The Role of Postoperative Radiotherapy for Large Nerve Perineural Spread of Cancer of the Head and Neck

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Abstract

Keywords

- ▶ perineural infiltration
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- ▶ adenoid cystic carcinoma

Large nerve perineural spread (LNPNS) is an uncommon but serious sequelae of cutaneous and salivary gland malignancies arising in the head and neck. This distinct clinical entity is caused by malignant cell spread along the course of larger (named) cranial nerves in a bidirectional pattern of spread toward the origins of the nerve in the brainstem and/or its most distal branches residing in the dermis. Untreated, LNPNS causes multiple cranial neuropathies that significantly impact on quality of life and ultimately is fatal. Curative treatment involves en bloc surgical resection of all known involved sites of gross disease followed by risk-adapted postoperative radiotherapy (PORT) to improve local control. We review the evidence for contemporary practice and outline the processes involved in the delivery of PORT using the zonal anatomical classification.

Introduction

Perineural infiltration (PNI) denotes direct malignant cell infiltration of the potential space surrounding neuronal axons and occurs in 2 to 6% of cutaneous head and neck squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs).¹ Major and minor salivary gland tumors, such as adenoid cystic carcinomas, are associated with PNI ranging from 29.4 to 62.5%,² whereas melanoma and cutaneous sarcomas are associated with a comparatively lower risk for PNI. Risk factors for PNI include high histologic grade, increasing tumor size, histology, immunosuppression, recurrent tumors, and those located in the midface region(s).³

PNI is classified into two categories. The most common scenario occurs when PNI is identified as an incidental finding in a resection specimen (known as *pathologic* or *incidental PNI*), and is more often observed with SCC histology.⁴ Incidental PNI occurs without preceding symptoms such as altered sensation or muscle weakness.

In the second scenario, motor or sensory symptoms arise as a result of cancer spread into larger and/or named nerves (clinical PNI). Large nerve perineural spread (LNPNS) is a distinct clinical entity whereby malignant cells metastasize along larger nerves in a bidirectional pattern toward the larger proximal branches of cranial nerves to their origins in the skull base (retrograde or centripetal spread), or alternatively, toward the smaller peripheral branches that extend throughout the dermis supplied by the named nerve (ante-grade spread). Retrograde spread is more common compared with spread to distal nerve endings.

A prior history of incidental PNI is not always present in patients with LNPNS. There is a direct relationship, however, between increasing involved nerve diameter, recurrence, and poorer clinical outcome with incidental PNI.⁵ In contrast, poorer outcomes occur with greater extent of spread along the nerve with LNPNS.

The type of LNPNS will depend on the location of the primary tumor and its relationship to the distal branches of

neurons that reside in the dermis. The most common involved cranial nerves are V (trigeminal) and VII (facial), but all cranial nerves and their divisions are at risk.^{6,7} Tumor spread usually occurs in a step-wise, contiguous pattern. Based on limited small series, skip lesions have been reported in the literature, however, in a series of 51 patients with clinical PNI from cutaneous SCC of the head and neck with detailed pathologic evaluation, no evidence of noncontiguous spread was demonstrated, suggesting skip lesions are a very rare occurrence.⁸

Patients with clinical PNI due to LNPNS may present with sensorimotor dysfunction in the distribution of large named cranial nerve(s) and are associated with a poor prognosis and survival.^{9,10} Sensorimotor symptoms can include numbness, paraesthesia, pain, and formication in the distribution of the involved nerve(s).¹¹ Disease may progress slowly over many months to years prior to a diagnosis, negatively impacting on outcome.¹² LNPNS of the facial nerve can often be misdiagnosed as Bell's palsy before the correct diagnosis is made. Magnetic resonance imaging (MRI) neurography is the investigation of choice to detect pathologically enlarged nerves in the setting of clinical PNI and LNPNS.¹³

Anatomy

A full description of cranial nerve anatomy is beyond the scope of this article so the reader is referred to the literature for further information.^{14,15} For surgical and radiotherapy (RT) treatment planning purposes, the zonal classification of LNPNS has emerged as a useful tool to guide clinicians in treatment recommendations.^{13,16} The zonal classification breaks the pathways of cranial nerves into three separate anatomical zones that are summarized for cranial nerves V and VII in ►Table 1. The reader is directed to the accompanying article by Gandhi et al for a detailed review of anatomical and radiological descriptions of LNPNS.

Pretreatment Assessment

Prior to any treatment, patients require a full history and examination with a detailed assessment of symptoms and signs. Particular questioning of any previously noted or treated skin lesions within the distribution of the nerve should be sought as symptoms and disease progression may occur years later. Patients require a careful assessment of all cranial nerves, as well as careful palpation to check for subcutaneous involvement. Potential skin primary sites should be identified and previous histologic reports obtained.

Patients should be assessed in a multidisciplinary team (MDT) with skull base surgeons, plastic and reconstructive surgeons, radiation oncologists, medical oncologists, neuro-radiologists, allied health, and nursing professionals in keeping with the National Comprehensive Cancer Network Guideline recommendation for complex skin cancers.¹⁷

Baseline assessment of audiometry and ophthalmology is recommended for patients who are to receive RT. Dental assessment is suggested to identify and treat at-risk dentition to mitigate late complications related to post-RT dental extractions or osteoradionecrosis of the jaw. If clinically sus-

pected, evaluation for locoregional and distant metastases with computed tomography (CT) of the head, neck, and chest is performed to assess for bone permeation, nodal involvement, and pulmonary metastases.

Referral to a psychosocial practitioner can be considered as anxiety and depression are common in patients with cancer.

Management

Historically, RT was the main treatment modality for LNPNS due to the limited ability to access the skull base surgically. With advances in skull base surgical expertise and techniques, surgery has an increasingly important role, which is discussed below.

Surgery

In operable patients, curative treatment for LNPNS is en bloc resection of the gross disease demonstrated on MRI neurography and subclinical disease proximally along the path of the affected nerve. The goal of surgical resection is to achieve a clear margin to prevent retrograde spread toward the proximal zone. It is preferable that surgery is undertaken at high-volume centers within an MDT. In patients deemed medically or technically inoperable (if disease extends proximally to zone 3, i.e., the gasserian ganglion of cranial nerve V or the geniculate ganglion of cranial nerve VII), definitive RT alone can be used after consideration of patient, tumor, and treatment factors.¹⁸ The reader is referred to the accompanying articles by Solares et al and Redmond et al for a detailed review of contemporary surgical treatments for LNPNS.

Thorough evaluation of the histopathology is essential to determine the final extent of gross and microscopically involved disease. Margin status on all resected specimens is required as this will determine RT target volumes, dose, and fractionation. Frozen sections at operation obtained at the most proximal aspects of the involved nerve require postsurgical correlation for concordance with the initial clinical and radiological diagnosis.

Radiotherapy

The principal aims of PORT for LNPNS are to prevent cutaneous relapse (in the distribution of the named nerve), extracranial skull base recurrence, and central intracranial progression. Consideration of the pathologically involved and at risk portion of the affected nerve is needed to inform the regions at risk of local recurrence. If more than one named nerve is involved (e.g., V1 and V2), the cutaneous branches of both nerves are treated. Crossover from one named nerve to another can occur in the dermis, in the watershed region bordering two dermatomes¹⁹ or via known conduits (e.g., vidian nerve and auriculotemporal nerve). In cases of LNPNS involving zones 2 and/or 3, the whole operative bed incorporating the path of the named nerve (including areas of known crossover, e.g., the infratemporal fossa for V2/V3) is treated back to the ganglion (for resected zone 1 disease) or prepontine region (for resected zone 2 disease).¹⁹

Table 1 Cranial nerve zonal classification of cranial nerves V and VII

	Zone 1 ^a	Zone 2 ^b	Zone 3 ^c
V1 (ophthalmic)	To superior orbital fissure	From zone 1 to the gasserian ganglion cistern	From zone 2 into the cisterns, or brainstem
V2 (maxillary)	To external aperture of foramen rotundum		
V3 (mandibular)	To external aperture of foramen ovale		
VII (facial)	To external aperture of stylo-mastoid foramen	From zone 1 to the lateral end of the internal auditory canal, including the geniculate ganglion and the labyrinthine segment	

V1, V2, V3 = cranial nerve 5 (trigeminal cranial nerve). VII = cranial nerve VII (facial cranial nerve).

^aZone 1 encompasses the course of the cranial nerve beyond its exit foramen in the skull base (V1 branch of cranial nerve V to the superior orbital fissure; V2 branch of cranial nerve V to the external aperture of foramen rotundum; V3 branch of cranial nerve 5 to the external aperture of foramen ovale; and cranial nerve 7 to the external aperture of the stylomastoid foramen).

^bZone 2 encompasses the nerve pathway within the skull base, largely within bony structures, prior to its connection at the ganglion (V1, V2, V3 branches of cranial nerve V from zone 1 to the gasserian ganglion cistern; and cranial nerve VII from zone 1 to the lateral end of the internal auditory canal, including the geniculate ganglion and labyrinthine segment).

^cZone 3 encompasses the nerve pathway from the ganglion into the cisterns or brainstem.

There are no data to support the use of concurrent chemotherapy with PORT in the treatment of LNPNS for cutaneous or salivary gland malignancies. In addition, the role of elective nodal RT in LNPNS in the absence of other adverse risk factors remains inconclusive. Elective nodal irradiation may be considered in some circumstances where there is a high risk of occult nodal involvement (e.g., larger primary tumors [> 2 cm], high-grade histology [poorly differentiated tumors], or immunosuppression).

Published Data on Surgery and Postoperative Radiotherapy

Published data on PORT for LNPNS are limited. McCord et al²⁰ reported on 62 patients treated at the University of Florida between 1965 and 1995 with clinical and/or gross evidence of cutaneous PNI of the head and neck with a minimum 1-year follow-up. Of those, 21 (34%) patients were treated with surgery and PORT, receiving a mean dose of 67.58 Gy using once daily standard fractionation, or 74.4 Gy if twice daily fractionation was used. For patients treated with surgery and PORT, local control (LC) was 53%. If there was evidence of gross LNPNS to the skull base, LC was lower at 25% with a recurrence pattern that was predominantly local, supporting the concept that even patients with advanced LNPNS are potentially curable.

Warren et al²¹ reported on 50 patients with clinical PNI from cutaneous SCC of the head and neck treated with curative-intent surgery between 2000 and 2011 at the Princess Alexandra Hospital, Brisbane. Median follow-up was 24 months. MRI neurography was positive in 95.8% of patients, and 5 (10%) patients had nodal disease at presentation. A total of 47 (94%) patients received PORT with a dose range of 50 to 63 Gy in 25 to 30 daily fractions. The 5-year outcomes were: recurrence-free survival, 62%; disease-specific survival, 75%; and overall survival 64% with no reported perioperative deaths. The predominant pattern of failure was local in-field (20%), followed by local out-of-field/peripheral (12%). The

authors concluded that long-term survival is possible in patients with LNPNS who undergo surgical and PORT.

Balamucki et al²² reported on 65 patients with clinical PNI from cutaneous SCC or BCC of the head and neck treated at the University of Florida between 1965 and 2009. Median follow-up periods for overall and living patients were 5.4 and 11.6 years, respectively. A variety of treatment regimens were used, including RT alone ($n = 18$), RT with concurrent chemotherapy ($n = 14$), surgery and PORT ($n = 26$), surgery and PORT with concurrent chemotherapy ($n = 5$), and preoperative RT followed by surgery ($n = 2$). Patients were stratified by imaging-negative disease ($n = 11$), minimal or moderate peripheral disease ($n = 18$), and macroscopic and/or central disease ($n = 36$). Median RT dose was 72.6 Gy (50.4–79.2 Gy). At 5 years, outcomes for imaging-negative disease versus minimal/moderate peripheral disease versus macroscopic/central disease were: LC, 81 versus 60 versus 47% ($p = 0.23$); locoregional control, 80 versus 54 versus 47% ($p = 0.22$); neck control, 100 versus 89 versus 93% ($p = 0.45$); distant metastasis-free survival, 89 versus 100 versus 93% ($p = 0.57$), overall survival, 82 versus 50 versus 52% ($p = 0.26$), and cause-specific survival, 100 versus 58 versus 65% ($p = 0.08$), respectively. Thirty-four per cent of patients had one or more severe (grade 3) late complications. These data suggested a nonsignificant trend toward improved LC for imaging-negative patients and patients with minimal/moderate peripheral disease compared with macroscopic/central disease. They also concluded that although survival appeared better for imaging-negative patients, the extent of imaging-positive PNI did not impact overall or cause-specific survival.

Lin et al²³ reported on 56 patients with cutaneous carcinoma of the head and neck with clinical PNI treated between 1991 and 2004 at Royal Brisbane and Women's Hospital, Brisbane. Of these, 41 (73%) were treated with surgery and PORT to a median dose of 60 Gy (range 48–74 Gy). Five-year relapse-free survival was 48% (SCC 39 vs. BCC 80%). Factors associated with an adverse outcome included SCC histology

(confirming previously reported data²⁴), tumors located in V1 and V2 distribution, and multiple nerve involvement. LR was the main pattern of recurrence (34%) and subsequent salvage was poor.

Gluck et al²⁵ reported on 11 patients with LNPNS treated at the University of Michigan between 2000 and 2007. A pattern of failure analysis was performed which demonstrated that the most prevalent site of relapse was along cranial nerves innervating the primary tumor site(s). In many cases, multiple cranial nerves (and communicating branches) were involved. As a result, the authors concluded that portions of the nerve proximal and distal to the tumor site, the skin innervated by the involved nerve, major communicating branches, and the compartment in which the nerve is embedded (e.g., parotid gland for CN VII) be included in the target volume.

Balamucki et al²⁶ reported on 120 patients with adenoid cystic carcinoma of the head and neck treated between 1966 and 2008. Clinical PNI was identified in 35 (29%) patients. On multivariate analysis, clinical PNI was negatively associated with LC ($p = 0.0488$), locoregional control ($p = 0.0487$), distant metastases-free survival ($p < 0.0001$), cause-specific survival ($p = 0.0002$), and overall survival ($p = 0.0002$). Distant metastasis-free survival at 5 years was 79% for patients with clinical PNI. The authors concluded that the combination of surgery and PORT offered the best outcome in terms of LC and cure for patients with resectable disease compared with RT alone.

Treatment Planning

Simulation

Prior to simulation, comorbid medical issues should be addressed prior to treatment, as rigorous treatment may exacerbate underlying illnesses. A multidisciplinary radiation oncology team including specialized nursing and allied health is needed to coordinate care, prevent treatment delays, and provide optimal RT planning.

Thermoplastic shell immobilization is required in all patients and consideration for upper body vacuum bag/cushion should be made to maximize reproducibility as per departmental protocol. Mouthpieces may be considered for treatment of palatal and paranasal sinus tumors to separate the palate from the tongue and floor of mouth and ensure separation of the lips, but this has to be individualized to patient tolerance and comfort.

All surgical wounds and/or biopsy scars are wired with radio-opaque materials to aid target volume delineation. The dermis and skin surface innervated by the affected nerve will need to be covered with bolus if zone 1 is being treated. This area can be wired at simulation and then correlated on the planning CT. Bolus/packing may need to be used to fill in air cavities/inhomogeneities and ensure total dose to the skin. If the orbit is away from the treatment volume, the patient can be treated with their eyes closed, remembering that this will result in the lens of the eye moving superiorly. If the eye is to be included in the treatment volume, the patient should keep their eyes open to help reduce conjunctival dose as closed

eyelids will act as bolus to the conjunctiva which can increase the morbidity or treatment.

A planning CT with contiguous axial slices (maximum slice thickness 2–3 mm) is acquired and fused with available pre- and postoperative imaging (diagnostic CT, MRI, and positron emission tomography [PET]) to aid in target delineation. We recommend the radiation oncologist check fusions prior to clinical use. IV contrast is recommended unless contraindicated (e.g., renal impairment, contrast allergy) for patients who are to receive elective nodal irradiation to define vascular anatomy. Clinical photography of the final clinical markup at simulation is highly recommended.

Volume Definition and Dose Fractionation

Operative notes should be obtained to carefully review the areas resected to correlate with pathological findings and determine areas at risk of recurrence. Contouring guidelines are available to guide radiation oncologists in the delineation of cranial nerve anatomy.^{27,28} When intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) is used, the margin for error is high due to the steep dose gradients achievable with these modulated techniques. Therefore, accurate delineation of the tumor volumes and organs at risk (OAR) is critical and can be facilitated with the assistance of the surgical oncologist and neuroradiologist.

The radiation volumes aim to treat the surgical bed and the involved nerves. This will include the dermatomal distributions as well as the proximal extent of disease. The resultant target volumes are complex three-dimensional shapes, complicated by sensitive OAR that lie immediately adjacent or in close proximity. OAR include the globes, lacrimal glands, optic nerves, chiasm, brainstem and brain.

The volumes should use established nomenclature and start with defining the high-risk tumor volume (HRTV). Several clinical target volumes (CTVs) with different dose levels are then determined according to disease burden. The CTV takes into account microscopic extension of disease. For example, the involved surgical margins will be treated to a dose of 66 Gy and this will be generated as CTV 66. Matching planning target volumes (PTVs) are generated for each CTV taking into account setup error.

The HRTV includes all areas of gross disease on preoperative imaging (MRI preferred) and the gross tumor volume (GTV) in patients with residual disease postoperatively. CTV 66/63 includes area of microscopic positive margins (if present) + 5- to 10-mm margin to account for microscopic spread of disease beyond the resection margin (►Table 2). If a specific area of positive margin cannot be identified, HRTV + 1 cm to be used for the CTV 63/66 and the CTV 60 is omitted. CTV 60 includes CTV 66/63 (if present), and HRTV + 1 cm constrained by anatomical boundaries and skin. CTV 56/54 includes CTV 60, and the entire operative bed as defined by postsurgical change seen on CT and the scar.

In cases where the primary lesion is within 2 cm of the midline (particularly in the midface), consideration should be given to extending the elective dose across the midline to prevent contralateral spread of cutaneous perineural disease.

Table 2 Doses for PORT for cutaneous (nonadenoid cystic carcinoma) malignancies with LNPNS of the head and neck

Schedule	Site	3D-CRT			IMRT		
		Dose (Gy)	Fractions	Weeks	Dose (Gy)	Fractions	Weeks
Conventional	Microscopic positive margin or gross (unresected or residual) LNPNS	66	33	6.4	63	30	6
	Tumor bed	60	30	6	60	30	6
	Operative bed	54	27	5.3	56	30	6
	Elective neck, ^a cutaneous distribution of named nerve, ^b and/or zone proximal to LNPNS	50	25	5	54	30	6

Abbreviations: IMRT, intensity-modulated radiotherapy; LNPNS, large nerve perineural spread; PORT, postoperative radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy.

^aElective neck RT can be considered in patients with tumors located in primary sites thought to be relatively rich in capillary lymphatics or in patients with nodal involvement in whom undissected nodal echelons remain at risk.

^bIn cases where the primary lesion is within 2 cm of the midline (particularly in the midface), consideration should be given to extending the elective dose across the midline to prevent contralateral spread of cutaneous perineural disease.

Where elective treatment to the nodes is being undertaken, CTV 54/50 includes CTV 56/54, and the first echelon of undissected, clinically uninvolved lymph nodes. Elective neck RT is used in patients with tumors located in primary sites thought to be relatively rich in capillary lymphatics or in patients with nodal involvement in whom undissected nodal echelons remain at risk.

PTVs are isotropic expansions for their corresponding CTVs, cropped to skin, and also named for their relevant dose levels (e.g., PTV 63). In most cases a 3- to 5-mm expansion will be appropriate. A representative case is provided illustrating MRI neurography findings, target volume delineations, and PORT dosimetry (►Fig. 1).

CTV Delineation for Adenoid Cystic Carcinoma

Treatment volumes need to be individualized in adenoid cystic carcinoma due to the diversity of locations of these tumors, (for example, major and minor salivary glands in the oral cavity and sinuses). The involved nerves to be treated will vary according to tumor site. The following CTVs are contoured in the following situations of radiological or pathological evidence of LNPNS involving CN V and/or VII and their branches (►Table 3). There is no role for elective treatment of larger (named) nerves if histopathology of the primary tumor demonstrates small nerve (incidental) PNI only (completely resected) without evidence of clinical PNI.

Normal Tissue Tolerances

The target volumes that are generated in patients in whom treatment of zone 2 or 3 is required lie in close proximity to critical OAR, including the retina, optic nerves, optic chiasm, medial temporal lobes, hypothalamus/pituitary, and brainstem. Updated normal tissue tolerances as described in QUANTEC should be respected.²⁹ However, in select cases, normal tissue tolerance may need to be exceeded when balanced against the risk of OAR injury from tumor progression. For example, in a patient with unresectable disease

involving zone 2, the risk of radiation-induced optic neuropathy if the optic nerve receives 60 Gy approaches 50%³⁰; however, if left untreated, the risk of tumor infiltration causing blindness or severe visual disturbances exceeds 50%.

Planning Techniques

In most cases, IMRT (static/step-and-shoot or rotational delivery with VMAT) should be used to maximize dose conformity. There are no data supporting the use of one particular technique over another in the treatment of LNPNS.³¹ A simultaneous integrated boost technique should be used, which recalculates conventional dose levels based on biological equivalent dose over the entire duration of treatment.

Image Guidance

Image-guided RT is essential in patients treated to high doses to the skull base that approach or exceed OAR tolerances. Departmental estimates of setup error are essential to estimate CTV to PTV margin expansion and to guide image guidance to avoid geographical miss. In our experience, daily online kV imaging with cone beam CT (CBCT) is used with a less than 2 mm action threshold. In the absence of CBCT capability, an alternative regimen of daily online EPI/kV imaging daily is acceptable.

Quality Assurance

Contouring variability among radiation oncologists is increasingly being identified as a weak link in terms of delivering reproducible, accurate RT.³² Just as the linear accelerators undergo strict quality assurance, it is important that contouring is also critically reviewed. All LNPNS patients treated with curative intent are recommended to undergo peer review of target volumes and final dosimetry as part of quality assurance, attended by head and neck radiation oncologists, radiation therapists (medical dosimetrists), and medical physicists to ensure consensus and improve consistency.

Fig. 1 Illustrative case. Case of a 52-year-old with cutaneous squamous cell carcinoma in the left cheek with V2 symptoms and magnetic resonance imaging confirmed infraorbital nerve involvement but no radiological evidence of zone 2 disease. Skull base surgery was performed demonstrating extensive large nerve perineural spread of V2 to the gasserian ganglion. The vidian, lesser, and greater palatine nerves were involved on pathologic examination with no evidence of geniculate ganglion spread, consistent with pathologic zone 2 disease. Postoperative radiotherapy was delivered to zones 1, 2, and 3 with bolus over the dermatomal distribution of V2 outlined at the time of planning computed tomography scanning. The patient was treated using volumetric modulated arc therapy using two coplanar arcs with 6 MV photons. Key organs at risk included the brainstem, optic chiasm, and optic nerves. (A) Magnetic resonance neurography illustrating 24 mm extension along the infraorbital nerve. (B) Axial view depicting three target volume delineations (clinical target volume [CTV] 63, CTV 60, and CTV 54 planned to receive 63, 60, and 54 Gy, respectively, delivered over 30 fractions, 5 fractions/wk, over 6 weeks. (C) Axial view illustrating brainstem avoidance and placement of bolus in V2 dermatomal distribution. (D) Coronal view. (E) Sagittal view.

There is evidence in other head and neck subsites that planning violations in a phase III clinical trial setting negatively impacts locoregional control and survival.³³

Treatment Duration and Interruptions

Every effort must be made to avoid protraction of treatment beyond 7 weeks for definitive therapy. In particular, treatment interruptions for toxicity or intercurrent illnesses should be avoided unless severe. In the event of a treatment interruption for any other reason, the missing dose fraction(s) should be made up by treatment on a weekend or by giving a second treatment on one or more of the remaining treatment

days with a minimum 6-hour interfraction interval. No more than seven fractions are given in any 1 week.

Management of Treatment Morbidity

Short-term side effects that arise during or within a few weeks of finishing RT are usually temporary. Complications of PORT vary according to primary site and are dose and volume dependent. Common adverse effects include dermatitis, conjunctivitis, mucositis, xerostomia, pain flare, and fatigue. Patients should be reviewed at least weekly by the treating clinician, with shorter intervals in patients who experience

Fig. 1 (Continued)

severe acute effects, with further support from specialized nursing and allied health. Intensive skin care and dietary support will assist in relieving patient symptoms and reduce the risk of admission to hospital.

Late-term effects occur 3 months (or later) after completion of treatment and may be progressive and permanent, and also vary according to site, dose, and volume. Late effects clinics for long-term survivors are not universally available

but may benefit patients who experience severe complications from treatment.

Follow-up

Follow-up of patients is important in terms of detecting early recurrence, providing the patient ongoing support, and management of the side effects of treatment. It also provides

Table 3 PORT doses for adenoid cystic carcinoma with LNPNS

	Radiologic PNI	Pathologic PNI
CTV 63	Abnormally thickened/enhancing nerve that is outside surgical field (i.e., gross disease)	Proximal cut edge is a positive margin; if accompanying radiology negative, treat entire zone of positive margin
CTV 60	N/A	Course of completely resected (R0) LNPNS
CTV 54	Zone proximal to abnormally thickened/enhancing nerve treated as positive above	Zone proximal to completely resected (R0) LNPNS

Abbreviations: CTV, clinical target volume; LNPNS, large nerve perineural spread; PNI, perineural infiltration; PORT, postoperative radiotherapy.

valuable information of the effectiveness of treatment and documents the timing and site of relapse. These patients have a very high risk of developing a separate unrelated skin cancer and a general skin check of sun-exposed areas should also be undertaken as part of the clinical review.

Progression will occur in one-third to one-half of patients. The most common site of relapse will be progression of the LNPNS component. Nodal relapse is uncommon. Relapse may be detected by the development of new symptoms or signs (e.g., increasing paresthesia, pain or new cranial nerve palsies). Periodic MRI scans are useful in detecting proximal spread.

During the review visit, the treatment area should be carefully evaluated and a full cranial nerve examination undertaken and the draining lymph nodes examined. Late effects of radiation should be recorded. The patient may require ongoing ophthalmic evaluation. Pituitary function should also be evaluated if this was included in the treatment volume.

Follow-up recommendations are risk-adapted based on the patient's baseline risk assessment, symptoms, and probable pattern of relapse. There are no data on the optimal follow-up in LNPNS. As a guide, clinical evaluation in the first year after completion of treatment is usually conducted every 3 months for the first 2 years, every 4 months in year 3, and every 6 months in years 4 and 5. Surveillance posttreatment MRI can be justified every 6 months for the first 2 years, then yearly thereafter, in patients in whom salvage treatment is possible. Depending on the clinical scenarios, reirradiation or surgery may be considered in highly select patients depending on the pattern or relapse.

Future Directions

In the future, there may be potential for dose escalation to decipher a dose response to higher doses, exploit altered fractionation to overcome tumor regeneration, reduce the volume of normal tissue damage by minimizing treatment margins with more sophisticated image guidance, or radiosensitize tumors with the use of concurrent systemic therapies. The incorporation of chemotherapy and biologic agents into RT protocols also needs to be explored to establish if additional control with acceptable toxicity can be achieved.

Conclusion

LNPNS represents one of the most challenging areas of head and neck surgery and RT. Successful treatment requires a

highly specialized team to coordinate the assessment, treatment and follow-up of patients. The potential to cause harm is significant and patients should be managed in centers with expertise in this area. Treatment with surgery and PORT is the current gold standard, but further research is needed to evaluate if other potential treatment modalities such as chemotherapy or biological agents improve clinical outcomes.

Highlights

- LNPNS is uncommon but serious sequelae of cutaneous and salivary gland malignancies arising in the head and neck.
- This distinct clinical entity is characterized by malignant cell spread along the course of larger (named) cranial nerve in a bidirectional pattern toward the origins of the nerve in the brainstem and/or its most distal branches residing in the dermis.
- Treatment involves en bloc surgical resection of all known involved sites followed by risk-adapted PORT to prevent cutaneous relapse, extracranial skull base recurrence, and central intracranial progression.
- PORT planning considers preoperative imaging findings, clinical symptoms, extent of disease resected, margin status, and patient factors including immunosuppression.
- Zone 1 is treated to the back of the ganglion, zone 2 to the preopontine region, and zone 3 to the brainstem as tolerated.
- To treat to suggested doses, modulated RT techniques are needed to maximize dose to the clinical target volume while sparing nearby OAR.
- Multidisciplinary management is critical to selecting patients suitable for curative versus palliative treatment.

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