



# Painful tongue lesion as an initial presentation of metastatic pancreatic ductal adenocarcinoma: a case report and review of the literature

Cynthia Mark<sup>1</sup>, Angela Minasyan<sup>1</sup>, Matthew I. Ebia<sup>1</sup>, Anser Abbas<sup>1</sup>, Ankona Ghosh<sup>2</sup>, Rabindra Watson<sup>3</sup>, Horacio M. Maluf<sup>4</sup>, Behrooz Hakimian<sup>5</sup>, Brent Larson<sup>4</sup>, Laura Elizabeth Mcvay<sup>1</sup>, Jun Gong<sup>1</sup>, Andrew Hendifar<sup>1</sup>, Arsen Osipov<sup>1</sup>

<sup>1</sup>Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; <sup>2</sup>Division of Otolaryngology, Department of Surgery, Los Angeles, CA, USA; <sup>3</sup>Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; <sup>4</sup>Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; <sup>5</sup>Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

*Contributions:* (I) Conception and design: C Mark, A Osipov; (II) Administrative support: All authors; (III) Provision of study materials or patients: A Osipov, MI Ebia; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Cynthia Mark, MD. Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Suite 5512, Los Angeles, CA 90048, USA. Email: [cynthia.mark@cshs.org](mailto:cynthia.mark@cshs.org).

**Background:** Metastasis of solid tumors to the tongue is a rare occurrence and makes up less than 1% of head and neck cancers. Given the treatment approach for a primary head and neck cancer would differ from metastasis to the tongue, an accurate diagnosis is critical. There are only a few reported cases of pancreatic cancer metastasizing to the head and neck region.

**Case Description:** This report presents a unique case of a 91-year-old man who initially presented with a painful tongue mass and ultimately was found to have metastatic pancreatic ductal adenocarcinoma. Comparison of a biopsy from the tongue mass and the pancreatic lesion showed they were morphologically identical and confirmed the diagnosis. Treatment of the tongue lesion with palliative radiation led to clinical improvement of difficulty and pain with swallowing.

**Conclusions:** Our case highlights a rare presentation of pancreatic cancer, as metastasis to the tongue has not been previously described as an initial presentation of pancreatic cancer. This report also discusses potential treatment strategies for this unique presentation. Head and neck lesions can greatly impact oral intake. Use of radiation therapy (RT) appears to alleviate some of these symptoms and lead to improved nutrition. Practitioners should consider palliative radiation as a potential treatment strategy in patients with tongue metastases.

**Keywords:** Pancreatic adenocarcinoma; tongue metastases; radiotherapy; case report

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## Introduction

Pancreatic adenocarcinoma is notoriously difficult to detect at an early stage given the location of the pancreas as a retroperitoneal organ, lack of screening tests, and often non-specific initial symptoms. Some of the most common

initial symptoms of pancreatic cancer are fatigue, anorexia, weight-loss, abdominal pain, dark urine, jaundice, nausea, or bloating (1,2). Therefore, by the time of diagnosis, many patients present with advanced stage disease. The most common sites for metastases being liver, followed by the

peritoneum, lung and pleura, bones, and adrenal glands (3).

Metastasis of solid cancer to the oral cavity is rare and represents less than 1% of neoplasms in the oral cavity (4). In the case of pancreatic cancer, there are only a few documented cases of metastasis of pancreatic cancer to the head and neck region, more specifically the oropharynx and esophagus (5-9). This is a rare way for pancreatic cancer to metastasize and is thought to occur through hematogenous spread from the lung (10). Another commonly discussed mechanism is spread through the Baston venous plexus, which is thought to occur when there is an absence of pulmonary metastases (11). In this case report, we discuss a rare case of pancreatic metastases to the tongue with the tongue lesion being the initial presenting symptom that led to diagnosis of pancreatic adenocarcinoma. We present this article in accordance with the CARE reporting checklist (available at <https://apc.amegroups.com/article/view/10.21037/apc-23-10/rc>).

### Case presentation

A 91-year-old man who is a former smoker with past medical history of hypertension and hypothyroidism presented to an otolaryngologist [ear, nose and throat (ENT)] office due to a painful left lateral tongue lesion that had been ongoing for approximately 3 weeks. Prior to presentation, his primary care provider (PCP) had prescribed two courses of antibiotics, including amoxicillin and levofloxacin without improvement. His PCP also attempted to drain the lesion with a needle but was unsuccessful given the solid state. He had visited a previous ENT who had obtained a computed



**Figure 1** Computed tomography soft tissue neck without contrast showing a 1.5-cm diameter thin-walled ring enhancing centrally hypodense lesion of the left lateral tongue (arrow).

tomography (CT) scan showing a 1.5-cm rim-enhancing well-circumscribed lesion in the submucosal left lateral tongue (*Figure 1*). Physical exam was notable for a firm submucosal lesion on the left lateral tongue with significant tenderness to palpation. Patient underwent an incisional biopsy which showed a moderately differentiated invasive adenocarcinoma without evidence of an associated precursor tumor. The biopsy was positive for cytokeratin 7 (CK7) and caudal-type homeobox 2 (CDX-2), which was suggestive of an upper gastrointestinal (GI) or pancreatobiliary primary, however, a primary salivary gland adenocarcinoma could not be excluded. Patient underwent a positron emission tomography (PET)-CT scan which was notable for a large hypodense lesion within the pancreatic head and tail concerning for a primary pancreatic neoplasm (*Figure 2*). PET-CT was also notable for metabolically active lesions in the left lateral anterior two-thirds of the tongue, multiple pulmonary nodules, left hilar lymph nodes, soft tissue foci (right shoulder, right lower back, left buttock, and left femur), and a large hypodense right hepatic lesion thought to represent a necrotic hepatic metastasis.

He later presented to the emergency room (ER) with significant tongue pain and poor oral intake resulting in a 20–25-pound weight loss over the past 6 months. Patient was otherwise asymptomatic. Physical exam was notable for the left lateral tongue lesion. Labs were notable for a mild leukocytosis to  $13.84 \times 10^3/\mu\text{L}$ , elevated alkaline phosphatase to 156 U/L, elevated alanine transaminase to

#### Highlight box

##### Key findings

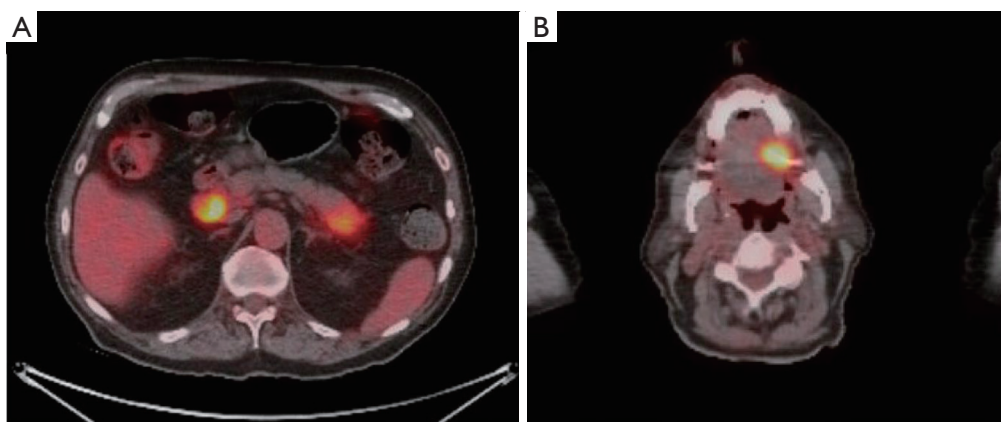
- Metastasis of pancreatic cancer to the oral cavity, specifically the tongue, is an incredibly rare occurrence.
- Radiation therapy may be beneficial for tongue metastasis.

##### What is known and what is new?

- This is a rare presentation of pancreatic cancer in which the patient presented with a tongue lesion and was found to have metastatic pancreatic cancer.

##### What is the implication, and what should change now?

- Consider a broad differential when presented with a patient with a new oral lesion.
- Consider palliative radiation for oral metastasis as a way to improve oral intake.



**Figure 2** Images from patient's full body PET-CT showing lesions in the pancreas and the tongue. PET-CT shows a large hypodense lesion with intensely increased FDG activity in the pancreatic head measuring 3.2 cm × 3.2 cm and pancreatic tail measuring 3.1 cm × 4.0 cm (A). Also, PET-CT shows a focal area of increased FDG activity within the left lateral anterior two-thirds of the tongue (B). PET, positron emission tomography; CT, computed tomography; FDG, fluorodeoxyglucose.

76 U/L and elevated aspartate aminotransferase to 73 U/L. Patient was treated with supportive measures including fluids and pain medications. Given the unusual location of suspected pancreatic metastasis, patient underwent an endoscopic ultrasound (EUS) with fine needle biopsy (FNB). The procedure showed a 3-cm hypoechoic poorly-demarcated pancreatic tail mass with evidence of extension into the gastric wall with encasement of the splenic vessels, gastric varices, one large 4-cm abnormal lymph node in the portocaval region, and a diffuse abnormal echotexture in the visualized portion of the liver. FNB obtained during the EUS showed invasive adenocarcinoma in the sample taken from the pancreatic tail mass and metastatic adenocarcinoma from the sample taken from the portocaval lymph node. Additional immunostains were performed and compared to the previous tongue biopsy. The tumor from the tongue and from the pancreatic tail lesion were found to be morphologically identical and were consistent with an invasive pancreatic ductal adenocarcinoma (PDAC) with metastasis (Table 1). Somatic testing of the portocaval lymph node specimen demonstrated *KRAS* G12V gain of function mutation, loss of function mutations in *CDKN2A* and *TP53*, copy number gain in *PIMI1*, microsatellite stable, and tumor mutational burden of 4.7 mutations/megabase.

After biopsy confirmed metastatic pancreatic cancer, he was started on gemcitabine monotherapy with plans to add nanoparticle albumin-bound (nab)-paclitaxel with cycle 2 if tolerated. Two weeks after the first dose of gemcitabine, patient developed significant lip swelling and mucositis and

was started on dexamethasone with improvement. He was also evaluated by infectious disease and was thought to have herpes of the lip and thrush and was started on acyclovir and fluconazole. The third dose of gemcitabine was held due to grade 3 thrombocytopenia. Additionally, given significant symptoms in his tongue, patient underwent a course of palliative radiation, 1,480 cGy divided in four fractions, quad shot, with improvement in pain and swallowing. Detailed radiation planning imaging is provided in Figure 3 and Figure S1. Moreover, given his poor oral intake, total parenteral nutrition was initiated and later a percutaneous endoscopic gastrostomy tube was placed to supplement nutrition. After two doses of gemcitabine, repeat CT of the abdomen and pelvis showed interval increase in size of the pancreatic mass and progressive hepatic metastatic disease despite chemotherapy. Given the lack of tumor response and poor tolerability to chemotherapy, decision was made to transition to hospice care.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

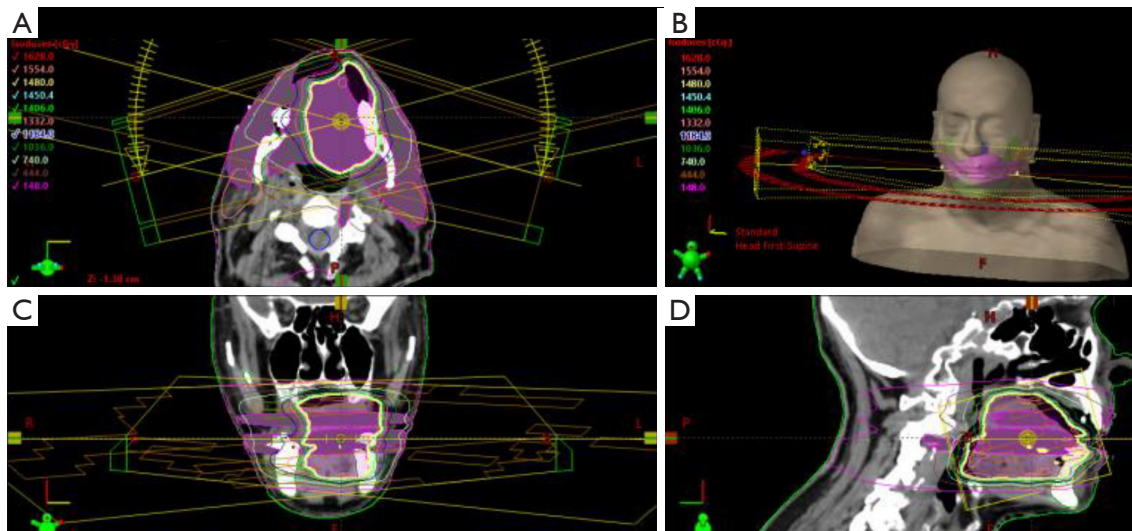
## Discussion

Metastases of pancreatic adenocarcinoma to the tongue

**Table 1** Immunohistochemical profile of tongue and pancreatic biopsy

Antibody [clone]	Tongue biopsy result	Pancreatic FNB result
TTF-1 [SP141]	Negative	–
Androgen receptor QL [SP107]	Negative	–
Cytokeratin 7 [RN7]	Positive	Positive
Cytokeratin 20 [SP33]	Negative	Negative
GATA-3 [L50-823]	Negative	–
CDX-2 [EPR2764Y]	Positive	Positive
DPC4/SMAD4 [B-8]	–	Intact (positive) in tumor cell nuclei
Napsin A [1P64]	Negative	–
Her2 [pathway]	Negative	–
MLH1 [G168-15]	Intact nuclear protein expression	Intact nuclear protein expression
PMS2 [A16-4]	Intact nuclear protein expression	Intact nuclear protein expression
MSH2 [G219-1129]	Intact nuclear protein expression	Intact nuclear protein expression
MSH6 [44]	Intact nuclear protein expression	Intact nuclear protein expression

FNB, fine needle biopsy; TTF-1, thyroid transcription factor 1; CDX-2, caudal-type homeobox 2.



**Figure 3** Image of isodose distributions from planning for radiation therapy. Images showing transversal (A), model (B), frontal (C), and sagittal (D) views.

is incredibly rare and has only previously occurred in the setting of known pancreatic cancer. To date, there are only two other described cases. Kucuktulu *et al.* 2013 presented a case of a patient with diagnosed pancreatic adenocarcinoma who had undergone chemotherapy with partial response who later developed a metastasis to the anterior one-third

of the tongue (12). The patient's tongue lesion was treated with radiotherapy and resulted in the mass disappearing macroscopically. de Souza *et al.* 2016 presented a case of a patient with stage IV pancreatic cancer who developed a lesion on his tongue 60 days into chemotherapy with biopsy proven metastatic pancreatic cancer to the tongue (13).

In both cases, these were patients with known pancreatic cancer who later developed lesions of the tongue. This contrasts with our case, where our patient presented with a tongue lesion without a prior diagnosis of pancreatic cancer. Given the rarity of this presentation, it is important to keep a broad differential even in patients with known cancer. In this case, tissue specimens from both the oral lesion and pancreatic lesion confirmed they were morphologically identical. Accurate diagnosis was crucial in prognosticating the patient's disease and setting an appropriate treatment course.

Adenocarcinomas of the tongue are uncommon, accounting for approximately 2% of all tongue malignancies, and usually follow well-recognized patterns of salivary gland derived carcinomas (14,15). This particular case did not have the appearance of a salivary gland tumor, so a metastasis from another primary tumor was highly suspected. Immunohistochemical stains can quickly identify possible sites of origin and exclude others. Negative thyroid transcription factor 1 (TTF-1) and napsin stain would make a lung primary unlikely (16), and negative GATA-3 and androgen receptor tend to exclude a salivary gland or breast primary (17,18). The combination of CDX-2 and CK7 is common in upper GI tract and pancreatobiliary tumors (19). Negative cytokeratin 20 makes a lower GI tract origin less likely (20). In this case, given the tissue sample was positive for CK7 and CDX-2, this was suggestive of an upper GI or pancreatobiliary primary (Table 1).

Distant spread of pancreatic adenocarcinoma is a poor prognostic sign and often treatments may transition to a more palliative approach depending on a patient's functional status. According to National Comprehensive Cancer Network (NCCN) guidelines of pancreatic metastatic disease, treatment decisions are based on a patient's performance status (PS) (21). In those with a good or intermediate PS, first-line therapy is a clinical trial or chemotherapy with FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin) or combination gemcitabine and nab-paclitaxel. However, if patients have disease progression, practitioners can still consider a clinical trial, switching to a different chemotherapy regimen based on tolerability, or supportive care. For patients with poor PS, NCCN guidelines recommend supportive care, single agent chemotherapy, and/or palliative radiation for local disease control.

Radiation therapy (RT) can be used as an adjunct to standard-of-care chemotherapy for metastatic pancreatic adenocarcinoma. According to NCCN guidelines, RT

is generally used in five clinical scenarios: resectable/borderline resectable disease, locally advanced disease, in the adjuvant setting after surgical resection, for palliation, or local control for oligometastatic disease recurrence (21). Given symptomatic tongue metastases can greatly impair a patient's quality of life, RT may be incredibly beneficial from the standpoint of a palliative approach. In the case presented by Kucuktulu *et al.* 2013, the patient was treated with radiotherapy, specifically a total of 4,320 cGy in 180 cGy fractions with image-guided, intensity-modulated radiation therapy (IG-IMRT) technique in Hi-Art TomoTherapy unit, with significant improvement in the tongue lesion. Similarly, the patient in our case presented with severe pain from his tongue metastasis and it was decided to treat him with a palliative course of "quad shot" radiation. He was treated with 370 cGy twice a day for 2 days with plans for a 3-week break followed by a second course. This regimen is used for quick relief of symptoms and minimizes the risk of mucositis associated with head and neck treatments. He received one round of quad shot RT with good response in the tongue lesion. Given lack of systemic response to chemotherapy, he was ultimately transitioned to hospice and did not undergo the second round of RT. If his response was suboptimal, we would have proceeded with a second cycle of RT and a third cycle could have been considered. Clinicians should consider a course of palliative radiation in these cases to improve symptoms and nutrition, as pain from the lesion could provide a significant barrier to oral intake.

In our case, given the extensive metastatic burden at the time of diagnosis, RT was used with a palliative goal. Given the good clinical response of the tongue metastasis to RT in these two cases, one could consider applications of RT to oligometastatic PDAC. Renz *et al.* 2017 reviewed data surrounding approaches to oligometastatic disease in pancreatic cancer (22). This study found that for oligometastatic PDAC, specifically with metastasis to the liver, it is not uncommon to use local radioablative techniques (22). Studies have shown that use of radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) in PDAC with oligometastatic disease to the liver could be feasible approaches and extend survival in these select patients (23,24).

Radioresistance is a known challenge for treating PDAC and is poorly understood, with many pathways being cited as possible resistance mechanisms (25). Some possible resistance mechanisms include overexpression of HOX transcript antisense intergenic RNA (HOTAIR), which was

shown to affect the radiosensitivity of the PDAC cells (26), and manipulation of microRNAs (miRs), specifically miR-31, which could promote a radiosensitive or radioresistant PDAC (27). Given the tongue metastasis had significant clinical response, this appears to be a radiosensitive site of PDAC metastasis. Although it is unknown as to why this would be a radiosensitive site, one could speculate on possible mechanisms. Given research on various resistance mechanisms for PDAC, it is possible that metastasis have a different tumor microenvironment (TME) as compared to the primary tumor that is more favorable for RT. Additionally, studies have pointed to a difficult anatomic location of the pancreas as a contributing factor to radioresistance (26). The anatomical location of the tongue could allow for improved accessibility without as much concern for damaging vital organs (Figure 3 and Figure S1).

In our case, the patient was treated initially with gemcitabine monotherapy with plans to add nab-paclitaxel, however, the disease quickly progressed despite therapy. Gemcitabine is a frequently used treatment option either as monotherapy or in combination based on tolerance (28). However, those on gemcitabine therapy often develop chemoresistance and there have been several postulated mechanisms as to how this happens (29). One of those mechanisms is loss of *TP53* function leading to activation of the *JAK2-STAT3* pathway. In mouse models, the downstream effects promote alterations in the tumor stroma and TME causing chemoresistance ultimately leading to tumor growth (30). In review of our patients next-generation sequencing (NGS), the tumor demonstrated a frameshift loss of function mutation in *TP53*, which may have contributed to tumor progression.

Furthermore, the TME of PDAC is characterized by desmoplastic stroma and a host of cells including cancer-associated fibroblasts, stellate cells, tumor-associated macrophages, and other regulatory immune cells that work in concert to promote tumor growth (31). Overexpression of TME regulators on pancreatic cancer cells consequently induces a more immunosuppressive TME and contributes to chemoresistance. Targeting various TME regulators such as focal adhesion kinase (FAK) (32,33) and C-X-C motif chemokine receptor 4 (CXCR4) (34,35) in combination with immunotherapy are active areas of ongoing research and clinical trials (NCT03727880, NCT02907099).

## Conclusions

Pancreatic cancer with metastasis to the oral cavity, specifically

the tongue, is an incredibly rare presentation. Accurate diagnosis is key to prognosis and appropriate treatment strategies. Given that pancreatic cancer with distant metastases has a poor prognosis, practitioners can consider a more palliative approach when faced with these clinical scenarios. Radiotherapy for symptomatic oral lesions should be highly considered to improve pain and dysphagia that could lead to reduced oral intake.

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*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 procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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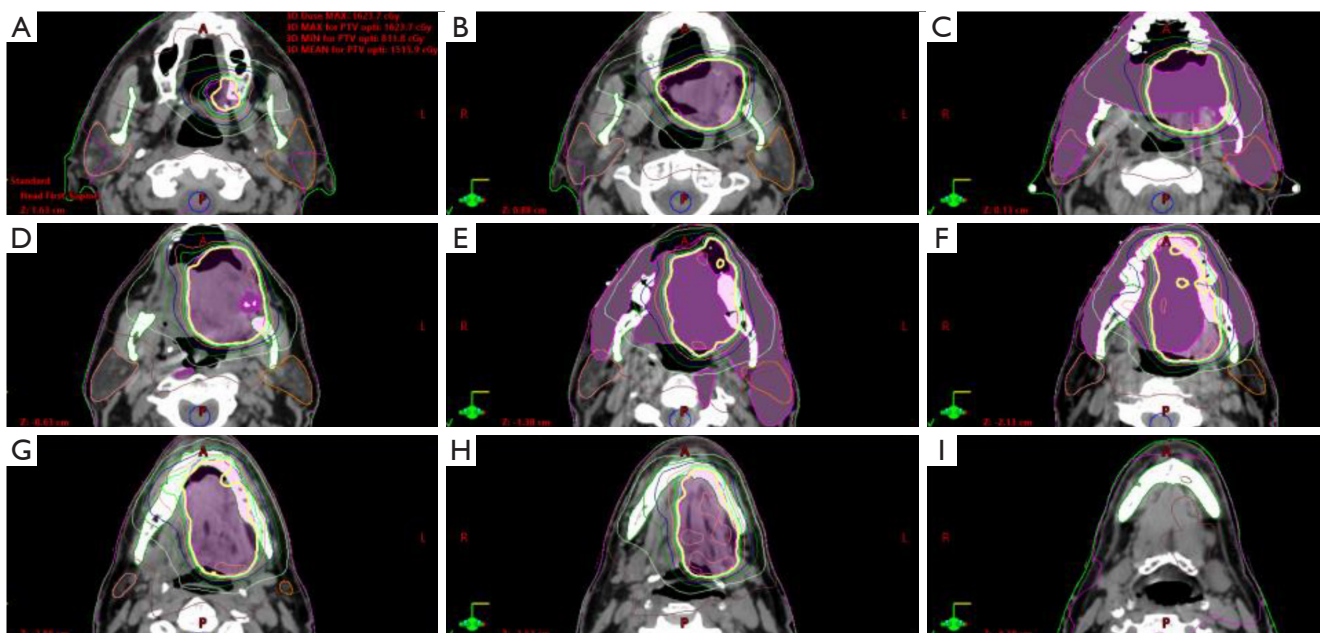
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**Figure S1** Additional images of isodose distributions for radiation planning. The figure shows sequential cross sections of the transversal view from most superior (A) to most inferior (I).