World Health Organization Classification of Tumors
Pathology and Genetics
Head and Neck Tumors

What's New

Leon Barnes, M.D.
Professor of Pathology and Otolaryngology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Introduction: The World Health Organization (WHO) "Blue Book" on the Pathology and Genetics of Head and Neck Tumors is the ninth in a series of ten books devoted to the classification of tumors. It was published in 2005 by the IARC Press in Lyon, France and edited by Barnes, Eveson, Reichart and Sidransky with the assistance of a 37 member Advisory Committee.

The book, with contributions from 130 authors from 28 countries, contains 890 colored illustrations, computer tomography –magnetic resonance images, and charts, 2918 references, and 430 pages. It sells for $110.00 (US).

Organization: In the past, the WHO used four different "Blue Books" to cover head and neck neoplasms:

(1) Oral and Oropharyngeal Tumors—published in 1971, 8 contributors, 48 pages and 40 illustrations
(2) Tumors of the Upper Respiratory Tract and Ear—published in 1991, 12 contributors, 201 pages and 200 illustrations
(3) Salivary Gland Tumors—published in 1991, 10 contributors, 113 pages, and 124 illustrations
(4) Odontogenic Tumors—published in 1991, 7 contributors, 119 pages and 142 illustrations.

The current "Blue Book" represents a combination of all four of the above books, and is organized into the following eight chapters: (1) Nasal Cavity and Paranasal Sinuses, (2) Nasopharynx, (3) Hypopharynx, Larynx and Trachea, (4) Oral Cavity and Oropharynx, (5) Salivary Glands, (6) Odontogenic Tumors, (7) Ear, and (8) Paraganglionic System.

In the old "Blue Book" each tumor was accompanied by a definition, a brief histologic description and usually a single illustration. This contrasts with the current "Blue Book" in which many of the tumors are thoroughly discussed and illustrated using the following subtitles: (1) definition, (2) epidemiology, (3) etiology, (4) clinical features, (5) gross and microscopic descriptions, (6) precursor lesions, (7) differential diagnosis, (8) immunohistochemistry, (9) electron microscopy, (10) molecular biology, (11) genetics, and (12) prognosis and predictive factors.

What's New:

1. Chapter on Nasal Cavity and Paranasal Sinuses

   A. Schneiderian Papillomas

      The Schneiderian papillomas are classified into three types—exophytic, inverted and oncocytic. The terms "exophytic" and "oncocytic" are now proposed to replace the old respective terms of "fungiform" and "columnar cell."

   B. Adenocarcinomas

      Adenocarcinomas, other than salivary-type, are more clearly defined and divided into intestinal and non-intestinal types based on morphology and immunohistochemistry. The intestinal-type are usually CK7+, CK20+, and CDX2+, while the non-intestinal types are CK7+, CK20-, and CDX2-.

   C. Glomangiopericytoma

      Glomangiopericytoma has emerged as the most preferred or at least an equivalent term for "sinonasal-type hemangiopericytoma."

   D. Nasal Chondromesenchymal Hamartoma (NCMH)

      NCMH is a newly recognized tumefactive lesion arising in the sinonasal tract with mixed chondroid, stromal and occasionally osseous components that is somewhat similar to the chest wall hamartoma.

   E. Respiratory Epithelial Adenomatoid Hamartoma (REAH)

      REAH is a benign non-neoplastic overgrowth of glands lined by ciliated respiratory epithelium that arises most often on the posterior nasal septum and less often in the paranasal sinuses or nasopharynx. The glands are surrounded by a hyalinized basement membrane and are associated with a background of polypoid rhinosinusitis. REAH is typically unilateral, rarely bilateral, and must be distinguished from the inverted papilloma. Conservative excision is curative.

2. Chapter on Nasopharynx

A. Nasopharyngeal Carcinoma

The classification of nasopharyngeal carcinoma is the same as proposed in 1991 with the exception that “basaloid squamous cell carcinoma” has been added.

Classification of Nasopharyngeal Carcinoma

(1) Keratinizing squamous cell carcinoma
(2) Non-keratinizing carcinoma
    (a) undifferentiated
    (b) differentiated
(3) Basaloid squamous cell carcinoma

B. Nasopharyngeal Papillary Adenocarcinoma (NPAC)

NPAC is a rare, recently described, low-grade, exophytic neoplasm comprised of papillary fronds and glands. The tumor may contain PAS-positive, diastase-resistant and mucicarminophilic intracytoplasmic secretions. EMA and cytokeratin stains are positive. Although psammoma bodies are occasionally seen, there is no reactivity for thyroglobulin and no association with the Epstein-Barr virus. NPAC is only locally invasive with no metastases recorded thus far. Complete excision is usually curative.

3. Chapter on Hypopharynx, Larynx and Trachea

A. Terminology of Premalignant Lesions

The terminology of premalignant mucosal lesions is controversial and not uniformly applied throughout the body. The three most common classifications in the head and neck and equivalent terms for each are given in the following table:

2005 WHO Classification	Squamous Intraepithelial Neoplasia (SIN)	Ljubljana Classification Squamous Intraepithelial Lesions (SIL)
Squamous cell hyperplasia		Squamous cell (simple) hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia*
Moderate dysplasia	SIN 2	Atypical hyperplasia**
Severe dysplasia	SIN 3***	Atypical hyperplasia**
Carcinoma in-situ	SIN 3***	Carcinoma in-situ
* Basal/Parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesions.		
** 'Risky epithelium'. The analogy to moderate and severe dysplasia is approximate.		
*** The advocates of SIN combine severe dysplasia and carcinoma in-situ		

B. Terminology of Neuroendocrine Tumors

The terminology of neuroendocrine tumors is another controversial issue. For consistency, the classification and terminology as used in the lung are applied to those in the head and neck.

Classification of Neuroendocrine Tumors

(1) Typical carcinoid
(2) Atypical carcinoid
(3) Small cell carcinoma, neuroendocrine type
(4) Combined small cell carcinoma, neuroendocrine type
(5) Paraganglioma
    (a) Benign
    (b) Malignant

4. Chapter on Oral Cavity and Oropharynx

A. Follicular Dendritic Cell Sarcoma/Tumor

This tumor is derived from follicular dendritic cells and may arise in nodal or extranodal sites. The oral cavity—oropharynx, especially the tongue and palate, is one of the most frequent extranodal sites of origin. The tumor typically grows beneath an intact mucosa and is comprised of fascicles, whorls, or nodules of spindle to ovoid cells with admixed, small lymphocytes. The cells possess poorly defined cell borders slightly vesicular nuclei and distinct nucleoli and are positive for CD21, CD23, and CD35. Most cases are treated by surgery, with or without adjuvant chemotherapy and radiotherapy. The tumors are regarded as low to intermediate grade with an overall recurrence rate of at least 40% and a metastatic rate of at least 28%.

5. Chapter on Salivary Glands

A. Carcinoma ex Pleomorphic Adenoma

Carcinoma ex pleomorphic adenoma is classified into three types based on the degree of invasion of its capsule:

(1) Non-invasive (in-situ carcinoma, intracapsular carcinoma)
(2) Minimally invasive (1.5 mm or less of invasion beyond the capsule)
(3) Invasive (more than 1.5 mm of invasion beyond the capsule)

B. Low-Grade Cribriform Cystadenocarcinoma (LGCCC)

The WHO has proposed that the tumor originally described as low-grade salivary duct carcinoma be renamed as LGCCC in order to avoid confusion with salivary duct carcinoma, a high-grade, aggressive tumor.

These tumors resemble the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in-situ. A few may be invasive. In contrast to salivary duct carcinoma, LGCCC is strongly positive for S-100 protein and negative for androgen receptor and HER2-neu. Following complete excision, the prognosis is excellent.

6. Chapter on Odontogenic Tumors

A. The lesion traditionally know as odontogenic keratocyst has been renamed as “keratocystic odontogenic tumor” as it more appropriately reflects its potential for local, destructive behavior.

7. Chapter on the Ear

A. Endolymphatic Sac Tumor (ELST)

ELST is a non-metastasizing, slowly-growing adenocarcinoma of endolymphatic sac origin which widely invades the temporal bone, and may have an association with von Hippel-Lindau disease. Although many names have been applied to this tumor, the WHO has endorsed ELST

B. Idiopathic Pseudocystic Chondromalacia (IPC)

IPC is a non-neoplastic painless swelling of the pinna due to a localized accumulation of fluid with the elastic cartilage. It most often occurs in young to middle-aged adults. Minor trauma may be an instigating factor. Microscopically, the lesion is a pseudocyst within the confines of the elastic cartilage. The cavity may be lined by cartilage, granulation and/or fibrous tissue.

8. Chapter on the Paraganglionic System

A. Laryngeal paragangliomas are distinctly unusual tumors, and in the past, have been erroneously assumed to be malignant in 25% of cases. Critical review of the alleged malignant cases has revealed that virtually all are actually unrecognized atypical carcinoid tumors.

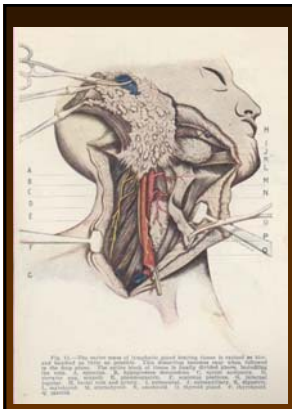
A Pathologist's Guide to Neck Dissection

North American Society for Head and Neck Pathology Companion Meeting 2006

Sigrid Wayne, M.D.
Department of Pathology
University of Iowa

The presence of cervical metastases is the most significant independent prognostic factor in squamous cell carcinoma of the head and neck

Decreases survival by almost 50%



- Oncologic importance of cervical lymph node excision recognized in late 19th century
- Radical neck dissection first described in 1906 by George Crile

Neck Dissections

- Anatomy
- Types of dissection
- Orientation
- Staging

Neck Dissections

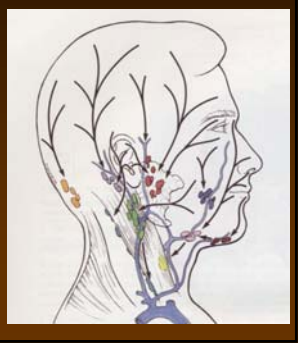
- Anatomy
- Types of dissection
- Orientation
- Staging

Lymphatics of head and neck

- Waldeyer's internal ring
  - Adenoids, lingual and palatine tonsils, posterior pharyngeal wall lymphoid aggregates
- Superficial lymph node system
- Deep lymph node system

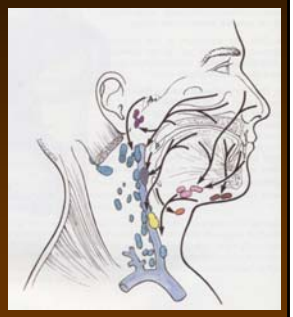
Superficial lymph node system

- Located at junction of head and neck
- Lymph node groups
  - Occipital
  - Post-auricular
  - Parotid
  - Buccal
  - Superficial cervical
  - Submental
  - Submandibular
  - Anterior cervical



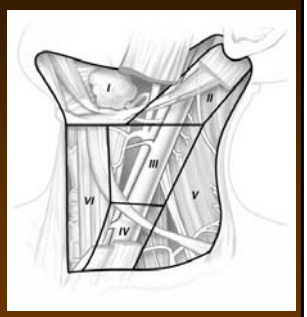
Deep lymph node system

- Located along internal jugular vein, within carotid sheath
- Lymph node groups
  - Upper jugular
  - Middle jugular
  - Lower jugular
- In general, lymph flows from superficial to deep, and from superior to inferior



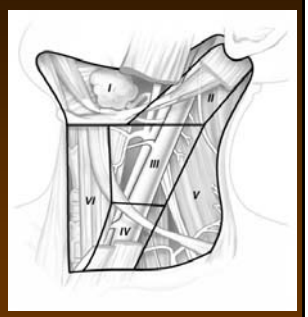
Surgical level system

- Lymph nodes categorized into 6 levels
- Includes deep and some superficial nodes



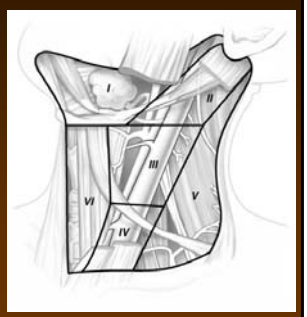
Level I

- Submental and submandibular nodes
- Boundaries
  - Submental and submandibular triangles
- Sites drained
  - Oral cavity, lower lip, anterior nasal cavity, submandibular gland, soft tissue of midface

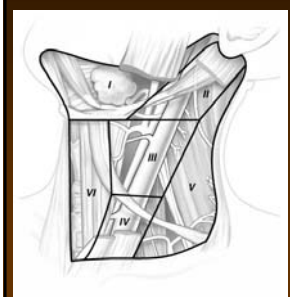


Level II

- Upper jugular nodes
- Boundaries
  - Superior: skull base
  - Inferior: inferior body of hyoid bone
  - Anterior: stylohoid muscle
  - Posterior: posterior border of sternocleidomastoid muscle
- Sites drained
  - Oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, parotid gland

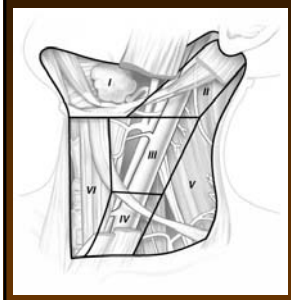


Level III



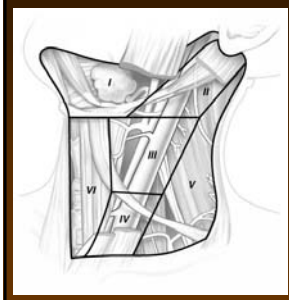
- Mid jugular nodes
- Boundaries
  - Superior: inferior body of hyoid
  - Inferior: inferior border of cricoid cartilage
  - Anterior: lateral border of sternohyoid muscle
  - Posterior: posterior border of sternocleidomastoid muscle
- Sites drained
  - Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx

Level IV



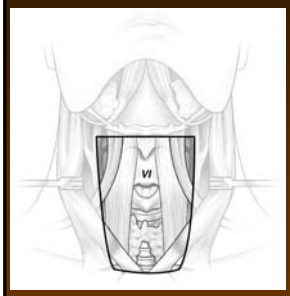
- Lower jugular nodes
- Boundaries
  - Superior: inferior border of cricoid cartilage
  - Inferior: clavicle
  - Anterior: lateral border of sternohyoid muscle
  - Posterior: posterior border of sternocleidomastoid muscle
- Sites drained
  - Hypopharynx, larynx, cervical esophagus, thyroid gland

Level V



- Posterior triangle nodes
- Boundaries
  - Inferior: clavicle
  - Anterior: posterior border of sternocleido-mastoid muscle
  - Posterior: anterior border of trapezius muslce
- Sites drained
  - Nasopharynx, oropharynx, cutaneous sites of posterior scalp and neck

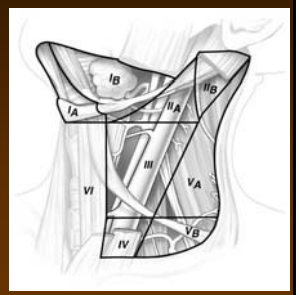
Level VI



- Pre- and paratracheal, precricoid (Delphian), and perithyroidal nodes
- Boundaries
  - Superior: hyoid bone
  - Inferior: suprasternal notch
  - Lateral: common carotid artery
- Sites drained
  - Thyroid gland, glottic/subglottic larynx, apex of pyriform sinus, cervical esophagus

American Academy of Otolaryngology-Head and Neck Surgery modification (1991)

- Subdivided levels I, II, and V
  - Level I: submental and submandibular
  - Level II: divided by plane defined by spinal accessory nerve
  - Level V: divided by plane defined by inferior border of cricoid cartilage
- Sublevels with different biological significance than larger level

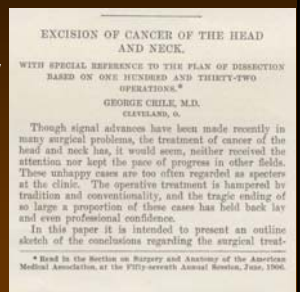


Neck Dissections

- Anatomy
- Types of dissection
- Orientation
- Staging

Neck dissection: *Historical perspective*

- Concept of cervical lymphadenectomy developed and reported by George Crile in 1906
- Article described resection of all cervical nodal groups
- Standard treatment for cervical metastases for over 60 years
- Basis for modern radical neck dissection



EXCISION OF CANCER OF THE HEAD AND NECK.

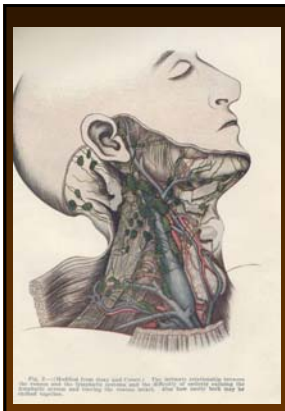
WITH SPECIAL REFERENCE TO THE PLAN OF DISSECTION BASED ON ONE HUNDRED AND THIRTY-TWO OPERATIONS.*

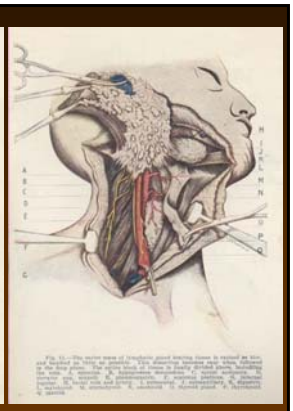
GEORGE CRILE, M.D.
CLEVELAND, O.

Though signal advances have been made recently in many surgical problems, the treatment of cancer of the head and neck has, it would seem, neither received the attention nor kept the pace of progress in other fields. These unhappy cases are too often regarded as specters at the clinic. The operative treatment is hampered by tradition and conventionality, and the tragic ending of so large a proportion of these cases has held back lay and even professional confidence.

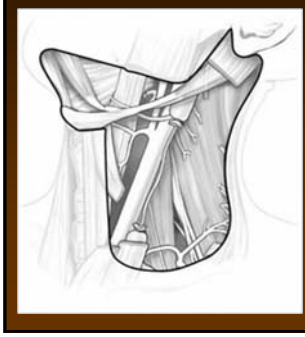
In this paper it is intended to present an outline sketch of the conclusions regarding the surgical treat-

* Read in the Section on Surgery and Anatomy of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.





Radical neck dissection (RND)



- Resection of:
  - All lymph node groups from levels I through V
  - Spinal accessory nerve
  - Internal jugular vein
  - Sternocleidomastoid muscle

Radical neck dissection (RND)

- Complications
  - Sacrifice of spinal accessory nerve and sternocleidomastoid
    - Weakness in turning head to opposite side
    - Inability to elevate and retract shoulder
    - Difficulty elevating arm above horizontal level
  - Disfiguring
    - Shoulder droop
    - Scapular winging

Development of conservation neck dissection

- Driving force behind development of conservation neck dissection was goal of preserving spinal accessory nerve
- 1950's: Ward and Robben reported that the spinal accessory nerve could be preserved in selected patients
- 1960's: Suarez popularized "functional neck dissection"
  - Demonstrated that lymphatics contained within fascial compartments, well defined from nonlymphatic structures
  - Nonlymphatic structures could be preserved during neck dissection

Evolution of neck dissection (1960's-1980's)

- Anatomic and clinical studies by Rouviere, Lindberg, Byers, and Shah
- Conclusion: squamous cell carcinoma of the head and neck metastasizes to regional lymph nodes in a predictable distribution

Frequency of cervical nodal metastases in floor of mouth carcinoma

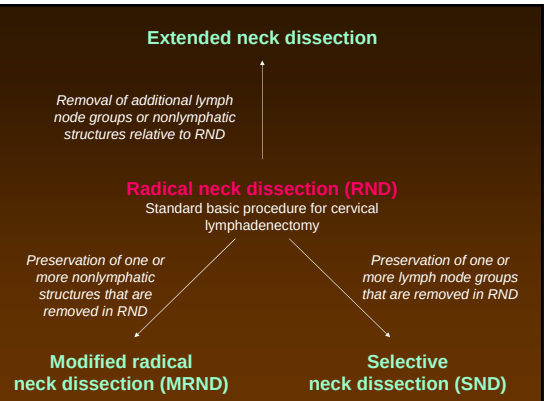
NODAL GROUP	IPSILATERAL (%)	CONTRALATERAL (%)
I	70	5
II	54	6
III	14	0
IV	6	1
V	3	0
Supraclavicular	1	0

Frequency of cervical nodal metastases in supraglottic carcinoma

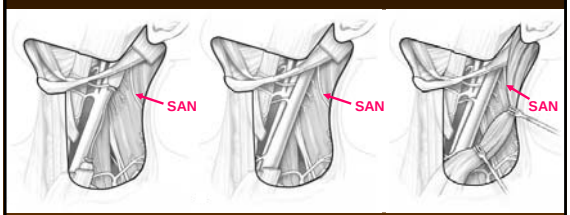
NODAL GROUP	IPSILATERAL (%)	CONTRALATERAL (%)
I	2	0
II	67	21
III	48	10
IV	15	5
V	9	4
Supraclavicular	3	

Proliferation of conservation neck dissections in 1980's

- Proliferation of nonstandardized, institution and surgeon specific eponyms and terms for types of neck dissection
- 1991: American Academy of Otolaryngology-Head and Neck Surgery issued a standardized classification of neck dissections
  - Updated in 2001



Modified radical neck dissection (MRND)



Type I: Preservation of spinal accessory nerve

Type II: Preservation of spinal accessory nerve and internal jugular vein

Type III: Preservation of spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle

- Excision of levels I – V
- Preservation of spinal accessory nerve (SAN) without or without internal jugular vein and sternocleidomastoid muscle

Which type of neck dissection to choose?

- Factors considered
  - Site of primary
  - Clincal status of neck (physical exam, radiologic studies)
    - Clinically negative = N_0
    - Clinically positive = N+
  - Previous treatment of neck
  - Patient preference
- General guidelines, but may be variations with region, institution, surgeon

The clinically N+ neck: *Therapeutic neck dissection*

- Radical neck dissection: Massive nodal disease with extensive soft tissue involvement
- Modified radical neck dissection: Lymph node metastases confined to nodes
- Selective neck dissection: May be used in carefully selected patients with limited nodal disease (N_1)

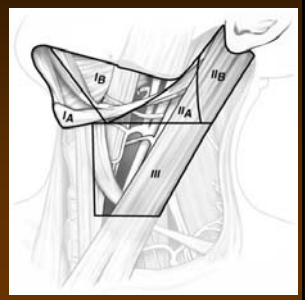
The clinically N_0 neck: *Elective neck dissection*

- Staging
- Treatment of occult metastases
  - Indicated when risk of metastases is > 20%
  - Factors determining risk
    - Site
    - Size
    - Thickness/depth of invasion (oral cavity)
    - Vascular/perineural invasion
- Modified radical neck dissection
- Selective neck dissection

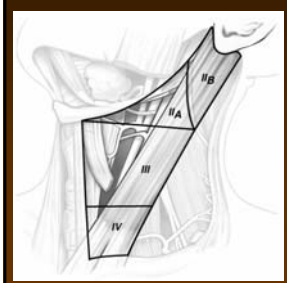
Nodal Group	Ipsilateral (%)	Contralateral (%)
I	70	5
II	54	6
III	14	0
IV	6	1
V	3	0
Supraclavicular	1	0

Primary site: *Oral cavity*

- Selective neck dissection (I-III)
- Selective neck dissection (I-IV) for tongue
- Bilateral dissections for floor of mouth and midline tongue



Primary site: *Oropharynx, hypopharynx, larynx*



- Oropharynx
  - Selective neck dissection (II-IV) or (I-IV)
  - Bilateral for base of tongue
- Hypopharynx and larynx
  - Selective neck dissection (II-IV) or (IIa, III, IV)
  - Bilateral for supraglottis

Primary site: *Thyroid gland*

- Papillary or follicular carcinoma
  - N_0 (Controversial): No neck dissection or selective neck dissection (VI)
  - N+: Selective neck dissection of involved levels
- Medullary carcinoma
  - N_0: Selective neck dissection (VI)
  - N+ or histologically positive nodes in VI: Radical or modified radical neck dissection
  - Bilateral radical or modified radical neck dissection if bilateral primary or nodal disease

Primary site: *Major salivary gland*

- N+ neck
  - Modified radical neck dissection
  - Selective neck dissection (I-III) or (I-IV)
- N_0 neck
  - Selective neck dissection (I-III) if:
    - High grade
    - T3/T4
    - Extraglandular spread
    - Age > 54 years
    - Lymphatic invasion

Neck Dissections

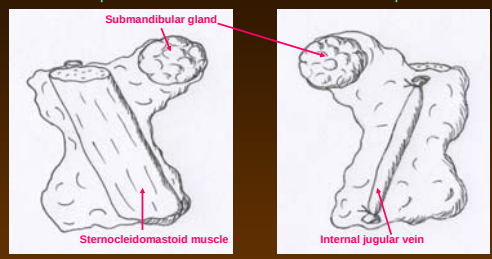
- Anatomy
- Types of dissection
- Orientation
- Staging

Orienting the neck dissection

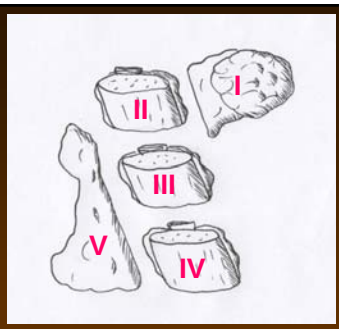
- Boundaries of neck levels are structures that mostly remain in patient
- Options for orienting specimen
  - Surgeon cuts specimen into levels prior to sending to pathology
  - Surgeon pins specimen to orienting board
  - What to do if specimen arrives in gross room unoriented…?

Right radical neck dissection: View of superficial surface

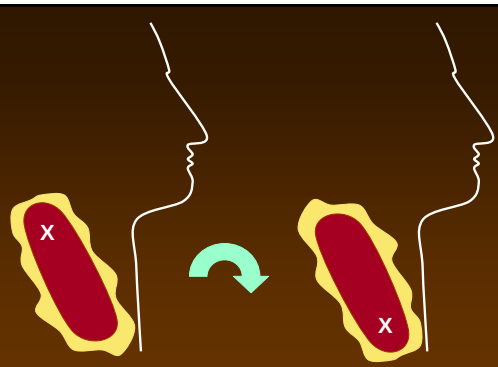
Right radical neck dissection: View of deep surface



- Neck dissections containing level I are easily oriented
  - Submandibular gland in level I gives anterior-superior aspect of specimen
  - Sternocleidomastoid muscle is on superficial aspect
  - Internal jugular vein is on deep aspect



- Level I: anterior to sternocleidomastoid
- Level V: posterior to sternocleidomastoid
- Levels II-IV: divide sternocleidomastoid and attached fibroadipose tissue into equal thirds



Cannot distinguish superior and inferior aspects without submandibular gland, even when sternocleidomastoid muscle is present.

- Check clinic notes and radiology reports to correlate location of any grossly positive nodes
- Ask the surgeon to orient the specimen

How many nodes?

- Sources of variability
  - Patient
    - Anatomic variation
    - Prior radiation therapy
  - Pathologist
  - Surgical technique

Mean number of nodes by procedure

Lymphography (I-V)	RND (I-V)	MRND (I-V)	SND (I-III)	SND (II-IV)
42	22 - 31	26 - 31	10 - 20	19 - 30

- Approximately 3-8 lymph nodes per level
- Prior radiotherapy can reduce yield by up to 50%

Neck Dissections

- Anatomy
- Types of dissection
- Orientation
- Staging

TMN Staging
American Joint Committee on Cancer 2002

N_0
No regional lymph node metastases

N_1
Metastasis in single ipsilateral node, 3 cm or less in greatest dimension

N_{2a}
Metastasis in single ipsilateral node, >3 cm but <6 cm in greatest dimension

TMN Staging
American Joint Committee on Cancer 2002

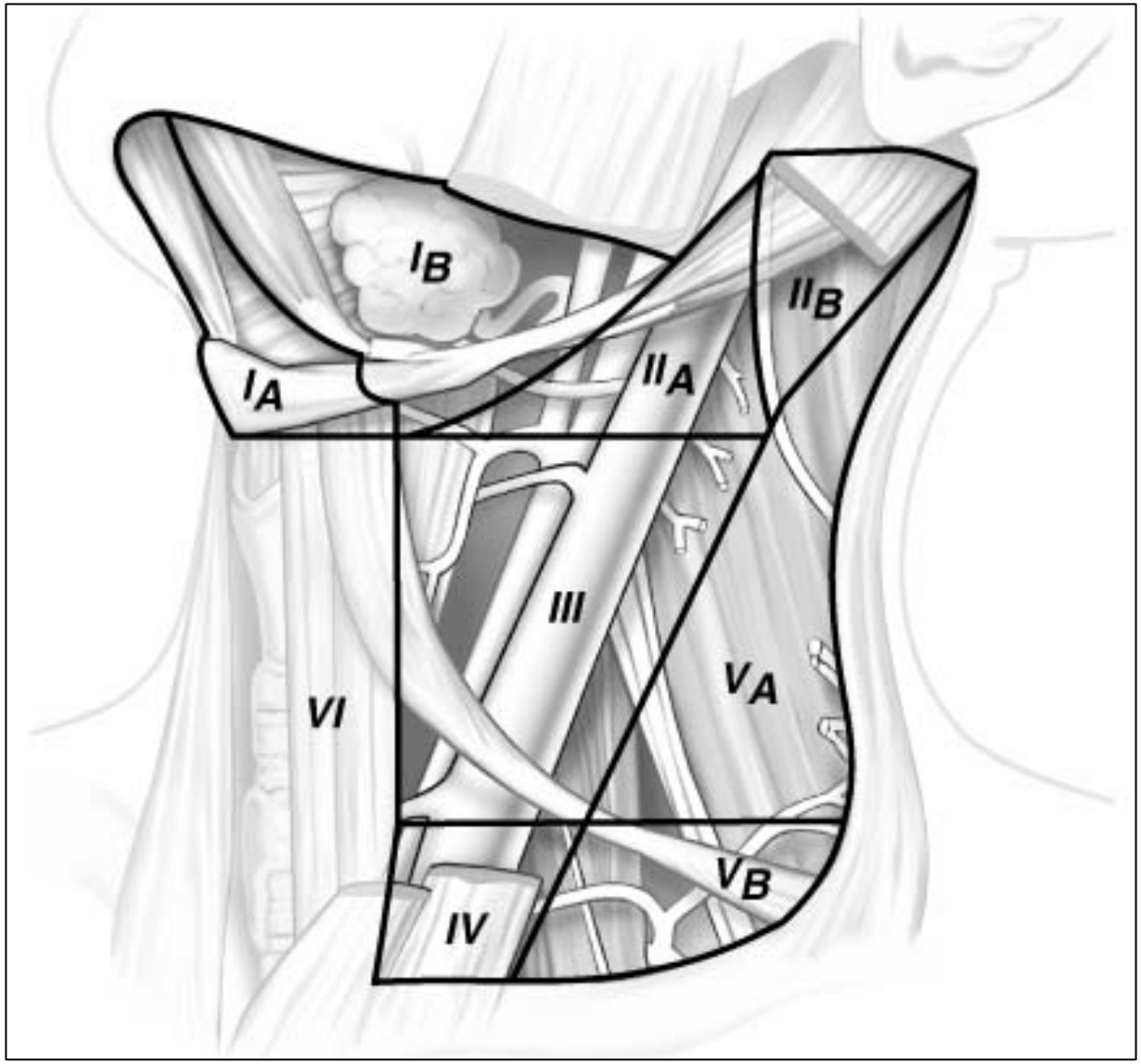
N_{2b}
Metastasis in multiple ipsilateral nodes, <6 cm in greatest dimension

N_{2c}
Metastasis in bilateral or contralateral nodes, <6 cm in greatest dimension

N_3
Metastasis in lymph node >6 cm in greatest dimension

Summary

- The surgical level system classifies cervical lymph nodes into 6 levels
- Neoplasms of the head and neck metastasize to regional lymph nodes in a predictable distribution according to site of primary
- Neck dissection has evolved from radical neck dissection to increasingly conservative procedures that strive to minimize functional and aesthetic complications
  - Future: Increasing role of sentinel node biopsy?



Cummings, CW. Cummings: Otolaryngology: Head and Neck Surgery, 4th ed. Mosby, Inc: 2005

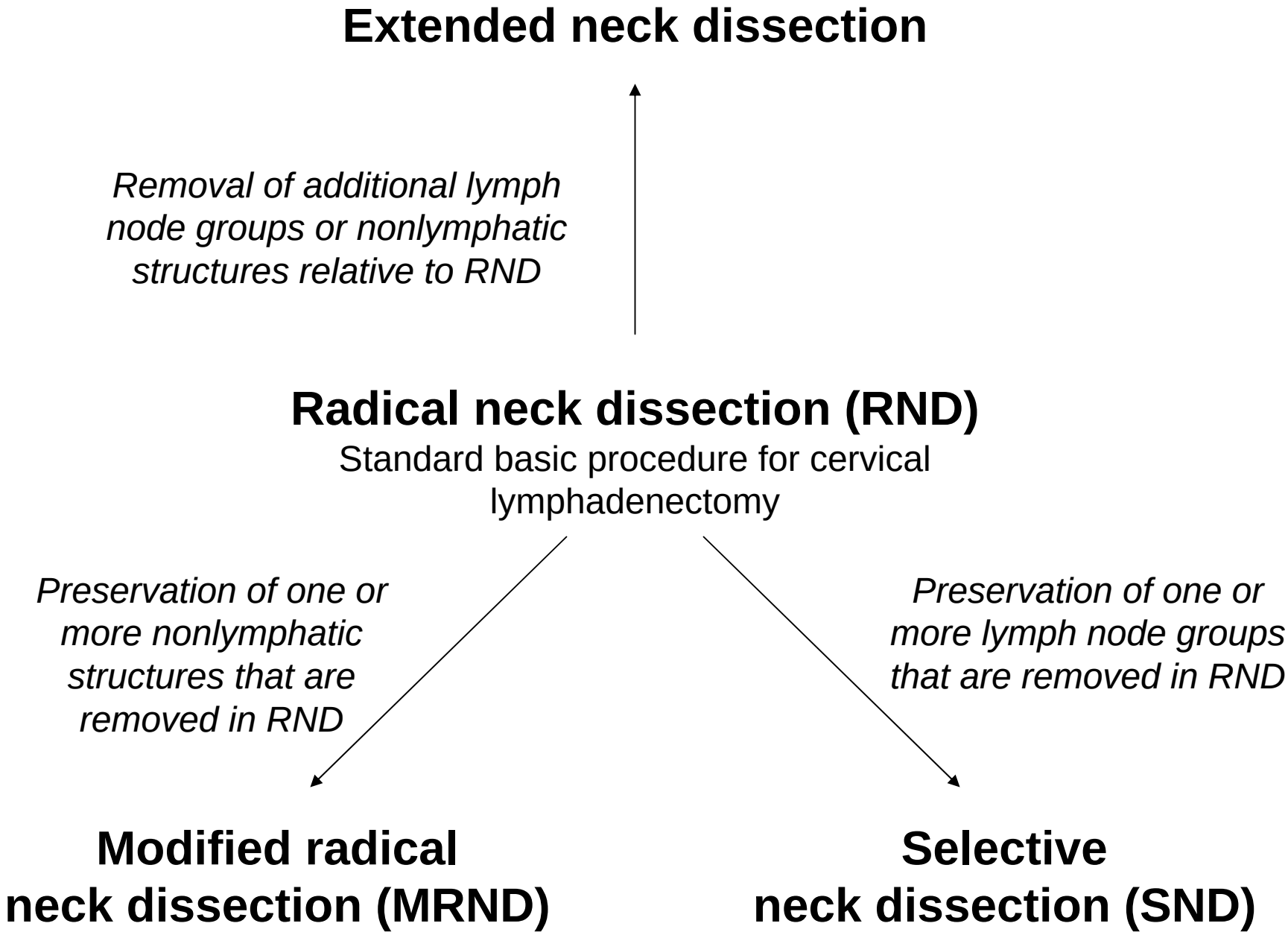
Summary of anatomic boundaries of neck levels

Level	Superior	Inferior	Anterior (medial)	Posterior (lateral)
IA	Symphysis of mandible	Body of hyoid	Anterior belly of contralateral digastric muscle	Anterior belly of ipsilateral digastric muscle
IB	Body of mandible	Posterior belly of digastric muscle	Anterior belly of digastric muscle	Stylohyoid muscle
IIA	Skull base	Horizontal plane defined by the inferior body of the hyoid bone	Stylohyoid muscle	Vertical plane defined by the spinal accessory nerve
IIB	Skull base	Horizontal plane defined by the inferior body of the hyoid bone	Vertical plane defined by the spinal accessory nerve	Lateral border of the sternocleidomastoid
III	Horizontal plane defined by inferior body of hyoid	Horizontal plane defined by the inferior border of the cricoid cartilage	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of cervical plexus
IV	Horizontal plane defined by the inferior border of the cricoid cartilage	Clavicle	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of cervical plexus
VA	Apex of the convergence of the sternocleidomastoid and trapezius muscles	Horizontal plane defined by the lower border of the cricoid cartilage	Posterior border of the sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VB	Horizontal plane defined by the lower border of the cricoid cartilage	Clavicle	Posterior border of the sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VI	Hyoid bone	Suprasternal	Common carotid artery	Common carotid artery

Robbins KT et al. The use and misuse of neck dissection for head and neck cancer. *J Am Coll Surg*, 193(1)91-102,2001

Summary of sites drained by nodal group and level

LEVEL	NODAL GROUPS	SITES DRAINED
IA	Submental	Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, lower lip
IB	Submandibular	Oral cavity, anterior nasal cavity, soft tissue of midface, submandibular gland
II (A+B)	Upper jugular	Oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, parotid gland
III	Middle jugular	Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx
IV	Lower jugular	Hypopharynx, thyroid, cervical esophagus, larynx
V (A+B)	Nodes around lower half of spinal accessory nerve and transverse cervical artery, supraclavicular nodes	Nasopharynx, cutaneous structures of posterior scalp and neck
VI	Pre- and paratracheal, precricoid (Delphian), and perithyroidal nodes	Thyroid gland, glottic/subglottic larynx, apex of pyriform sinus, cervical esophagus


Extended neck dissection
Removal of additional lymph node groups or nonlymphatic structures relative to RND
Radical neck dissection (RND)
Standard basic procedure for cervical lymphadenectomy
Preservation of one or more nonlymphatic structures that are removed in RND
Preservation of one or more lymph node groups that are removed in RND
Modified radical neck dissection (MRND)
Selective neck dissection (SND)

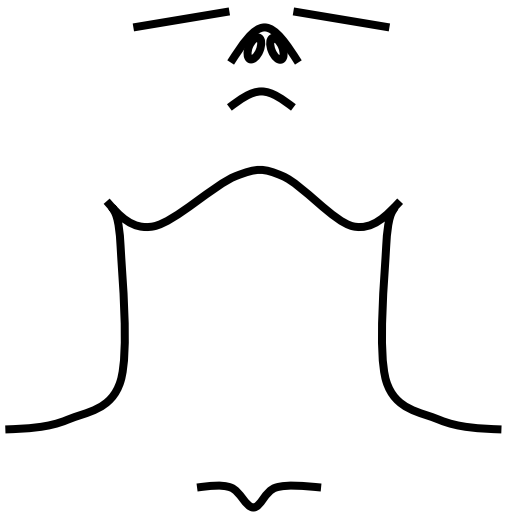
Classification of neck dissection

1991 Classification	2001 Classification	Lymph node levels removed	Other structures removed
Radical neck dissection (RND)	Radical neck dissection (RND)	I-V	SAN, SCM, IJV
Modified radical neck dissection (MRND)	Modified radical neck dissection (MRND)	I-V	Type 1: SCM, IJV Type 2: SCM Type 3: None
Selective neck dissection (SND)	Selective neck dissection (SND)	Specify in parentheses	None
Supraomohyoid (SOHND)	SND(I-III)	I-III	None
Lateral (LND)	SND(II-IV)	II-IV	None
Posterolateral (PLND)	SND(II-V)	II-V	None
Anterior	SND(VI)	VI	None
Extended neck dissection	Extended neck dissection	I-V +/- other lymph node groups (eg retropharyngeal nodes)	SAN, SCM, IJV +/- other nonlymphatic structures (eg skin)

SAN = Spinal accessory nerve; **SCM** = Sternocleidomastoid muscle; **IJV** = Internal jugular vein

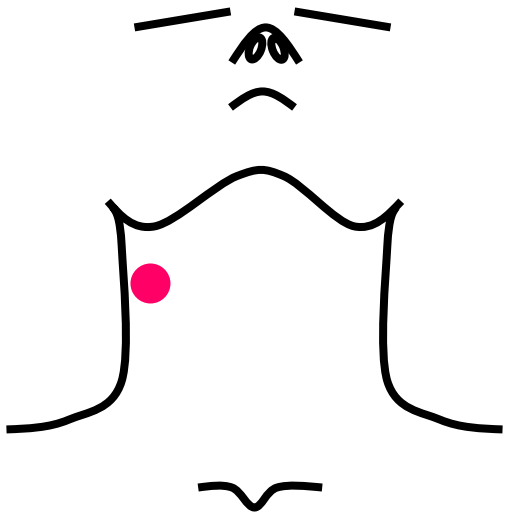
TMN Staging

American Joint Committee on Cancer 2002



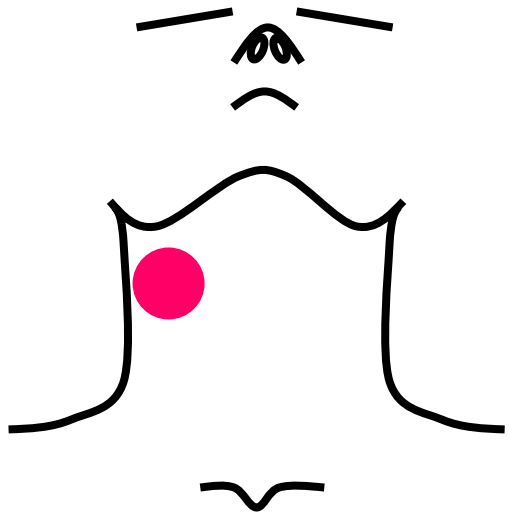
N_0

No regional lymph node metastases



N_1

Metastasis in single ipsilateral node, 3 cm or less in greatest dimension

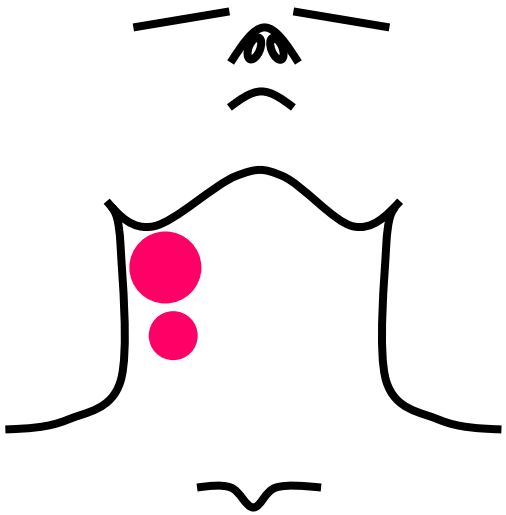


N_{2a}

Metastasis in single ipsilateral node, >3 cm but <6 cm in greatest dimension

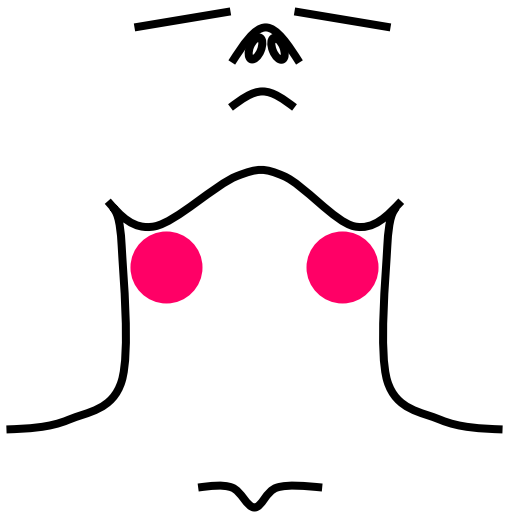
TMN Staging

American Joint Committee on Cancer 2002



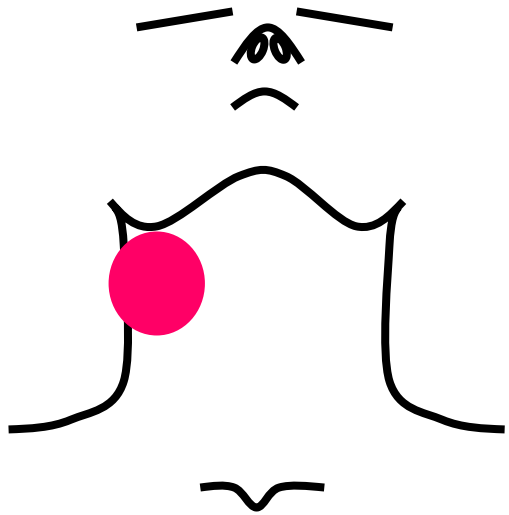
N_{2b}

Metastasis in multiple ipsilateral nodes, <6 cm in greatest dimension



N_{2c}

Metastasis in bilateral or contralateral nodes, <6 cm in greatest dimension



N_3

Metastasis in lymph node >6 cm in greatest dimension

LITERATURE CITED

1. Crile G. Excision of cancer of head and neck. With special reference to the plan of dissection based on 132 patients. JAMA. 47:1780-1786, 1906.

2. Agur, A.M.R. Grant's Atlas of Anatomy, 9th ed. Williams and Wilkins:1991.

3. Cummings, CW. Cummings: Otolaryngology: Head and Neck Surgery, 4th ed. Mosby, Inc: 2005.

4. Shah JP et al. Neck dissection: current status and future possibilities. *Clin Bull* 11:25, 1981.

5. Robbins KT et al. Standardizing neck dissection terminology. *Arch Otolaryngol* 117:601, 1991.

6. Robbins KT et al. The use and misuse of neck dissection for head and neck cancer. J Am Coll Surg, 193(1)91-102,2001

7. Werning J. Modified Radical Neck Dissection. medicine.com, 2004.

8. Rouviere H. Lymphatics of the head and neck. Tobias MJ, trans. Ann Arbor, Mich: Edwards Brothers: 1938.

9. Ward GE, Robben JO. A composite operation for radical neck dissection and removal of cancer of the mouth. *Cancer* 4:98, 1951.

10. Suarez O. El problema de las metastasis linfáticas y alejadas del cancer de laringe e hipofaringe. Rev Otorhinolaringol 23:83, 1963.

11. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446, 1972.

12. Shah JP. Patterns of lymph node metastases from squamous carcinomas of the upper aerodigestive tract. Am J Surg 160:405, 1990.

13. Byers, RM, et al, Rationale for elective modified neck dissection. Head and Neck Surgery 1988; 10:160-167

14. Lindberg J et al. Treatment of cervical lymph node metastases from primary lesions of the oropharynx, supraglottic laryx, and hypopharynx. Am J Roentgen Rad Ther Nucl Med. 102:132-137, 1968.

15. Shah J and Anderson PE. Impact of patterns of nodal metastases on modifications of neck dissections. Ann Surg Oncol. 1:521-532, 1994.

16. Mukherji SK et al. Cervical nodal metastases in squamous cell carcinoma of the head and neck: what to expect. Head & Neck. 23(11)995-1005, 2001.

17. Robbins KT et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology – Head and Neck Surgery. Arch Otolaryngol Head Neck Surg. 128:751-758, 2002.

18. Chummun S et al. Surgical education: neck dissection. Br Assoc Plast Surg 57:610-623, 2004.
Ferlito A et al. Current considerations in neck dissection. Acta Otolaryngol. 122:323-329, 2002.

19. Ferlito A et al. Is the standard radical neck dissection no longer standard? Acta Otolaryngol. 122:792-795, 2002.

20. Shaha AR. Neck dissection: an operation in evolution. Wor J Surg Onc. 3:22, 2005.

21. Gold DR et al. Management of the neck in salivary gland carcinoma. Otolaryngol Clin N Am. 38:99-105, 2005.

22. Hurban RH et al. Surgical Pathology Dissection: an illustrated guide. Springer-Verlag New York, Inc, 1996.

23. Greene FL et al, eds. American Joint Committee on Cancer: Cancer staging manual, 6th ed. Springer-Verlag, 2002.

24. Fisch UP and Sigel ME. Cervical lymphatic system as visualized by lymphography. Annals Oto Rhino Laryngol. 73:869-882, 1964.

25. Agrama MT et al. Node counts in neck dissection: are they useful in outcomes research? Otolaryngol Head Neck Surg. 124:433-435, 2001.

26. Friedman M et al. Quantification of lymph nodes in selective neck dissection. Laryngoscope. 109:368-370, 1999.

27. Bhattacharyya N. The effects of more conservative neck dissection and radiotherapy on nodal yields from the neck. Arch Otolaryngol Head Neck Surg. 124:412-416, 1998.

PATHOLOGY OF NECK DISSECTIONS

Mario A. Luna M.D.
The University of Texas MD. Anderson Cancer Center
Houston, Texas

The presence of cervical lymph node metastasis at the time of presentation and treatment is the main adverse prognostic factor for patients with squamous cell carcinoma of the upper aerodigestive tract: its presence reduces the 5-year survival by approximately 50%, irrespective of the primary site.[1] However, clinical and pathologic findings specific to lymph node metastasis provide additional prognostic information related to tumor recurrence and overall survival. The basic histopathologic features of cervical lymph node metastasis of prognostic significance are: extracapsular spread (ECS) ; the level , number, and size of positive lymph nodes; pattern of lymph node response; and soft tissue deposits. [2-6] Furthermore, accurate pathologic staging of the neck of patients with head and neck cancer is important for providing information and optimizing the treatment plan.[6]

Gross examination of specimens

Because the main anatomic and radiologic landmarks are lacking in neck dissection specimens, the orientation and labeling of the lymph node levels must be performed by the surgeon. Ideally, each level and sublevel of lymph nodes should be labeled and submitted to the pathology laboratory in separate containers, one container for each level or sublevel of lymph nodes removed.[7] The pathologist has a choice of two methods for examination of the specimens [6,8.]

The traditional method of assessing dissected nodes relies on the identification of lymph nodes by dissection of the received specimen.[8] All lymph nodes visible or palpable in each specimen are carefully dissected from connective tissue with a rim of perinodal connective tissue or fat. The number of lymph nodes should be noted; if tumor is present, the size in centimeters of the metastases and presence of ECS are also noted and recorded. Nodes greater than 2 to 3 cm are bisected along their longest axis plane, and both halves are submitted. Smaller nodes are submitted in toto. If a group of matted lymph nodes is present, two to three sections through the nodes often are adequate to document the extent of tumor.[8]

In 2003, Jose et al [6] designed a new method for pathologic examination of neck dissections. In this method; the node levels and sublevels are sent to the laboratory in separately labeled containers and fixed in formalin. Each specimen is cut into 2- mm-thick blocks, embedded in paraffin and sectioned at 6 microns thickness and stained with hematoxylin and eosin. Any macroscopically enlarged lymph nodes present are noted and embedded in their entirety. Care must be taken to count only once those lymph nodes that appear in multiple sections . With this method, the lymph node yield obtained is 50.4 nodes per neck dissection and the average number of microscopic slides generated is 63 (Level l-IV dissection). This technique allows accurate and comprehensive pathologic staging of cervical metastases, because the entire neck dissection specimen is examined rather than only apparent lymph nodes. [6]

The following method for the pathologic examination the neck dissections is recommended when they are submitted to the pathology laboratory as a single surgical specimen rather than in separate containers. It pertains to standard radical neck dissection and needs to be modified for the other subtypes.[8] After the tissue specimen has been oriented and the platysma muscle has been removed, the first step in a gross examination is to measure the dimensions of the sternocleidomastoid muscle and the internal jugular vein and describe their involvement by the tumor. Next, the pathologist should dissect and divide the submandibular gland, sternocleidomastoid muscle, and internal jugular vein and separate the fat-containing nodes into five levels: sublingual and submandibular, superior jugular, middle jugular, lower jugular, and posterior. The presence of tumor in soft tissues, submandibular gland, and muscle should be described. The number of lymph nodes (by level) should be noted ; if tumor tissue is present, the size of the metastases and presence of extracapsular extension are likewise indicated. Tissue sections of all lymph nodes (separated by level), the submandibular gland, the sternocleidomastoid muscle, and the internal jugular vein are then submitted for microscopic examination. If the neck dissection is of the extended type, sections of all extra lymph node groups and nonlymphatic structures that were removed also should be submitted for microscopic examination [8,9]

It is important to distinguish lymphoid aggregates from true lymph nodes. Lymph nodes are defined as an aggregate of encapsulated lymphoid tissue of any size with a peripheral sinus present. Microscopic ECS is diagnosed when the tumor extends beyond the lymph node capsule and a desmoplastic stromal response is observed. A soft tissue deposit of carcinoma is identified as metastatic squamous carcinoma in the soft tissues of the neck, with no evidence of a lymph node present. Soft tissue deposits may represent extralymphatic deposits of squamous carcinoma or a totally effaced lymph node.[6,8]

MICROSCOPIC EXAMINATION AND DETERMINANTS OF PROGNOSIS

The aim of the microscopic examination is to discover the histologic features that are important in predicting patient outcome or that may determine whether the patient should be given adjuvant therapy. The seven important parameters are the number of positive lymph nodes, the presence of metastasis in different groups of lymph nodes, the presence or absence of ECS, the size of the metastasis, the presence of metastasis in soft tissues, invasion of jugular vein and the presence of desmoplastic reaction in metastatic tissue. [2-7]

Of these parameters, ECS has been increasingly identified as a major prognostic factor in terms of recurrent disease in the neck and overall survival.[2,3] In a study by Johnson et al,[3] histopathologic evidence of ECS was associated with a statistically significant reduction in the survival rate. Thirty–nine per cent of patients whose metastases showed evidence of ECS survived 5 years, whereas 75% of those without evidence of ECS survived 5 years. Patients with ECS had an increased risk of disease recurrence and a shorter time to disease recurrence. Local disease recurred within 6 months in 42% of patients with ECS and in 18% of patients without ECS, and distant metastases occurred within 18 months in 14% of patients with ECS and in 4% of patients without ECS.Similar results were observed by Woolgar et al,[4] in patients whose tumors showed only microscopic evidence of ECS. Carter et al.[2] demonstrated a 10-fold

difference in the risk of disease recurrence in the neck between patients with macroscopic ECS and patients with only microscopic ECS or no ECS at all.

Prognostic significance has often attributed to the number of lymph nodes and the number on involved nodal group. In a multivariate analysis performed by Carter et al [2] using Cox regression methods, the important factors in predicting survival time were the number of involved nodes and the number of involved anatomic groups.

Involvement of the lower jugular and posterior triangle nodes and noncontiguous or multiple disease sites have been associated with poorer prognoses.[2,7] Estimated 2-year survival rates in patients with one positive lymph node were 68.8%, 56.3% in patients with 2 to 4 positive nodes, and 28.6% when more than four lymph nodes were involved by metastatic carcinoma. [4,5].Also, Woolgar et al [4] found a correlation between the size of the metastatic lymph node deposits and 5-year survival when the deposits measured less than 3 mm the survival rate was 80% compared with 55% when the metastatic deposits were grossly appreciated.

In a study by Olsen et al [5] a desmoplastic stromal pattern in a lymph node metastasis was associated with a nearly sevenfold increase in the risk of recurrent neck disease. In the same study, the authors demonstrated that metastasis to soft tissue and /or invasion of the jugular vein were associated with a high rates of neck recurrences (50% and 27%, respectively) compared with rates for patients with neither of these two factors (84% and 75%, respectively)..

INCIDENTAL FINDINGS IN LYMPH NODES OF NECK DISSECTIONS FOR SQUAMOUS CARCINOMA

During the pathologic examination of neck dissection specimens, unexpected findings within the lymph nodes may occasionally be discovered. [9-11] Such findings may include the presence of a second primary tumor (thyroid, lymphoma, chronic lymphocytic leukemia and Warthin's tumor are the most common) , chronic infectious or inflammatory diseases (tuberculosis, sarcoidosis), benign ectopic inclusions (nevus cells, salivary glands, thymus, bronchial or parathyroid heterotopias) or keratin granulomas.[2] Such incidental findings during neck dissection occur in 2% to 5% of patients with carcinoma of the upper aerodigestive tract [9-11] Malignant tumors may be present in nearly half of these. [9,11] Thyroid tissue within lymph nodes is the most common incidental finding and may present management dilemmas.[9,11]

References

1 Hahn SS, Spauldings CA, Kim JA, et al. The prognostic significance of lymph node involvement in pyriform sinus and supraglottic cancers. Int J Radiat Oncol Biol Phys 1987;13:1143-1147.

2 Carter RL, Bliss JM, Soo KH, et al. Radical neck dissection for squamous cell carcinoma. Pathologic findings and their clinical implications, with particular reference to transcapsular spread. Int J Radiat Oncol Biol Phys 1987;13 :825-832.

3 Johnson JT, Meyers EN, Bedetti CT, et al. Cervical lymph node metastasis and implications of extracapsular carcinoma. Arch Otolaryngol 1985;111: 534-537.

4 Woolgar JA, Rogers SN, Lowe D, et al. Cervical lymph node metastasis in oral cancer: the impotance of even microscopic extracapsular spread. Oral Oncol 2003;39:130-137.
5 Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement. Arch Otolaryngol Head Neck Surg 1994;120: 1370-1374.
6 Jose J, Coatesworth AP, McLennan K. Cervical metastases in upper aerodigestive tract squamous cell carcinoma: histopathologic analysis and reporting. Head Neck 2003; 25:194-197.
7 Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update:revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngol-Head Neck Surgery. Arch Otolaryngol Head Neck Surg 2002;128:751-758.
8 Gilles EM , Luna MA. Histologic evaluation of neck dissection specimens. Otolaryngol Clin North Am 1998;31: 759-771.
9 Sheehan P, Hafidh M, Toner M. Unexpected findings in neck dissection for squamous cell carcinoma: incidence and implications. Head Neck 2005;27:28-35.
10 Ratcliffe RJ, Soutar DS. Unexpected lymph node pathology in neck dissection for head and neck cancer. Head Neck 1990;12:244-246.
11 Ansari-Lari MA, Westra WH. The prevalence of clinically unsuspected neoplasms in cervical lymph nodes. Head Neck 2003;25:841-847.

Jennifer L. Hunt, MD, MEd
Cleveland Clinic Foundation

Sentinel Lymph Node Biopsy in Head and Neck Cancers

Background

Tumor metastasis is one of the most important predictive factors in most solid tumors. In head and neck squamous cell carcinoma (HNSCC) survival is strongly affected by regional lymph node metastases, most commonly in the cervical chain [1, 2]. The treatment of metastatic disease can include surgery (neck dissection) or radiation [3, 4]. There are two arguments for treating metastatic lymph node disease surgically. First, this procedure is done for staging [5]. The number, size, location, and invasive characteristics of positive nodes all have impact on prognosis and are used to determine the post-operative treatment regimen [5]. The second argument for neck dissection is that it improves locoregional control of tumor, though not necessarily long-term survival [6, 7]. Thus, in head and neck cancer, neck dissection is said to serve two purposes: improved staging and potential therapeutic advantages [8].

Treatment of the clinically node positive (cN+) neck with surgery and/or radiation is the standard of care. The real area of controversy is the elective treatment of the clinically negative neck (cN0). The overall risk of occult metastases or neck recurrence in the cN0 neck with lower stage tumors is significant, estimated at between 10 and 30%, depending on tumor characteristics [9, 10]. Authors have argued extensively both for and against elective selective neck dissection in these cN0 patients [1, 8, 9, 11]. With the increased utilization of selective neck dissections, morbidity is even lower, with the most common post-operative complaints being from nerve damage, particularly the spinal accessory nerve [8, 12-15].

The strongest arguments for treatment of the cN0 neck revolve around the poor outcome for recurrence in the neck, the low morbidity of the selective procedures, and improved locoregional control [8]. However, other authors have argued for “watchful waiting”, which entails careful monitoring of the neck for the appearance of clinical metastases. This clinical monitoring relies on clinical examination and radiological surveys such as CT scans, MRI, and ultrasound. In scans, the only variables that correlate with the presence of carcinoma are the size and the shape of the lymph nodes, where nodes >1 cm and nodes that are round instead of oval are suspicious [16-18]. Very advanced metastatic disease may show central necrosis. Newer monitoring has been described using CT scans paired with PET scanning which appears to improve the detection rate for metastases and improves the lower limits of the size of detectable metastases [18].

Despite advances in our understanding of which patients will benefit from neck dissection, advances in lowering the morbidity of treating the neck, and advances of detection of metastatic disease, treatment of the cN0 neck remains a controversial issue. Performance of elective neck dissection or neck irradiation in the cN0 neck is over-treatment for the majority of patients, but undetected and untreated neck metastases are associated with an unacceptably high failure rates. For these reasons, the sentinel lymph node procedure has been inviting for the treatment of the cN0 neck.

Sentinel Lymph Node Procedures

Many tumors are treated with primary surgery for tumor control and lymphadenectomy of the draining lymph nodes, which are evident by the routes of common metastases (Figure 1). The sentinel lymph node (SLN) procedure is really a "super-selective" nodal dissection. Head and neck surgeons have dramatically decreased the amount of tissue removed in nodal neck dissections, in converting from radical to selective neck dissections [7]. In breast carcinoma and melanoma treatment, where a lymphadenectomy used to be routine, the sentinel lymph node procedure is now commonly used as a selective procedure that has a lower morbidity [19]. This procedure was first popularized in the 1977 by Cabanas for staging of penile carcinoma [20], but was first described in parotid tumors in 1960 by Gould [21]. The procedure has now been attempted in nearly every type of tumor, and reported with varying success rates [22].

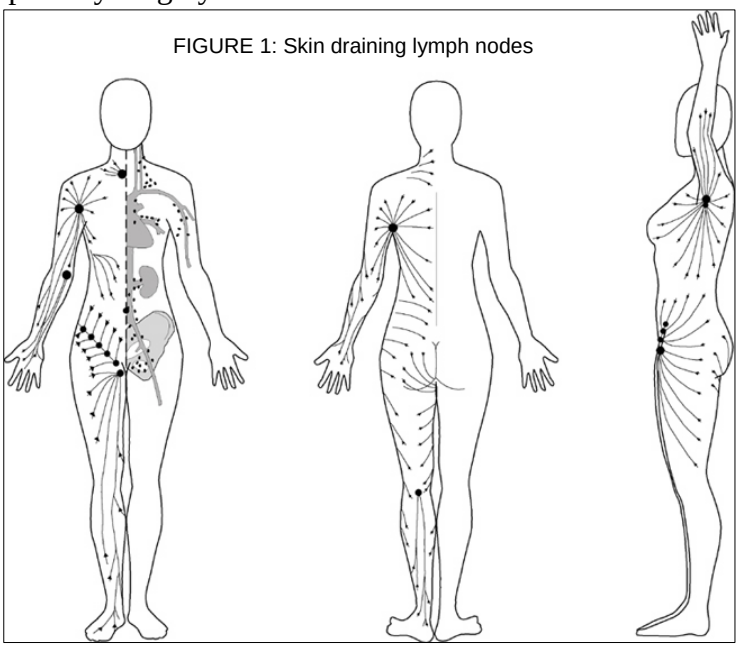


FIGURE 1: Skin draining lymph nodes

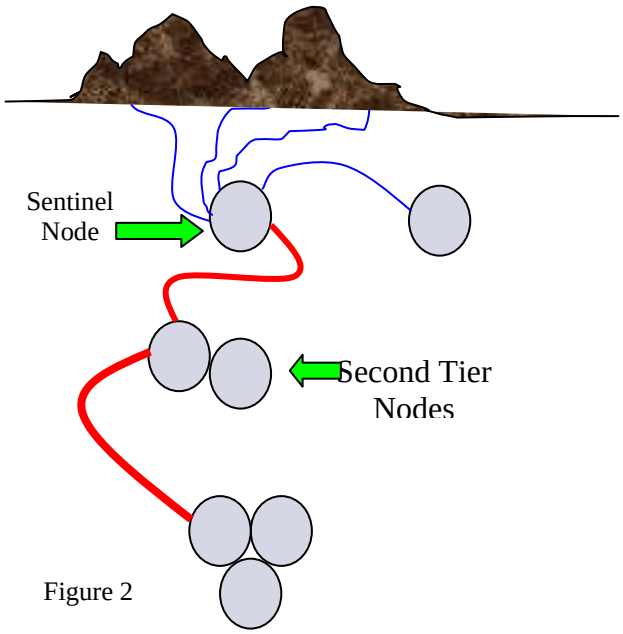
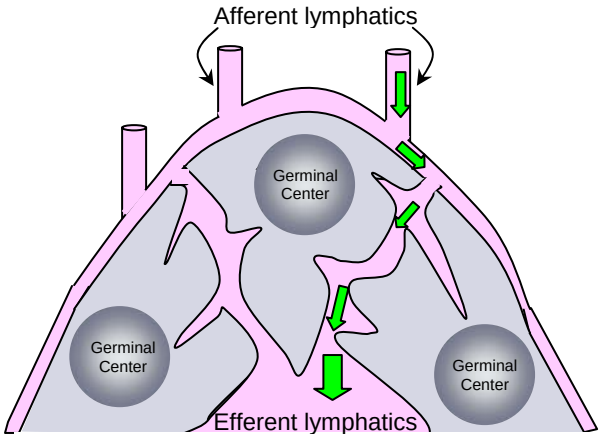


Figure 2

The theory behind the use of the SLN procedure is the assumption that lymphatic drainage from a particular anatomic site is predictable and hierarchical in nature. In other words, lymph from a certain anatomical site drains to predictable lymph node basins. It follows that tumor cells from a tumor in that location will gain access to the lymphatics and will become deposited in the same consistent regional lymph node basins (Figure 2). The lymph nodes in this basin are thought to be connected in series, meaning that the lymph flows into the first node in the chain (the sentinel lymph node, SLN), and then sequentially flows into the next lymph nodes in the chain (second tier nodes). The examination of this very first lymph node for metastases is therefore theoretically predictive of the status of all remaining lymph nodes.

The procedures utilized for identification of the SLN have involved two types of models: blue dye and radioactive injectable substances [23]. In both models, the

substance is injected in the peritumoral tissues, where the lymphatics are preserved and are thought to be draining the tumor region. Both substances have particle sizes that



enable them to enter into the afferent lymphatics of the lymph node, and become trapped within the lymph node parenchyma (Figure 3). This enables the detection of the lymph node with the highest signal, either radioactivity measured by a gamma probe, or visually as the blue node. The size of the radiocolloid particles is different in the various radiocolloid preparations that are commercially available, and smaller particles pass through to the second tier nodes more easily and rapidly [24]. Many investigators have supported the use of both detection methods simultaneously, for increased specificity and sensitivity [23].

Methods to measure the success of the SLN procedure are variable. In early studies, patients were consented for an investigational trial and the SLN procedure followed by a typical lymph node dissection. The detection rate of at least one or more sentinel node(s) is the first variable that is measured; some patients will not have an SLN that is detectable using the methods described above. Most studies report high (>90-95%) detection rates for most tumor types [25]. The predictive power of the SLN should also be measured. In other words, how well does the SLN predict the status of the entire regional lymph node basin? The endpoints of the effect of SLN on survival and regional recurrence can only be assessed in randomized trial assessing the SLN procedure alone vs. the full lymph node dissection. In breast cancer and in melanoma, the risk of regional recurrence in SLN alone is low (usually <5%) [26-28]. The SLN is often the only positive node in the majority of the patients [29], and because of this, some studies have questioned the necessity of the completion procedure in patients with a positive SLN [30, 31]. Importantly, morbidity is reduced when a complete lymph node dissection is not performed [19]. Despite all of the literature that suggests the SLN procedure is safe, beneficial, and decreases morbidity, there are investigators and clinicians who do not believe that it should be the standard of care and that it was prematurely adopted [19, 22, 25, 32-35].

From the pathologist's perspective, handling of the sentinel node is important because it requires special care. One concern that pathologists may have is the safety of handling the radioactive sentinel lymph node. Some departments require quarantine of the tissues for a period of time, which makes intraoperative margin assessment by frozen section impossible. The literature on the safety of handling these specimens demonstrates that there is negligible risk to the person doing gross examination, except in the unlikely scenario of very high specimen volume handled all by one person [36]. Therefore, it is probably not necessarily to delay processing or to store the specimens in any special type of container. It is recommended to have radiation safety training for all

individuals who come into contact with these specimens, from transport staff to the person performing the gross examination. There is essentially no risk in the histology laboratory or for other downstream processes.

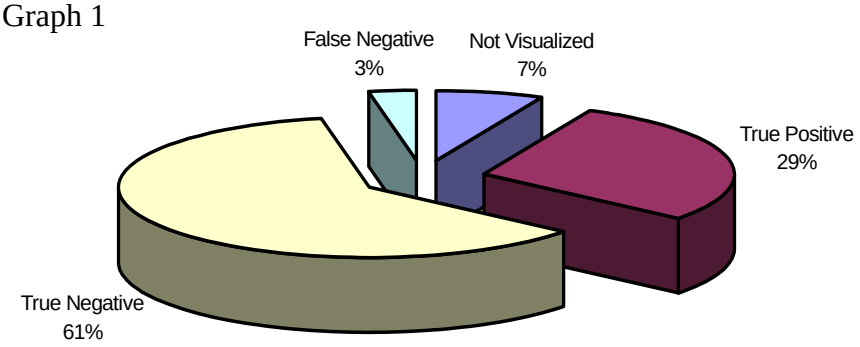
The role for intra-operative assessment is unclear. In breast cancer and melanoma, grossly positive nodes are usually easily diagnosed intra-operatively by frozen section or imprint cytology [37]. The false negative rate for micrometastases, however, is high [38]. The gross and histological handling of sentinel lymph nodes is far from standardized [39]. It is clear from the vast literature on this subject that the more sections that are examined and the finer the detail at which they are examined (i.e., immunohistochemistry), the more micrometastases will be picked up [27, 40]. And, it is also clear that missed micro-metastases are responsible for a significant number of failures of the SLN procedure with recurrence in the lymph node basin [27, 28]. The important role for IHC in detection of micro-metastases has been clearly established, but again, no standardized approach has been adopted.

Sentinel Lymph Nodes in Head and Neck Cancers

In the head and neck, we are in the initial phases of investigation of the SLN procedure for treatment of the neck. Multiple small series have been published that have shown the feasibility of the procedure and initial results were considered to be promising. Initial studies determined that the SLN was not effective in patients with clinically positive necks and may not detect grossly positive lymph nodes. This is most likely due to utilization of alternate lymphatic channels when metastases replacing lymph nodes and tumor plugs in the lymphatic channels block lymphatic flow [41, 42]. Obviously, in this situation, the blue dye or radio-colloid will not flow through these lymphatic channels either. Therefore, it has become clear that the SLN in head and neck cancer will be most useful in clinically N0 necks and in patients with relatively small primary tumors (T1 or T2).

Clearly, the SLN procedure in HNSCC is feasible. Seventeen studies of SLN procedures in HNSCC have been summarized in Table 1 and Graph 1. An analysis of all of the data presented in those studies shows that the sensitivity in picking up at least one sentinel lymph node in HNSCC of various sites, by various detection methods, is approximately 93%. Almost all studies found more than 1 SLN per neck examined, with an overall average of 1.6 nodes SLNs per neck. The SLN harbored metastases in a mean of 29% of patients. The false negative rate of the SLN in these procedures showed a mean of 3.2%, with a range of 0-10%.

Graph 1



Several studies have highlighted the fact that experience in performing the SLN procedure is critical [43]. One author has recommended that at least 10 SLN with completion neck dissection before attempting the SLN procedure without subsequent neck dissection [41, 44]. Other authors have argued that the SLN procedure should only be performed as part of clinical trials, since it is far too premature for it to become an acceptable option for routine therapy [45].

Pathologic analysis of sentinel lymph nodes in head and neck cancer is variable in the reported studies, from those studies that examine one routine H&E from the nodes, to those that utilize step sections through the node, to studies that utilize a combination of step sections and immunohistochemistry. The studies that have utilized step sections and IHC to detect metastatic disease show an increased number of micro-metastases or isolated tumor cells that are detected only on these additional studies [46, 47]. In breast cancer, the definition of isolated tumor cells is a cluster that measures <.2 mm. Though the significance of micrometastatic disease is not entirely understood, it does appear to portend a worse prognosis [48-50].

In head and neck cancer, the incidence of micrometastases is relatively high, with up to 10% of patients with metastasis having small tumor foci (identified with standard pathologic analysis). The incidence increases when additional levels and immunohistochemistry are added to the workup. We do not fully understand the clinical importance of micrometastatic disease in HNSCC but is likely to have significant prognostic implications [44].

Problems in SLN for head and neck cancers

The most significant arguments against using SLN for head and neck cancer have arisen from the anatomical variation and the inconsistent drainage basins in the head and neck. The presence of "skip metastases" and aberrant drainage patterns has been regularly described in the literature [51]. This has led to some concern that the nodal hierarchy may not be consistent and that the "sentinel" nodes may be falsely negative, resulting in the skip patterns have been seen infrequently [52].

Interestingly, the argument of inconsistent drainage patterns is used to argue against SLN, but it could just as easily be used to support the use of SLN. Since the SLN procedure allows the surgeon to map and identify unusual drainage sites, it may allow for more extensive dissection in high risk areas that would not usually be sampled in a routine selective neck dissection [44, 53, 54]. Studies in other organ systems have shown that there is increased pick-up of positive nodes when the SLN procedure is used as opposed to lymph node dissection [55]. In some ways, the argument for using SLN in the head and neck may become that it will allow directed specialized study of high-risk nodes in patients who are otherwise at lower risk for occult metastases. This is a similar argument that has been used for SLN in colon cancer, where the lymph nodes are removed anyway, but the procedure will allow the pathologist to examine certain nodes in greater detail [56-58].

Another area of concern in the use of SLN in HNSCC is the fact that radiated tissues are not suitable for the procedure since the drainage flow patterns are greatly altered or even destroyed by the radiation induced tissue damage. In today's era of treating HNSCC, primary radiation is becoming a main-stay of treatment for some cancers, and this will certainly affect the applicability of SLN procedures [9, 59]. It appears that prior chemotherapy may also increase the risk of false negative SLN [58, 60]. Interestingly, however, the SLN procedure has been also proposed to be helpful in identifying unusual patterns of lymphatics in post-radiation patients that are being treated by salvage surgery [61].

The recurrence of carcinoma in the neck with the need for salvage surgery has a poor prognosis [8, 62]. Therefore, some authors have expressed concern that false negatives in SLN would be unacceptable. This argument may be counteracted, however, by the fact that using immunohistochemistry can up-stage lymph nodes significantly, with one study suggesting detection of metastases in 2/24 patients with H&E increased to 14/24 patients with IHC [63]. Therefore, patients may actually be staged more accurately by use of the SLN procedure when a specific protocol including IHC is used for examining the pathology specimens [44, 64].

Finally, several studies have highlighted the fact that floor of mouth cancers have produced significantly high false negative rates in using the SLN procedure. The authors have postulated that the primary tumor signal masks the signal of the SLN [24].

Recommendations for practice

SLN procedure for HNSCC will more than likely come into use in some centers, but is unlikely to become the standard of care within the next five years. Although initial results are promising, there are still some unresolved problems with the procedure, including the issues with certain sub-sites, previously treated patients, and most authors are suggesting caution before making the SLN standard of care [64]. Some authors have described enhanced procedures that combine the use of SLN localization with the results of pre-procedure PET scanning or combine SLN with fine needle aspiration [65, 66]

For the pathologist, the question will become how to properly analyze the SLN for HNSCC. From all of the literature in breast cancer and melanoma on handling SLNs, it is clear that specialized assessment for SLNs is needed. The most appropriate handling will include specialized fresh assessment, grossing, multiple histological sections, and immuhistochemistry.

The first question is whether the SLN should be assessed in the intra-operative setting and how. In the breast and melanoma literature, the intra-operative assessment of the SLN has been shown to be fraught with error using either touch/imprint cytology or frozen sections [38, 67, 68]. The low sensitivity and high specificity are thought to be because of sampling errors, particularly for micrometastases, and also because the morphology of breast and melanoma cells can be subtle. In HNSCC, sensitivity and specificity is likely to be somewhat higher, since the morphology of metastatic SCC is usually not subtle [69]. The risks of inadequate sampling of micro-metastatic lesions will still remain high.

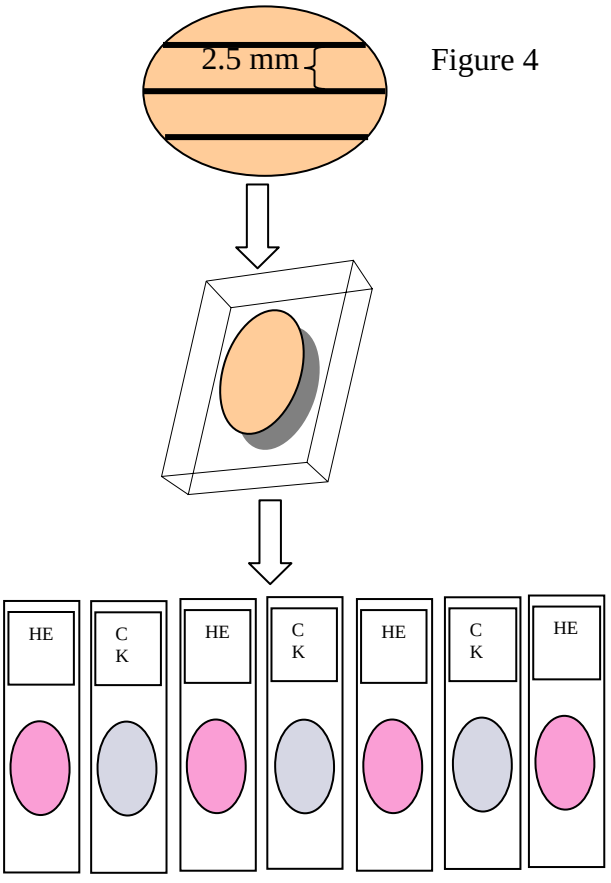


Figure 4

Grossing and histology of the SLN should also be standardized, at least within each institution. Ideally, the pathologist will visualize of as much as the node as possible (Figure 4). Serially sectioning larger SLNs at cassette-appropriate intervals (i.e., 2.5 mm thickness slices) and submission of the entire node are important. If the node is positive on initial H&E section, no further workup is necessary. If the initial H&E is negative, additional H&E sections (step sections) and intervening immunohistochemical staining will optimize detection of micrometastases. In many practices with turnaround time concerns, however, waiting to review the initial section before obtaining additional levels and immunohistochemical stains could result in a significant delays, and therefore up front SLN protocols may be implemented. The optimal number of slides to be examined and the number of IHC stains has not been determined, though it is clear from the literature that the more sections the pathologists sees, smaller and smaller tumor deposit will not escape detection. If SLN becomes an acceptable

alternative to elective selective neck dissection in HNSCC, discussions between pathologists, surgeons, oncologists and radiation oncologists and close interactions between these physicians will become critical. All of our clinician colleagues should be aware of the false negative rate of intraoperative assessment (frozen section and cytology), because there will be a need for a completion neck dissection as a second procedure in these intraoperative false negative cases.

Despite the initial promising results in these studies of SLN in HNSCC, it still remains to be seen with larger clinical trials and randomized studies, whether the SLN procedure will serve the purpose of adequately staging patients and with no negative effects on long-term survival [70-72]. Furthermore, standardization of the approach and protocols, and determination of the optimal pathologic workup should precede widespread implantation of the SLN procedure in head and neck surgery practices.

Table 1: Studies of SLN in head and neck cancers. The detection methods utilized radiocolloid (RC) with or without the addition of blue dye (Dye). The number of patients with an identifiable SLN is given, as is the average number of SLNs detected per patient. The number of SLNs that were positive, of the total number detected in the study and the number of patients who had a negative SLN and another positive node in the neck dissection are both listed. The type of pathologic analysis, when described, is listed.

Author	Year	Method	Number	Identification of an SLN in the patients	Avg # of nodes	Positive SLN in pt	SLN- (pN+)	Pathology
Koch [73]	1998	RC	5	3/5	2.3	2/3	0/3	
Shoaib [74]	2001	Dye/RC	40	36/40	2.2	16/36	1/36	One H&E
Alex [75]	2001	RC	15	14/15	3.1	1/14	0/14	
Taylor [76]	2001	RC	11	9/11	2.0	4/9	0/9	One H&E
Werner [77]	2001	RC	48	48/48	NA	10/48	5/48	NA
Ross^ [64]	2002	RC	316	301/316	NA	76/301	8/301	Variable
Pitman [42]	2002	RC	20	19/20	2.9	2/19	1/19	
Ionna [53]	2002	Dye/RC	41	39/41	1.1	4/39	0/39	
Civantos [66]	2003	RC	18	18/18	NA	10/18	2/18	One H&E & IHC
Asthana[#] [78]	2003	Dye	32	30/32	NA	8/32	2/32	H&E
Kontio [47]	2004	Dye/RC	15	14/15	3.1	3/14	1/14	One H&E & IHC
Ross [44]	2004	Dye/RC	57	43/48	2.4	15/43	1/43*	Steps & IHC
Ross^ [79]	2004	Dye/RC	134	125/134	2.8	59/125	3/55**	Steps & IHC
Hoft [80]	2004	RC	50	46/50	3.2	12/46	0/36	Steps & IHC
Alex [24]	2004	RC	20	20/20	NA	3/20	0/20	NA
Niewuenhuis [81]	2005	RC	27	22/27	1.1	8/22	1/22	Steps & IHC
Payoux [82]	2005	RC	37	36/37	1.8	6/36	1/36	2 H&E
Total			886	823/886 (93%)	1.6	239/823 (29%)	26/823 (3.2%)	

*=no neck dissection performed, but patient recurred in the neck
[#]=Patient sample included both clinically N0 and clinically N+ necks
**=neck dissection only performed in subset (55/134) patients
^=Multiple centers participated
NA=Not available
H&E=Hematoxylin and eosin; Steps=step sections; IHC=immunohistochemistry stains

References

1. Smith, G.I., et al., *Management of the neck in patients with T1 and T2 cancer in the mouth.* British Journal of Oral & Maxillofacial Surgery, 2004. **42**(6): p. 494-500.
2. Mastronikolis, N.S., et al., *The management of squamous cell carcinoma of the neck. The Birmingham UK experience.* European Journal of Surgical Oncology, 2005. **31**(5): p. 461-6.
3. Moore, M.G. and N. Bhattacharyya, *Effectiveness of chemotherapy and radiotherapy in sterilizing cervical nodal disease in squamous cell carcinoma of the head and neck.* Laryngoscope, 2005. **115**(4): p. 570-3.
4. Hosal, A.S., et al., *Selective neck dissection in the management of the clinically node-negative neck.* Laryngoscope, 2000. **110**(12): p. 2037-40.
5. Jose, J., A.P. Coatesworth, and K. MacLennan, *Cervical metastases in upper aerodigestive tract squamous cell carcinoma: histopathologic analysis and reporting.* Head & Neck, 2003. **25**(3): p. 194-7.
6. Clark, J., et al., *Outcome of treatment for advanced cervical metastatic squamous cell carcinoma.* Head & Neck, 2005. **27**(2): p. 87-94.
7. Mira, E., et al., *Efficacy of selective lymph node dissection in clinically negative neck.* Otolaryngology Head & Neck Surgery, 2002. **127**(4): p. 279-83.
8. Duvvuri, U., et al., *Elective neck dissection and survival in patients with squamous cell carcinoma of the oral cavity and oropharynx.* Laryngoscope, 2004. **114**(12): p. 2228-34.
9. Andry, G., M. Hamoir, and C.R. Leemans, *The evolving role of surgery in the management of head and neck tumors.* Current Opinion in Oncology, 2005. **17**(3): p. 241-8.
10. Sparano, A., et al., *Multivariate predictors of occult neck metastasis in early oral tongue cancer.* Otolaryngology Head & Neck Surgery, 2004. **131**(4): p. 472-6.
11. Sarno, A., et al., *Does unnecessary elective neck treatment affect the prognosis of N0 laryngeal cancer patients?* Acta Oto Laryngologica, 2004. **124**(8): p. 980-5.
12. van Wilgen, C.P., et al., *Shoulder and neck morbidity in quality of life after surgery for head and neck cancer.* Head & Neck, 2004. **26**(10): p. 839-44.
13. El Ghani, F., et al., *Shoulder function and patient well-being after various types of neck dissections.* Clinical Otolaryngology & Allied Sciences, 2002. **27**(5): p. 403-8.
14. Cappiello, J., et al., *Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study.* Laryngoscope, 2005. **115**(2): p. 259-63.
15. Genden, E.M., et al., *Complications of neck dissection.* Acta Oto Laryngologica, 2003. **123**(7): p. 795-801.
16. Kovacs, A.F., et al., *Positron emission tomography in combination with sentinel node biopsy reduces the rate of elective neck dissections in the treatment of oral and oropharyngeal cancer.* Journal of Clinical Oncology, 2004. **22**(19): p. 3973-80.
17. Ojiri, H., et al., *Lymph nodes of patients with regional metastases from head and neck squamous cell carcinoma as a predictor of pathologic outcome: size changes*

at CT before and after radiation therapy.[see comment]. Ajnr: American Journal of Neuroradiology, 2002. **23**(10): p. 1627-31.
18. Schwartz, D.L., et al., *FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma.* International Journal of Radiation Oncology, Biology, Physics, 2005. **61**(1): p. 129-36.
19. Lee, K.K., et al., *Sentinel lymph node biopsy.* Clinics in Dermatology, 2004. **22**(3): p. 234-9.
20. Cabanas, R.M., *An approach for the treatment of penile carcinoma.* Cancer, 1977. **39**(2): p. 456-66.
21. Gould, E.A., et al., *Observations on a "sentinel node" in cancer of the parotid.* Cancer, 1960. **13**: p. 77-8.
22. Schulze, T., A. Bembenek, and P.M. Schlag, *Sentinel lymph node biopsy progress in surgical treatment of cancer.* Langenbecks Archives of Surgery, 2004. **389**(6): p. 532-50.
23. Radovanovic, Z., et al., *Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer*. European Journal of Surgical Oncology, 2004. **30**(9): p. 913-7.
24. Alex, J.C., *The application of sentinel node radiolocalization to solid tumors of the head and neck: a 10-year experience.* Laryngoscope, 2004. **114**(1): p. 2-19.
25. Singh-Ranger, G. and K. Mokbel, *The sentinel node biopsy is a new standard of care for patients with early breast cancer.* International Journal of Fertility & Womens Medicine, 2004. **49**(5): p. 225-7.
26. Morton, D.L., et al., *Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial.* Annals of Surgery, 2005. **242**(3): p. 302-11.
27. Li, L.X., et al., *Pathologic review of negative sentinel lymph nodes in melanoma patients with regional recurrence: a clinicopathologic study of 1152 patients undergoing sentinel lymph node biopsy.* American Journal of Surgical Pathology, 2003. **27**(9): p. 1197-202.
28. Jeruss, J.S., et al., *Axillary recurrence after sentinel node biopsy.* Annals of Surgical Oncology, 2005. **12**(1): p. 34-40.
29. Cox, C., et al., *The clinical relevance of positive sentinel nodes only versus positive nonsentinel lymph nodes in breast cancer patients.* American Journal of Surgery, 2003. **186**(4): p. 333-6.
30. Pu, L.L., et al., *Prevalence of additional positive lymph nodes in complete lymphadenectomy specimens after positive sentinel lymphadenectomy findings for early-stage melanoma of the head and neck.[see comment]*. Plastic & Reconstructive Surgery, 2003. **112**(1): p. 43-9.
31. Mack, L.A. and J.G. McKinnon, *Controversies in the management of metastatic melanoma to regional lymphatic basins.* Journal of Surgical Oncology, 2004. **86**(4): p. 189-99.
32. Kell, M.R. and M.J. Kerin, *Sentinel lymph node biopsy.* Bmj, 2004. **328**(7452): p. 1330-1.
33. Gipponi, M., et al., *New fields of application of the sentinel lymph node biopsy in the pathologic staging of solid neoplasms: review of literature and surgical perspectives.* Journal of Surgical Oncology, 2004. **85**(3): p. 171-9.

34. Schwartz, G.F., *Clinical practice guidelines for the use of axillary sentinel lymph node biopsy in carcinoma of the breast: current update.* Breast Journal, 2004. **10**(2): p. 85-8.
35. Thomas, J.M. and M.A. Clark, *Sentinel lymph node biopsy: not yet standard of care for melanoma.[see comment][comment]*. Bmj, 2004. **329**(7458): p. 170-1.
36. Hunt, J.L., Z.W. Baloch, and V.A. LiVolsi, *Sentinel lymph node evaluation for tumor metastasis.* Seminars in Diagnostic Pathology, 2002. **19**(4): p. 263-77.
37. Wada, N., et al., *Evaluation of intraoperative frozen section diagnosis of sentinel lymph nodes in breast cancer.* Japanese Journal of Clinical Oncology, 2004. **34**(3): p. 113-7.
38. Schrenk, P., et al., *Intraoperative frozen section examination of the sentinel lymph node in breast cancer.* Rozhledy, 2005: p. 217-22.
39. Viale, G., et al., *Histopathologic examination of axillary sentinel lymph nodes in breast carcinoma patients.* Journal of Surgical Oncology, 2004. **85**(3): p. 123-8.
40. Cohen, C., et al., *Immunohistochemical evaluation of sentinel lymph nodes in breast carcinoma patients.* Applied Immunohistochemistry & Molecular Morphology, 2002. **10**(4): p. 296-303.
41. Ross, G.L., et al., *The First International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer and adoption of a multicenter trial protocol.* Annals of Surgical Oncology, 2002. **9**(4): p. 406-10.
42. Pitman, K.T., et al., *Sentinel lymph node biopsy in head and neck squamous cell carcinoma.* Laryngoscope, 2002. **112**(12): p. 2101-13.
43. Posther, K.E., et al., *Sentinel node skills verification and surgeon performance: data from a multicenter clinical trial for early-stage breast cancer.* Annals of Surgery, 2005. **242**(4): p. 593-9.
44. Ross, G.L., et al., *Improved staging of cervical metastases in clinically node-negative patients with head and neck squamous cell carcinoma.* Annals of Surgical Oncology, 2004. **11**(2): p. 213-8.
45. Rigual, N.R. and S.M. Wiseman, *Neck dissection: current concepts and future directions.* Surgical Oncology Clinics of North America, 2004. **13**(1): p. 151-66.
46. Stoeckli, S.J., et al., *Histopathological features of occult metastasis detected by sentinel lymph node biopsy in oral and oropharyngeal squamous cell carcinoma.* Laryngoscope, 2002. **112**(1): p. 111-5.
47. Kontio, R., et al., *Sentinel lymph node biopsy in oral cavity squamous cell carcinoma without clinically evident metastasis.* Head & Neck, 2004. **26**(1): p. 16-21.
48. Rivera, M., et al., *Controversies in surgical pathology: minimal involvement of sentinel lymph node in breast carcinoma: prevailing concepts and challenging problems.* International Journal of Surgical Pathology, 2004. **12**(4): p. 301-6.
49. Calhoun, K.E., et al., *Nonsentinel node metastases in breast cancer patients with isolated tumor cells in the sentinel node: implications for completion axillary node dissection.* American Journal of Surgery, 2005. **190**(4): p. 588-91.
50. Kuijt, G.P., et al., *The prognostic significance of axillary lymph-node micrometastases in breast cancer patients.* European Journal of Surgical Oncology, 2005. **31**(5): p. 500-5.

51. Byers, R.M., et al., *Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue.* Head & Neck, 1997. **19**(1): p. 14-9.
52. Mamelle, G., *Selective neck dissection and sentinel node biopsy in head and neck squamous cell carcinomas.* Recent Results in Cancer Research, 2000. **157**: p. 193-200.
53. Ionna, F., et al., *Prognostic value of sentinel node in oral cancer.* Tumori, 2002. **88**(3): p. May-Jun.
54. Mozzillo, N., et al., *Therapeutic implications of sentinel lymph node biopsy in the staging of oral cancer.* Annals of Surgical Oncology, 2004. **11**(3 Suppl).
55. Doubrovsky, A., et al., *Sentinel node biopsy provides more accurate staging than elective lymph node dissection in patients with cutaneous melanoma.* Annals of Surgical Oncology, 2004. **11**(9): p. 829-36.
56. Bilchik, A.J., et al., *Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial.* Journal of Clinical Oncology, 2001. **19**(4): p. 1128-36.
57. Smith, F.M., et al., *Sentinel nodes are identifiable in formalin-fixed specimens after surgeon-performed ex vivo sentinel lymph node mapping in colorectal cancer.* Annals of Surgical Oncology, 2005. **12**(6): p. 504-9.
58. Kovacs, A.F., et al., *Sentinel node biopsy as staging tool in a multimodality treatment approach to cancer of the oral cavity and the oropharynx.* Otolaryngology Head & Neck Surgery, 2005. **132**(4): p. 570-6.
59. Bernardi, D., et al., *Treatment of head and neck cancer in elderly patients: state of the art and guidelines.* Critical Reviews in Oncology Hematology, 2005. **53**(1): p. 71-80.
60. Kovacs, A.F., et al., *Pattern of drainage in sentinel lymph nodes after intra-arterial chemotherapy for oral and oropharyngeal cancer.* Journal of Oral & Maxillofacial Surgery, 2005. **63**(2): p. 185-90.
61. Pitman, K.T., *Sentinel node localization in head and neck tumors.* Seminars in Nuclear Medicine, 2005. **35**(4): p. 253-6.
62. Smith, B.D., et al., *Do PET and SNB reduce the rate of elective neck dissection? A hypothesis still in need of validation.* Journal of Clinical Oncology, 2005. **23**(12): p. 2874-5.
63. Yoshida, K., et al., *Immunohistochemical detection of cervical lymph node micrometastases from T2N0 tongue cancer.* Acta Oto Laryngologica, 2005. **125**(6): p. 654-8.
64. Ross, G., et al., *The use of sentinel node biopsy to upstage the clinically N0 neck in head and neck cancer.* Archives of Otolaryngology Head & Neck Surgery, 2002. **128**(11): p. 1287-91.
65. Nieuwenhuis, E.J., et al., *Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node?* Head & Neck, 2002. **24**(3): p. 282-9.
66. Civantos, F.J., et al., *Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry.* Head & Neck, 2003. **25**(1): p. 1-9.

67. Khalifa, K., et al., *The accuracy of intraoperative frozen section analysis of the sentinel lymph nodes during breast cancer surgery.* International Journal of Fertility & Womens Medicine, 2004. **49**(5): p. 208-11.
68. Gipponi, M., et al., *Sentinel lymph node biopsy in patients with Stage I/II melanoma: Clinical experience and literature review.* Journal of Surgical Oncology, 2004. **85**(3): p. 133-40.
69. Tschopp, L., et al., *The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx.* Otolaryngology Head & Neck Surgery, 2005. **132**(1): p. 99-102.
70. Dulguerov, P., I. Leuchter, and W. Lehmann, *Sentinel lymph node radiolocalization in head and neck squamous carcinoma: curious methods.* Laryngoscope, 2001. **111**(10): p. 1866-7.
71. Loree, T.R., *Sentinel lymph node biopsy for early stage clinical n0 squamous cell carcinoma of the oral cavity.* Annals of Surgical Oncology, 2004. **11**(8): p. 725-6.
72. Shah, J.P., *Extent of surgical intervention in case of N0 neck in head and neck cancer patients.* European Archives of Oto Rhino Laryngology, 2004. **261**(6): p. 293-4.
73. Koch, W.M., et al., *Gamma probe-directed biopsy of the sentinel node in oral squamous cell carcinoma.* Archives of Otolaryngology Head & Neck Surgery, 1998. **124**(4): p. 455-9.
74. Shoaib, T., et al., *The accuracy of head and neck carcinoma sentinel lymph node biopsy in the clinically N0 neck.* Cancer, 2001. **91**(11): p. 2077-83.
75. Alex, J.C., et al., *Sentinel lymph node radiolocalization in head and neck squamous cell carcinoma.* Laryngoscope, 2000. **110**(2 Pt 1): p. 198-203.
76. Taylor, R.J., et al., *Sentinel node localization in oral cavity and oropharynx squamous cell cancer.* Archives of Otolaryngology Head & Neck Surgery, 2001. **127**(8): p. 970-4.
77. Werner, J.A., et al., *Number and location of radiolabeled, intraoperatively identified sentinel nodes in 48 head and neck cancer patients with clinically staged N0 and N1 neck.* European Archives of Oto Rhino Laryngology, 2002. **259**(2): p. 91-6.
78. Asthana, S., et al., *Intraoperative neck staging using sentinel node biopsy and imprint cytology in oral cancer.* Head & Neck, 2003. **25**(5): p. 368-72.
79. Ross, G.L., et al., *Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial.[see comment].* Annals of Surgical Oncology, 2004. **11**(7): p. 690-6.
80. Hoft, S., et al., *Sentinel lymph-node biopsy in head and neck cancer.[see comment].* British Journal of Cancer, 2004. **91**(1): p. 124-8.
81. Nieuwenhuis, E.J., et al., *Histopathologic validation of the sentinel node concept in oral and oropharyngeal squamous cell carcinoma.* Head & Neck, 2005. **27**(2): p. 150-8.
82. Payoux, P., et al., *Effectiveness of lymphoscintigraphic sentinel node detection for cervical staging of patients with squamous cell carcinoma of the head and neck.* Journal of Oral & Maxillofacial Surgery, 2005. **63**(8): p. 1091-5.