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Well-differentiated neuroendocrine tumour (WDNET) of Jugular foramen treated with radiotherapy – A rare case-report

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Case Report

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Abstract

Neuroendocrine tumors (NETs) are rare entity and most common location in head and neck region is larynx. Given the rare occurrence, only few studies exist describing prognosis and management of these cancers. The case presented below is a grade 2 well-differentiated NET which is unique in its location, grade discordance and intermediate prognosis. Additionally, we reviewed the existing literature for tumour characteristics, diagnosis, grouping, treatment modalities and prognosis.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a rare and heterogenous group of tumours. They account for less than 2% of all malignancies in the United States. It is most commonly found in the lung [1]. Extrapulmonary sites include gastrointestinal, head and neck, thyroid, thymus, breast, genitourinary system and skin. SEER data analysis suggest that in the head and neck region, larynx (especially epiglottis and supraglottic region), trachea, salivary glands and para-nasal sinuses are the most common sites [2]. The 5th edition of WHO Classification for Head and Neck Tumours (2022) recognizes two broad categories of NENs based on histologic differentiation and mitotic count: 1) well-differentiated neuroendocrine tumours (WDNET), and 2) neuroendocrine carcinomas (NEC). Further, WDNETs are graded into three grades, 1–3, based on mitotic counts (< 2/2mm^2, 2–10/2mm^2, and > 10/2mm^2, respectively) [3]. We here present a case report of a 46-year-old male with right jugular foramen lesion, that eventually revealed to be a Grade 2 WDNET, with an unusually high Ki67 index and high mitotic activity.

CASE PRESENTATION

A 46-year-old gentleman presented to a high-volume Tertiary care centre in India with a feeling of fullness in right ear for three years. He also gave history of diplopia, dizziness and loss of taste sensation in right side of tongue for 2 months. He had signs of lower motor neuron (LMN) palsy of facial nerve. Local examination revealed postoperative healed scar in right temporal region.

The patient was evaluated and managed at a local hospital in month of December 2022. His index magnetic resonance imaging (MRI) brain with high-resolution computed tomography (HRCT) of the temporal bone revealed a fairly large lesion, measuring 3.7x2.9x4.5 cm in region of right jugular foramen extending into the carotid space, middle ear cavity, mastoid air cells, external auditory canal (EAC), and adhered to dura.

The differential diagnosis at the presenting centre was a paraganglioma and he underwent a craniotomy and excision of right jugular foramen lesion on January 23, 2023 at a local hospital. Outside surgical pathology report revealed paraganglioma of jugular foramen. Slides and block of outside operated surgical specimen were reviewed at our institute as part of central pathology review protocol. Microscopic evaluation revealed a hypercellular tumour arranged as nests and sheets. Tumour cells

were monotonous in appearance and possessed rounded nuclei with stippled chromatin and scant to moderate eosinophilic cytoplasm. Necrosis was not seen. Mitotic count was 6/2mm^2. On immunohistochemistry, the tumour cells were positive for AE1/AE3, synaptophysin, chromogranin, INSM1, and SDHB, while were negative for GATA3 and lacked S100 positive sustentacular cells. Ki-67 (Mib1) labeling index in the tumor cells was 10%. Based on the positivity of epithelial markers, negativity for GATA3, and lack of S100 positive sustentacular cells, a diagnosis of WD-NET, grade 2, was made (Fig. 1).

Thereafter, patient underwent ^{68}Gallium-DOTANOC positron emission tomography/ computed tomography (PET/CT) and MRI which showed SSTR expressing residual disease of 5.1 x 3.8 x 6.3 cm at the right jugular foramen involving the entire petrous bone, middle ear and internal auditory canal (IAC), EAC, mastoid cavity and encasing cervical ICA. No suspicious cervical nodes were seen (Fig. 2).

The case was further discussed in the multi-disciplinary skull base tumour board at our hospital and with the patient as well, regarding further management of the residual lesion. The lesion was deemed unresectable and was referred to radiation oncology for fractionated conformal radiotherapy. He thereafter received adjuvant radiotherapy to residual disease to a dose of 66 Gray in 33 fractions using volumetric modulated arc therapy (VMAT) technique with overall treatment time was 47 days (Fig. 3).

DISCUSSION

NENs can arise from any anatomical site, share common histology, immunophenotype, ultrastructural neuroendocrine features but their natural history varies and also prognosis is widely different. NENs can arise from various sites, most common being bronchial (pulmonary) and gastroenteropancreatic (GEP) system. There exists confusion in literature regarding the classification of NENs. Neuroendocrine neoplasms (NEN) of the head and neck include two groups: the epithelial NENs and the non-epithelial (neuronal) paragangliomas. Further, the epithelial NENs of the head and neck region encompass two distinctive neoplasms, i.e. WDNET and NEC, that are separable by their cellular differentiation, molecular genetic alterations, aggressiveness, and response to treatments. In the recent fifth-edition WHO classification of head and neck tumours, the NENs classification has been revised to reflect both the WHO / International Agency for Research on Cancer (IARC) unified terminology framework [4]. The WDNET are graded into three grades (1–3) based on mitotic count, presence of necrosis and Ki67 labelling index, whereas, NECs are by definition, poorly differentiated and high-grade. Further, based on cellular morphology, NECs can be small cell NEC or large cell NEC (Table 1).

Table 1
WHO 2022 neuroendocrine neoplasms classification (WHO 5th edition) [3]

Neuroendocrine neoplasm (NEN)	Tumour category	Diagnostic criteria
Well- differentiated NEN (NET)	Well-differentiated NET, grade 1 (G1 NET)	No necrosis and < 2 mitosis/ $2mm^2$ Ki67 < 20%
	Well-differentiated NET, grade 2 (G2 NET)	Necrosis and/ or 2–10 mitosis/ $2mm^2$ Ki67 < 20%
	Well-differentiated NET, grade 3 (G3 NET)	> 10 mitosis/ $2mm^2$ Ki67 > 20% Absence of NEC cytomorphology
Poorly differentiated NEN (NEC)	Small cell NEC	> 10 mitosis/ $2mm^2$ Ki67 > 20% (often > 70%) Small cell NEC cytomorphology
	Large cell NEC	> 10 mitosis/ $2mm^2$ Ki67 > 20% (often > 50%) Large cell NEC cytomorphology

NENs are characterized by organoid pattern of growth, absence of keratinization, granular chromatin, and increased mitotic index. On immunohistochemistry, they express neuroendocrine markers such as, synaptophysin, chromogranin A, and INSM1. IHC is essential for diagnosis of NENs. Epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) are also commonly found to be positive. Serotonin markers like somatostatin receptors (SSTR2A) are also expressed in WDNETs and maybe more focal to absent in the NECs.

MRI as compared to CT provides superior soft tissue delineation, which makes it an ideal technique for imaging especially defining intracranial extension of tumours [5]. Functional imaging with radiopharmaceuticals, e.g. ^{68}Ga-DOTA-NOC, in conjugate with anatomical imaging (CT or MRI) is used to evaluate multifocal disease and distant metastases [6]. Their uptake also provides surrogate for tumour differentiation, biologic behaviour and prognosis of NENs [7].

As stated above, larynx is the most common site of NENs. NEC comprises of 0.5 to 1% of all laryngeal neoplasm, second only to squamous cell carcinoma (SCC), while WDNETs are among the least common

NENs to be found [8], [9].

WD-NETs of larynx have good prognosis and have excellent overall outcomes with surgery alone. The incidence of nodal disease is low, hence there appears to be no role of elective neck dissection or adjuvant therapy [8], [10]. Ferlito *et al* recommend elective neck dissection in higher grade tumours. A more recent retrospective analysis of advanced stage laryngeal NENs showed high incidence of nodal metastasis (63%, 83%, and 100% in WDNET, SCNEC, and LCNEC, respectively) [9]. Adjuvant radiotherapy is recommended in lymph node positive metastasis [10] while, Gillenwater *et al* also demonstrated response to chemoradiotherapy, suggesting a combined approach is needed [11]. It is not yet known that traditional pathological features like, positive margins, perineural invasion, and lymphovascular invasion have any impact on recurrence and survival outcomes in these patients. Further studies are indicated to recognize impact of adjuvant therapy.

Non-laryngeal NETs in head and neck region are very sparsely reported in literature, hence further lack of evidence supporting optimum management in these tumours. Paranasal NETs represent less than 5% of malignancies. It has increased propensity of regional and distant spread [12]. Middle ear NETs are very rare and are generally benign in nature. These tumours can sometimes be invasive and occasionally metastatic. Asa *et al* noted that that these tumours usually have low proliferative index similar to grade 1 NETs of GI tract. They may occasionally have higher KI67 labelling index that enables them to be classified under grade 2 and 3 NETs [13]. Complete surgical resection remains treatment of choice [14], [15] [16], while radiotherapy is reserved for unresectable and metastatic cases. Role of chemotherapy is not well defined in current literature [17]. A review by Furata *et al* proposed role of post-operative chemoradiation in cases of incomplete resection, although efficacy is yet to be proved [18].

Results of phase 3 landmark trial, NETTER-1 established the role of PRRT ^{177}Lu-DOTATATE using in treatment of locally advanced and metastatic grade 1 and 2 GEP NETs [19]. This data can be extrapolated to head and neck NETs; however, further studies are warranted. Retrospective review by Chen *et al* of 45 patients treated by high dose radiation therapy demonstrated ORR rates of 68% compared to about 15% seen in patients receiving PRRT [20]. Thus, high dose radiation therapy is an important option to consider in management of selected patients with NENs.

CONCLUSIONS

NENs of head and neck region require precise diagnosis and aggressive management which is a challenge for both the pathologists and oncologists. Their clinical behavior ranges from benign to lethal depending upon histology and grade. Further larger prospective studies are needed with well-defined homogeneous population to better establish the role of radiation therapy in management of NENs.

Declarations

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Competing Interests

The authors declare that they have no competing financial or non-financial interests that are relevant to the content of this article.

Ethics Approval

This article is a case report and does not contain any studies involving human participants or animals performed by any of the authors. Ethics committee approval was not required.

Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed.

Authors' Contributions

R.M. and S.G.L. conceived the case report and drafted the main manuscript text. M.B. performed the central histopathological and immunohistochemical review and provided the pathology figure. S.S., A.K., S.M., A.B., and M.S. were involved in the clinical management of the patient and contributed to critical revision of the manuscript. S.G.L. supervised the study and provided final critical revision of the manuscript. All authors reviewed and approved the final manuscript.

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Figures

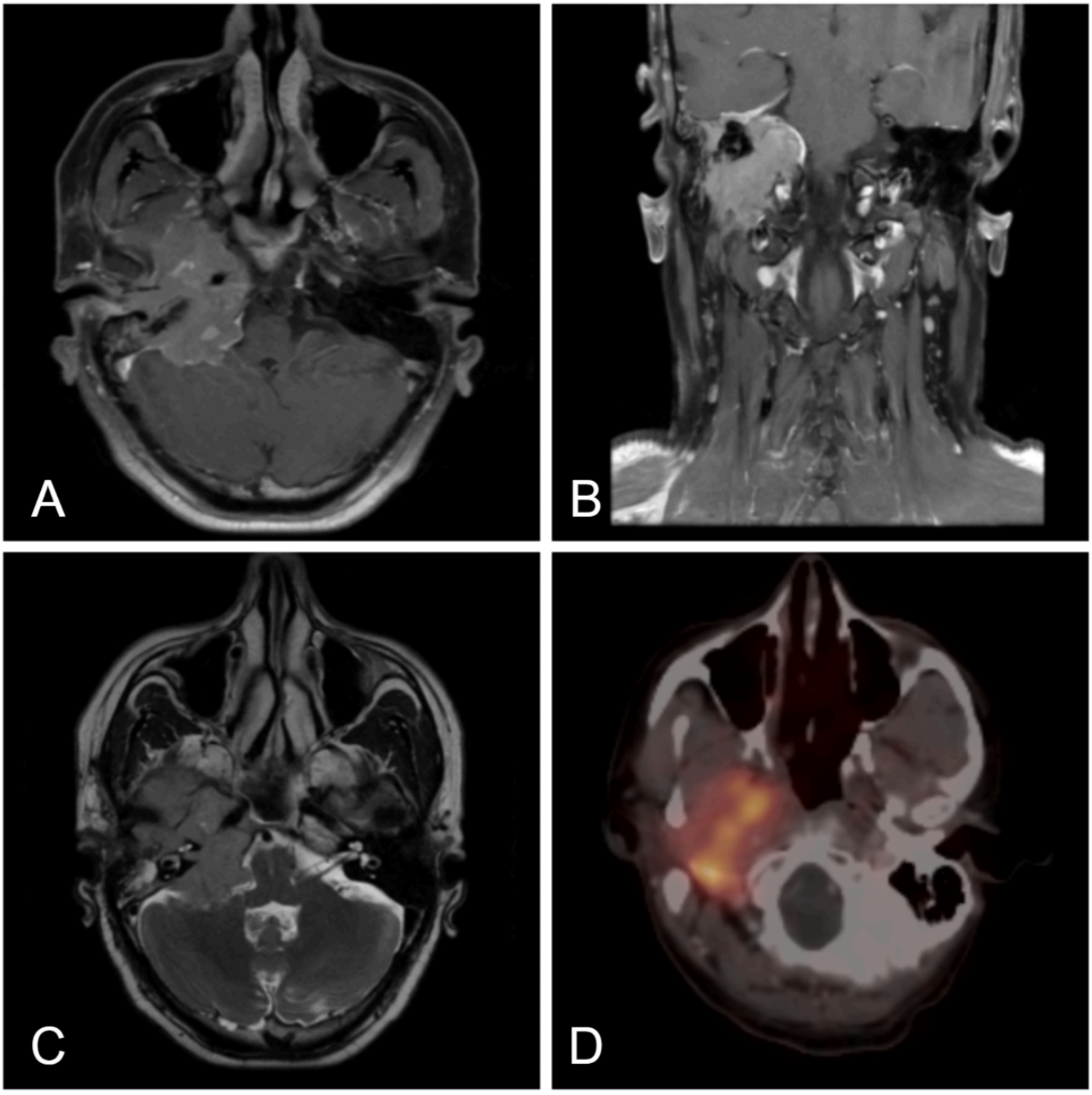


Figure 1

Post-contrast T1 sequence axial (A) and coronal (B). T2 hyperintense heterogeneously enhancing soft tissue mass (C). DOTANOC avid heterogeneously enhancing soft tissue mass (D).

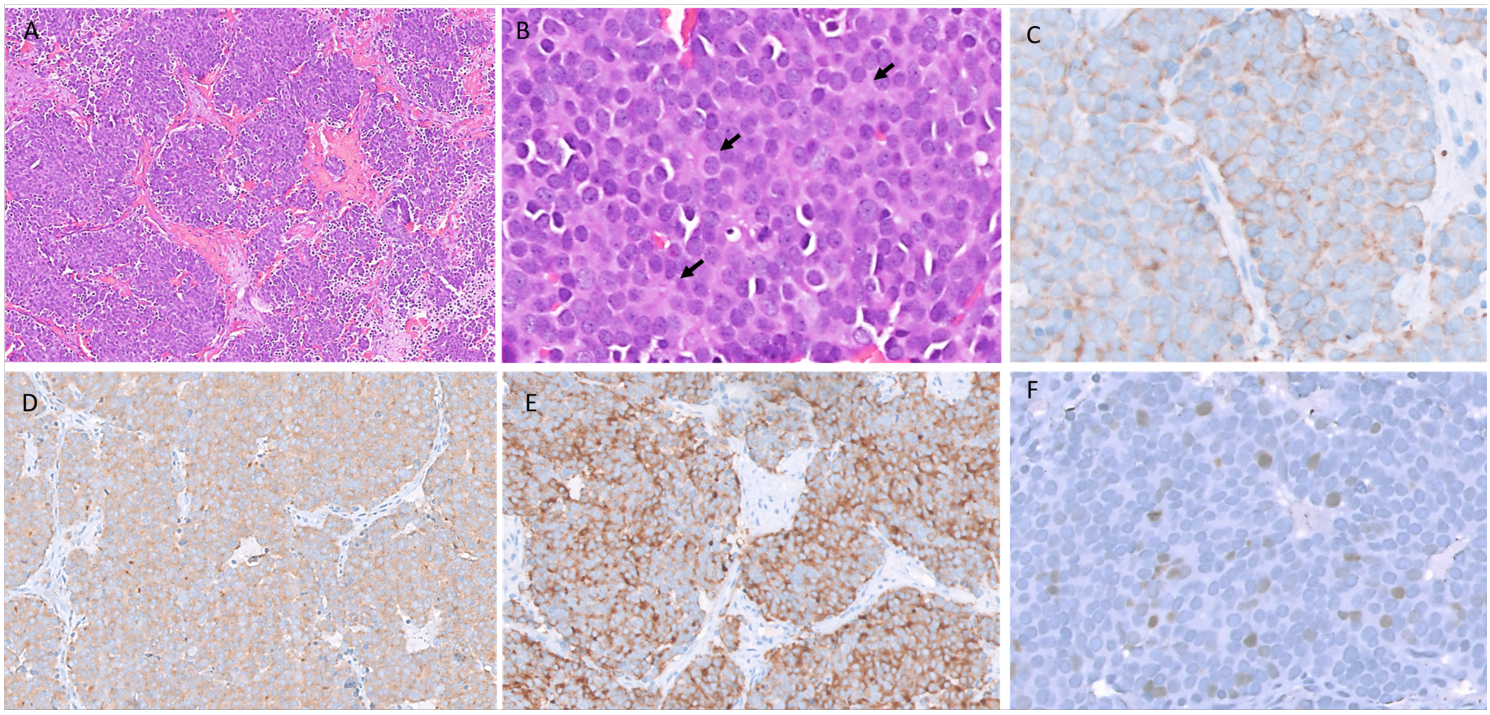


Figure 2

Pathologic features of well-differentiated neuroendocrine tumor. A) Microscopy showed a tumor arranged in nested architecture (hematoxylin and eosin, x100X). B) Higher magnification revealed uniform cells, stippled chromatin, and rosettes (arrow) (hematoxylin and eosin, x 400X). C-D). Tumor cells are positive for cytokeratin (C), synaptophysin (D), and chromogranin (E) on immunohistochemistry. Tumor nuclei showing Ki67 labeling index of 8% on immunohistochemistry.

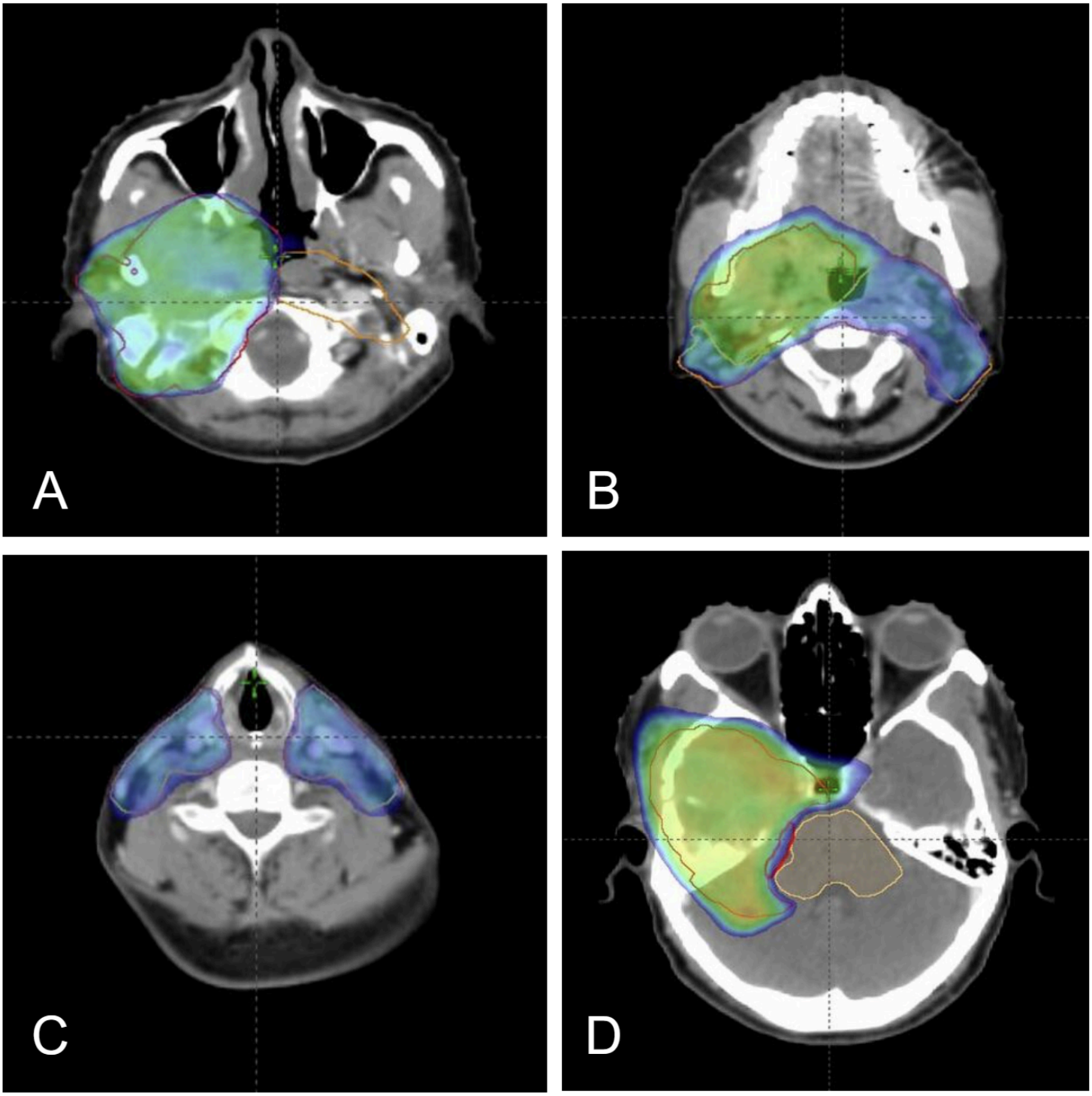


Figure 3

95% dose color wash of 66Gy (A), 59.4Gy (B, C) and 56.1Gy (D). Note – The primary gross disease was prescribed to 66Gy (A), bilateral uninvolved neck to 59.4Gy (C), while area close to brainstem was underdosed to 56.1Gy (D).