Squamous Cell Carcinoma with Clinical Perineural Invasion: Challenges and Review in Single Case Study

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ABSTRACT

Perineural invasion is a rare prognostic finding of squamous cell carcinomas that is associated with a poor prognosis. Early recognition of perineural invasion is imperative to improving treatment and lowering recurrence. Here we report the case of a 77-year-old Caucasian male with a suspicious mass on his forehead. Diagnosis confirms a squamous cell carcinoma with T1-weighted MRI findings significant for perineural invasion of the right supratrochlear nerve based on nerve thickening with loss of fat. Due to his immunocompromised status and the presence of positive margins after wide local excision, the patient is treated with adjuvant external beam radiotherapy of the nerve course. Risks of radiation-induced optic neuropathy should be weighed against recurrence in tumors that invade the trigeminal nerve.

CASE REPORT

CASE REPORT

A 77-year-old Caucasian man with past medical history of rheumatoid arthritis, chronic pain, osteopenia, hypertension, and hyperlipidemia presented to the clinic with a suspicious mass on his left forehead. Current home medications consisted of etodolac, tramadol, alendronate, atorvastatin, and hydrochlorothiazide. Patient had no relevant surgical history. On review of systems, patient denied fever, chills, night sweats, recent weight loss, or changes in his appetite. Patient had a social history that includes a 13 pack-year history of smoking, though patient denied recent tobacco use. Patient denied history of alcohol use.

On physical examination, a suspicious mass on his left forehead to midline area was noted with symmetric facial tone, good brow function, and absent ptosis. Sensation throughout the face, including V1, V2, and V3 was normal. No parotid masses or tenderness over the frontal/maxillary sinuses were noted. Examination of the head, ears, nose, and throat showed normal findings with no cervical lymphadenopathy identified. Neurologic exam revealed normal cranial nerves III-XII with both motor and sensory responses intact. Reflexes were 2+ and symmetrical.

Patient was treated with wide-local excision. Later pathology showed a 0.7 cm poorly differentiated cutaneous squamous cell carcinoma (cSCC). Due to midface location of the mass and immunosuppression, Magnetic Resonance

Imaging (MRI) was ordered that showed asymmetric enhancement of the right supratrochlear neurovascular bundle, concerning for perineural spread of the tumor (Fig 1 and 2) with the tumor staged at T3N0M0. Combination immunosuppressive rheumatoid arthritis therapy of anti-TNF and methotrexate was modified to abatacept and prednisone due to the patient's cancer diagnosis. MRI and skin surveillance was recommended for the next two months.

Based on radiological and pathological findings, patient was recommended treatment of the scalp surgical bed to the bilateral supratrochlear and supraorbital nerve bundles with electron beam radiotherapy. Due to the sensitive location of the tumor near the optic nerve, extreme care was given in planning the target volume to extend up to the inward branch points of the superior orbital fissure. As the supratrochlear and supraorbital nerves are branches of the trigeminal V1 nerve, full radiation doses up to the superior orbital fissure had an extreme risk of optic neuropathy due to the path of the optic nerve. After the risks and benefits of radiotherapy were discussed, the patient elected radiotherapy. Subsequently the patient received a course of 6,600 centigray (cGy) in 33 fractions over multiple sessions without complication (Figure 3).

DISCUSSION

Etiology & Demographics:

The annual incidence of cSCC in the United States is 700,000 cases, accounting for the second most common nonmelanoma skin cancer [1]. cSCC is commonly divided into low-risk or high-risk groups for treatment. The AJCC recognizes several key factors on pathology that increase the likelihood the cancer will recur or be metastatic including poor differentiation, high-risk subtypes, depth >6 cm, invasion past subcutaneous fat, and involvement of either the perineural, lymphatic, or vascular systems [2]. Although only accounting for 1-2% of cSCC cases, perineural invasion (PNI) is associated with a poor prognosis with a 30% associated risk of death in some studies [2]. The finding of a cancer invading and spreading along a nerve is a poor prognostic factor that has a 16% decrease in 5-year recurrence-free survival and 18% decrease in 5-year disease-specific survival compared to non-perineural invading tumors [3]. Unless found on incidental findings, PNI can be asymptomatic in as many as 60-70% of cases and may not be found until invasion of the orbit and cavernous sinus when clinical exam findings are present [4].

Clinical & Imaging Findings:

Clinical PNI is recognized when either radiographic evidence or physical symptoms are identified. On physical exam, PNI is associated with findings of neuropathy such as pain, tingling, abnormal sensation, or loss of motor function, especially along cranial nerve V and VII tracts, among cSCC patients with recurrent disease [5]. The finding of PNI can often be surreptitious with the tumor invading small cutaneous nerves peripherally and tracing proximally along bigger nerve towards the brain stem if untreated. Compared to patients, however, with incidental PNI found either by imaging or pathology, patients with clinical PNI have higher rates of local recurrence and poor survival outcomes over 5 years [6].

PNI recognition is of the utmost importance in improving survival and lowering recurrence. Careful consideration with imaging examination should be given early in patients with cSCC greater than 2 cm on either the forehead or brow [7]. Some reports suggest that PNI can be negative in as many as 45% of cases [8]. Magnetic resonance imaging (MRI) with contrast is the preferred imaging modality, however sensitivity has been shown to be equal at 76% for both MRI and CT [9]. MRI diffusion tractography for visualization of tumor infiltration is promising for clinical practice in order to improve detection of PNI and has shown success in increasing sensitivity in a small cohort study of facial nerve invasion in parotid cancers [10-11].

Treatment & Prognosis:

Mohs micrographic surgery (MMS) with frozen tissue sectioning is the preferred method of surgical resection in order to minimize recurrence. In a study performed by Leibovitch et al., recurrence was found to be 47.2% when wide local excision was applied compared to a recurrence of 0-8% with MMS [12]. In fact, MMS in incidental PNI can be curative with no significant benefit of radiotherapy over observation in patients that involve <2 nerves microscopically [13]. The presence though of PNI infiltration can also be detected by MMS and can be an additional indicator suggestive for PNI in cases that is often helpful beyond radiographic imaging alone [14]. Often wide local excision is used, however, due to lack of physical exam features indicating PNI.

Due to the high local recurrence of PNI, adjuvant radiotherapy is indicated along the course of the nerve to the skull base especially for patients that have positive margins after excision, immunocompromised states, or involve >2 nerves microscopically [13, 15-16]. Although there are no randomized clinical trials comparing surgery alone to surgery with postoperative radiotherapy, combined modality therapy has been recommended in major practice guidelines such as the NCCN. Several cohort studies have compared outcomes of surgery alone versus surgery with adjuvant radiotherapy. While an earlier study found no significant difference between the two groups, in a later larger study that included 122 patients, 5-year overall and disease-free survival was found to be significantly improved in patients treated with tumor resection with adjuvant radiotherapy [17-18]. Adjuvant radiotherapy in PNI should target the course of the specific nerve involved from its effector location up to its path to the base of the skull. For tumors that involve the trigeminal nerve, care must be taken near the superior orbital fissure due to severe risk of radiation-induced optic neuropathy that presents with irreversible vision loss [19].

Tumor invasion into nerves, as opposed to typical modes of cancer progression along hematogenous or lymphatic systems, depends on a complex microenvironment that has just begun to be understood in recent years. Cancer invasion and migration along a nerve relies on the predilection of the tumor to activate a RET tyrosine kinase pathway, through secretion of GDNF [20]. Cancer cell progression has also

been shown to be aided by Schwann cell and monocytes. In particular, Schwann cells have been shown to be inappropriately activated by cancer cells to aid in cancer progression [21]. Similarly, tumors have been shown to promote cancer cell invasion by the expression of monocytes into CCL2-expressing inflammatory macrophages that can degrade the basement membrane around the perineum [22].

Understanding of the tumor microenvironment offers not only promising opportunities for improvement on current treatment modalities but also for future therapeutic targets. According to Bakst et al., radiotherapy impairs tumor invasion directly as well as through the interruption of paracrine signaling—low doses of radiation led to a decrease in expression of GDNF [23]. While currently, however, there are no targeted therapies for PNI several promising therapies have been suggested including the use of immunotherapy, checkpoint inhibitors and CCR2 signaling targets to downregulate monocyte recruitment [24-25]. Overall, treating tumors that display PNI is still challenging due to its aggressiveness and diagnoses that are often missed or delayed; however, large cutaneous squamous cell carcinomas of the brow whether in the past or present should be monitored regularly for risk of PNI.

Differential Diagnoses:

A primary neural tumor such as a schwannoma should be considered especially as it can often remain asymptomatic. The presence of symptoms is often due to a local mass effect or a deficit in the cranial nerve involved. Imaging of a schwannoma on CT imaging shows low-to-intermediate attenuation with variable enhancement. MRI shows iso-to-hypointense lesions on T1 and hyperintense on T2-weighted sequences.

An invasive fungal infection such as neuroaspergillosis should be considered especially in an immunocompromised patient as it represents one of the most common opportunistic infections in the central nervous system. On physical exam, neuroaspergillosis can present with a range of symptoms including a fever, focal neurological deficits, headache, or a seizure among others. Imaging of neuroaspergillosis on CT often can be non-specific, but in the presence of findings such as a brain abscess it will typically have a hyperdense lesion with a surrounding hypodense region (edema). MRI findings show iso-to-hypointense lesions on T1-weighted sequences. If aspergillus is suspected, chest radiography would typically demonstrate nodular consolidation with surrounding ground glass opacities.

A traumatic neuroma is a consideration in an elderly patient especially with history to trauma to the area. Although the clinical course varies, typical signs of a traumatic neuroma include paresthesia specifically in the local region of the injury. CT imaging of a traumatic neuroma is oftentimes non-specific, whereas MRI typically features hyperintense lesions on T2-weighted sequences.

Ultimately, the definitive diagnosis of perineural invasion from a tumor depends not only on diagnostic imaging but histopathological findings. CT imaging demonstrates asymmetric soft-tissue thickening of a nerve. T1-weighted MRI sequences demonstrate an avidly enhancing nerve. Although the absence of physical exam findings is inconclusive, key points to consider in a patient's history, including our own, is male gender, immunocompromised status, lesion involving the midface region, and pathological findings significant for cSCC.

TEACHING POINT

Perineural invasion of a cutaneous squamous cell carcinoma should be considered, even in the absence of neuropathic physical exam findings based on location and size radiographically. As perineural invasion is associated with a high risk of recurrence, radiologic follow-up is important.

REFERENCES

1. Karia PS, Morgan FC, Ruiz ES, Schmults CD. Clinical and Incidental Perineural Invasion of Cutaneous Squamous Cell Carcinoma: A Systematic Review and Pooled Analysis of Outcomes Data. JAMA Dermatol. 2017 Aug 1;153(8):781-788. PMID: 28678985.

2. Chu MB, Slutsky JB, Dhandha MM, Beal BT, Armbrecht ES, Walker RJ, Varvares MA, Fosko SW. Evaluation of the definitions of "high-risk" cutaneous squamous cell carcinoma using the american joint committee on cancer staging criteria and national comprehensive cancer network guidelines. J Skin Cancer. 2014; 2014:154340. PMID: 25309755.

3. Karia PS, Morgan FC, Ruiz ES, Schmults CD. Clinical and Incidental Perineural Invasion of Cutaneous Squamous Cell Carcinoma: A Systematic Review and Pooled Analysis of Outcomes Data. JAMA Dermatol. 2017 Aug 1;153(8):781-788. PMID: 28678985.

4. Koukkoulli A, Koutroumanos N, Kidd D. Perineural Spread of Cutaneous Squamous Cell Carcinoma Manifesting as Ophthalmoplegia. Neuroophthalmology. 2015 Jun 17;39(3):144-146. PMID: 27928347.

5. Garcia-Serra A, Hinerman RW, Mendenhall WM, Amdur RJ, Morris CG, Williams LS, Mancuso AA. Carcinoma of the skin with perineural invasion. Head Neck. 2003 Dec;25(12):1027-33. PMID: 14648861.

6. Karia PS, Morgan FC, Ruiz ES, Schmults CD. Clinical and Incidental Perineural Invasion of Cutaneous Squamous Cell Carcinoma: A Systematic Review and Pooled Analysis of Outcomes Data. JAMA Dermatol. 2017 Aug 1;153(8):781-788. PMID: 28678985.

7. McNab AA, Francis IC, Benger R, Crompton JL. Perineural spread of cutaneous squamous cell carcinoma via the orbit. Clinical features and outcome in 21 cases. Ophthalmology. 1997 Sep;104(9):1457-62. PMID: 9307641.

8. Chen VH, Hayek BR, Grossniklaus HE, Wojno TH, Kim HJ. Review of periorbital nerve enlargement and biopsy techniques. Orbit. 2017 Oct;36(5):293-297. PMID: 28820280.

9. Bowyer JD, Sullivan TJ, Whitehead KJ, Kelly LE, Allison RW. The management of perineural spread of squamous cell carcinoma to the ocular adnexae. Ophthalmic Plast Reconstr Surg. 2003 Jul;19(4):275-81. PMID: 12878875.

10. Krainik A, Casselman JW. Imaging Evaluation of Patients with Cranial Nerve Disorders. 2020 Feb 15. In: Hodler J, Kubik-Huch RA, von Schulthess GK, editors. Diseases of the Brain, Head and Neck, Spine 2020-2023: Diagnostic Imaging [Internet]. Cham (CH): Springer; 2020. Chapter 12. PMID: 32119250.

11. Rouchy RC, Attyé A, Medici M, Renard F, Kastler A, Grand S, Tropres I, Righini CA, Krainik A. Facial nerve tractography: A new tool for the detection of perineural spread in parotid cancers. Eur Radiol. 2018 Sep;28(9):3861-3871. PMID: 29633003.

12. Cernea SS, Gontijo G, Pimentel ER, Tarlé RG, Tassara G, Ferreira JA, Fernandes VM, Bernardo WM. Indication guidelines for Mohs micrographic surgery in skin tumors. An Bras Dermatol. 2016 Sep-Oct;91(5):621-627. PMID: 27828636.

13. Sapir E, Tolpadi A, McHugh J, Samuels SE, Elalfy E, Spector M, Shuman AG, Malloy KM, Prince ME, Bradford CR, Worden FP, Schipper M, Eisbruch A. Skin cancer of the head and neck with gross or microscopic perineural involvement: Patterns of failure. Radiother Oncol. 2016 Jul;120(1):81-6. PMID: 27475277.

14. Green JS, Tournas JA, Allen EJ, Youker SR, Fosko SW. Mohs frozen tissue sections in comparison to similar paraffin-embedded tissue sections in identifying perineural tumor invasion in cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2012 Jul;67(1):113-21. PMID: 22533992.

15. Mendenhall WM, Amdur RJ, Williams LS, Mancuso AA, Stringer SP, Price Mendenhall N. Carcinoma of the skin of the head and neck with perineural invasion. Head Neck. 2002 Jan;24(1):78-83. PMID: 11774406.

16. Koyfman SA, Joshi N, Vidimos A. Adjuvant radiotherapy in high-risk cutaneous squamous cell cancer of the head and neck in immunosuppressed patients. JAAD Case Rep. 2015 Nov 24;1(6):S5-7. PMID: 27051809.

17. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. Dermatol Surg. 2009 Apr;35(4):574-85. PMID: 19415791.

18. Wang JT, Palme CE, Morgan GJ, Gebski V, Wang AY, Veness MJ. Predictors of outcome in patients with metastatic cutaneous head and neck squamous cell carcinoma involving cervical lymph nodes: Improved survival with the addition of adjuvant radiotherapy. Head Neck. 2012 Nov;34(11):1524-8. PMID: 22109745.

19. Wang W, Yang H, Guo L, Su H, Wei S, Zhang X. Radiation-induced optic neuropathy following external beam radiation therapy for nasopharyngeal carcinoma: A retrospective case-control study. Mol Clin Oncol. 2016 May;4(5):868-872. PMID: 27123298.

20. Bakst RL, Lee N, He S, Chernichenko N, Chen CH, Linkov G, Le HC, Koutcher J, Vakiani E, Wong RJ. Radiation impairs perineural invasion by modulating the nerve microenvironment. PLoS One. 2012;7(6):e39925. PMID: 22768171.

21. Deborde S, Omelchenko T, Lyubchik A, Zhou Y, He S, McNamara WF, Chernichenko N, Lee SY, Barajas F, Chen CH, Bakst RL, Vakiani E, He S, Hall A, Wong RJ. Schwann cells induce cancer cell dispersion and invasion. J Clin Invest. 2016 Apr 1;126(4):1538-54. PMID: 26999607.

22. Bakst RL, Xiong H, Chen CH, Deborde S, Lyubchik A, Zhou Y, He S, McNamara W, Lee SY, Olson OC, Leiner IM, Marcadis AR, Keith JW, Al-Ahmadie HA, Katabi N, Gil Z, Vakiani E, Joyce JA, Pamer E, Wong RJ. Inflammatory Monocytes Promote Perineural Invasion via CCL2-Mediated Recruitment and Cathepsin B Expression. Cancer Res. 2017 Nov 15;77(22):6400-6414. PMID: 28951461.

23. Bakst RL, Lee N, He S, Chernichenko N, Chen CH, Linkov G, Le HC, Koutcher J, Vakiani E, Wong RJ. Radiation impairs perineural invasion by modulating the nerve microenvironment. PLoS One. 2012;7(6):e39925. PMID: 22768171.

24. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, Chung CH, Hernandez-Aya L, Lim AM, Chang ALS, Rabinowits G, Thai AA, Dunn LA, Hughes BGM, Khushalani NI, Modi B, Schadendorf D, Gao B, Seebach F, Li S, Li J, Mathias M, Booth J, Mohan K, Stankevich E, Babiker HM, Brana I, Gil-Martin M, Homsi J, Johnson ML, Moreno V, Niu J, Owonikoko TK, Papadopoulos KP, Yancopoulos GD, Lowy I, Fury MG. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018 Jul 26;379(4):341-351. PMID: 29863979.

25. Pienta KJ, Machiels JP, Schrijvers D, Alekseev B, Shkolnik M, Crabb SJ, Li S, Seetharam S, Puchalski TA, Takimoto C, Elsayed Y, Dawkins F, de Bono JS. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Invest New Drugs. 2013 Jun;31(3):760-8. PMID: 22907596.

FIGURES

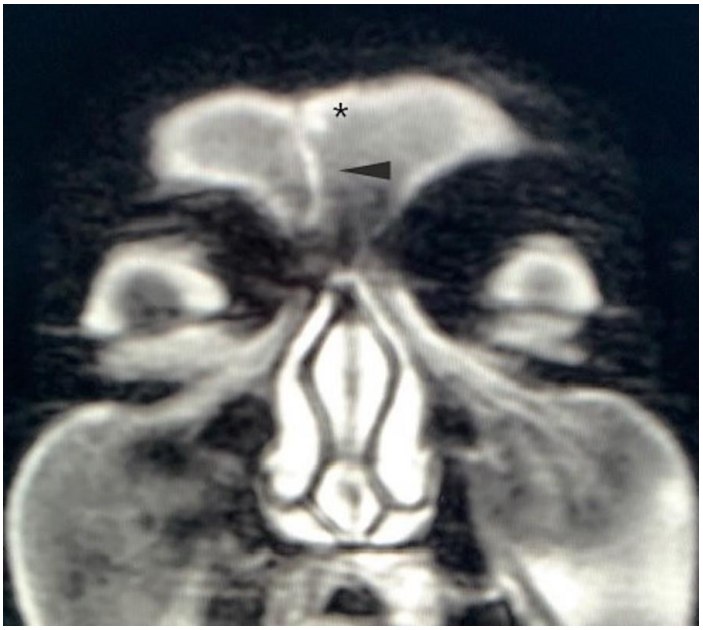

Figure 1 (left): 77-year-old male with perineural invasion of the trochlear nerve from cutaneous squamous cell carcinoma.

FINDINGS: Coronal T1-weighted post contrast with fat-saturation demonstrates the avidly enhancing supratrochlear nerve (arrow) at the inferior aspect of the surgical bed (*).

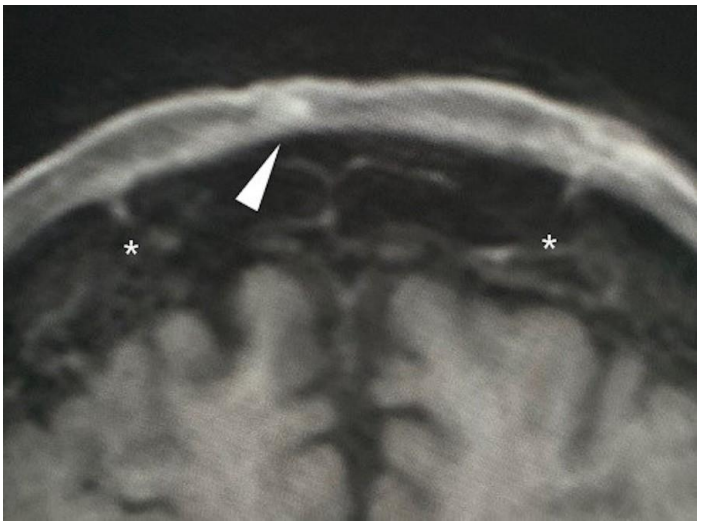

Figure 2 (left): 77-year-old male with perineural invasion of the trochlear nerve from cutaneous squamous cell carcinoma.

FINDINGS: Axial T1-weighted post contrast with fat-saturation shows the normal enhancement of the supraorbital nerves (*) juxtaposed against the intense enhancement of the supratrochlear nerve (arrow).

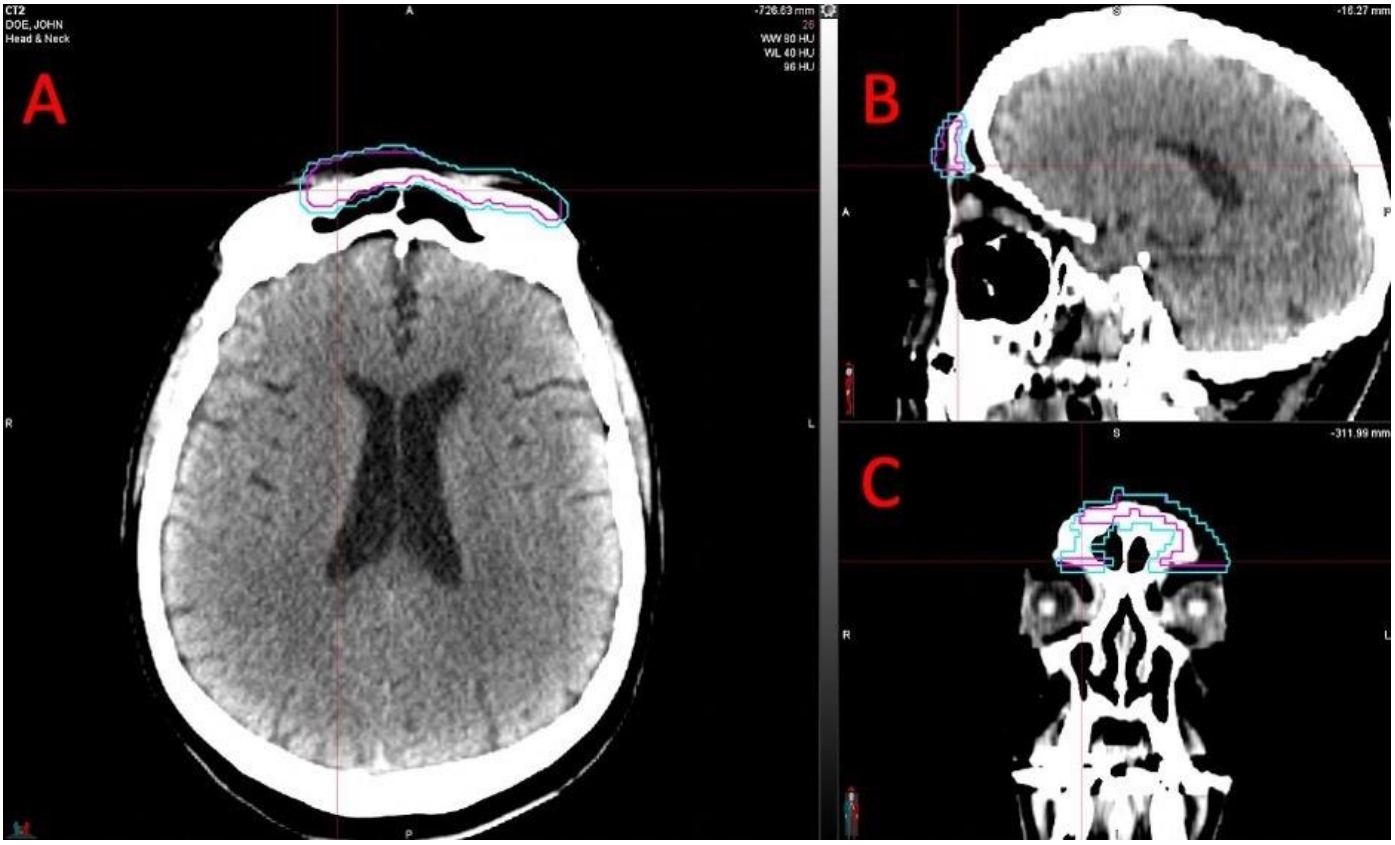

Figure 3: 77-year-old male with perineural invasion of the trochlear nerve from cutaneous squamous cell carcinoma.

FINDINGS: External beam radiotherapy treatment field, shows the intended target area (red arrows) of the supratrochlear nerves in transverse (a), sagittal (b), and coronal (c) planes.

Etiology	Unknown
Incidence	2.4-14%
Gender ratio	Unknown
Age predilection	64 years old
Risk factors	Recurrent cutaneous squamous cell carcinoma, prior treatment, midface location of tumor, size greater than >2 cm or male gender
Treatment	Surgery and radiation
Prognosis	Poor
Imaging findings	CT: Asymmetric soft-tissue thickening with hypointense lesions due to volume loss. Neural foramen widening. Resurfacing phenomenon where tumor reappears after traversing bone canal. MRI: T1 or T2-weighted hyperintense lesions with nerve thickening and loss of fat. May show retrograde tumor enhancement. In the muscle, T2-weighted hyperintense signals may be seen.

Table 1: Summary table of perineural invasion amongst cutaneous squamous cell carcinoma of head and neck cancers.

	CT	MRI
Perineural Invasion	Asymmetric soft-tissue thickening with hypodense lesions due to volume loss. Neural foramen widening. Resurfacing phenomenon where tumor reappears after traversing bone canal.	T1 or T2-weighted hyperdense lesions with nerve thickening and loss of fat. May show retrograde tumor enhancement. In the muscle, T2-weighted hyperdense signals may be seen.
Primary neural tumor	Low to intermediate attenuation.	T1-weighted sequences demonstrate hypodense (if cystic areas present). T2-weighted sequences demonstrate hyperdense lesions.
Invasive Fungal Infection	Hyperdense lesion with surrounding hypodense region (edema).	Hypodense on T1-weighted sequences.
Mycobacterial (i.e., Tuberculosis)	Low to intermediate attenuation with surrounding edema.	T1-weighted sequences demonstrate hyperdense lesions.
Lyme Disease	Not visible.	Often non-specific findings, but T1 and T2-weighted sequence may demonstrate hyperdense lesions.
Syphilis	Not visible.	On T1-weighted sequences may demonstrate hypodense lesions while on T2-weighted sequence may demonstrate hyperdense lesions.
Sarcoidosis	Not visible.	Hypodense on T1-weighted sequences while hyperdense on T2-weighted sequences.
Varicella Zoster Virus Myelitis	Not visible.	Hypodense on T1-weighted sequences while hyperdense on T2-weighted sequences.
Traumatic Neuroma	Not visible.	T1-weighted sequences not visible. T2-weighted sequences demonstrate hyperdense lesions.

Table 2: Differential diagnosis table for enhancement of the trochlear cranial nerve.

ABBREVIATIONS

cGy = Centigray
cSCC = Cutaneous Squamous Cell Carcinoma
MMS = Mohs Micrographic Surgery
MRI = Magnetic Resonance Imaging
PNI = Perineural Invasion

KEYWORDS

Cutaneous Squamous Cell Carcinoma with clinical Perineural Invasion of the Supratrochlear Nerve; CT; External Beam Radiotherapy, Oncology; Head & Neck Cancer; Adjuvant radiotherapy

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