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Neuroendocrine, Sensory, Trabecular: Merkel Cell Carcinoma

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Preface

Afferent sensory mechano- receptors situated in the basal layer of the epidermis are designated as Merkel cells [1]. The malignant conversion of the merkel cells the pleuri-potent stem cells may engender the Merkel cell carcinoma [2,3]. A neuro-endocrine tumour frequently located in the head and neck of fair skinned adults or elderly males, Merkel cell carcinoma is a contemporary designation for a cutaneous malignancy, previously termed as a trabecular carcinoma, small cell carcinoma, neuro-endocrine or an endocrine carcinoma [4]. Analogous with adjunctive cutaneous malignancies, the sun-exposed regions, face and extremities are commonly implicated. The disease prevalence may be elevated in the immune - suppressed patients. The infrequent, asymptomatic malignancy has amplified up-to four times in the preceding decades [5]. Tumours of the lip, scalp, on-site invasion, lymph node or distant metastasis, tumour reoccurrence and lymphatic-vascular invasion are indicators of a poor prognosis. Merkel cell carcinoma may be collated with the malignant melanoma on account of the tumour aggression and an unfavourable outcome. The epidemiology, diagnostic evaluation and therapeutic options are debatable by virtue of the infrequency of the tumour.

Tumour Incidence

An up-surge in the last two decades, Merkel cell carcinoma displays an estimated prevalence of 0.6 per 100,000 [6]. Majority (80%) of the tumour specimens delineate a polyoma virus, designated the Merkel cell carcinoma polyoma virus [6,7]. The virus may be discovered in roughly 16% of healthy skin [8]. Environmental aspects such as ultraviolet exposure, immune suppression and viral mutations may assist the tumour

progression. Merkel cell carcinoma is frequent in the head and neck(41.8%), followed by the upper extremities(24.6%) [1,4]. The majority of the lesions (81%) emerge in the regions of sun exposure. The condition is prevalent in the Caucasians(90%-95%) and males (59%) of around 50 years of age (90%) [1,4]. The miniature lesions of the head and neck may probably metastasize to the regional lymph nodes (50.1%) with the tumour infiltrating the bone, cartilage or muscle (7.9%). Tumours confined to the lip may invade locally (89.8%), extensive scalp tumours may exhibit distant metastasis (8.7%) and lesion of the external auditory canal exemplify nodal metastasis (63.2%) [1,4].

Clinical Aspects

A red or violet nodular lesion with a tendency to ulcerate, Merkel cell carcinoma is an aggressive neoplasm, metastasizing to the regional lymph nodes and distant organs such as the lungs, liver and bone or testis. The acronym "AEIOU" may enunciate the clinical elements of the neoplasm: asymptomatic / non-tender, expanding quickly, immune suppressed, older than 50 years of age and ultra- violet exposure for fair skinned individuals [8]. The lesions may be deemed innocuous(56%) or benign, prior to tissue sampling. Immune compromised patients, organ transplant recipients, immune - deficiency syndrome(AIDS) or autoimmune disorders demonstrate an elevated (13.4%) probability of tumour occurrence, in contrast to the normal population [1]. The telangiectatic lesions are characteristically bluish red with an uninvolved epidermis and infrequently ulcerating giant tumours [8]. The tumour may be suspected by the virtue of the enlarged regional lymph nodes. The head and neck neoplasm with implication of the lip, scalp, local invasion, regional node metastasis and distant metastasis usually indicate an enhanced mortality [1,4]. Tumour thickness is an insensitive predictor of clinical stage and metastatic potential of the tumour. A tumour thickness of > 10mm, the absence of a regional lymph node dissection or elective radiation therapy, may exhibit a decline in the 5 year survival of the patient [1,4]. Primary tumour size, lymphatic and vascular invasion may compound the probable regional metastasis and may concur with the decline in the patient survival [4].

Analysis and Attributes

The evaluation of Merkel cell carcinoma requires a detailed history and physical exam, the assessment of the extent of the primary tumour, regional lymphatic spread, satellite nodules and the occurrence of immune suppression. Unconventional lesions may be sampled for histology. Radiographic imaging may include the primary tumour, regional lymphatic, lymph nodes and lungs. Positron emission tomography (PET-CT) is a sensitive and specific technique, which may be applicable for the preliminary staging, surveillance of the neoplasm and outlining the therapeutic protocol [9].

Tumour Staging

The metastatic potential of the disease may mandate a precise staging of the malignancy. Merkel cell carcinoma may be analyzed with a TNM classification system comprising of the tumour magnitude, extent of tumour invasion, microscopic and macroscopic lymph node metastasis, the presence of satellite nodules and distant metastasis.

Table 1: *Staging of Merkel Cell Carcinoma (American Joint Committee of Cancer AJCC)[1]*

Primary Tumour	Regional Lymph Node	Distant Metastasis
Tx: Primary tumour cannot be assessed	Nx: Lymph nodes cannot be assessed	Mx: Metastasis cannot be assessed
T0: No evidence of primary tumour	cN0: Nodes negative by clinical exam	M0: No distant metastasis
Tis: In situ primary tumour	pN0: Nodes negative by pathologic exam.	M1a: Metastasis to skin, subcutaneous tissue or distant lymph node.
T1:≤ 2cm maximum tumour diameter	N1a: Micro-metastasis identified by lymph node exam.	M1b: Metastasis to lungs.
T2:≥ 2cm but ≤ 5cm maximum tumour diameter	N1b:Macrometastasis with clinically detectable nodes, confirmed on biopsy	M1c: Metastasis to other visceral sites.
T3:≥ 5cm maximum tumour diameter	N2: In transit lesion- Tumour distal to primary lesion.	
T4: Primary tumour invades bone, muscle, fascia or cartilage		

Histo - Morphology

On microscopy, the tumour is situated in the dermis or subcutaneous tissue with an uninvolved superficial epidermis. The diffuse, homogeneous round cell infiltrate with a focal trabecular pattern, predominantly occupying the subcutaneous region may be misinterpreted as a malignant lymphoma. Distinctive cytological aspects include a scanty cytoplasm appearing as a thin, acidophilic rim, typically round and vesicular nuclei with a fine, granular (dusty) chromatin and multiple nucleoli. Mitotic figures and fragmented, apoptotic bodies are numerous [2]. An infrequent Azzopardi's phenomenon (haematoxyphilic staining of the blood vessel wall and fibrous septa) may appear along with necrosis. A plump endothelium laminating the blood vessels with prominent vascular proliferation is demonstrated in the stroma, analogous to the malignant tumours of the primitive neural phenotype. Merkel cell carcinoma may co-exist with foci of in-situ or invasive squamous cell carcinoma, eccrine duct like configurations or a basal cell carcinoma. Thus it may be surmised that the neoplasm commences from a multi-potent ectodermal stem cell. Extensive intra-epidermal pagetoid dissemination or a purely intra-epidermal tumour accompanied by a squamous cell carcinoma in situ may emerge infrequently. Merkel cell carcinoma may exceptionally simulate a leiomyosarcoma, rhabdomyosarcoma or atypical fibro-xanthoma either in the primary tumour or with the tumour reappearance because of de-differentiation or dissimilar differentiation [2]. The reciprocal phenomenon must then be excluded, such as the existence of a rhabdomyosarcoma with anomalous neuro-endocrine markers.

Ultrastructural Features

The tumour cells harbour dense core neuro-secretory granules (abutting the cell membrane) and compact peri-nuclear intermediate filaments. Spikes of the cytoplasm (filament rich stiff spinous protuberances) and innumerable filiform extensions of the cell (anemone like presentation) are exceptional [2]. The tumour cells appear argyrophilic with the Grimelius reaction to the tissue fixed in Bouin's fluid.

Immunohistochemistry

The tumour cells are reactive for low molecular weight cytokeratin (CK20- in a peri-nuclear dot like fashion), neuro-filaments and neuron specific enolase(NSE). The tumour cells are negative for thyroid transcription factor 1(TTF-1), which may aid the differentiation from the metastatic small cell neuro-endocrine carcinoma of the lung. Merkel cell carcinoma is immune-reactive for chromogranin, synaptophysin, pancreatic polypeptide, vaso-active intestinal polypeptide, substance P, somatostatin, adreno-cortico-trophic hormone (ACTH), peptide hormones, PAX-5 (a B cell transcription factor), terminal deoxynucleotidyl transferase (TdT), CD 117 and glypican -3 [2].

Genetic Anomalies

Discerned in the neoplasm are the loss of heterozygosity (LOH) in 1p35-36 depicted in about three fourth (70%) instances, a trisomy 6 (50% cases) and a promoter hypermethylation of P14/ARF (42%) in the patients.

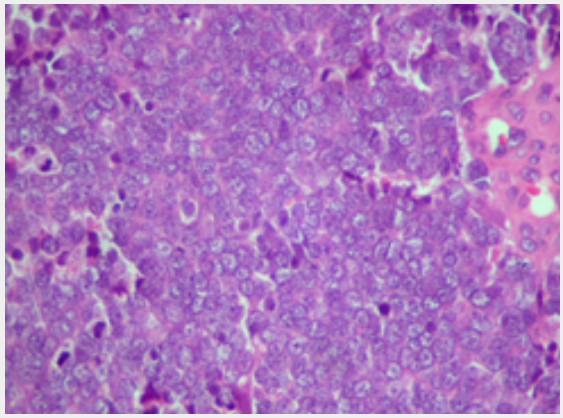

Figure 1: *Merkel Cell Carcinoma - round cells with indistinct cytoplasm*

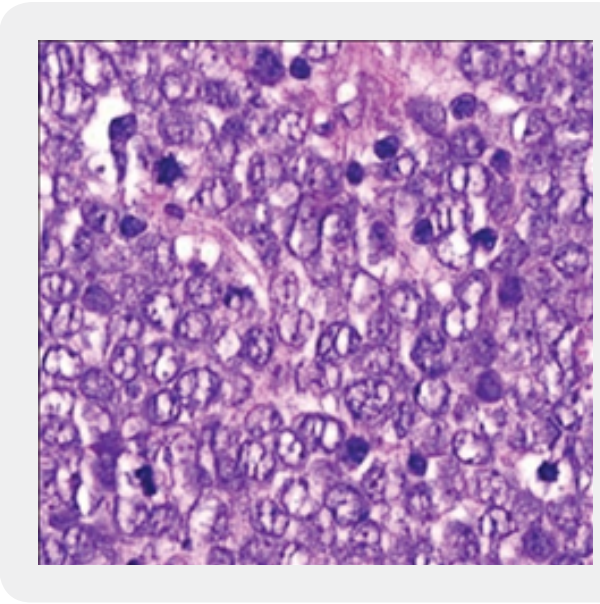

Figure 2: *Merkel Cell Carcinoma- vesicular nuclei with indistinct nucleoli*

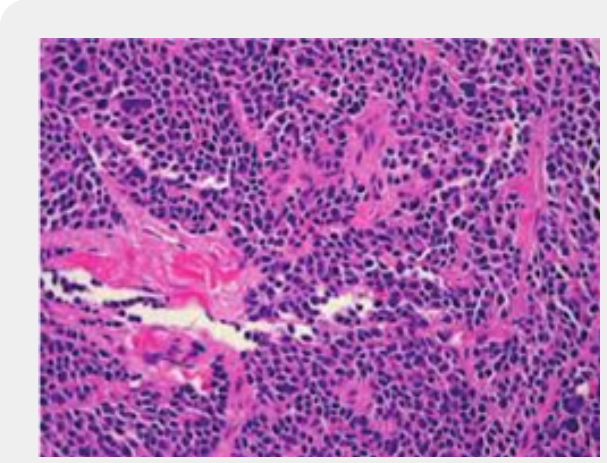

Figure 3: *Merkel Cell Carcinoma - trabecular pattern*

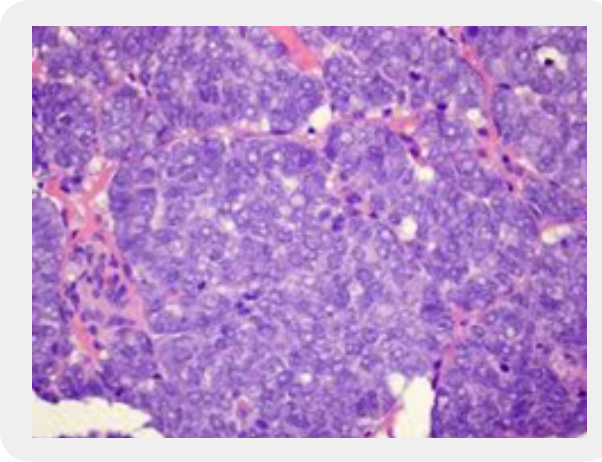

Figure 4: *Merkel Cell Carcinoma-zellballen with a prominent vascular outline*

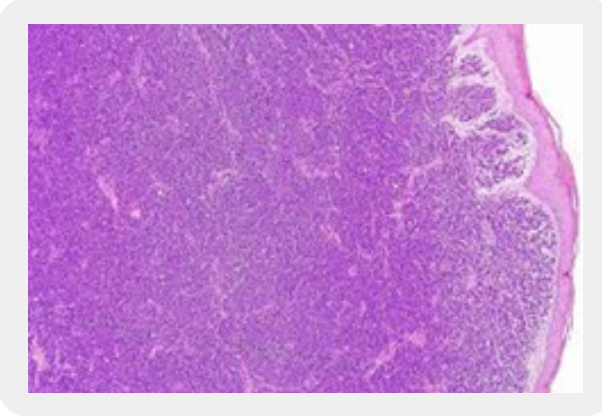

Figure 5: *Merkel Cell Carcinoma with epidermotropism*

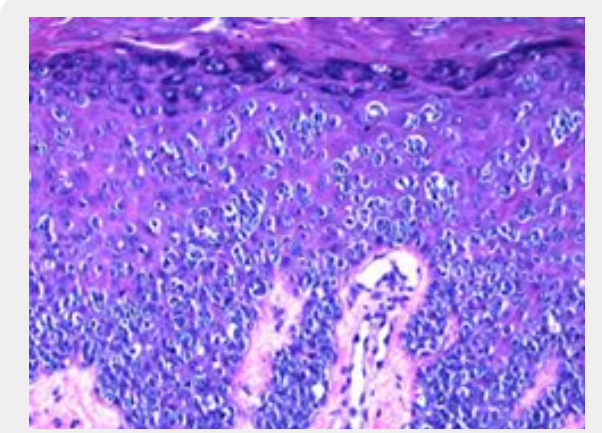

Figure 6: *Merkel Cell Carcinoma -In situ with an intact basement membrane*

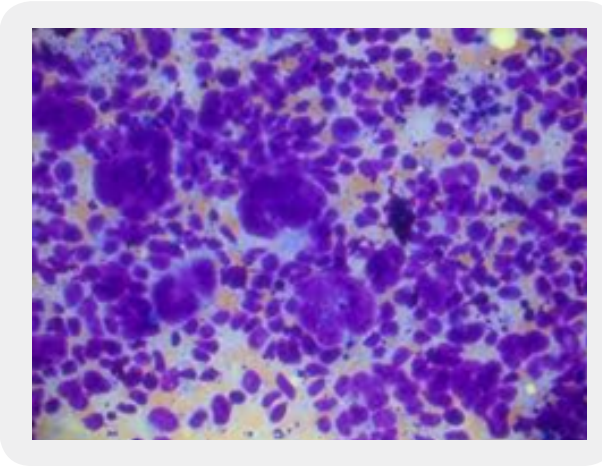

Figure 7: *Merkel Cell Carcinoma- aggregates of small round cells-aspiration cytology*

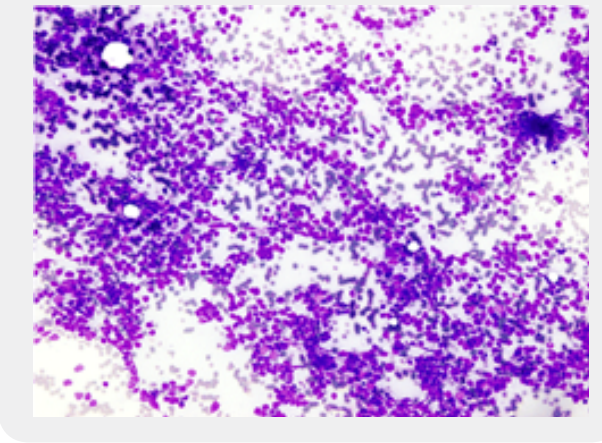

Figure 8: *Merkel Cell Carcinoma- random spheroid cell clusters- aspiration cytology*

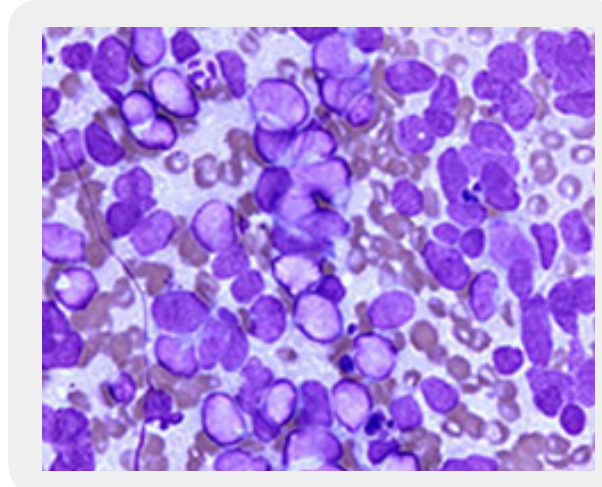

Figure 9: *Merkel Cell Carcinoma- cellular globules, indistinct cytoplasm-aspiration cytology*

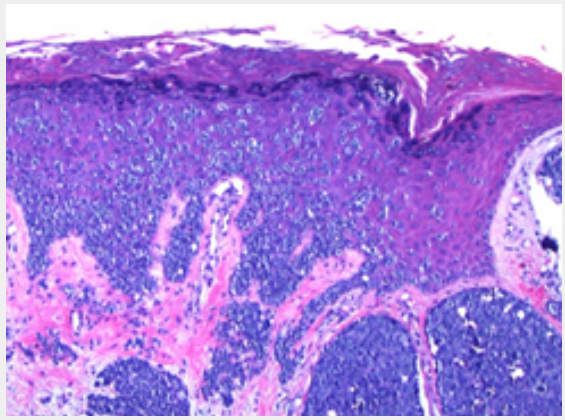

Figure 10: *Merkel Cell Carcinoma- in situ tumour with epidermotropism*

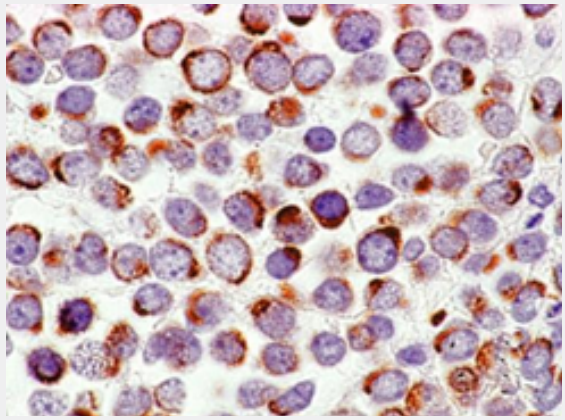

Figure 11: *Merkel Cell Carcinoma-perinuclear CK 20 immune staining*

Radiographic Elucidation

Fluorine-18- fluorodeoxyglucose positron emission tomography (FDG-PET & PET -CT) may be employed for staging the accelerated, metabolically active neoplasm [9,10]. Positron emission tomography (PET) delineates a 90% sensitivity and 98% specificity for the metabolically active neoplasm. The physiologically metabolic brain metastasis may not be adequately evaluated [9]. Analogy of the fluorodeoxyglucose positron emission tomography(FDG-PET), in contrast to the ultrasound, computerized tomography and magnetic resonance imaging, elucidated an enhanced specificity for the positron emission (96.2% versus 89.1%) with a reduced sensitivity (85.7% versus 95.5%) [1]. Contrary to the traditional positron emission (PET), the PET-CT may elaborate an effective and precise anatomic localization of the lesion. Though a positron emission scan (PET) is beneficial in exposing metastatic disease, it may not enhance patient survival [9,10]. FDG -PET is an advantageous modality for diagnosing Merkel cell carcinoma as it may analyze the cellular

proliferation and elevated glucose uptake of the tumour [9]. Modalities such as F-DOPA or conventional PET may also be employed. The somatostatin receptor scintigraphy may elucidate false positives and negatives. Thus these techniques may not be beneficial.

Obscure Primary Tumour

A pathologic lymph node enlargement with an unknown cutaneous lesion may be defined as an obscure primary skin tumour. A regional inguinal lymph node metastasis may be discerned subsequent to the spontaneous retrogression of the primary tumour. The implicated lymph nodes may arise from an undiscovered skin lesion, a de novo malignancy, a primary in the nodal basin/ site or from the secondary involvement of a sub-dermal lesion [11]. Up to 12% individuals may elucidate regional or remote metastasis with an obscure primary tumour. The management of an obscure primary tumour is inadequately scripted with insufficient data. The initial investigation should include a staging PET-CT and a comprehensive skin exam abutting the incriminated lymph node drainage and the discovery of the neoplasm by an aspiration cytology (FNAC) or an excision biopsy [1].

Therapeutic Options

of an unknown primary are identical to an analogous, staged and established primary condition. Patients with an obscure primary tumour present with a survival advantage (36.4% versus 76.9%) [11].

The Sentinel Lymph Node Biopsy

The international committees and institutions may differ on the therapeutic methodologies and the employment of the sentinel lymph node biopsy for a diagnostic tumour staging, in contrast to the elective radiation or a comprehensive neck dissection. Sentinel lymph node evaluation is beneficial for the primary melanomas of the head and neck. However, the advantage of the procedure in the categorization of Merkel cell carcinoma is dubious [12]. Merkel cell carcinoma is an aggressive neoplasm with extensive localized, distant and in-transit lymph node metastasis. The clinical or radiologic N0 neck may present with undiscovered micro-metastasis to the draining lymph nodes. Determination of metastasis in the first lymph node (sentinel) may indicate the occurrence of malignancy in the lymph node pool. With a positive sentinel lymph node, an estimated one fourth (25%) probability arises of localizing the micro-metastasis in the remaining lymph nodes [1]. If the sentinel lymph node is negative for micro-metastasis, the existing residual lymph node pool requires an evaluation. A comprehensive neck dissection or radiation therapy may also be recommended for a metastatic sentinel lymph node. A clinical N0 stage may be an unsatisfactory pointer of absent nodal metastasis as 23%-32% of N0 necks may carry occult metastatic disease [1]. Attributes of histological prognosis such as tumour depth or ulceration or mitotic figures may not be enunciated by the tumour. Features such as lymphatic and vascular invasion, tumour size > 2cm, tumour thickness and mitotic rate may be implicated in predicting tumour outcomes. Minimal probabilities of tumour metastasis may, however, depict neck metastasis in a substantial number of cases. The application of sentinel lymph node analysis may diminish the prevalence of neck dissection and adjuvant therapy. An elective radiation of comprehensive N0 regional nodes may be recommended, in the absence of the lymph node biopsy,

considering the incidence of regional metastasis [1]. Since the head and neck has an exclusive lymphatic drainage, multiple sentinel lymph nodes may be situated within the various lymph node groups.

Therapeutic Decisions

The habitually aggressive Merkel cell carcinoma responds appropriately to multimodal therapy. A suitable preliminary therapy is an adequate loco regional control achieved by a combination of excised one centimetre wide surgical perimeter, radiotherapy and regional lymph node dissection. Adjuvant radiotherapy may be employed for non-eradicable neoplasm [1]

Primary Tumour

A substantial surgical perimeter may be employed with a wide, localized excision. Amputation of the surgical periphery by > 1cm may not reduce the localized relapse in miniature tumours. A one centimetre tumour perimeter may justify the resection of tumours < 2cm in diameter or a 2cm margin may be endorsed for tumours >2cms magnitude [13]. The investing fascia or the peri-cranium with a perimeter for a frozen section may be incorporated in the base of the incision [13]. An aggressive loco-regional management may be mandated. Prompt reconstruction of the surgical incision is desirable - a simple closure may be accomplished following the conclusive histopathology. Tumour implicated surgical perimeter following a complicated reconstruction may be managed by singular radiotherapy, though concomitant tumour excision and adjuvant radiation may enhance the loco-regional outcome [1].

Lymph Nodes

The regional lymph nodes necessitate therapy as the nodes are prone to occult metastasis. The patient survival may decimate if the primary tumour is singularly addressed. Possible treatment may involve elective irradiation of stage N0 necks, a surgical neck dissection or a sentinel lymph node evaluation in order to initiate and instruct the therapies. Stage N0 neck may be addressed by mono-therapy. A lack of treatment of the lymph node group in a clinical N0 neck may terminate in a 33.3% decline of survival and is greater than N0 necks subjected to elective radiotherapy [1]. The lymph nodes may depict a 73%-78% macroscopic eradication of disease with singular radiotherapy. With concurrent cervical lymph node dissection and radiotherapy, a superior outcome may be delineated. Neoplasm with distant metastasis may be administered concomitant radiotherapy, chemotherapy and surgery [13]. Elective neck dissection, optional radiotherapy and an sentinel lymph node assessment are suitable for alleviating the lymph node group and regulating the regional disease.

Functions of Chemotherapy

Tumour relapse, lymph nodes metastasis, neoplasm > 1cm and a malignant surgical perimeter are indications for the employment of agents such as carboplatin or etoposide. Surgery and radiation may elucidate analogous results as with concurrent chemo-radiation. The 5 year survival, loco- regional disease containment or distant metastasis may not be significantly impacted with solitary chemotherapy [14].

Radiotherapy: may be applicable for non-eradicable tumours as chemotherapy may not be beneficial in curtailing the regional or distant disease emergence.

Sequels to Therapy: Merkel cell carcinoma exhibits a 5 year survival of 30-64% for undetermined neoplasm of the body. The estimates may differ with distant and regional metastasis [1]. An approximate 9 month survival period is achieved with the detection of distant metastasis [14].

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