Review Article

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Management of Metastatic Cervical Lymphadenopathy with Unknown Primary

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Abstract

Neck lymph node metastases from occult primary constitute about 5%-10% of all patients with carcinoma of unknown primary site. Metastases in the upper and middle neck (levels I-II-III-V) are generally attributed to head and neck cancers, whereas the lower neck (level IV) involvement is often associated with primaries below the clavicles. Diagnostic procedures include a careful clinical evaluation and a fiberoptic endoscopic examination of the head and neck mucosa, biopsies from all suspicious sites or blindly from the sites of possible origin of the primary, computerized tomography scan, and magnetic resonance. The most frequent histological finding is Squamous Cell Carcinoma, particularly when the upper neck is involved. Thoracic, and abdominal primaries (especially from lung, oesophagus, stomach, ovary or pancreas) should be sought in the case of adenocarcinoma and involvement of the lower neck. Positron emission tomography with fluoro-2-deoxy-D-glucose allows detection of primary tumour in about 25% of cases, but this procedure is still considered investigational. Therapeutic approaches include surgery (neck dissection), with or without post-operative radiotherapy, radiotherapy alone and radiotherapy followed by surgery. In early stages (N1), neck dissection and radiotherapy seem to have similar efficacy, whereas more advanced cases (N2, N3) require combined approaches. The extent of radiotherapy (irradiation of bilateral neck and mucosa versus ipsilateral neck radiotherapy) remains debatable.

Keywords: Unknown Primary; Diagnosis; Surgery; Radiotherapy.

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Introduction

Carcinoma of Unknown Primary (CUP) are metastatic solid tumors (hematopoietic malignancies and lymphomas excluded) for which the site of origin is not identified despite history, physical examination, imaging, blood and urine studies and thorough histologic evaluation.

Cervical nodal metastases with unknown primary accounts for 3-9 % of head and neck cancers. The occurrence of CUP to cervical lymph nodes is six times more common in men than women. Metastases are located in the jugular chain in most patients [1]. Patients are usually smokers and heavy drinkers who have noted the mass for several months.

When evaluating a patient with a neck mass suspicious for cervical nodal metastases, one cannot overemphasize the need for a systematic, comprehensive medical history and physical examination of the head and neck. The salient features in the history and physical examination of a patient presenting with a cervical nodal mass are as follows:

Clinical History

- Otalgia
- Epistaxis
- Trismus
- Dysphagia
- Odynophagia
- Dysarthria
- Hoarseness
- Dyspnea
- Weight loss or other constitutional symptoms

Past History

Previous history of malignancy

Previous history of radiation exposure

Social History

Tobacco use

Alcohol use

Occupational exposures, including sun exposure

Family History

Family history of malignancy

Physical Examination

- Overview of functional status and nourishment
- Comprehensive examination of the skin of the scalp, face and neck
- Otoscopy
- Anterior rhinoscopy
- Test maximal interincisal distance
- Assess dentition
- Assess voluntary movement of tongue
- Examination of oral cavity and oropharynx
- Indirect mirror laryngoscopy or fibreoptic
- Nasopharyngolaryngoscopy
- Examination of thyroid gland, salivary glands
- Examination of all cervical lymph node levels
- Examination of the chest, breast, arms, abdomen and the genitalia

The patients are usually in the age group of55-65 years with an exception of papillary carcinoma of the thyroid. Most head and neck cancers are more common in males except thyroid malignancies. Typically the lump is painless and sloe growing with new lumps appearing over time. The patients may have symptoms related to the primary with are mentioned above. Head and neck cancers usually do not cause significant anorexia or weight loss.

On examination, the site of the lymph nodes is indicative of the primary tumor.

Table: Relationship between level of lymph node and possible location of primary tumor [2]

Level of lymph nodes	Location of primary tumor
Level i Submental Submandibular	Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, lower lip Oral cavity, anterior nasal cavity, soft tissues and structures of mid face, submandibular gland, maxillary sinus.
Level II	Oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, parotid
Level III	Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx
Level IV	hypopharynx, larynx, cervical oesophagus
Level V Level VI	nasopharynx, oropharynx, Thyroid gland, larynx/apex of pyriformfossa,cervical oesophagus

Involved nodes are single in 75% of patients, multiple but ipsilateral in 15% and bilateral in 10%[1]. Multiplicity is often associated with adenocarcinoma. Fixed nodes are associated with an advanced primary lesion. Fixed nodes on one side of the neck have poor prognosis than mobile bilateral neck nodes.

Carcinoma of the nasopharynx, hypopharynx, base of the tongue, larynx and tonsil present with upper cervical node metastasis as the first manifestation of disease in 30-50% cases [1]. These sites harbor the primary 95% of the time when the primary site is ultimately found after initially manifesting as CUP to neck nodes.

About 65% of the metastases to the lower cervical nodes originate in sites below the clavicle, most commonly the lung. Supraclavicular nodal involvement almost always indicates disease which is far advanced. The primary site is the lung, breast or gastrointestinal tract.

Should the primary tumor prove elusive during the physical exam, particular attention must be directed to sites of the head and the neck where a primary lesion may remain occult, for example the tonsil and the base of tongue. The fiberoptic laryngoscope has proven invaluable in examining and photographically documenting the nasopharynx, laryngopharynx and pyriform sinuses in the office setting.

Histologic Diagnosis

The diagnosis of metastatic cancer is made histologically, and so pathologic confirmation should be obtained for clinically and radiologically

suspicious nodes, when other non-invasive diagnostic modalities fail to demonstrate any hint of primary cancer.

Fine Needle Aspiration Cytology

Fine-needle aspiration (FNA) is an accurate, reliable procedure with minimal morbidity and may be performed in an outpatient setting, allowing for quick cytologic interpretation of suspicious neck masses. A diagnosis of metastatic epidermoid carcinoma may be distinguished from other malignant conditions such as lymphoma, adenocarcinoma, or thyroid carcinoma. In addition, benign conditions, such as tuberculosis, chronic lymphadenitis, and hyperplastic lymph nodes, may be ruled out [3]. Sensitivity and specificity of FNA of masses of the head and neck have been reported as 97 and 96% respectively. Immunohistochemical staining for markers such as thyroglobulin, calcitonin, cytokeratin and mucin may be performed on the cellular aspirate to classify the histology if necessary.

Masses at sites in the head and neck inaccessible on routine examination e.g. retropharyngeal lymph nodes) may be sampled under image guidance using CT, MRI, or ultrasonography.

An important caveat to remember regarding FNA concerns misinterpretation of cytologic results. A finding of epithelial cells in the presence of clear or straw-colored fluid on aspiration is occasionally misinterpreted as branchial cleft carcinoma, rather than cystic degeneration of a metastatic lymph node which is the more likely diagnosis in an adult. Metastases from squamous carcinoma of certain sites, such as the tonsil or base of tongue, and from well-differentiated thyroid carcinomas are often cystic and therefore more likely to such misinterpretation. Repeat fine-needle aspiration, using image guidance if appropriate, should be considered following an initial non-diagnostic FNA. A metastatic lymph node with a necrotic center may occasionally yield a non-diagnostic specimen because of cellular debris in the hypoxic core, with viable tumor cells undetected at the periphery of the lymph node. The following table represents the histology of neck node metastases from unknown primary site [3].

Lymph node	SCC	Adenocarcinoma	Undifferentiated carcinoma	Other
Upper to middle cervical	60%	10%	25%	5%
Lower cervical	45%	5%	40%	10%
Supraclavicular	20%	35%	45%	

Diagnostic Imaging

In patients with cancer of the neck, imaging of cervical lymphatics is almost always performed and it alters the estimated clinical stage in 20% to 30% of patients [2]. In the clinically N_0 neck, imaging is used to evaluate subclinical disease and to verify the absence of contralateral disease. In the clinically N+ neck, imaging should be considered to assess resectability in advanced nodal disease, to assist in the detection of primary tumors not identified on physical examination, and to act as a baseline study for palpable tumors when non-surgical therapy is contemplated. It is also useful in patients with metastatic lymph nodes at sites typically inaccessible to routine physical examination, such as the parapharyngeal space.

Imaging modalities currently available in routine clinical practice include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) scans, and positron emission tomography (PET) scans. Other modalities, such as single positron emission computed tomography (SPECT) scans are currently under evaluation and presently have little application in clinical practice. PET / CT is often useful if the CT or MRI fails to identify the primary site.

Relevant imaging should be undertaken prior to manipulation of the neck nodes in order to maximize the information obtained from these studies. Inflammation and obliteration of tissue planes from a recent biopsy may not only create difficulty in interpreting anatomic relations, but also cause artefacts on functional imaging studies such as PET scans.

Computed Tomography and Magnetic Resonance Imaging

Imaging studies provide valuable supplemental information of regional lymph node status as well as may herald the position of the primary tumor not amenable to physical examination. Although the presence of metastatic involvement of a lymph node is a histologic, not a radiologic diagnosis, there are characteristic changes apparent on CT and MRI suggestive of metastatic squamous cell carcinoma,

including rim enhancement, central necrosis, and nodal size in excess of lcm in diameter. Lymphoma of the head and neck typically presents radiographically as solid, homogeneous lymph nodes that are iso-intense with muscle. Despite the advantages afforded by these imaging modalities, limitations of both CT and MRI include difficulty differentiating reactive soft tissue inflammation or postradiotherapy fibrosis from residual or recurrent carcinoma. Furthermore, cervical lymph node size does not always correlate with the presence of tumor involvement. Although larger metastatic lymph nodes indicate greater tumor volume, a small lymph node less than lcm in diameter may still harbor foci of tumor cells. Conversely, lymph node size greater than 1cm in diameter does not automatically herald metastatic cancer, since reactive lymphadenopathy following infection, inflammation or surgical intervention may result in lymph nodes of such size. Another disadvantage of CT is that scatter artefact from dental fillings may result in poor image resolution.

Ultrasonograpy

Ultrasonography is a useful diagnostic, imaging modality, which has been reported to be extremely sensitive in accurately characterizing cervical lymph nodes metastatic for SCC as well in assessing the thyroid gland for suspicious areas[4]. Advantages of ultrasonography include its relative low cost, easy onscreen nodal measurement, low patient burden and facility for guided fine-needle aspiration. In spite of its high sensitivity (97%), a potential confounding factor in Ultrasound examination of cervical lymph nodes is a low rate of specificity (32%) for the evaluation of metastatis[4]. Another disadvantage of ultrasonography is that the results are dependent on the experience of the investigator.

Positron Emission Tomography

PET scanning is a functional imaging modality that measures the metabolic rate of tissue using radioisotopes and is based on the principle that malignant tumors have higher metabolic rates compared to normal tissues. Glucose metabolism can be characterized following the administration of radiolabeled 18 F-2-fluoro-2-deoxy-D-glucose (FDG). Although 18 FDG-PET imaging lacks the anatomic detail afforded by CT or MRI scans, it relies on metabolic activity from glucose transport, rather than gross lymph node or primary tumor size, to indicate tumor foci. Sites of increased metabolic activity are reflected on PET scans by higher body weight-based standardized uptake values (SUV_{bw}). Such a physiologic study aims to reduce the false-negative rate of CT and MRI by identifying primary tumor and metastatic lymphnodes smaller than 1 cm. However, like these conventional imaging techniques, FDG-PET is prone to the false-positive tendency of suggesting erroneously that reactive lymphadenopathy may be metastatic cancer.

Evaluation of 18FDG-PET for accurately identifying nodal metastases demonstrates results comparable to those of CT or MRI Prospective comparison of PET with CT, MRI, and ultrasound demonstrated superior sensitivity and specificity of "FDG-PET for detecting cervical lymph node metastases and occult primary" [5]. Other reports have suggested that PET is particularly useful when the findings on conventional CT imaging are equivocal for nodal metastases or occult primary [6]. The lowerlimit in terms of resolution of 18FDG-PET for detection of malignant site has not been clearly delineated, but accurate identification of tumor rests of SCC less than 5mm in diameter has been reported.

Newer technologies are aimed at improving accuracy by combining functional information from FDG -PET with the anatomic resolution of MRI or CT scans.

Some studies have suggested a beneficial contribution of "FDG-PET in elucidating the primary tumor." while other reports have concluded that it did not significantly improve detection of the primary tumor and was hindered by false-positive results.[7] However, an area where PET seems particularly beneficial is the detection of recurrent tumor following radiation therapy. To the extent that PET imaging is predicated on tissue metabolism, tumor cells should theoretically possess greater metabolic activity and express increased levels of glucose transporters, compared to edematous, scarred, or most normal tissues.

Open Biopsy

The prognostic impact of open biopsy of a metastatic neck node during the work-up of patient with squamous cell carcinoma of the head and neck remains controversial. Unfortunately, data from retrospective reviews[8,9] have shown 'no adverse impact on overall outcome,' are quoted to justify the practice. III-planned biopsy incisions create unwarranted difficulties with surgical planning during the definitive surgical operation. If the patient needs a subsequent neck dissection it may need resection of structures that would ordinarily be spared, in order to fully excise contaminated tissue planes and scar from the previous open biopsy.

Modality	Advantages	Disadvantages	Sensitivity	Specificity
Ultrasound	Noninvasive Inexpensive Useful for guided Biopsy	Operator-dependent, Poor for deep nodes	69-78%	30-56%
CT	Noninvasive Relatively inexpensive Easy to perform Easy to interpret	Exposure to ionizing radiation ,Reactions to iodine, Iodine interferes with thyroid work	40-68%	78-92%
MRI	NoninvasiveMultiplanar imaging No radiation Perineural spread	Expensive Subject to motion artifact	55-66%	82-92%
PET	Higher sensivity and specificty	Expensive Limited availability	63-100%	90-94%

In addition, therapy may be delayed if the patient develops wound complications from the biopsy and there have been anecdotal reports of fungation of the tumor through the biopsy site. An open biopsy of a suspicious neck node should therefore be discouraged in most instances.

The open biopsy of the suspect node should be done only when:

- FNA cytology fails to reveal a diagnosis.
- Panendoscopy fails to reveal a primary site.
- Lymphoma is suspected.

In cases of indeterminate or equivocal histology, Immunoperoxidase staining and other special studies may be helpful. Immunoperoxidase antibodies are either monoclonal or polyclonal and are directed against cell components or products which include enzymes (e.g., prostatic acid phosphatase, neron-specific enolase(NSE) normal tissue components (e.g., keratin, desmin, vimentin,neurofilaments, leukocyte common antigen (LCA) hormones and hormone receptors (e.g., estrogen receptor *ER+, progesterone receptor *PR+), oncofetal antigens (e.g., a-fetoprotein [AFP]), carcinoembryonic antigen (CEA),and other substances (e.g., S 100 protein, chromogranin).

Endoscopy

When imaging studies and a detailed clinical examination of the head and neck fail to reveal a primary, examination under anaesthesia should be done. The examinations which are done include nasopharyngoscopy, laryngoscopy with tracheoscopy, bronchoscopy and esophagoscopy. All suspected lesions and random areas of apparently normal tissue at the base of the tongue, pyriform fossa and the nasopharynx are subject to biopsy in search of a primary source. Ipsilateral tonsillectomyhas a better yield thantonsillar fossa biopsy and is often performed as well. If a primary is found, treatment is planned with consideration of the primary site and neck metastasis.

Staging and Prognosis

The staging system of regional metastases to cervical lymph nodes established by the 7th American Joint Committee on Cancer (AJCC) is outlined in the table.

- N_x Regional lymph nodes cannot be assessed
- N_0 No regional lymph node metastasis
- N_1 Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension
- N_{2a} Metastasis in a single ipsilateral lymph node more than 3cm but not more than 6cm in greatest dimension
- N_{2b} Metastasis in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension
- N_{2c} Metastasis in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension
- N_3 Metastasis in a lymph node more than 6 in greatest dimension

The prognostic factors which are considered are as follows:

1. N stage of the disease

2. Location in the neck

As a general rule, the incidence of distant metastases increases with, and prognosis worsens with more inferiorly located cervical metastases.

3. Histopathology

Adenocarcinoma is associated with a poor prognosis than the SCC metastases [2].

4. Whether the primary site is ever found

The prognosis is much better when the primary tumor never becomes manifest [1].

The extracapsular spread (ECS) of carcinoma in cervical lymph nodes, which is probably the single-most important predictor of poor prognosis has not been included as a predictor of prognosis as per the current TNM staging. However, multivariate analysis has demonstrated that extra-capsular spread is an independent predictor of survival.

Principles of Treatment

The treatment for a CUP with neck node metastases is primarily directed towards the management as adenocarcinoma is usually associated with advanced disease and has a poor prognosis.

Metastasis from Squamous Cell Carcinoma

The management of the neck in these patients follows similar principles as those in patients with a clinically positive neck and an identified primary i.e. locally advanced. As a general rule, even patients with Ni diseasefrom an unknown primary benefit from neck dissection rather than radiation alone because the additional pathologic information that becomes available may help plan further treatment. However, metastatic lymph nodes at level IV are not recommended for neck dissection if the primary site is believed to lie below the level of the clavicles,unless the patient complains of compressive symptoms.Treatment must be comprehensive at the outset because salvage therapy has a low yield.

Surgery

Traditional surgical management of cervical nodal metastases entails comprehensive neck dissection with or without preservation of certain anatomic structures, such as the spinal accessory nerve (XI), internal jugular vein (UV), and the sternocleidomastoid muscle (SCM) when technically and oncologically feasible. There has been a continuing trend towards more selective procedures, sparing not only the XI, UV, and SCM, but also lymph node groups thought to be at low risk for metastases in cases where the primary has been identified.

The standard type of neck dissection employed for cervical metastases with an occult primary involves comprehensive neck dissection, with or without preservation of the spinal accessory nerve.

Classification of neck dissections

The classical radical neck dissection is the gold standard of lymphadenectomy for clinically apparent lymphatic metastases and consists of surgical clearing of nodal lymphatics from all five levels of the from the inferior border of the mandible superiorly to the clavicle inferiorly, and from the lateral border of the sternohyoid muscle, hyoid bone, and contralateral anterior belly of the digastric muscle, medially, to the anterior border of the trapezius muscle laterally. Included in the specimen with the cervical lymphatic s are the sternocleidomastoid and omohyoid muscles, spinal accessory nerve, internal jugular vein, submandibular gland and tail of the parotid.

Functional morbidity associated with radical neck dissection arises primarily from sacrifice of one or more of the following structures: the spinal accessory nerve, the sternocleidomastoid muscle, and the internal jugular vein. Sacrifice of the spinal accessory nerve results in loss of innervation to the trapezius muscle. The patient is unable to abduct the arm fully and suffers from chronic Pain and stiffness of the shoulder. Destabilization of the shoulder results in a 'winged scapula ' deformity and increases the risk for sternoclavicular subluxation. Resection of the sternocleidomastoid muscle gives the appearance of platysmal handing and removes a layer of cover for the carotid artery, potentially important in the irradiated neck. Sacrifice of the internal jugular vein may result in significant facial edema and possibly neurovascular compromise, particularly following bilateral radical neck dissection and laryngopharyngectomy, that disrupts collateral drainage into Batson's prevertebral venous plexus.

Comprehensive neck dissection:

1. Classical radical neck dissection (RND)
2. Type I modified radical neck dissection (MRND I)
3. Type II modified radical neck dissection (MRND II)
4. Type III modified radical neck dissection (MRND III)
5. Extended radical neck dissection (ERND)

Comprehensive Neck Dissection

Comprehensive neck dissection refers to those procedures that remove cervical lymph nodes from

levels I through V. This category includes the aforementioned radical neck dissection, as well as the following modifications to this technique. Type I modified radical neck dissection selectively preserves the spinal accessory nerve. Type II modifiedradical neck dissection preserves the spinal accessory nerve and sternocleidomastoid muscle but sacrifices the internal jugular vein. Type III modified neck dissection (functional neck dissection) preserves the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. Extended radical neck dissection is also included in the category of comprehensive neck dissection . In addition to those structures removed in the standard radical neck dissection, extended radical neck dissection includes nodal groups not typically removed during the dissection, such as retropharyngeal or parapharyngeal lymph nodes. Alternatively, extended radical neck dissection includes non lymphatic structures not typically removed during the dissection, such as the carotid artery or hypoglossal nerve. The routine reporting of structures preserved or resected in comparison to the standard neck dissection is paramount for all procedures included in the category of comprehensive neck dissection.

'Functional neck dissection', as popularised by Bocca, is the same as type III MRND, except that as originally described Boccadid not excise the submandibular salivary gland.

Selective Neck Dissection

In contrast to comprehensive neck dissections, procedures in this category selectively remove cervical lymph node groups at certain levels, while preserving the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. Supraomohyoid neck dissection removes lymph nodes at levels I, II, and III. Lateral neck dissection (jugular neck dissection) removes lymph nodes at levels II III, and IV. Posterolateral neck dissection removes lymph nodes at levels II through V, as well as suboccipital nodes and postauricular nodes. The selective neck dissection are usually opted for cases with a known primary and more often favoured for N1 disease with a single, small, mobile node.

Complications of Surgery

Sacrifice of the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein during radical neck dissection results in functionalmorbidity and cosmetic deformity. Air embolismrefers to inadvertent entry of air into the cervical venous system and may occur following laceration of the internal jugular vein. Clinical signs include a precipitous drop in systolic blood pressure, cardiac output, and oxygen saturation, and an audible 'to-and-fro' murmur. Further operating should cease immediately, and the following steps instituted: nitrous inhalation anesthesia should be terminated and the patient ventilated with 100% oxygen; the patient should be positioned in the left lateral decubitus position to trap the air embolus in the right atrium; aspiration of the air embolus may then be performed through cardiac puncture or central venous catheterization.

Chylous fistulae may be prevented by meticulous identification and ligation of the thoracic duct prior to division. The terminal branches of the thoracic duct on the left neck are at risk for inadvertent injury during dissection of lymph nodes at level IV. Intraoperativechylous leaks may be recognized by the extravasation of milky fluid at the lower neck, particularly with increased intrathoracic pressure by the Valsalva maneuver. Recognition of chylous fistulae intraoperatively should be treated immediately with suture ligatures orhemoclips. Postoperative chylous fistulae manifest with marked increase in output of milky fluid in suction drains. Conservative management of postoperative chylous fistulae includes cessation of wall suction, with drains on self suction only, pressure dressings; and low-fat nutritional support. Failure of conservative measures warrants return to the operatingfor surgical intervention.

Radiation Therapy

General principles of radiotherapy include; the generally favorable radio-responsiveness of most early stage head and neck squamous cell carcinomas; a well oxygenated environment provides an ideal setting for therapeutic radiation; invasion of bone or deep muscle portends a poorer response to radiotherapy; and neck dissection, with or without adjuvant irradiation, is the preferred treatment for large cervical metastases. Heterogeneity among radiosensitivity may be due to several factors, including tumor volume, intrinsic cellular radiosensitivity, clonogen density, and hypoxia. In light of this heterogeneity, molecular markers to predict radiosensitivity have been investigated, including Ki-67 immunohistochemistry, as well as assays for p53 mutation, or bc1-2 expression. The prognostic significance of such molecular markers has yet to be determined.

Definitive Radiation Therapy

Definitive radiotherapy shares comparable results with surgical treatment for NO and Ni neck disease. SCC arising from certain subsites in the head and

neck is particularly radiosensitive, such as the nasopharynx and lymphoepithelial carcinoma of the tonsil. Even advanced cervical metastases from these primary tumors respond well to definitive radiotherapy, reserving planned neck dissection for residual disease. Although a variety of fractionation schemes may be employed, definitive radiotherapy generally delivers 60-70 Gy through a shrinking field technique over 6-7.5 weeks.

In theory, RT fields should encompass the undiscovered primary tumor encompassing the nasopharynx, oropharynx, hypopharynx and both sides of the neck.

After completion of RT, clinical assessment is done at 4-8 weeks. If there is suspected progression, then CT and/or MRI with contrast is performed. If the neck is positive, neck dissection should be done. If disease is stable or has responded, PET-CT should be done after a minimum of 12 weeks. If there are no lymph nodes or nodes<1cm and PET negative then one can observe the patient. If there are lymph node < 1 cm and PET positive, then one can either observe them for any increase in size or increased uptake on subsequent PET scans, or consider an ultrasound guided FNA followed by surgery as required, or do a neck dissection straightaway. When the lymph node is more than 1 cm and PET negative, the above protocol may be followed. Also, depending on the initial nodal size, the surgeon may consider a neck dissection. If the lymph nodes are greater than 1cm and PET positive, then a neck dissection is recommended. If PET is unavailable, then CT and/or MRI with contrast is performed about 6-12 weeks after treatment. If they are negative for nodes then patient is observed, but if the nodes are positive then a neck dissection is done. Neck dissection is the preferred modality for salvage. Irradiation for surgical failure in the neck is associated with worst survival rates compared to salvage neck dissection following failed radiotherapy.

Adjuvant Radiation Therapy

Advanced cervical lymphatic metastasis (N_2 or N_3) from most sites of the head and neck usually require a combination of neck dissection and radiotherapy. Early reports combining neck dissection andpreoperative radiation therapy demonstrated reduction in regional recurrence; particularly for advanced nodal disease.The final report of study of the Radiation Therapy Oncology Group did not demonstrate a statistically significant difference in survival between preoperative versus postoperative radiation therapy for advanced stage, although Loco-regional control was improved in the patients receiving postoperative radiation therapy [10]. The standard timing of radiation therapy when combined with neck dissection is currently an adjuvant setting. The advantages of delivering radiation therapy after surgery include the ability to deliver a greater dose of radiation in the postoperative setting (usually 60-70Gy over 6-7 weeks), than preoperatively (typically 45Gy over 4-5 weeks); and the additional information gleaned during neck dissection to plan for appropriate portals of radiation therapy, based on the surgical extent of tumor. Potential disadvantages associated with postoperative radiation therapy include possible contamination of tissue planes with tumor during surgical manipulation, or delayed wound healing from complications following neck dissection may delay the adminstrationof radiation therapy. The ideal time to initiate postoperative radiotherapy has been recommended as between 4 and 6 weeks following surgery, in light of the risk for increased locoregional failure.

Adjuvant radiation therapyhas been shown to improve loco-regional control and survival in the presence of extracapsular spread or positive resection margins following surgery [11]. Postoperative radiotherapy however should not be construed as a panacea for an inadequate operation. Silver clips placed intraoperatively are useful to mark the extent of gross residual disease if adjuvant radiation therapy is planned, in order to facilitate planning for electron boost.

Neck dissection with brachytherapy is indicated for patients with nodal recurrence or gross persistent disease following previous irradiation to the neck.

Complications of Radiation Therapy

In addition to side-effects of mucositis and xerostomia, major complications of external beam radiotherapy for SCC of the oral cavity and oropharynx include osteoradionecrosis, pathologic fracture, or ulceration of mucous membranes. The risk of osteoradionecrosisnecessitates fracture, dental care prior to the initiation of radiotherapy.

Concurrent Chemoradiation Therapy

Concurrent chemotherapy and radiation therapy has been demonstrated to provide improved disease control and survival rates over sequential chemoradiation or radiation therapy alone, when utilized in an organ preservation approach for advanced SCC of the head and neck. However,

despite the improved benefit of concurrent chemoradiation, an area for which very little data exists is the optimal management of nodal metastases in a concurrent approach. Overall survival and disease-free survival were also improved in the concurrent chmoradiatioa arm compared to the arm treated with radiation therapy alone [12]. The addition of chemotherapy however was not found to improve the rate of distant metastases.

For fixed unresectable nodes and for metastasis with occult primary, primary systemic therapy and concurrent radiotherapy, include the following drugs:

1. *Cisplatin alone (preferred)*

   100mg/sq.m ,IV ON day 1. Given in 21 day cycles for 3 cycles with RT.

2. *Cetuximab*

   400 mg/sq.mIV loading dose given on the week before RT starts, then 250 mg/ sq.mIV weekly for 7 days

3. *Cisplatin/infusional 5-FU*

Management of Cup to Cervical Lymph Nodes [13]

Early stage (N_1) regional lymph node metastasis of the upper or middle cervical group may be treated equally well with surgery (particularly when the metastasis <3 cm) or radiation therapy. A modified radical neck dissection or a functional neck dissection usually suffices, without need for RND. Indications for adjuvant RT includemetastatic lymph node size greater than 3cm, multiple positive nodes or extracapsular lymph node extension.

For more advanced cervical metastases of N_2 and N_3, combined therapy with surgery and postoperative radiation therapy is indicated. In N_2 disease, surgery may vary from MRND to RND based on the size, mobility and anatomic site of the metastatic nodes. However for patients with N_3 disease, RND is most often required. The presence of fixed nodes precludes surgery.

For unresectable disease, radiation is recommended, often with concurrent chemotherapy followed by salvage surgery if required.

Lymphoepithelioma or poorly differentiated SCC with a strong suspicion of nasopharyngeal origin is usually treated with radiotherapy to the nasopharynx and both sides of the neck.

For SCC of lower cervical or supraclavicular nodes or adenocarcinomas administer RT alone, as the survival rates are poor no matter what is done; due to the systemic tumor dissemination present in these cases. The goal of treatment is local control of the disease. However in the presence of metastasis only in the neck, surgery along with post-operative radiotherapy may be recommended. When adenocarcinomatous lymph nodes of level I-III are found, a neck dissection with parotidectomyis sometimes indicated. This is followed by adjuvant radiation if indicated by the pathological status of the neck mentioned above.

Results of Treatment

Survival outcomes are influenced by clinical stage at time of diagnosis and the presence of extracapsular extension [3]. No significant 5 year survival difference has been seen between patients treated with chemotherapy with radiation alone when compared to patients who also received surgical treatment.

- Patient with upper cervical nodal metastases. The 5 year survival for all patients is 50% if the primary tumor is eventually found and 60% if it is never found.

  1. Stage N_1 or N_{2a}: The 5 and 10 year survival rates are both 70-80%. At 10 years of treatment the risk of finding a primary site is 30%, which is the same as the odds of developing a second cancer after successful treatment.

  2. Stage 2_b: Variable survival rates reported.

  3. Stage N_3: the 5 year survival rate is about 20%.

- Patients with low cervical or supraclavicular lymph node metastases: the 5 year survival rate is 5% (median survival time is 7 months).

Follow-Up Recommendations [13]

1. History and physical examination
   - Every 1-3 months for first year
   - Every 2-4 months for second year
   - Every 4-6 months from 3rd to 5th year
   - Every 6-12 months, after 5 years
2. Post-treatment baseline imaging of the treated neck is recommended within 6 months of treatment. And further imaging is done as indicated on signs/symptoms. It is not routinely recommended for asymptomatic patients.
3. Chest imaging as clinically indicated.
4. Thyroid-stimulating hormone (TSH) every 6-12 months if the neck has been irradiated.

5. Smoking cessation and alcohol counseling as clinically indicated.

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