 days at 31 days after treatment started, at a total irradiation dose of 42 Gy. Because stomatitis then improved, combined treatment was restarted.

Stomatitis disappeared completely on day 84 after the initial medical examination, and the therapeutic outcome was confirmed as CR. TS-1 continued to be administered until day 194 under the same regimen. SCC lesions were absent on MRI evaluation of concurrent radiotherapy and S-1 chemotherapy at 4 and 12 months after treatment had ended. Right upper superior internal jugular node that was judged as metastasis at baseline decreased to a long diameter of 5 mm, and typical findings of metastasis were not noted. Thus, outcome was judged as CR.

When the combined treatment was stopped (on day 62), hematological toxicity was Grade 2, which was the most severe level observed. Neither recurrence nor metastasis was noted, and patient condition remains excellent at 3 years after concurrent radiotherapy and S-1 chemotherapy. No adverse reactions were observed. The primary lesion and the lymph node metastasis disappeared after treatment (Fig. 3A-F). This patient also achieved CR.

Discussion

It has previously been reported that even advanced oral squamous cell carcinoma shows a good response to TS-1 therapy;[12-15] moreover, a radiation sensitization effect can be expected.[16,17] The mechanism by which TS-1 exerts its radiosensitization effect in oral squamous carcinoma is reported to be the result of repressing survival signal Akt/PKB expression.[6-7] Moreover, it has been reported that concurrent radiotherapy and S-1 chemotherapy is effective

for oral SCC and for other cancers, including hypopharyngeal, glottic, urachal, pancreatic, and gastric.[18-23]

Recently, Tsukuda et al. reported that 2 weeks of S-1 followed by a 1-week rest period was more feasible for adjuvant chemotherapy of locoregionally advanced squamous cell carcinoma of the head and neck region than 4 weeks of S-1 followed by a 2-week rest period.[24,25] Therefore, we selected 2 weeks of S-1 followed by a 1-week rest period as the regimen for our patients.

If more than three hematological side effects or greater than Grade 2 non-hematological side effects occurred, the following protocol was followed. First, chemoradiation therapy was stopped, and the patients were observed for 2 weeks while they recovered from the side effects. If the side effect did not improve, treatment was discontinued. Although both patients experienced grade 2 oral stomatitis, the stomatitis decreased to grade 1 within 2 weeks, and

therapy was restarted. Throughout therapy, patients were able to eat, as they had oral care, which included gargling with xylocaine and polyacrylic acid sodium.

Although we were concerned about the need to interrupt treatment due to the potential of severe side effects in these elderly patients with generally decreased systemic functions,[26, 27] concurrent radiation therapy and S-1 chemotherapy was completed, and the patients were able to maintain their activities of daily living (ADL) without serious side effects.

The following advantages are associated with concurrent radiotherapy and S-1 chemotherapy.

1) Because it is an oral medicine rather than injection, psychological stress to the patient is reduced.

2) Side effects are easier to deal with due to the washout period.

3) There are comparatively high antitumor and radiosensitization effects with a single agent.

4) Outpatient care is possible.

For elderly patients with advanced oral cancer, surgical resection can lead to severe adverse effects on ADL, for example, affecting mastication, deglutition, swallowing and speech, and recovery is generally not expected. It is therefore important to consider both surgical treatment and chemoradiotherapy in elderly patients with advanced oral caner. Concurrent radiotherapy and S-1 chemotherapy offers the possibility of radical cure while maintaining ADL, and is expected to result in a lower histological malignancy grade, as invasive capacity is poor, even in advanced cancer.

Conclusion

This therapy may be feasible for elderly patients with advanced oral cancer and complications and become a curative treatment considering ADL in some patients. However, Further studies with a larger number of cases are necessary in order to establish the role of concurrent radiotherapy and S-1 chemotherapy for elderly cancer patients.

Acknowledgments

The authors would like to thank all members of the department of Oral and Maxillofacial Surgery, School of Medicine, Kanazawa University for their helpful suggestions and support.

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Figure Legends

Figure 1. (A). Microscopic findings indicated atypia squamous cell infiltrate under the epithelial membrane with abundant pearls of keratinization. (B). Microscopic findings of the insicional specimen. Atypia squamous cell infiltrate under the epithelial membrane with abundant pearls of keratinization was noted. Inflammatory granulation tissue was seen in the tumor surroundings.

Figure 2. Patient 1: Images obtained during initial visit and after treatment.

Photograph of the mouth at initial visit (A). Photograph of the mouth after treatment (B). MRI of primary region at the time of initial visit (C). MRI of primary region after treatment (D). MRI of lymph node metastasis at the time of initial visit (E). MRI image of lymph node metastasis after treatment (F).

Figure 3. Patient 2: Images obtained during initial visit and after treatment.

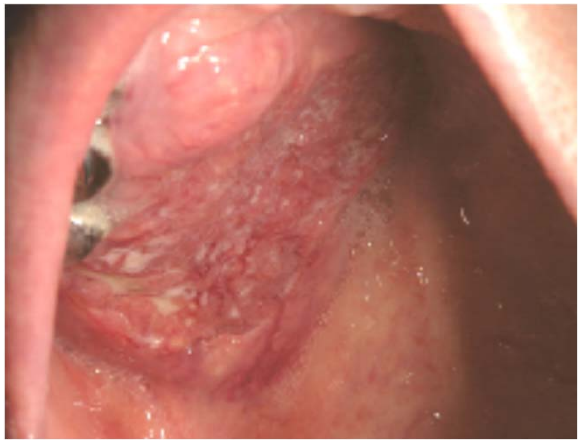
Photograph of the mouth at the time of initial visit (A). Photograph of the mouth after treatment

(B). MRI of primary region at the time of initial visit (C). MRI of primary region after treatment

(D). MRI of lymph node metastasis at the time of initial visit (E). MRI of lymph node metastasis

after treatment (F).

Fig.2. Patient 1



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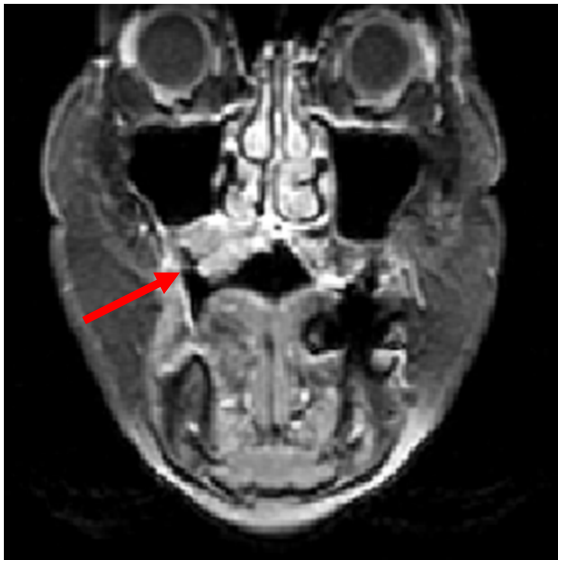

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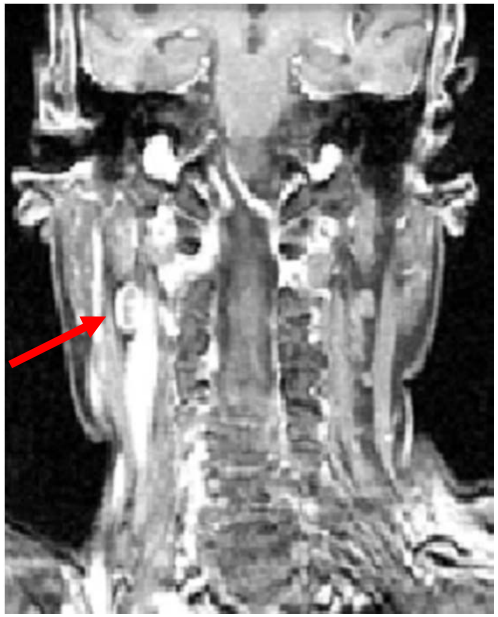

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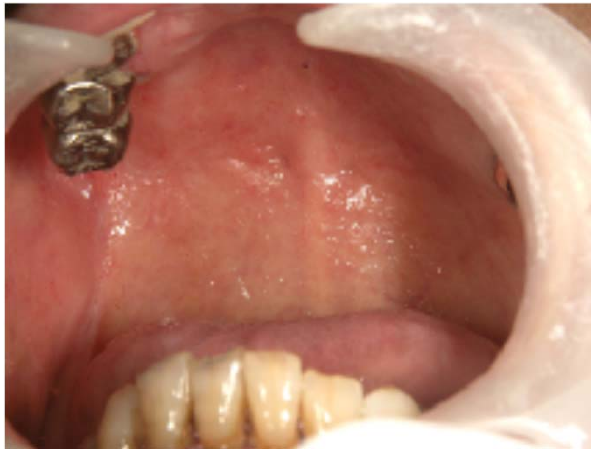

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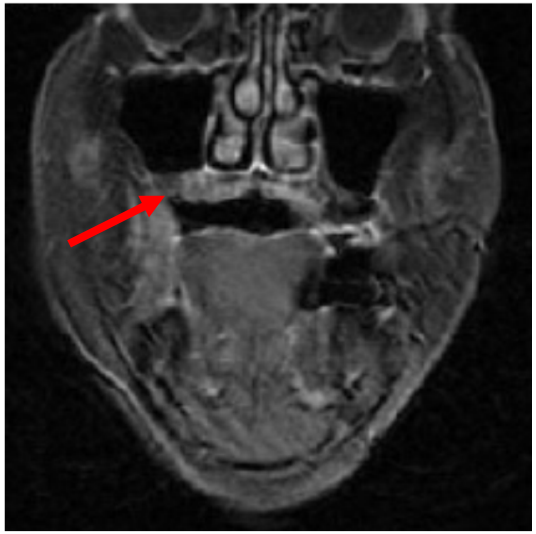

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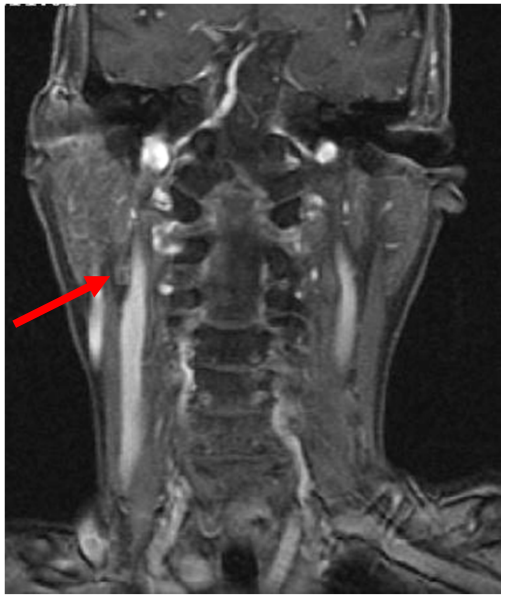

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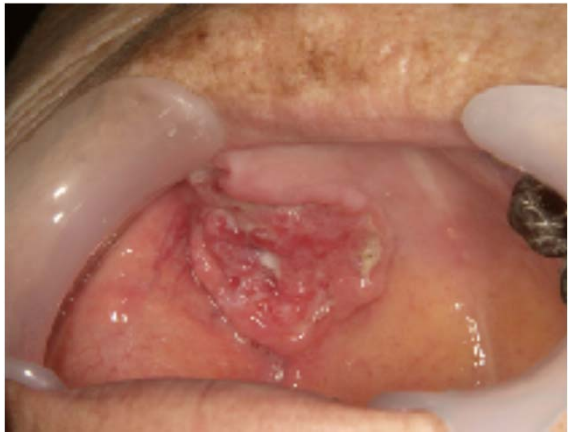
Fig.3. Patient 2



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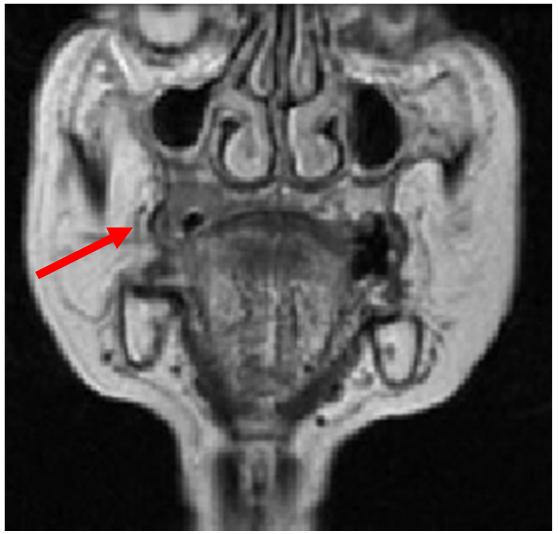

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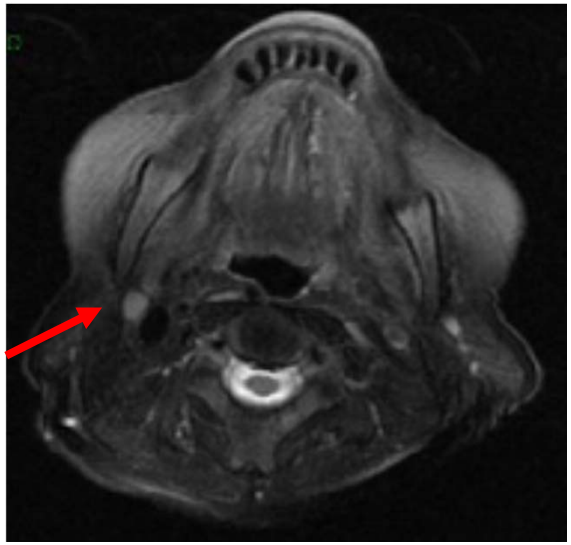

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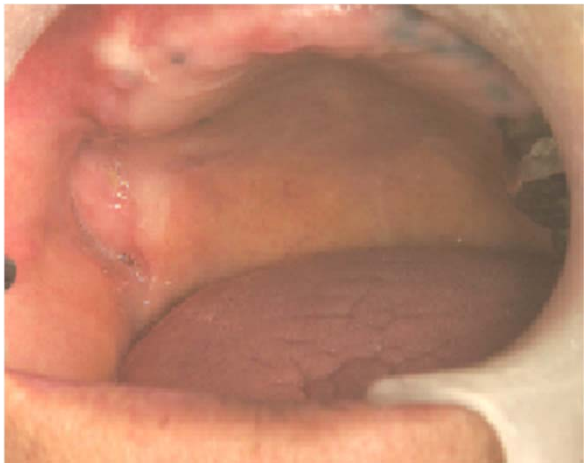

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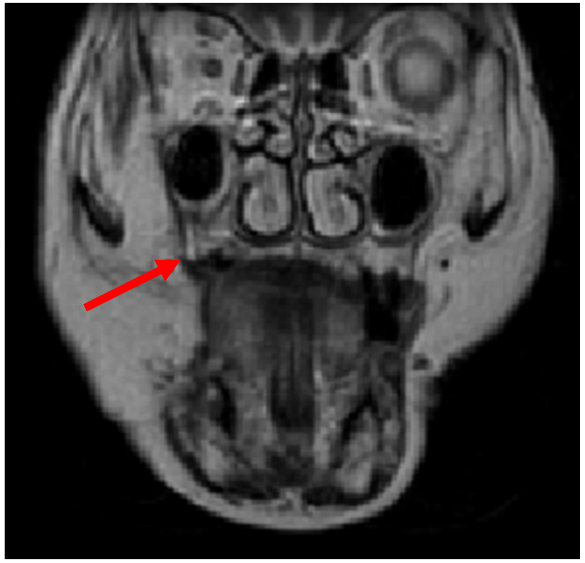

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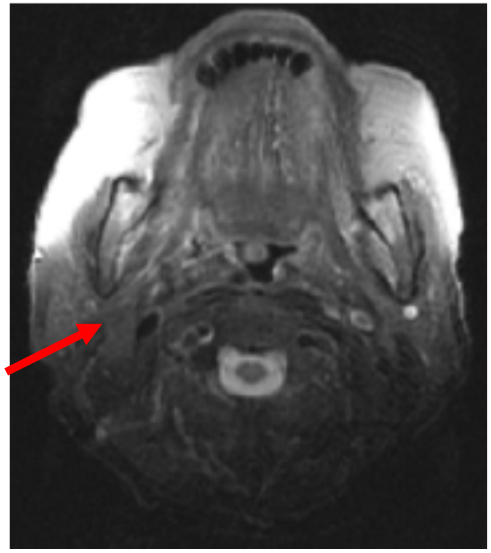

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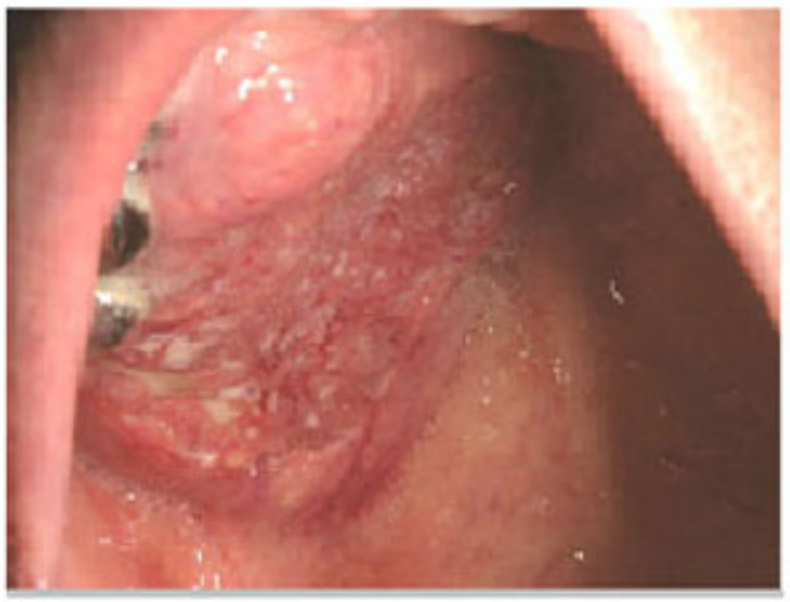
Fig.2. Patient 1



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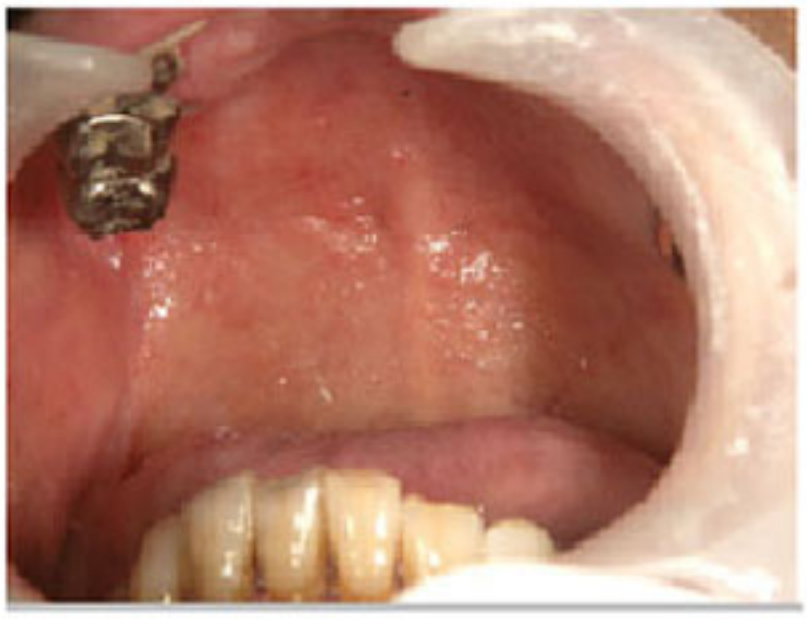

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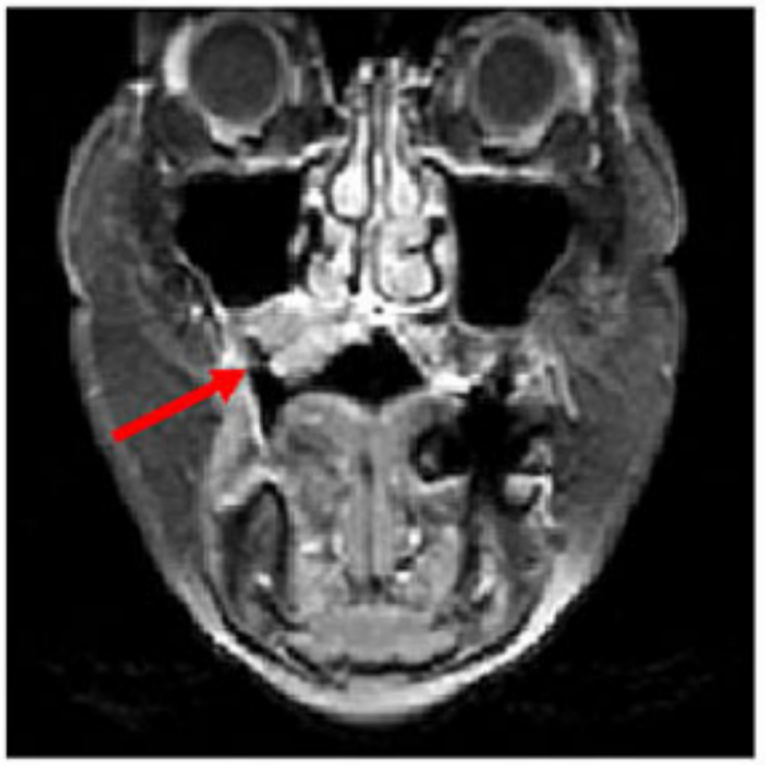

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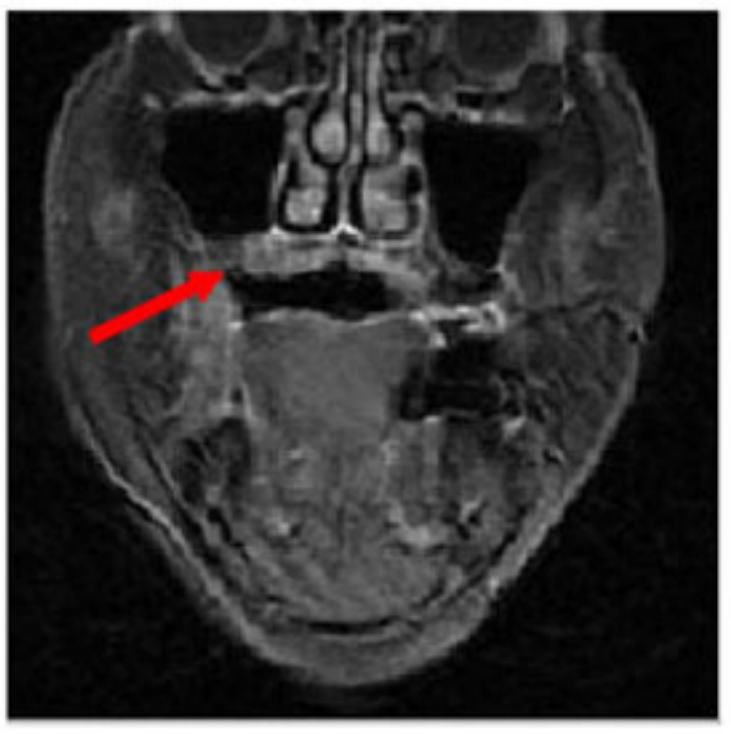

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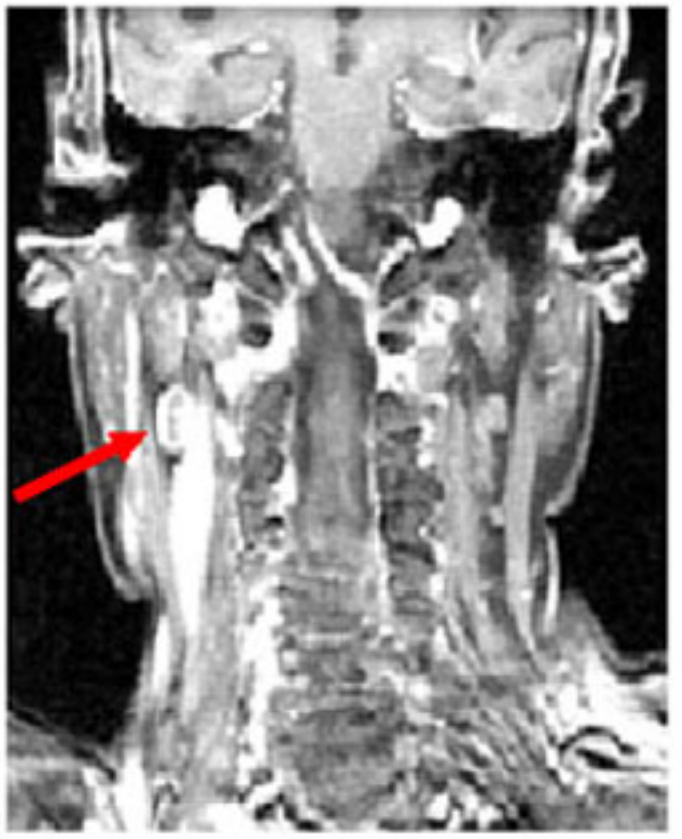

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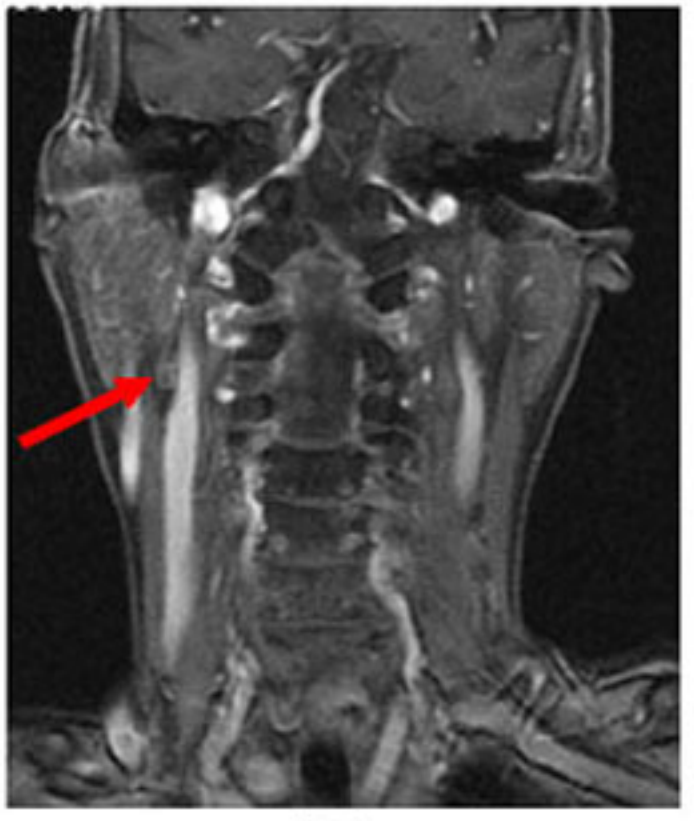

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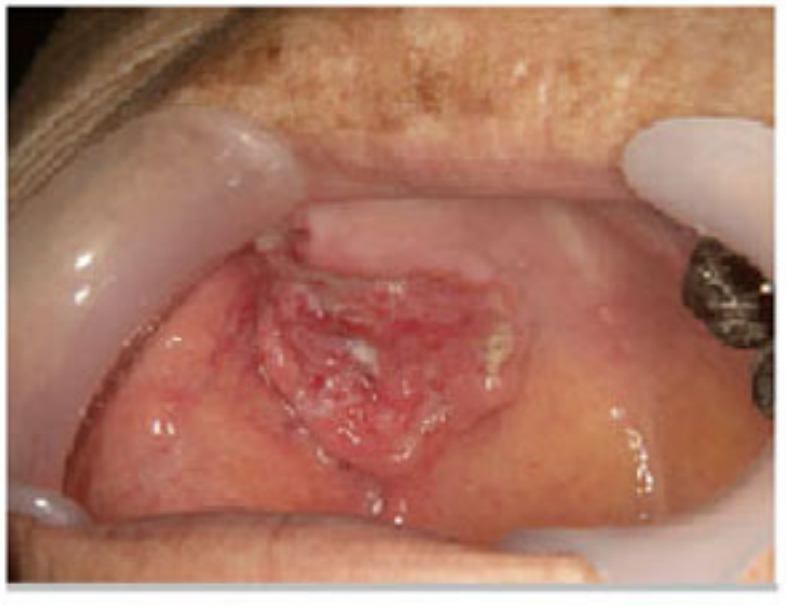
Fig.3. Patient 2



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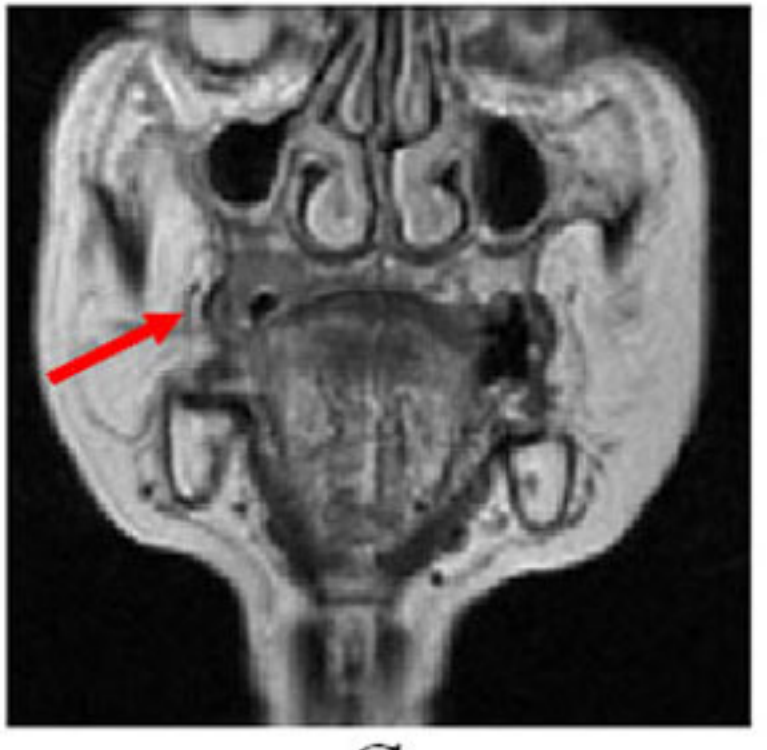

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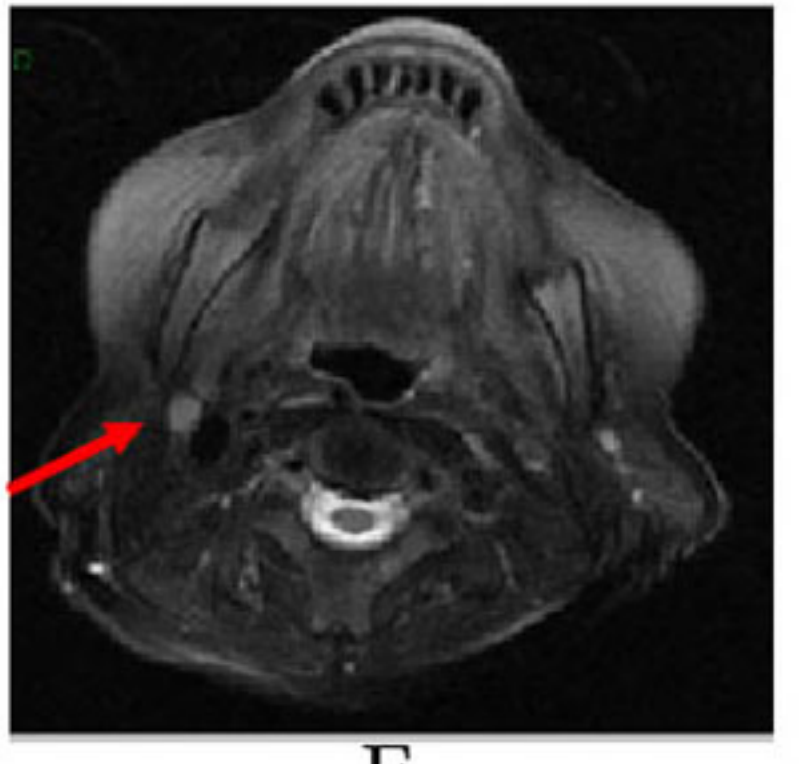

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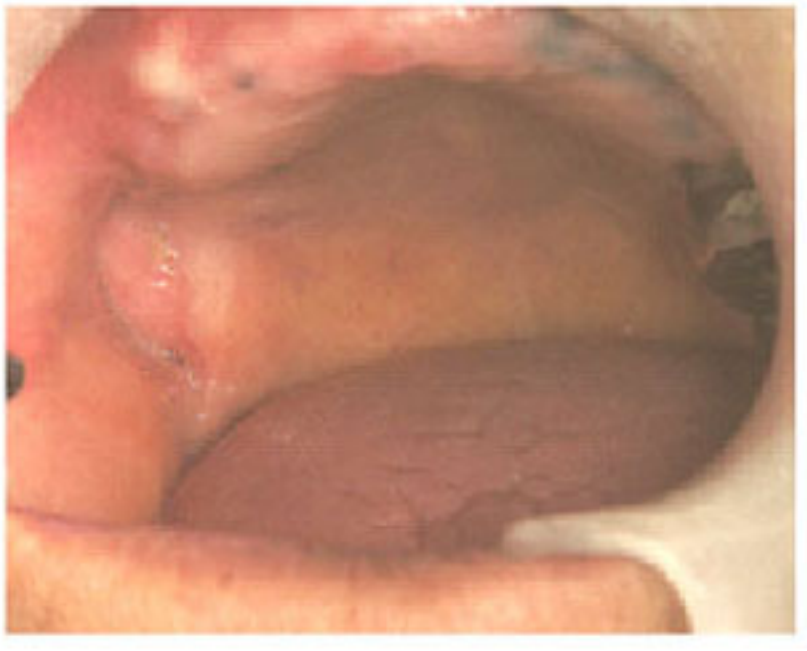

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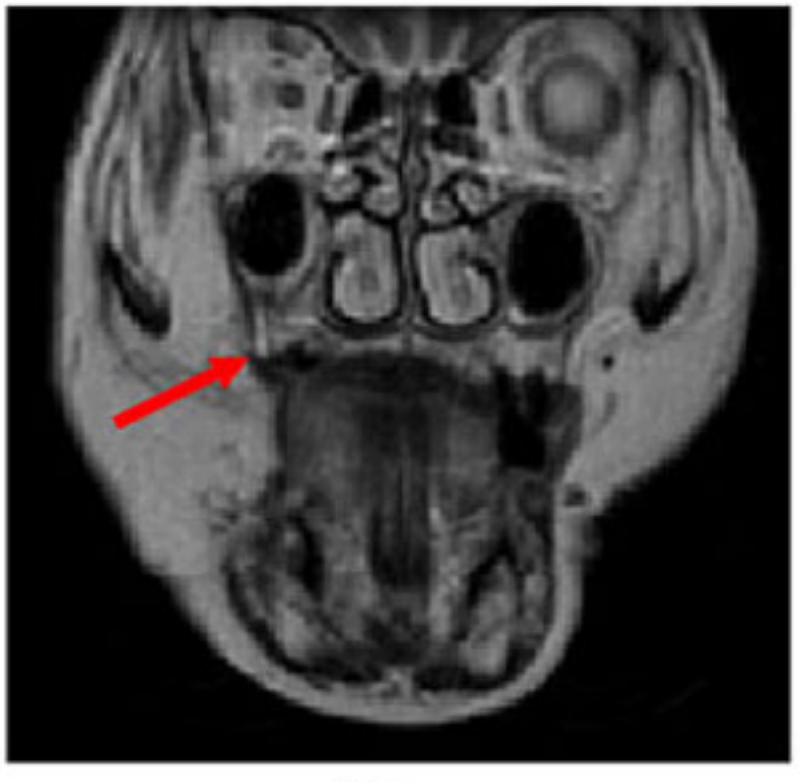

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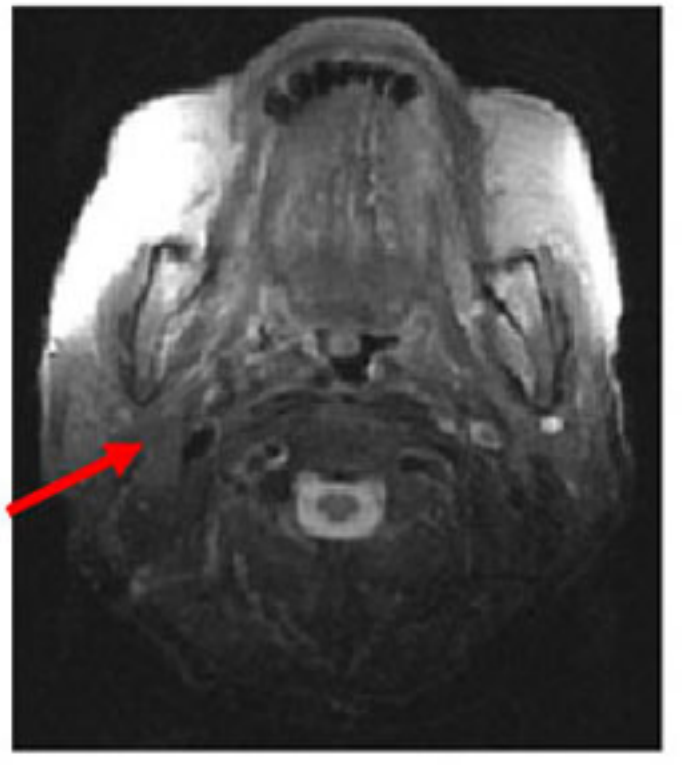

F