

# Successful surgical management of a patient with osteoradionecrosis of the jaw with RET fusion-positive advanced thyroid cancer: A case report

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Received December 27, 2024; Accepted May 6, 2025

DOI: 10.3892/etm.2025.12898

**Abstract.** Osteoradionecrosis (ORN) of the jaw is a severe complication of radiotherapy for head and neck cancer. Extensive surgical resection has shown promising outcomes; however, patients' prognosis must be considered. Papillary thyroid carcinoma (PTC) generally has a favorable prognosis, whereas metastatic PTC is considered a refractory disease against conventional treatment. Recently, comprehensive genomic profiling (CGP) has enabled clinicians to provide personalized medicine, offering patients with intractable disease further therapeutic options. The present case study reported on a patient with advanced PTC who developed ORN during lenvatinib treatment; extensive surgical treatment with submandibular dissection for ORN provided a favorable outcome. Pathological examination unexpectedly revealed PTC metastases in the dissected right submandibular gland. Postoperatively, the patient experienced worsening metastases to the lung and liver. CGP identified a CCDC6-RET fusion, prompting selpercatinib treatment, which achieved a partial response. This report aims to emphasize that extensive surgical treatment for ORN should be considered, even in patients with advanced cancer, if the patients' condition is stable. In addition, submandibular dissection is warranted in selected patients, particularly when thyroid cancer exhibits an aggressive phenotype with occult metastases. Furthermore,

this report highlights the importance of integrating personalized medicine in the management of advanced cancer cases and emphasizes the availability of genomic profiling to guide treatment decisions.

## Introduction

Osteoradionecrosis (ORN) of the jaw is a major complication of radiotherapy for head and neck cancer (HNC) (1,2). ORN is characterized by persistent bone exposure lasting over three months in patients with a history of radiotherapy to the orofacial region (3-5). The advent of intensity-modulated radiotherapy (IMRT) and widespread use of prophylactic tooth extractions before radiotherapy have reduced the incidence of ORN; however, its incidence rate remains between 4 and 8% (6). The risk factors for ORN include radiotherapy-related factors, such as radiation dose exceeding 60 Gy and the type of radiation modality, as well as patient-related factors, including poor oral hygiene, and dental extractions within the irradiated area, particularly involving the mandible (7-9). It is still controversial to determine the appropriate timing of dental extractions among patients undergoing radiotherapy; however, the National Comprehensive Cancer Network guidelines propose that dental extraction should be performed at least 2 weeks prior to the initiation of radiotherapy (1). A previous study demonstrated that the prognosis of ORN varies, with a survival rate of 96% at 12 months and 73% at 60 months after the diagnosis of ORN, indicating that ORN can have a significant impact on long-term survival (10). Hence, effective ORN management is also crucial for improving long-term outcomes and quality of life of patients with HNC. Conventional treatments for ORN include conservative and surgical approaches. Conservative treatments, such as pentoxifylline and tocopherol, clodronate potentiation and hyperbaric oxygen (HBO) therapy, offer limited efficacy as ORN advances (1,11-14). By contrast, surgical treatments, particularly segmental mandibulectomy, are now regarded as favorable options for advanced ORN (1,15-17). Although evidence increasingly supports

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**Key words:** osteoradionecrosis of the jaw, multiple primary malignant neoplasms, companion diagnostics, comprehensive genomic profiling, RET fusion

surgical treatment, patients with ORN often undergo other cancer therapies, such as surgery or chemoradiotherapy, for their primary HNC. Thus, the patients' overall prognosis must be considered when managing ORN.

Comprehensive genomic profiling (CGP) technologies have provided critical insights into tumorigenesis mechanisms and identified potent therapeutic targets, advancing precision medicine (18,19). These technologies are also employed in companion diagnostics, helping predict therapeutic efficacy (19,20). The present study presents a case of ORN coinciding with thyroid cancer metastasis to the submandibular gland. Subsequent CGP identified a RET fusion as a therapeutic target, and treatment with its inhibitor, selpercatinib, resulted in a partial response.

The present case report highlighted the necessity of extensive surgical treatment for ORN among those with advanced cancer, as well as the clinical utility of submandibular dissection in the surgical treatment of ORN, particularly thyroid cancer exhibiting an aggressive phenotype. Furthermore, the study emphasized the novelty of managing ORN in patients with advanced cancer using CGP testing. Through this strategy, the patient of the present study successfully underwent management of ORN with extensive surgery, while concurrently receiving treatment for advanced PTC based on genomic profiling. The effectiveness of this novel management approach was demonstrated by improving the patient's condition. This suggests that the combined approach may offer a promising treatment option for patients with both ORN and advanced PTC.

## Case presentation

A 58-year-old Japanese male was referred to the Department of Oral Diagnosis and Medicine in Hokkaido University Hospital (Hokkaido, Japan) by his family dentist in July 2020 for evaluation of bone exposure in the mandible. The patient reported severe spontaneous pain in the right mandibular area. The patient had a history of smoking for 18 years (ages 20 to 38 years) and of drinking alcohol regularly for 38 years. The medical family history included no cancer cases; however, the patient's medical history included left-sided thyroid cancer and right-sided oropharyngeal cancer.

For thyroid cancer, the patient had undergone a left hemithyroidectomy and was diagnosed with papillary thyroid carcinoma (PTC; TNM stage unknown) in 1998 (Fig. 1A). In March 2012, routine computed tomography (CT) identified a mass in the right lung. The patient underwent thoracoscopic right lower lobectomy and the lesion was diagnosed as PTC metastasis. The patient received postoperative radioactive iodine (RI) therapy with I-131 (Fig. 1B). After three sessions of RI therapy, a partial response was achieved and the patient was monitored regularly. In March 2020, routine CT revealed worsening PTC metastases in the lung, leading to initiation of lenvatinib treatment (24 mg/day) (Fig. 1C).

Regarding oropharyngeal cancer, the patient first experienced right neck pain and a swollen cervical lymph node in February 2017. Fine-needle aspiration suggested squamous cell carcinoma (SCC) (Fig. 1D). The patient also reported discomfort in the right palatine tonsil. Biopsy confirmed right oropharyngeal SCC with p16+/human papillomavirus +

(cT2N1M0, stage I). The patient opted for IMRT alone to treat the oropharyngeal cancer. In March 2017, prior to IMRT, the right-sided wisdom tooth, which was scheduled to be in the irradiation field (Fig. 1E), was extracted. In June 2017, the patient completed IMRT with a dose of 70 Gy in 35 fractions and showed no evidence of recurrence on follow-up positron emission tomography (PET)/CT.

In July 2020, extraoral examination revealed swollen, reddened skin over the right mandible. The patient also experienced trismus, with a maximal interincisal distance of 22 mm. Intraoral examination showed exposed bone (4 mm in diameter) in the right mandibular gingiva (Fig. 2A). A panoramic X-ray revealed mild sclerosis around the exposed area (Fig. 2B), and CT also showed marked sclerosis and a partial cortical irregularity without apparent mandibular fracture (Fig. 2C). Considering these clinical manifestations, the patient was diagnosed with ORN in the right mandible (Grade III according to Notani's classification) (21) (Fig. 1F). Initial antimicrobial therapy with amoxicillin (AMPC; 1,000 mg/day) and clavulanic acid/AMPC (1,000 mg/day) relieved the swollen gingiva; however, the patient still suffered pain during meals. In October 2020, the patient underwent extraction of the right second mandibular molar and sequestrectomy (Fig. 1G), followed by 10 sessions of HBO therapy. During the treatment, the patient did not feel any benefit and therefore chose to discontinue further sessions, resulting in a total of 10 sessions.

In April 2021, the patient reported severe pain and pus discharge from the wound, with exposed bone observed at the site. Given the poor response to conservative treatment, the patient consented to right segmental mandibulectomy. At that time, the patient had been receiving lenvatinib for 18 months, which was discontinued one week before surgery for ORN. In September 2021, the patient underwent right segmental mandibulectomy and right submandibular dissection (levels I and II), including right submandibular gland resection (Figs. 1H and 3A and B). As for determining the extent of mandibulectomy, the resected area included the bone sclerotic area observed in the CT images, the area irradiated >45 Gy and the area where punctuate bleeding is observed during the surgery. Reconstruction involved a vascularized fibular free flap and concurrent right inferior alveolar nerve repair using Renuve® (Nipro Medical Corp.), a bioresorbable allograft material (Fig. 3C). Pathological examination confirmed sequestrum with bacterial colonies in the bone lacunae, consistent with osteonecrosis (Fig. 4A and B). In this examination, formalin-fixed tissue sections were processed and embedded in paraffin. Subsequently, 4- $\mu$ m sections were prepared for staining with hematoxylin and eosin according to standard procedures. Unexpectedly, the pathological examination also revealed tumor cells that showed optically clear nuclei, characteristic of PTC, in the resected right submandibular gland, which had not been identified in the previous CT images (Fig. 5A). In addition, immunohistochemical staining was positive for thyroglobulin, thyroid transcription factor 1 (TTF1) and paired-box 8 (PAX8), confirming PTC metastasis (Fig. 5B-D). Regarding the immunohistochemical staining, 4- $\mu$ m paraffin sections were prepared from blocks of tumor

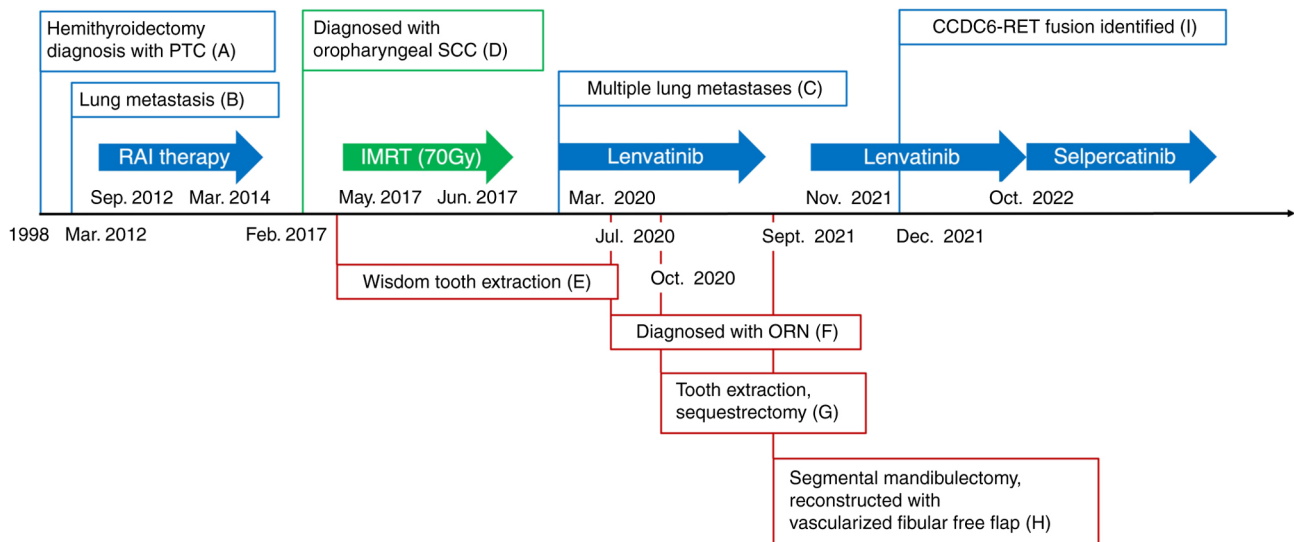


Figure 1. Summary of the patient's clinical course. The clinical course related to PTC is indicated in blue, oropharyngeal cancer in green and ORN of the jaw in red. (A) The patient was subjected to left hemithyroidectomy and pathological examination revealed PTC. (B) The patient displayed lung metastasis unveiled by thoracoscopic right lower lobectomy. (C) The patient showed worsening PTC metastases in the lung. (D) The patient underwent fine-needle aspiration, revealing oropharyngeal SCC. (E) The patient received right-sided wisdom tooth extraction two months prior to the initiation of radiotherapy. (F) At three years after the completion of radiotherapy, the patient had developed ORN. (G) The patient underwent right-sided second mandibular molar extraction and sequestrectomy. (H) The patient experienced right segmental mandibulectomy and right submandibular dissection (levels I and II), including right submandibular gland resection. The patient also underwent reconstructive surgery with vascularized fibular free flap. (I) Comprehensive genomic profiling test identified CCDC6-RET fusion as an actionable target. ORN, osteoradionecrosis; PTC, papillary thyroid carcinoma; SCC, squamous cell carcinoma; IMRT, intensity-modulated radiotherapy; RAI, radioactive iodine.



Figure 2. Clinical manifestations at the first visit. (A) Bone exposure was observed in the right mandibular gingiva, with a diameter of ~4 mm. Arrow indicates bone exposure (mirror image). (B) Panoramic X-ray revealed mildly increased radiopacity around the right mandibular alveolar bone. (C) Computed tomography showed sclerotic changes around the bone exposure site, along with a partial cortical irregularity (marked by a yellow arrow).

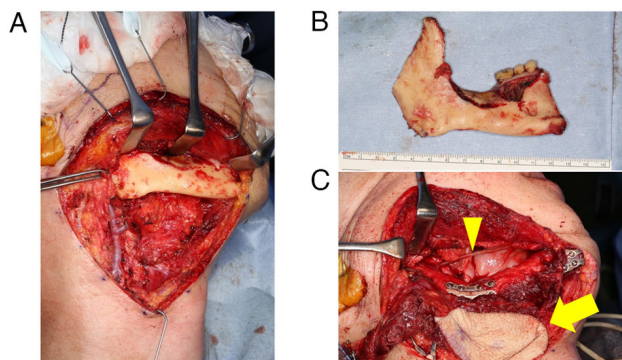


Figure 3. Surgical procedures. (A) The patient underwent right segmental mandibulectomy and concurrent right submandibular dissection. During surgery, the right submandibular gland was resected. (B) The mandibulectomy extended from the coronoid process superiorly, through the area between the lingula and mandibular notch, and anteriorly to the right mandibular canine (scale in cm). (C) Reconstructive surgery was performed using a vascularized fibular free flap (arrowhead) and included right inferior alveolar nerve reconstruction with Renuve® (Nipro Medical Corp.).

tissues using a microtome. The antigen was activated by heat treatment at 97°C for 20 min in Tris/EDTA buffer solution (pH 9.0) after deparaffinization and dehydration. The antibodies used were as follows: Anti-thyroglobulin (cat. no. M078101-2; Dako; Agilent Technologies, Inc.), anti-TTF-1 (cat. no. M3575; Dako; Agilent Technologies, Inc.) and anti-PAX8 (363M-14-RUO; Sigma-Aldrich; Merck KGaA) antibodies. Immunoreaction was visualized with horseradish peroxidase-linked secondary antibody (cat. no. K4001; Dako; Agilent Technologies, Inc.) and 3,3'-diaminobenzidine substrate (cat. no. GV82511-2; Dako; Agilent Technologies, Inc.). All sections were observed under a fluorescence microscope (ECLIPSE Ci; Nikon Corp.).

At four weeks post-surgery, lenvatinib treatment (8 mg/day) was resumed, but subsequent CT revealed further metastases to the lungs and liver (Fig. 6A). In December 2021, CGP using FoundationOne® CDx (performed externally at Foundation Medicine, Inc.) identified a CCDC6-RET fusion in tumor cells from the submandibular gland metastasis (Fig. 1I, Table I).

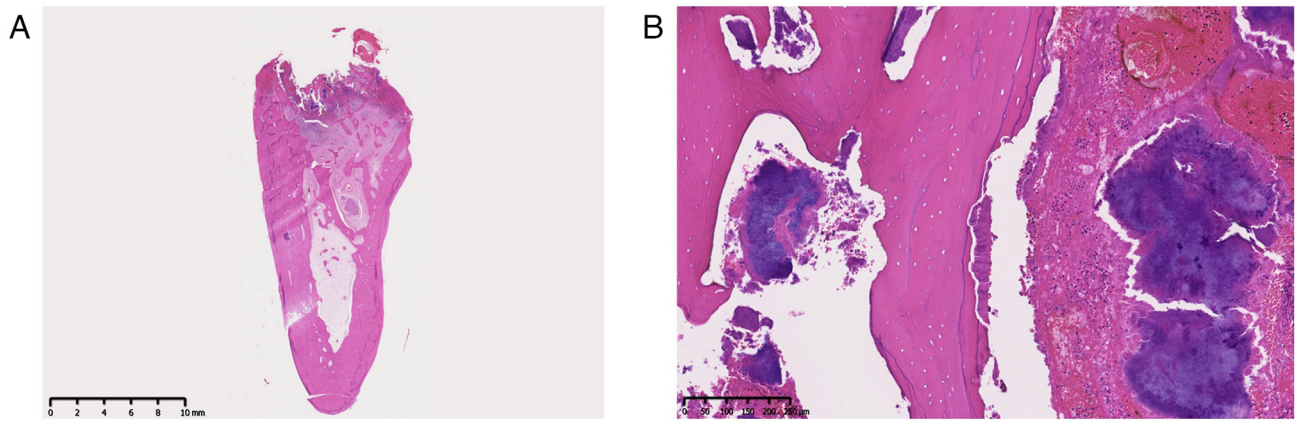


Figure 4. Pathological findings for bone. Pathological examination revealed a bony sequestrum containing bacterial colonies within the bone lacunae in the exposed bone area. (A) Original magnification, x1 (scale bar, 10 mm); (B) original magnification, x200 (scale bar, 250  $\mu$ m) (hematoxylin-eosin staining).

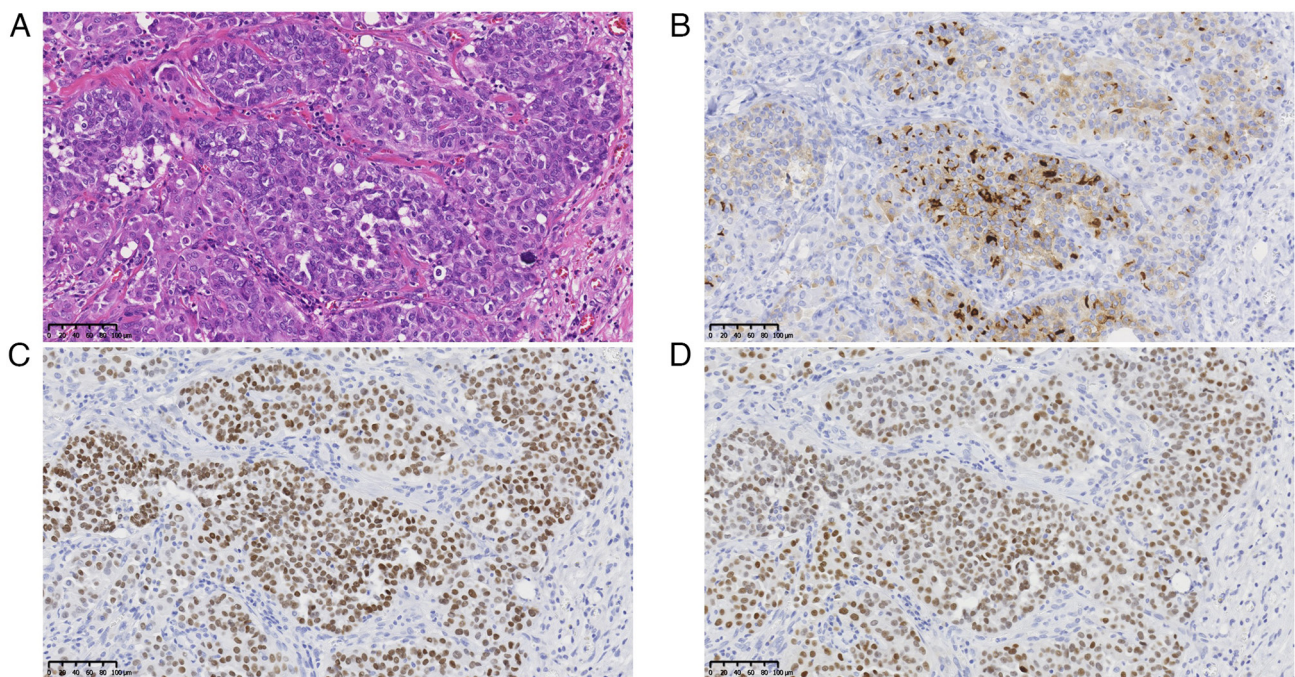


Figure 5. Pathological findings for the submandibular gland. (A) Pathological examination detected tumor cells in the submandibular gland with optically clear nuclei characteristic of PTC (hematoxylin-eosin staining). (B-D) Immunohistochemical analysis confirmed PTC metastasis in the submandibular gland, with positive staining for (B) thyroglobulin, (C) thyroid transcription factor 1 and (D) paired-box 8 (original magnification, x400; scale bars, 100  $\mu$ m). PTC, papillary thyroid carcinoma.

Consequently, the patient was switched to selpercatinib, a selective RET inhibitor, (320 mg/day) in October 2022, achieving a partial response with reduced metastatic lesions in the lungs and liver (Fig. 6B).

At three years after the ORN surgery, the patient remains under regular monitoring with no signs of recurrence on panoramic X-ray (Fig. 7A), and the patient's occlusion has been restored with dentures (Fig. 7B). Furthermore, nerve reconstruction has successfully preserved sensation of the skin area around the mental region. The patient continues selpercatinib treatment without showing any severe adverse effects, maintaining stable disease. The patient is now being monitored regularly with panoramic X-ray once a year for ORN and CT scans every three months for PTC.

## Discussion

This report describes a rare clinical course in a patient with ORN of the jaw who unexpectedly presented with PTC metastasis to the submandibular gland. The patient underwent extensive surgical treatment for ORN, resulting in a favorable outcome without any severe postoperative complications. Furthermore, due to the detection of PTC metastases in the submandibular gland, CGP was called upon, revealing RET fusion as a therapeutic target. As a result, treatment with selpercatinib, a selective RET inhibitor, led to the successful management of advanced PTC with the patient showing a partial response. This case highlights the value of extensive surgical treatment for patients with ORN even

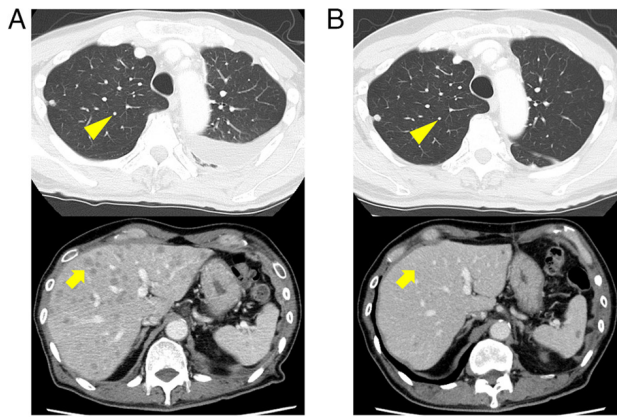


Figure 6. Response to selpercatinib treatment. (A) Computed tomography revealed exacerbated papillary thyroid carcinoma metastases to the lungs and liver after the extensive surgery for osteoradionecrosis of the jaw compared to the condition before the surgery. (B) At one month after the initiation of selpercatinib therapy, the size of the metastatic lesions was markedly reduced as indicated with arrowhead and arrow, respectively, achieving a partial response. Upper panels indicate the lung fields and lower panels the hepatic regions. Yellow arrowheads indicate a representative lung metastatic lesion, displaying with high density, while the yellow arrows indicate a representative liver metastatic lesion, displaying with low density.

when they have aggressive cancer phenotypes, and of the utility of CGP in identifying therapeutic targets, particularly in patients with cancer who generally harbor well-known actionable targets.

Thyroid cancer is the most prevalent endocrine malignancy (22), with PTC accounting for ~80% of all thyroid cancers (23). The prognosis for PTC is generally favorable, with the 10-year survival rate exceeding 90%, making it a controllable cancer (24,25). However, ~40% of PTC cases metastasize to the cervical lymph nodes, lungs, liver and bones, leading to intractable disease and a 10-year survival rate <60% (26,27). Of note, PTC metastasis to the submandibular gland is rare, with only a few reports describing such occurrences (28-32). In the patient of the present study, preoperative CT scans failed to detect the metastasis. Given his multiple lung PTC metastases despite ongoing lenvatinib treatment, it was decided to perform submandibular dissection during the surgery for ORN and the right submandibular gland was resected, as occult PTC metastasis was suspected. Previously, it was reported that ultrasound (US) would be highly effective in detecting a submandibular gland metastasis that cannot be identified by CT or PET/CT (32). Therefore, it should be considered to perform not only regular CT but also US for monitoring patients with thyroid cancer to detect metastasis around the neck region in the early period.

The CGP test is a next-generation sequencing approach that analyzes the genomic landscape of patients with cancer, which enables the detection of potential therapeutic targets, leading to personalized medicine. Currently, our hospital offers two CGP platforms, FoundationOne® CDx and OncoGuide™ National Cancer Center (NCC) OncoPanel, to those who complete or are expected to complete standard treatment for solid tumors. FoundationOne® CDx examining based on formalin-fixed, paraffin-embedded (FFPE)

samples, enables the analysis of a total of 324 genes covering various somatic mutations in 309 genes and 36 fusion genes in addition to microsatellite instability and tumor mutation burden (TMB), while the OncoGuide™ NCC OncoPanel test based on both FFPE and blood samples allows analyzing 126 genes, including various somatic/germline mutations in 114 genes and 12 fusion genes and TMB (33,34). As for the patient of the present study, his desire to undergo CGP with a broader gene analysis led to analysis with the FoundationOne® CDx platform, which eventually identified a CCDC6-RET fusion that is covered in these CGP platforms.

The *RET* proto-oncogene encodes a transmembrane tyrosine kinase receptor protein (35). RET regulates cellular proliferation, differentiation and apoptosis through binding with its ligands, the glial cell line-derived neurotrophic factor family (36,37). Genetic aberrations, including RET alterations, fusions and amplifications, have been observed in various cancers (38,39). These RET aberrations lead to ligand-independent hyperactivation of downstream signaling pathways, contributing to tumorigenesis (40). RET aberrations have become major therapeutic targets, with several multi-kinase inhibitors, including lenvatinib, and selective RET inhibitors, such as selpercatinib and pralsetinib, having received Food and Drug Administration approval (41-43). Prior studies have shown that these selective RET inhibitors offer substantial benefits with manageable toxicity in patients with thyroid and lung cancers harboring RET aberrations (44,45). Of note, patients with thyroid cancer often exhibit RET aberrations, with ~50% of medullary thyroid carcinoma and 30% of PTC cases exhibiting such alterations (38,46,47). Therefore, early CGP testing is valuable for identifying actionable targets, such as RET aberrations, in thyroid cancer cases not well-controlled by ongoing treatments.

Management of ORN remains challenging, as conventional treatments are often insufficient for this intractable disease. Treatment strategies, including conservative and surgical options, depend on disease severity (1). Several reports have described ORN grade classification based on clinical manifestations, radiological findings, duration of bone exposure and response to HBO therapy (4). In our department, Notani's classification is used, which considers the extent of bone involvement to guide treatment decisions for patients with ORN (Table I) (21). Accordingly, the patient of the present study was classified as Grade III. Notani *et al* (21) demonstrated that patients with Grade III ORN show favorable outcomes with segmental resection. Consequently, the patient of the present study underwent segmental mandibulectomy followed by reconstruction with a vascularized fibular free flap. Furthermore, previous studies have emphasized early surgical intervention when conservative treatments fail to show improvement in clinical and radiographic findings (17,21,48). Although the decision to perform extensive surgery in patients with cancer is controversial, the response of the patient of the present study indicated limited efficacy with antimicrobial treatment and sequestrectomy. Given the patient's strong desire to alleviate the severe pain from mandibular inflammation and the limited success of conservative treatments, it was decided to perform surgery.

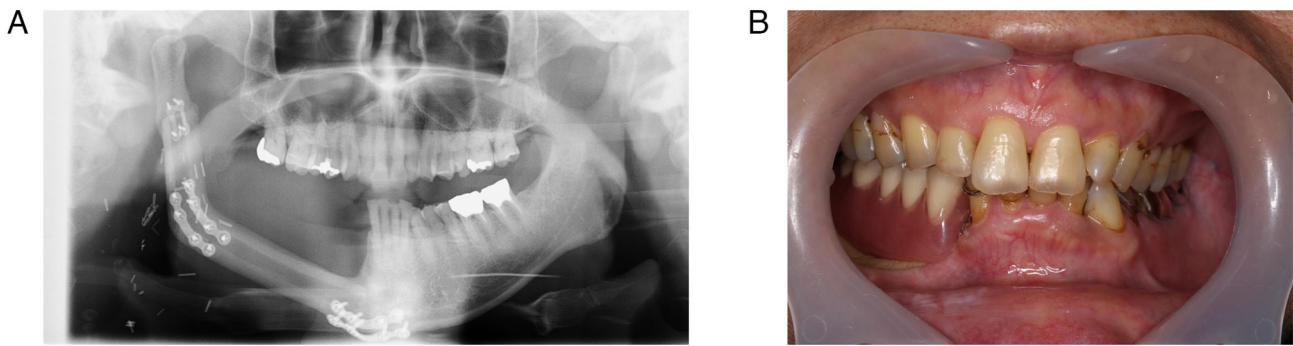


Figure 7. Postoperative outcomes. (A) Postoperative panoramic X-ray showed no signs of recurrence. (B) Extensive surgery for osteoradionecrosis successfully restored the patient's occlusion, enabling the use of dentures.

The decision to perform extensive surgery on cancer patients should always be carefully weighed against potential risks and benefits. This is because those who receive anti-angiogenic inhibitors would likely show delayed wound healing as described previously (49). Lenvatinib is a multi-kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor- $\alpha$ , RET and KIT proto-oncogene receptor tyrosine kinases (50). From the perspective of bone remodeling, lenvatinib can impair the normal remodeling process by inhibiting angiogenesis. In general, bone remodeling primarily involves two key processes: Vigorous angiogenesis and regulation of basic multicellular units (BMUs), including osteogenic cell activity (51). Angiogenesis plays crucial roles in bone remodeling by recruiting osteogenic cells toward the remodeling site and by supplying oxygen and growth factors essential for bone regeneration (52). Although it remains elusive whether lenvatinib directly affects BMUs, its inhibition of VEGF may disrupt angiogenesis. Therefore, lenvatinib treatment may have contributed to the worsening of ORN by impairing bone healing. Furthermore, it has been reported that lenvatinib bears a risk of developing medication osteonecrosis of the jaw (MRONJ) (53,54). In the present study, the patient had been subjected to radiotherapy and lenvatinib treatment, both of which can contribute to the onset of osteonecrosis. As for the differential diagnosis, it is noteworthy that MRONJ specifically presents as an apparent periosteal reaction on CT imaging (55,56). In the patient of the present study, CT revealed osteolytic lesions accompanied by sclerotic changes around the exposed bone without showing any apparent periosteal reaction. Thereafter, the patient was eventually diagnosed with ORN.

Regarding segmental mandibulectomy for ORN treatment, there are no clear guidelines on the ideal resection area. A previous study suggested that preoperative radiographic findings and intraoperative bleeding from native bone may help define resection borders (1). At our department, criteria for determining the extent of mandibulectomy for ORN have been established (Table II). These include occlusal factors, radiographic findings, radiation dose, intraoperative observations and consideration of autologous bone reconstruction. Based on these guidelines, early surgical intervention is suitable, as previously recommended

when conservative treatments failed to yield substantial benefits (48). In the patient of the present study, the extent of mandibulectomy was determined by the extent of sclerotic changes observed on CT, the area irradiated >45 Gy, intraoperative findings to observe bleeding and availability of autologous bone that includes patients' surgical tolerance. Nevertheless, further research is necessary to refine these criteria for more sophisticated decision-making regarding ORN surgery.

Despite the success of the present strategy in preventing postoperative complications and recurrence, there are certain limitations to address. First, the extensive surgery for ORN led to discontinuation of the patient's treatment for PTC metastases, ultimately worsening the progression of PTC. The withdrawal of tyrosine kinase inhibitors (TKIs) can trigger a rapid disease progression known as the flare phenomenon, characterized by an aggressive resurgence of cancer symptoms (57,58). Specifically, patients with thyroid cancer treated with lenvatinib have a 14.3% incidence rate of the flare phenomenon (59). Furthermore, previous studies have shown that patients experiencing the flare phenomenon tend to have a worse prognosis compared with those who do not exhibit this phenomenon (59). Considering these facts, it is highly important to manage the lenvatinib treatment course properly in the surgical setting. Thus far, guidelines for the perioperative discontinuation of lenvatinib and resumption remain to be established. Several reports have recommended the discontinuation period as seven days prior to surgery based on the half-life of lenvatinib, 34.5 h (60-62). As for the timing of lenvatinib resumption, a recent paper demonstrated that the timing for resumption should be four to six weeks after the surgery when wound healing is generally confirmed (60). Accordingly, the patient of the present study stopped lenvatinib treatment one week before ORN surgery and resumed treatment four weeks post-surgery. Given the progression of PTC metastases during this period, the timing of TKI treatment resumption or an alternative strategy should be reconsidered. Previously, a paper demonstrated that the personalized treatment schedule of lenvatinib led to the successful management of a patient with thyroid cancer who responded well to lenvatinib; however, severe adverse effects occurred (63). Hence, when a patient exhibits an apparent disease flare following lenvatinib discontinuation, it should be considered to resume

Table I. Comprehensive genomic profiling results.

| Gene  | Variant            | Variant type      | Interpretation |
|-------|--------------------|-------------------|----------------|
| RET   | CCDC6-RET          | Fusion            | Actionable     |
| BRCA2 | V2687I (c.8059G>A) | Missense mutation | VUS            |
| BRD4  | P1091S (c.3271C>T) | Missense mutation | VUS            |
| SDHD  | A90E (c.269C>A)    | Missense mutation | VUS            |
| TBX3  | M608T (c.1823T>C)  | Missense mutation | VUS            |

VUS, variant of uncertain significance.

Table II. Clinical/radiographic factors for determining the extent of mandibular resection required to treat jaw osteoradionecrosis.

| Factors determining the extent of mandibulectomy | Context                                                                                                                                                  |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral hygiene/denture assessment                  | Preservation of occlusal contact                                                                                                                         |
| Imaging assessment                               | CT; presence of osteomyelitis and/or peritoneal reaction<br>MRI; hypointensity region in T1-weighted images<br>PET/CT; accumulation of FDG uptake region |
| Radiation amount                                 | Affected bone irradiated >45 Gy                                                                                                                          |
| Intraoperative findings                          | Punctate bleeding at the wound edge of the affected bone                                                                                                 |
| Reconstruction method                            | Availability of autologous bones                                                                                                                         |

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG, [<sup>18</sup>F]-fluorodeoxyglucose.

lenvatinib immediately with a low dose after surgery with careful attention to wound management. As a second limitation of the study, the CGP testing successfully identified the actionable target; however, this technique has several limitations. CGP requires an adequate quantity and quality of tumor samples defined as the tumor cell content ratio, DNA amount and tissue size, which would narrow down the patients' accessibility to this analysis (34,64). Furthermore, CGP testing can detect druggable gene mutations, in other words, it cannot detect gene mutations beyond the scope of the CGP panels (65). In addition, the prevalence of CGP testing can have an economic impact, increasing the financial burden on health systems (34,66). Of note, a recent paper demonstrated that CGP testing may be cost-effective compared with conventional single-gene testing (65). This is proposed to be due to the increased possibility of identifying actionable targets, resulting in patients receiving genotype-matched therapy, which may provide better outcomes than traditional chemotherapies (65). Furthermore, since the CGP testing generally takes four to six weeks to get results (65), it would be preferable to perform this analysis before the completion of standard treatment. Therefore, based on these facts, early CGP testing should be considered among patients with cancer harboring potentially actionable targets. In particular, as mentioned earlier, effective RET inhibitors have already been developed and shown therapeutic efficacy in patients with thyroid cancer harboring RET aberrations (67,68). Therefore, early CGP testing should be encouraged for patients with refractory thyroid

cancer to identify actionable targets and guide personalized treatment plans. Based on the rationale for early CGP testing, the present analysis also identified missense forms of four genes, BRCA2, BRD4, SDHD and TBX3, in addition to the CCDC6-RET fusion. According to the previous papers, BRCA2 primarily functions in DNA repair pathways (69). BRD4 is involved in the NF-κB-mediated inflammatory gene expression system, thereby regulating inflammation and promoting fibrosis (70). Furthermore, TBX3 facilitated epithelial wound healing in mouse experiments (71). Although no reports describing a relationship between SDHD function and wound healing exist, to the best of our knowledge, it is noteworthy to consider how these genetic alterations may influence clinical outcomes, particularly postoperative wound healing. As a third limitation of the present study, the patient did not receive any quantitative analyses to assess the preservation of oral and sensory functions after the reconstructive surgery. To support the effectiveness of the present treatment strategy, further examinations, including repetitive saliva swallowing test, glucose measurement by chewing gummy jelly and Semmes Weinstein monofilament test for sensory testing, for instance, should be performed (72-74).

In conclusion, extensive surgical treatment should be considered for managing patients with ORN even in those with advanced cancer. In particular, submandibular dissection should also be included as part of the extensive surgery, particularly when patients with thyroid cancer exhibit an aggressive phenotype, to detect occult metastases. Lastly, the present

case also highlights the utility of CGP in managing aggressive cancers with specific gene aberrations, underscoring its potential role in precision medicine.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

The comprehensive genomic profiling data generated in the present study are available in the Figshare repository at <https://doi.org/10.6084/m9.figshare.28890965.v1>.

## Authors' contributions

TK collected the clinical data. TK and KIS wrote the manuscript. TK, KIS, KY, TMu, TI, TMa, JK and YK acquired and interpreted clinical data. AYM performed the pathological examination. KIS, JS and YK revised the manuscript. KIS and JS checked and confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

The present report was approved by Hokkaido University Hospital Independent Clinical Research Review Committee (Sapporo, Japan; approval no. 023-0364).

## Patient consent for publication

Written informed consent for the publication of the clinical data, including photos and images, was obtained from the patient.

## Competing interests

The authors declare that they have no competing interests.

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