Management of Oral Cancer

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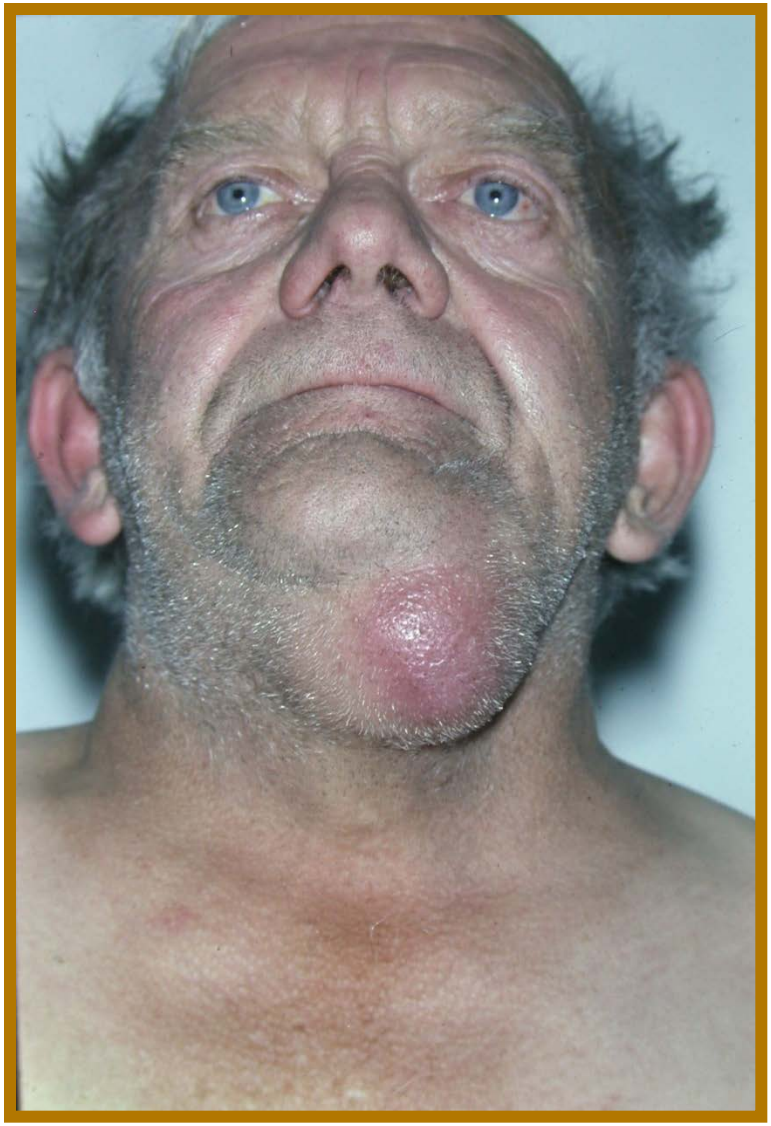
May 2013

Lecture Goals

- Diagnosis of Oral Cancer
- Surgical Management of Oral Cancer
- Management of the Neck
- Role of Adjuvant Therapy of Oral Cancer



- Worldwide: 640, 000 new cases each year
- US: 41,380 new cases each year(oral cavity and pharynx)
- Maryland: Approximately 650 new cases each year
- Deaths: 7,890 (oral cavity and pharynx)
- Approximately 50% of will survive 5 years

National Cancer Institute, 2013

Oral/Jaw Cancer 1991-2008
University of Maryland 2,554 patients

Cancer Oral Cavity/Jaws			
Epidermoid carcinoma.		1,044	
CIS		83	76%
Salivary (intra-oral)	147		
Sarcomas		48	
Lymphomas		35	
Metastatic		29	
Others		17	
		1,363	

Epidemiology

- Increase in Female patients
- Increase in young (<40 years) patients
- Increase in Non-smokers (Non-drinkers)

Relative 5-Year Survival Rate (%)

Oral Cavity

	1975-77	1984-86	1996-02
White	55	57	62*
Black	36	36	40
All rates	53	55	60*

*Rates 75-77 : 96-02 significant (p< 0.0.5)

CA Cancer J Clin 2007

- African American
- Lower income
- Higher grade tumor
- Male
- Less than 50% 5-year survival
- Age – not an independent predictor of disease free survival

Funk et. al Head & Neck Feb 2002

- Myth - Oral cancer is a disease of elderly men who abuse tobacco and alcohol and usually present with advanced disease

- Approximately 30% of new cases occur in young patients (less than 45 years of age)

- Human papillomavirus (HPV)

Diagnosis

- Ulceration
- Toothache
- Tooth mobility
- Pain
- Erythro/Leukoplakia
- Bleeding
- Otalgia
- Paresthesia
- Rolled border
- Non-healing extraction socket

- Any solitary lump, ulcer, white or red lesion persisting for more than 3 weeks or non-healing socket, numbness or unexplained loose tooth should be regarded as cancer until proven otherwise

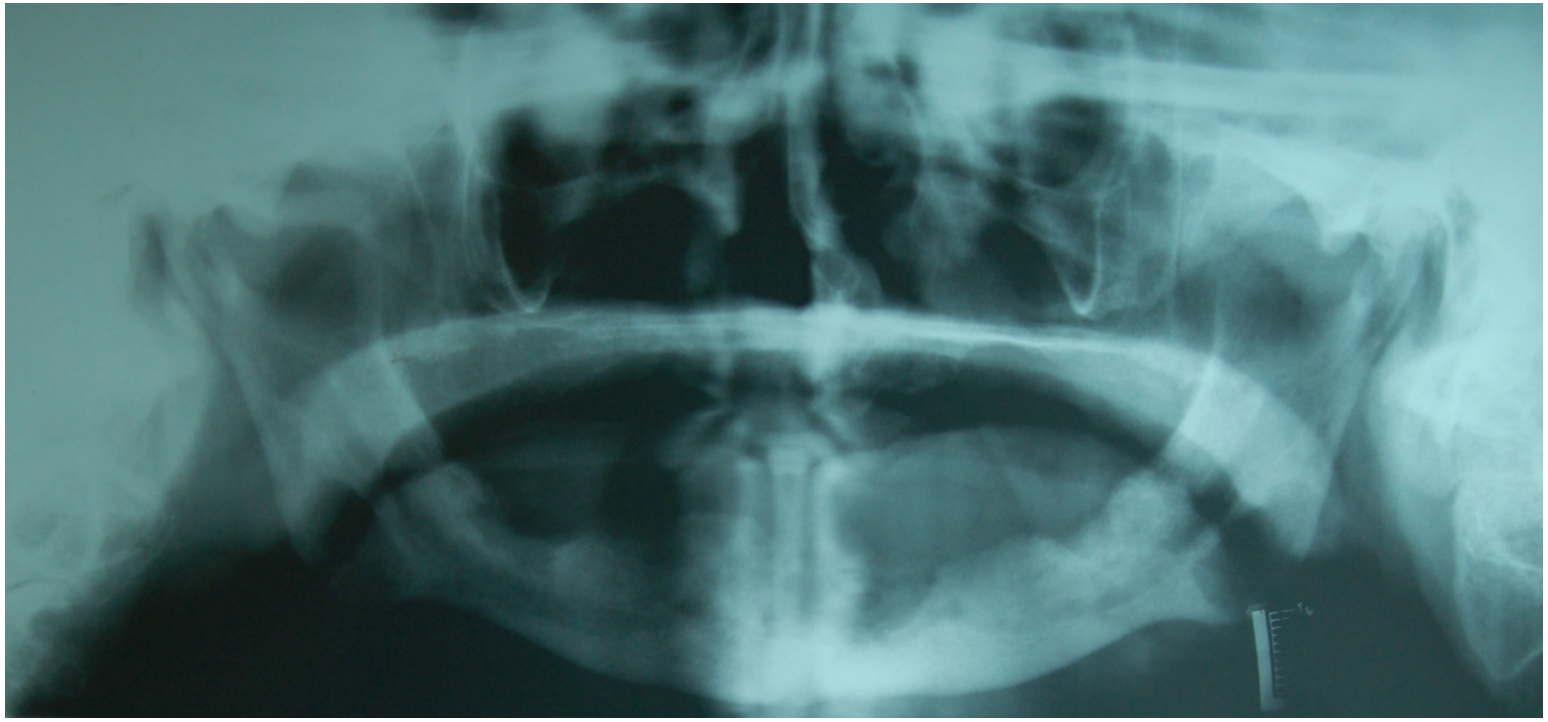
Scully C, Bagan J Oral Oncology 2009

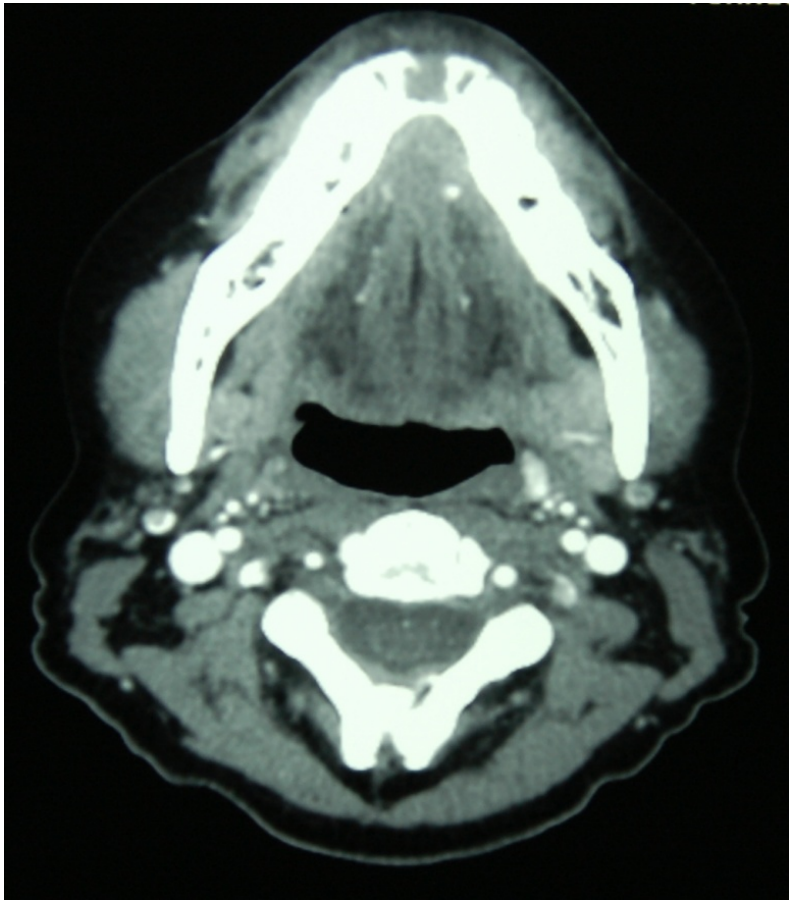
Imaging for Oral Cancer

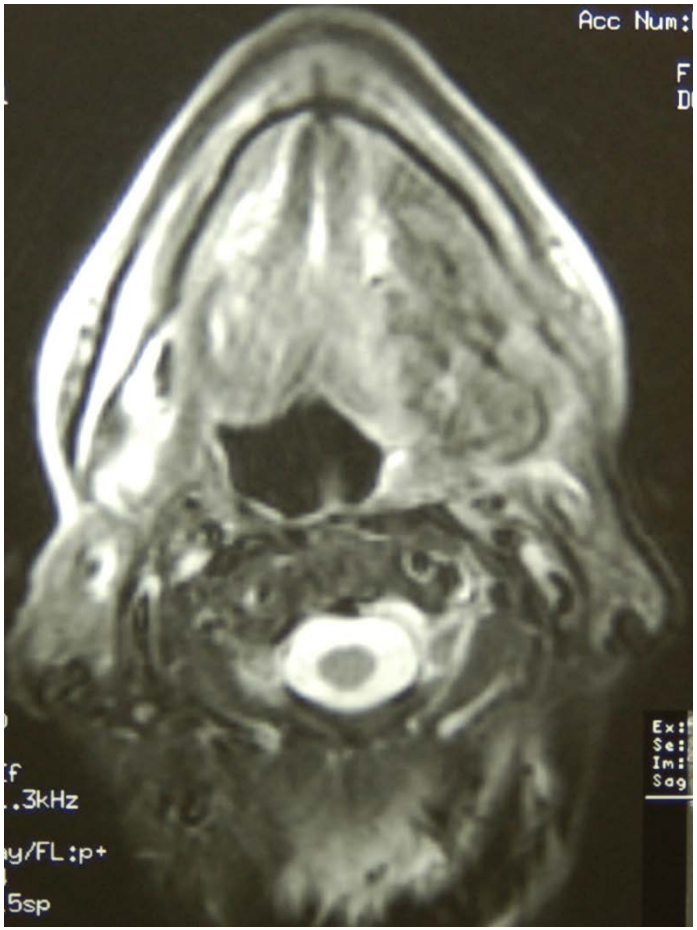
- Clinical exam is at best 70% accurate in detecting disease within the neck
- Help define margins/extent of disease/bony involvement
- Identify distant metastatic disease

Imaging

- Panorex
- CT scan with contrast
- MRI
- PET scan
- Bone Scan
- Ultrasound



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PET Scan

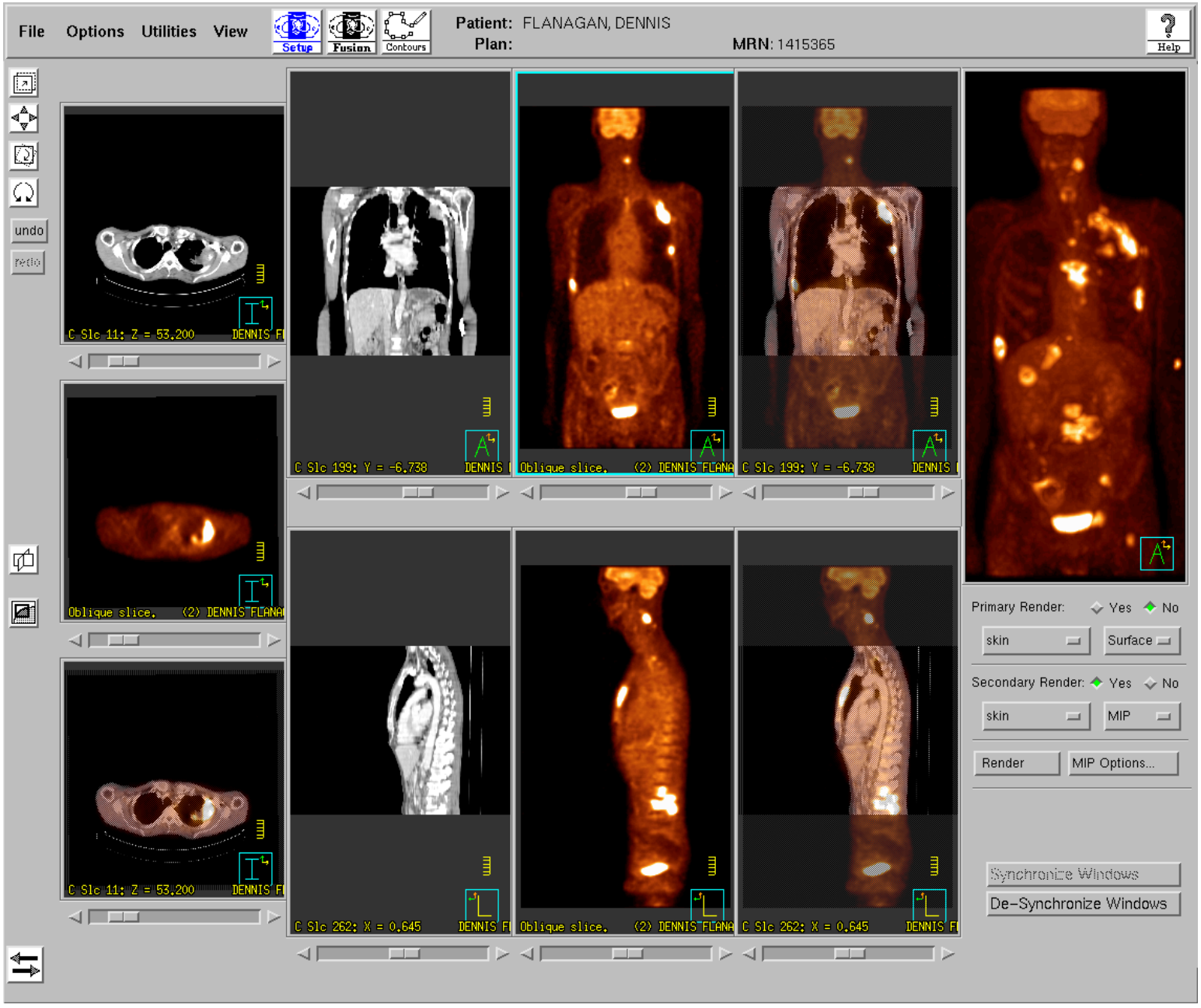
- Head and Neck Cancer – Diagnosis

	PET	CT
– Sensitivity	93%	66%
– Specificity	70%	56%

- Head and Neck Cancer – Staging

	PET	CT
– Sensitivity	87%	62%
– Specificity	89%	73%

Gambhir et al. J. of Nuclear Medicine Vol 42-Number 5 – May 2001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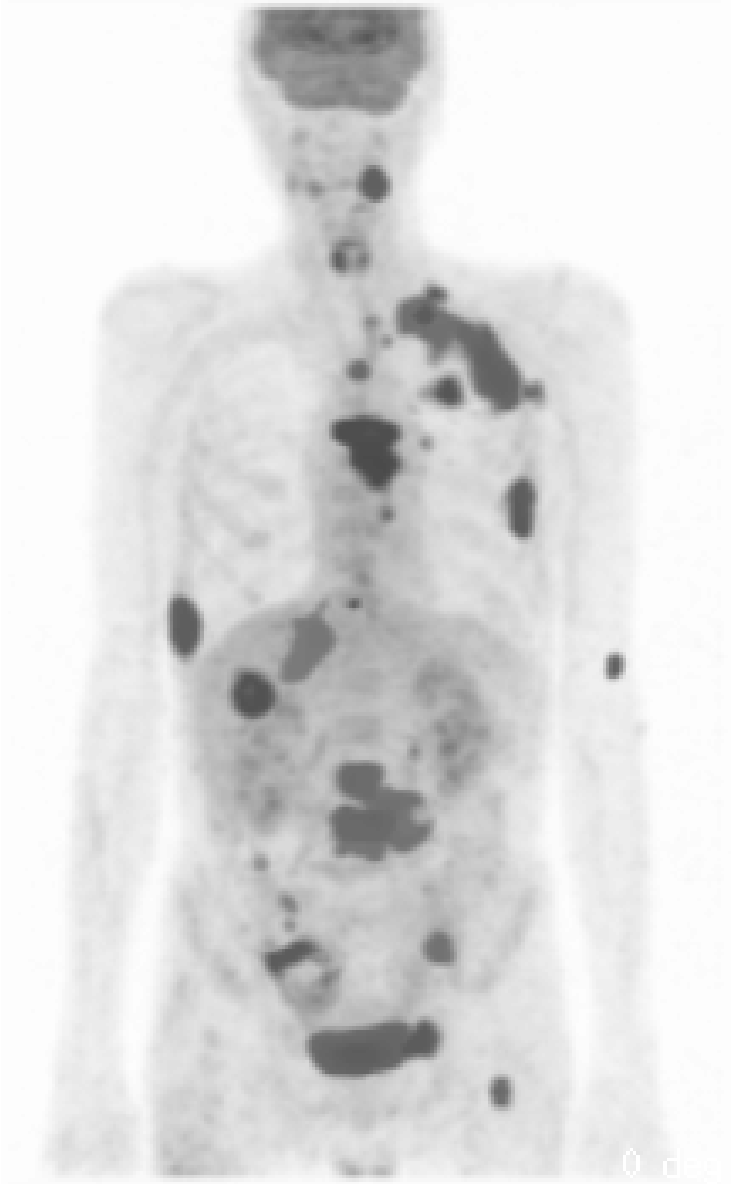


PET Scan in N0 Neck

- It is unlikely FDG-PET is superior in the detection of occult lymph node metastases in a palpably negative neck.

  Browner J et al Eur Arch Otolaryngol 2004

- Not sufficiently accurate in the N0 neck to rule out nodal metastases.

  Menda and Graham Semin Nuc Med 2005

PET Scan in N0 Neck

- In oral cancer 18FDG-PET Sensitivity 67% and Specificity 85% for neck sides.
- 3 False negatives <3mm.
- Negative test can exclude metastatic disease with high specificity.
- Surgical management of N0 necks should not be based on PET/CT alone due to a limited sensitivity for small deposits and a relatively high number of false positives.

Schoder H et al J Nuc Med 2006

PET Scan in Surveillance

Overall sensitivity and NPV of PET scans for recurrence were 92.5% and 94.8%, compared with 55.0% and 76.9% for conventional evaluation methods. In 156 routine scans, the diagnostic sensitivity, specificity, and NPV for locoregional recurrence were 90%, 91% and 97%, respectively, and the values for distant metastases and second primary cancers were 100%, 97% and 100%, respectively. PET scan may be a useful tool in routine surveillance for recurrence. The initial PET scan should be performed within 6months after completion of treatment and the proper timing of next routine PET scan for subclinical patient with initial negative PET might be 1year after initial PET scan.

Lee JC et al Oral Oncol 2007

PET Scan

- Currently in the 2007 NCCN Practice Guidelines for Oral Cancer PET Scanning is not recommended for diagnosis or follow up surveillance

TNM staging – Oral Cancer

- Tumor Size
  - T1 –T4
- Nodal Metastases
  - N1, N2a, N2b, N2c, N3
- Distant Metastases
  - M0, M1

- Attempt to stratify risk of recurrence and overall survival

TNM staging – Oral Cancer

- 5 year survival
  - Stage I
    - 75-90%
  - Stage II
    - 70%
  - Stage III
    - 50%
  - Stage IV
    - 30%

Clinical Management of Oral Cancer

- Oral Cancer is a Multidisciplinary disease and may involve therapy with surgery, RT and chemotherapy with novel therapies based on advances in molecular biology and gene therapy being increasingly introduced in clinical trials.

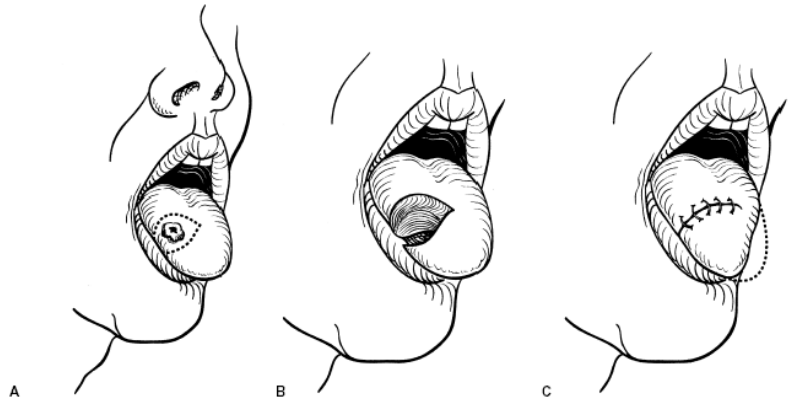
Clinical Management of Oral Cancer

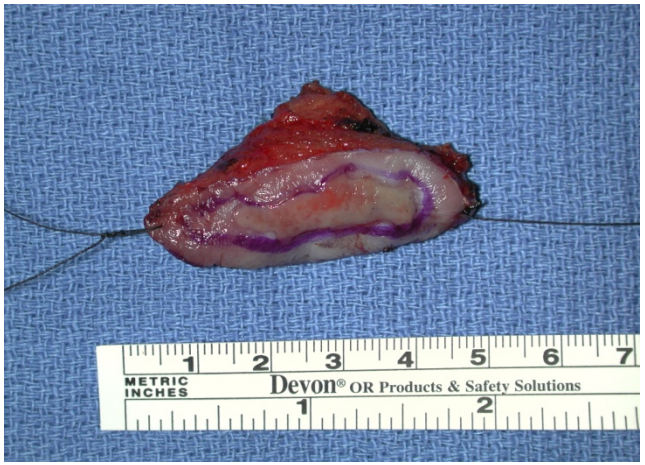
- Stage I/II disease is currently managed with one modality and although survival rates are comparable between Surgery vs Radiation therapy, surgery is the preferred primary modality for Oral Cancer in the USA
- Increasing use of elective neck dissection has lead to approximately 33% of “early” stage disease being upstaged

Clinical Management of oral cancer

- Stage III/IV is usually treated with multimodality treatment. In resectable disease primary surgery with post-operative RT or post operative concomitant Chemo/RT in cases at high risk for failure is used.
- In **Oral** cancer Chemo/RT is reserved for unresectable disease.

SCCA of the Tongue





- Peroral resection is the most common approach for T1 and T2 lesions.
- Perform a partial glossectomy with a 1 to 1.5 cm margin
- Defect is closed primarily
- Anterior tip defects will lead to speech defects
- Posterior defects may interfere with swallowing

SCCA of the Tongue

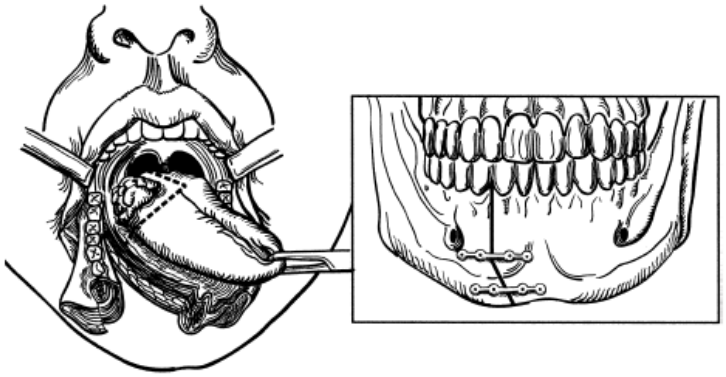


Figure 5–10. The mandibulotomy approach to tumors of the posterior oral cavity. Biplane fixation of the mandible is necessary.

- Posterior defects often require a mandibulotomy for improved access
- Resection is carried out as normal
- Mandible is fixed with rigid fixation

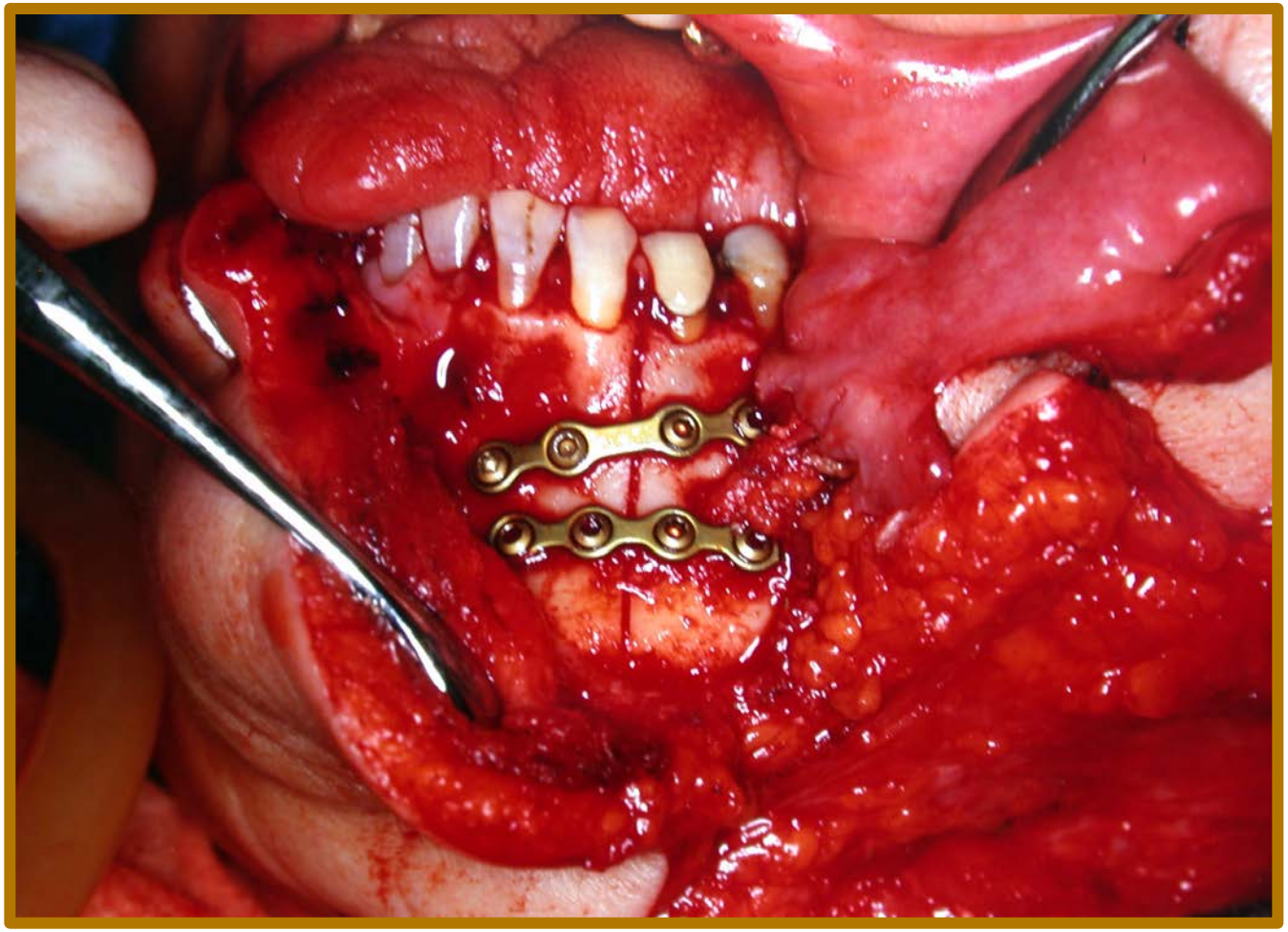
Access Surgery

- Lip-split mandibulotomy
- Pull-through
- Intra-oral
- Trans-oral (robotic assist)

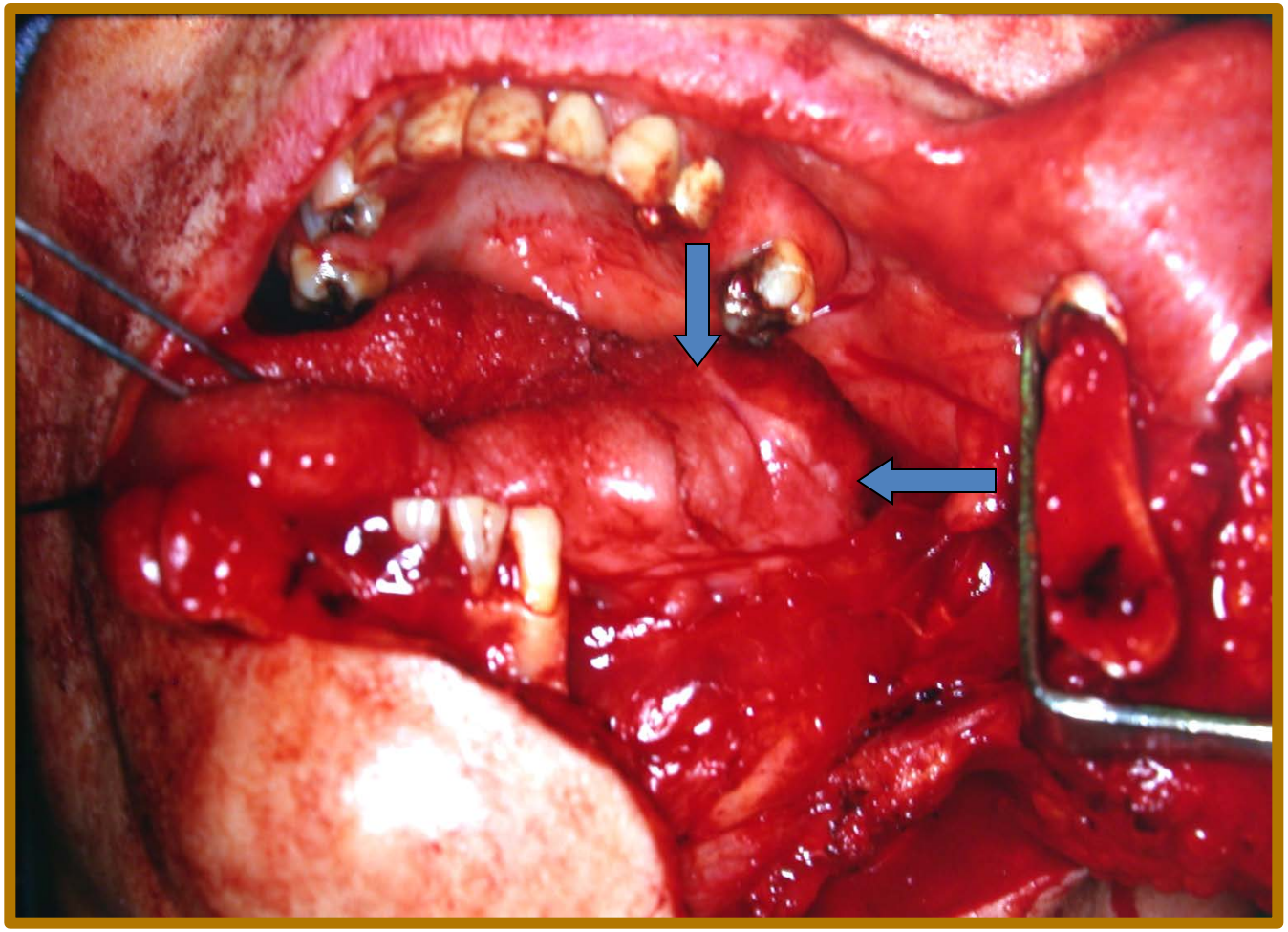
Mandibulotomy Approach

Mandibulotomy Approach

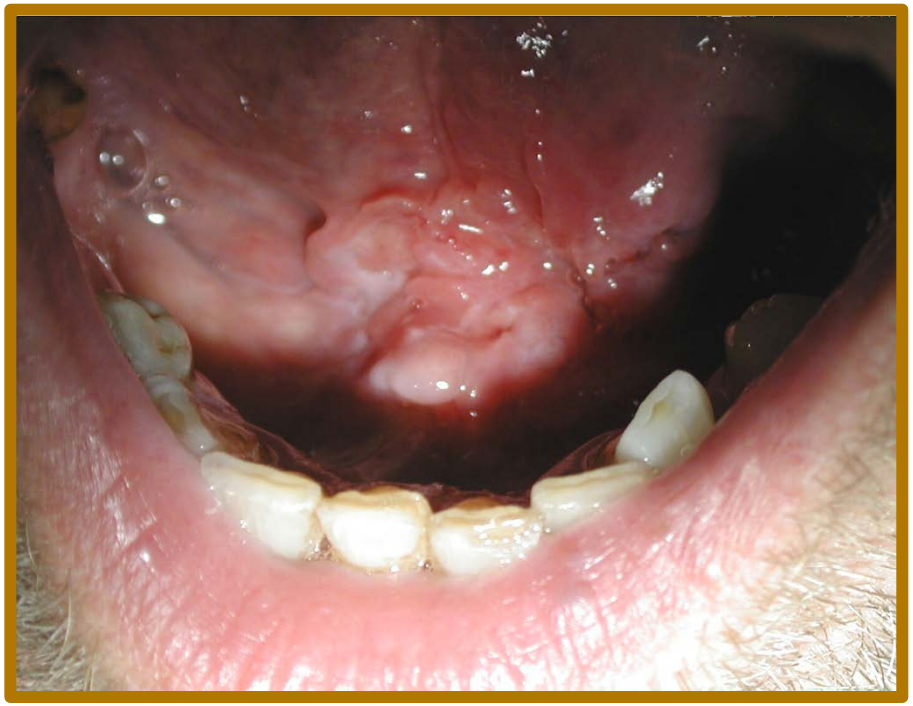
Mandibulotomy Approach

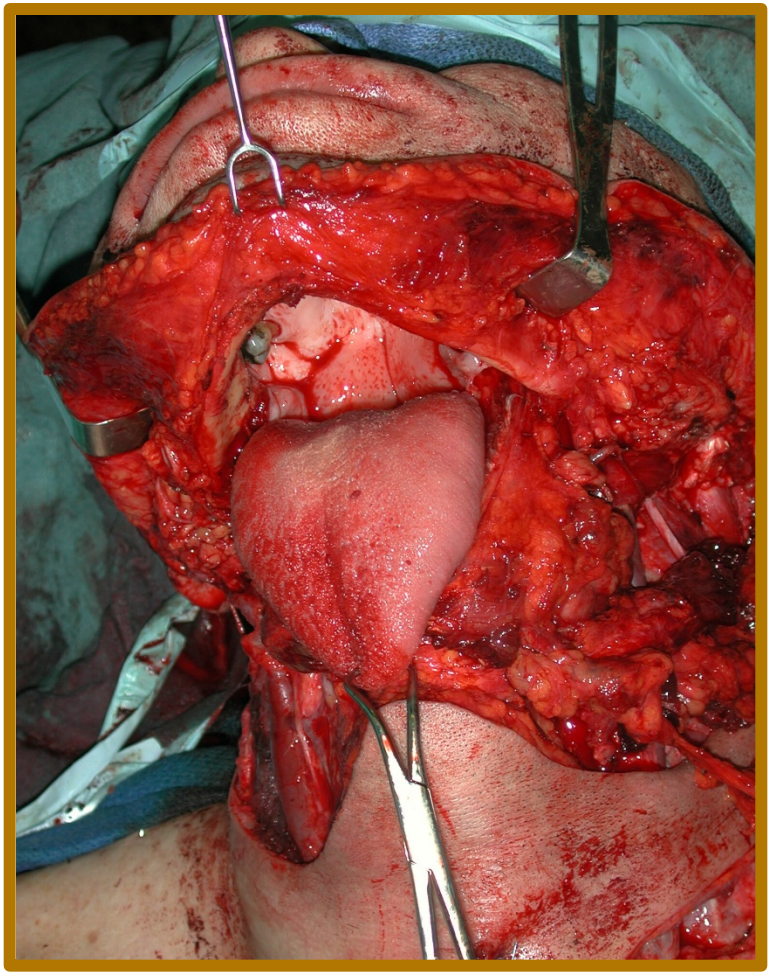


Mandibulotomy Approach

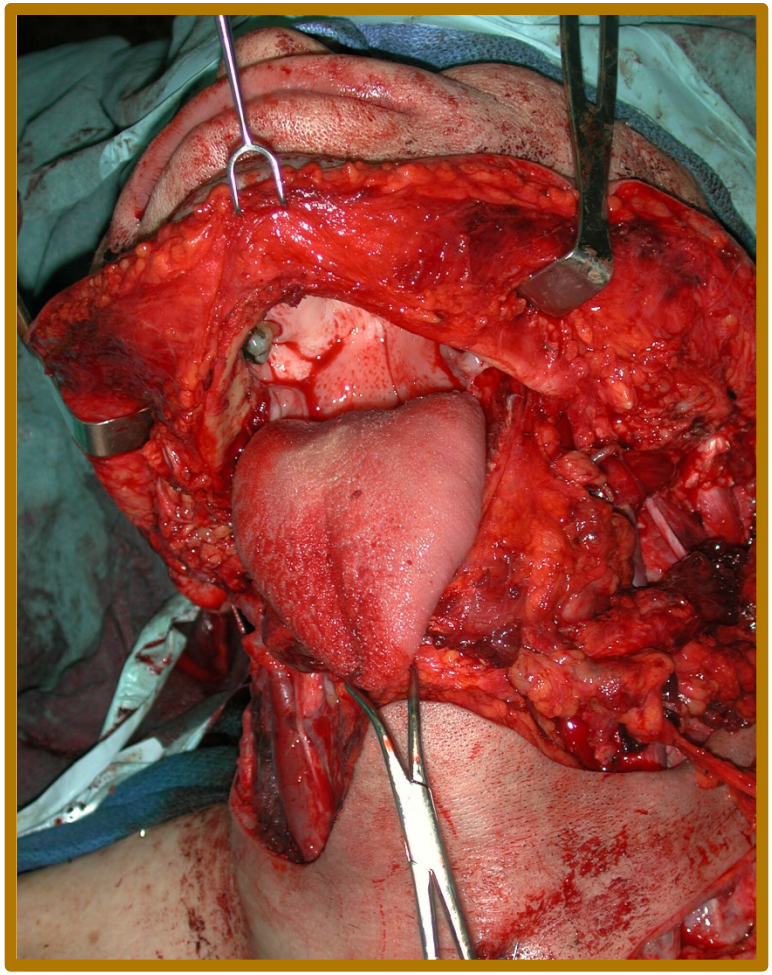


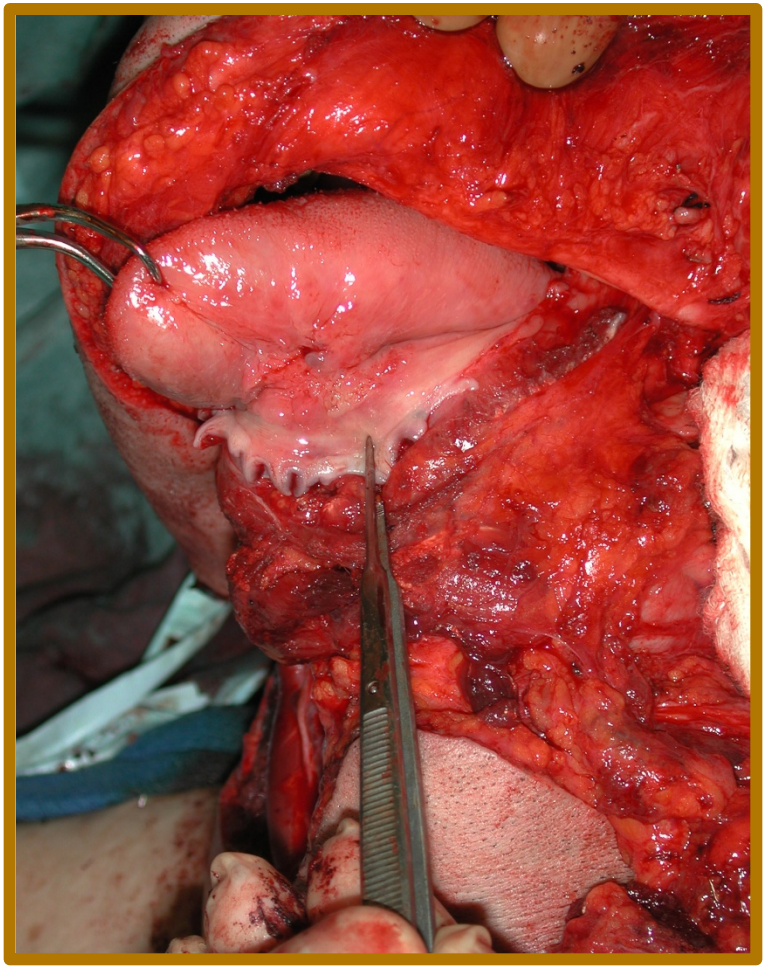
Mandibular Pull-Through





Mandibular Pull-Through





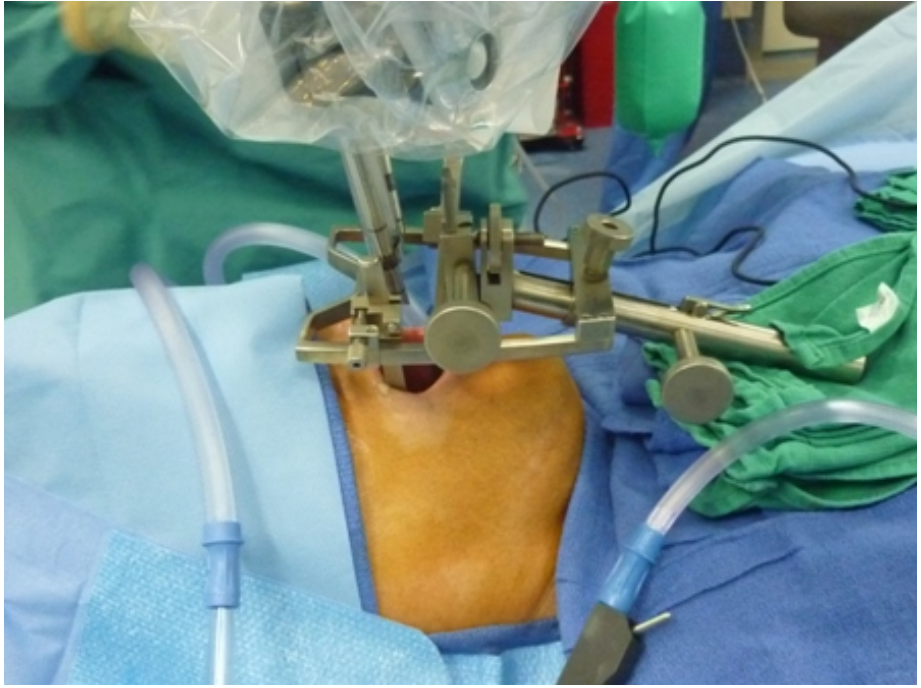
Mandibulotomy vs Pull Through

- Resection margins the same
- Clinical Exam, No difference in function
- Mandibulotomy patients had significantly better speech, swallowing and chewing.
- No significant difference esthetically.

Devine JC et al IJOMS 2001

Robotic Surgery


da Vinci S

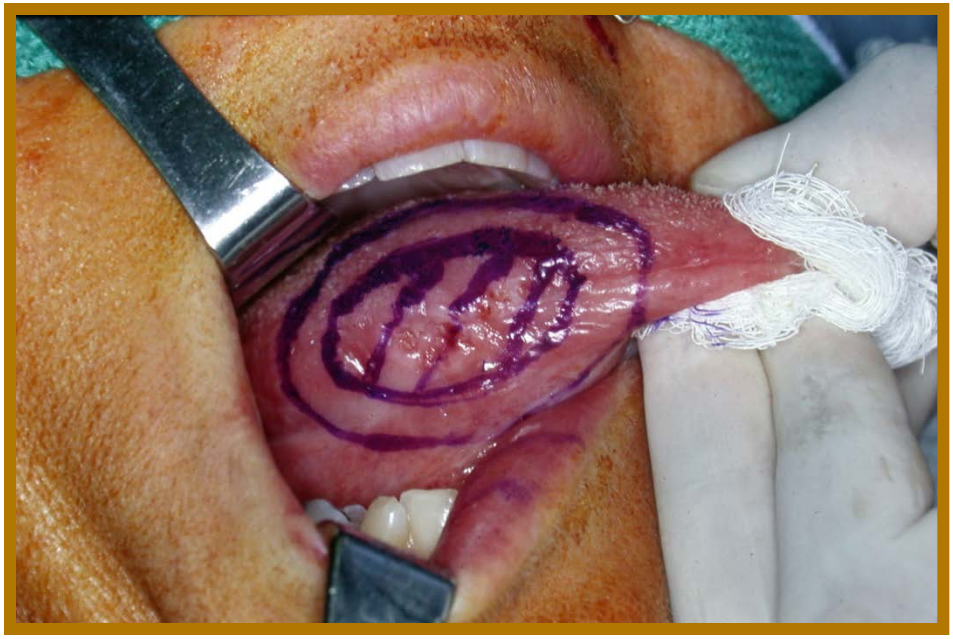


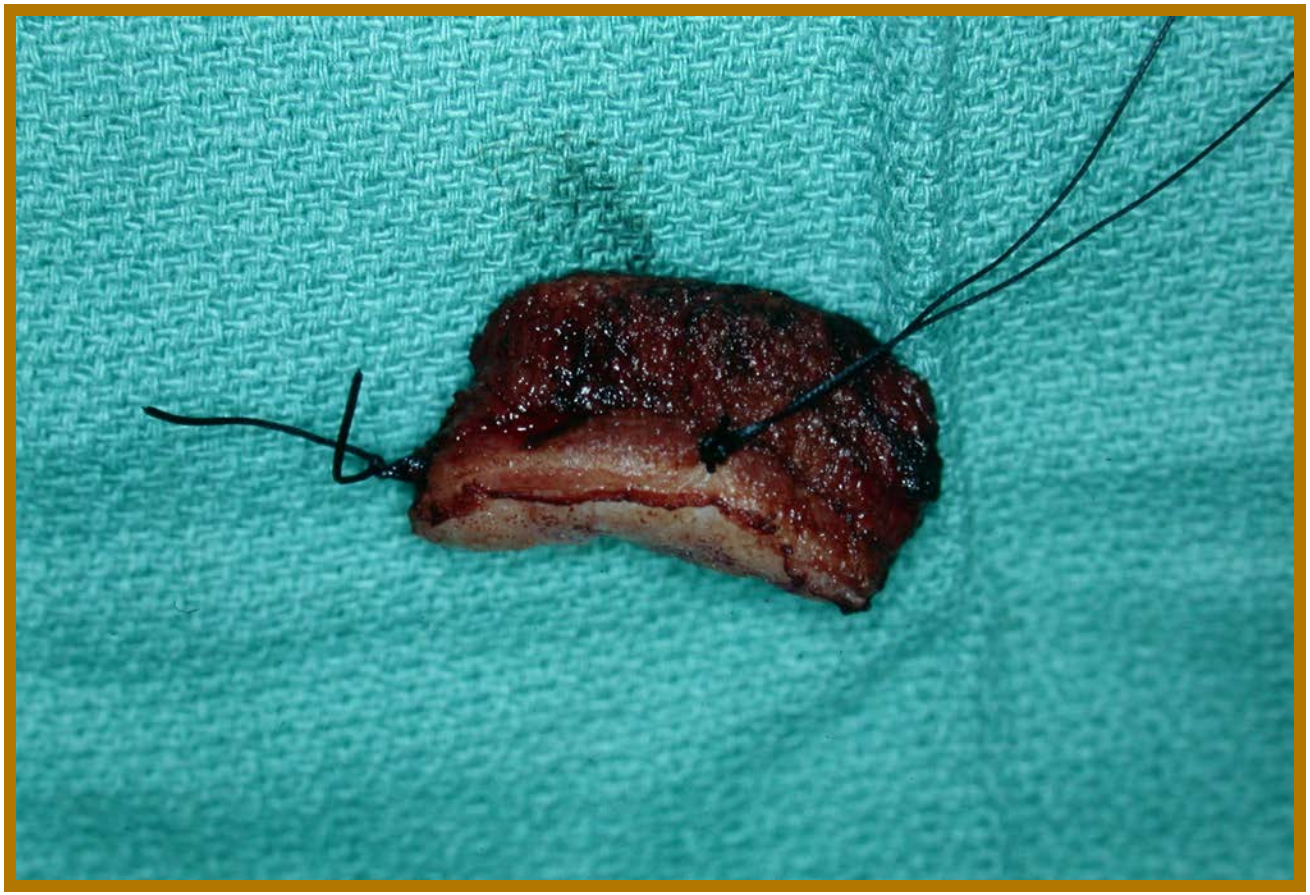

U.S. Patent

Management of the Primary Site

Surgical Margins

- Clear margin
  - 5mm
- Close Margin
  - 1-5mm
- Positive Margin
  - < 1 mm





Surgical Margins ???

- False margins
  - surgeon/pathologist error
- Tissue shrinkage
  - 15-70% shrinkage
- Effects of radiotherapy/chemotherapy
- Molecular margins

- Molecular assessment of surgical margins
  - 78 surgical margins in 30 patients with invasive SCC
  - 25 patients reported to have negative margins
  - p53 molecular analysis
  - 52% of patients with negative surgical margins found to have neoplastic cells with the p53 mutation

Brennan et al. NEJM 1995

Bone Invasion

- Attached gingiva does not exceed 2-3mm in thickness and therefore bone invasion can occur early
- Many of these cancers are T4 by the time they are diagnosed due to this rapid invasion
- Previous dental extractions can in theory “seed” the open socket and allow deep bony involvement

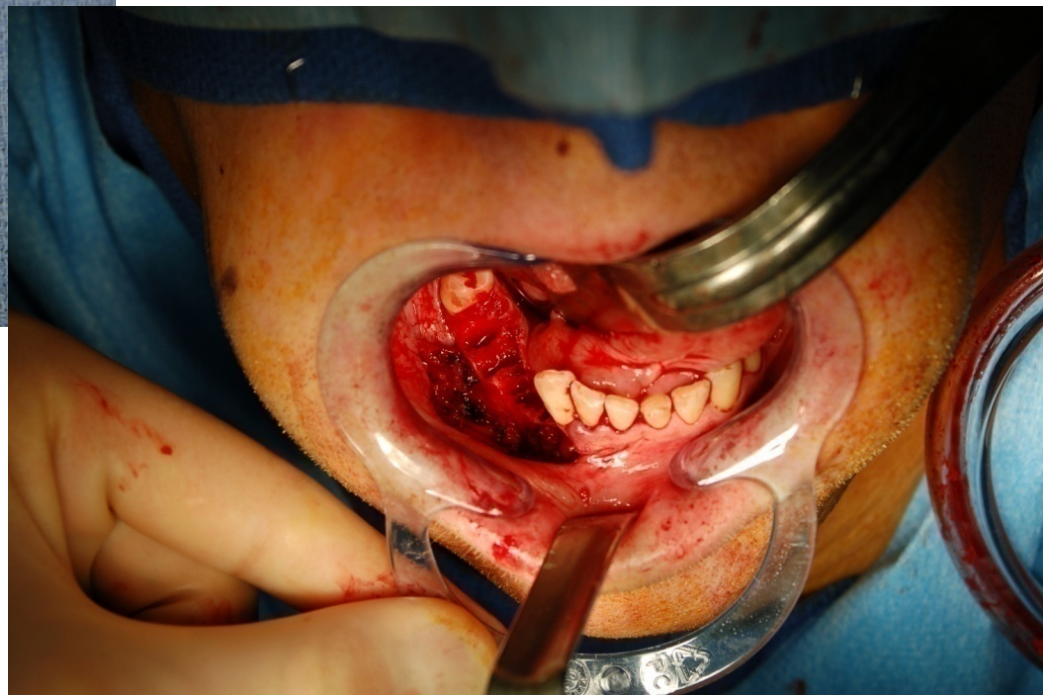
- High percentage of resected mandibles without evidence of mandibular invasion (35-78%)

Ellen M Van Cann et al. IJOMS 2008

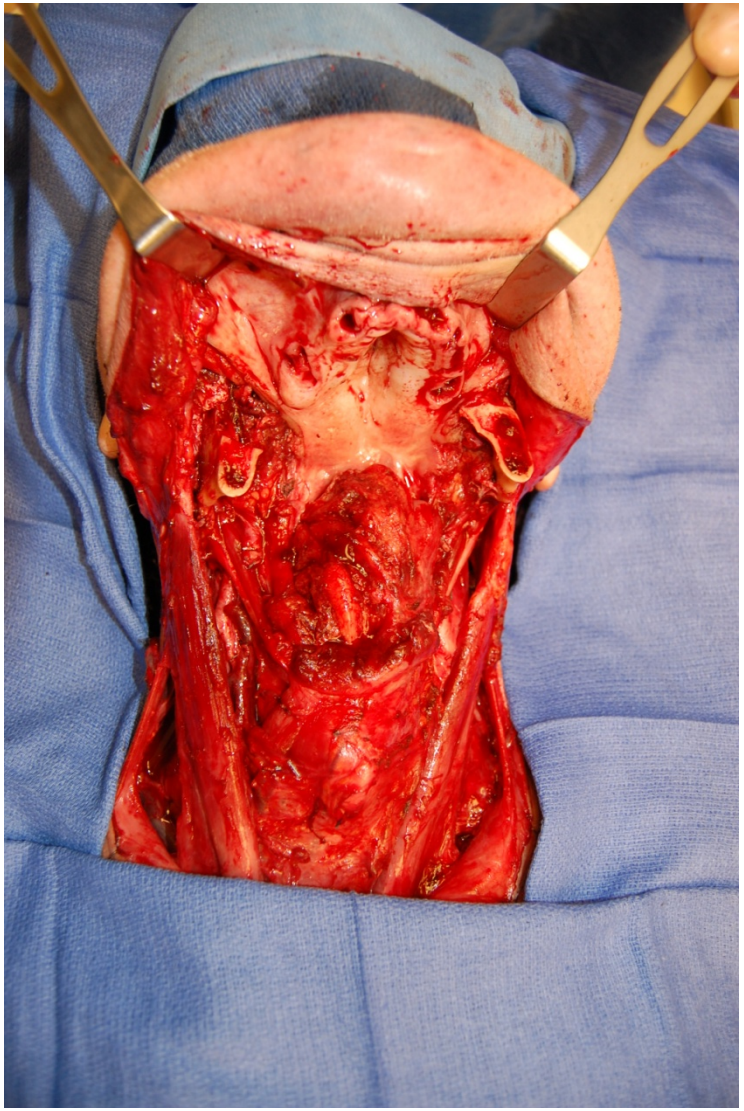
- Tumors involving the attached gingiva had a significantly greater risk of bone invasion

MJ Imola et al. Laryngoscope 2001

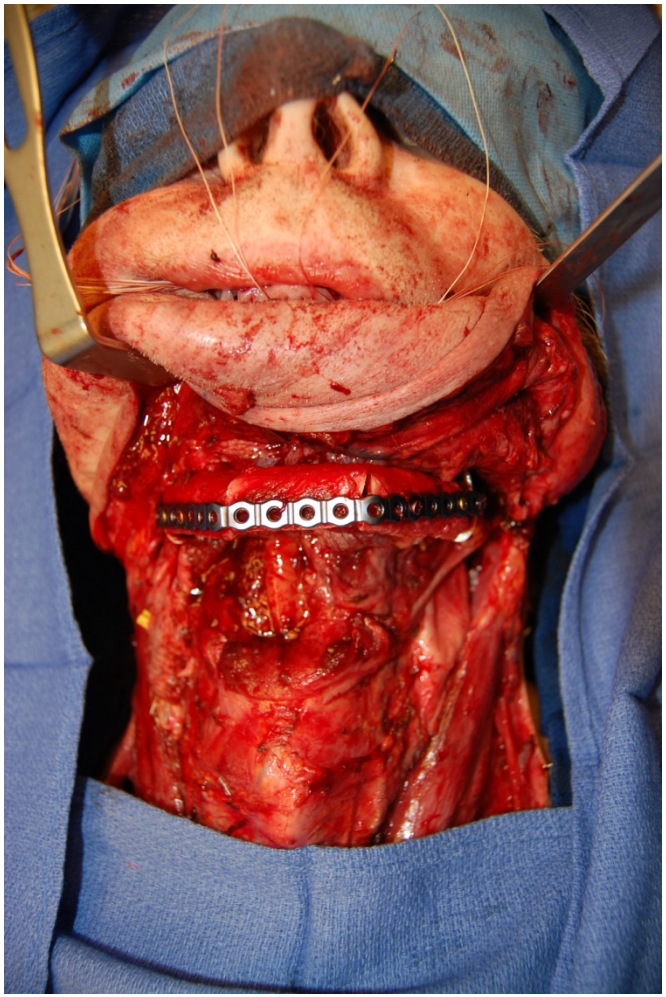
Marginal Resection

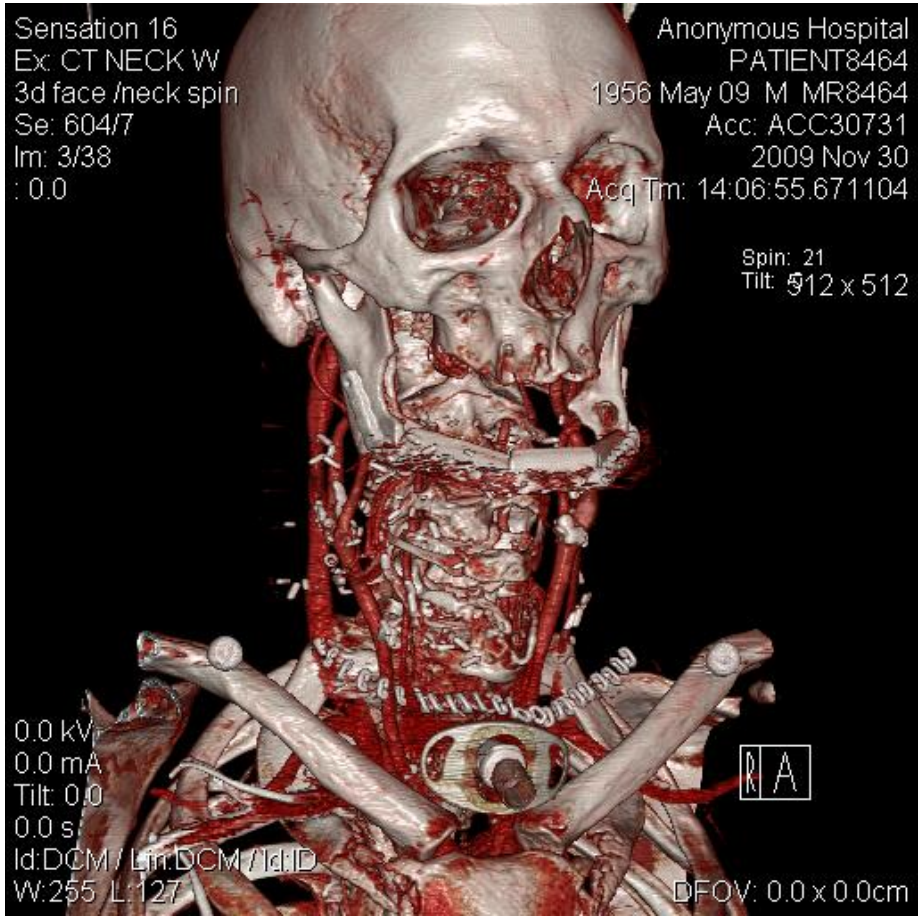


Segmental/Composite Resection



Reconstruction of a Composite Mandibular Defect





Marginal vs. Segmental Mandibular Resection

- Ability to achieve negative margin
- Previous extraction with invasion along periodontal ligament
- Previous radiotherapy
  - Periosteal ability to resist invasion
- Thickness/Stability of mandibular bone remaining

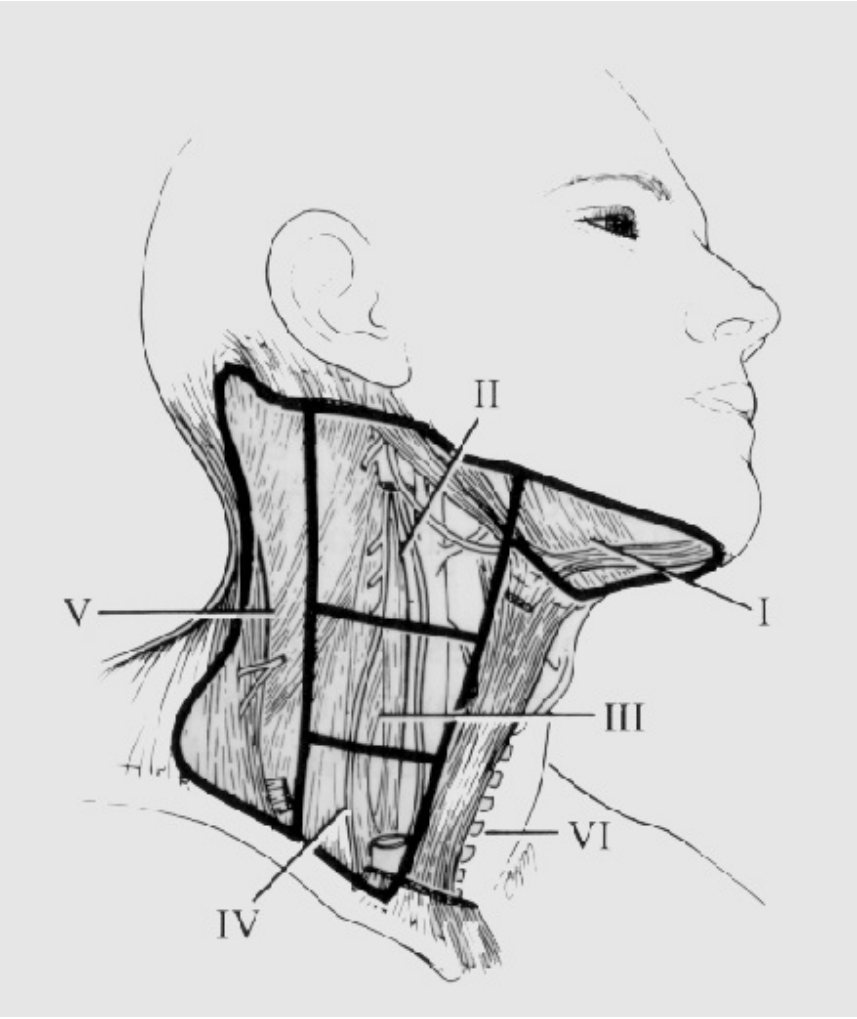
Management of the Neck

Lymph node metastases

- Single positive node decreases survival by 50%
- Contralateral positive node decreases survival by 50%
- Extracapsular spread decreases survival by 25-50%

Cervical Metastases

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- **N2a**: Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
- **N2b**: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- **N2c**: Metastasis in bilateral or contralateral nodes, no more than 6 cm in greatest dimension
- **N3**: Metastasis in a lymph node more than 6 cm in greatest dimension



Neck Dissection (Lymphadenectomy)

- Elective neck dissection
  - Remove the lymph nodes with the highest risk of having occult metastatic disease
- Therapeutic neck dissection
  - Remove the lymph nodes with positive metastatic disease

- “if the probability of occult metastases is greater than 20% then a neck dissection should be undertaken”

Weiss MH et al. Arch Otolaryngol Head Neck Surg 1994

Study Design - Prospective Randomized Study

- 75 patients T1-T3 N0 (tongue/floor of mouth)
- 39 elective radical neck dissection
- 36 watch and therapeutic neck dissection

Vandenbrouk et al., Cancer, 1980

- 39 elective 49% +ve 13% ECS
- 17/36 therapeutic 47% +ve 25% ECS
- 2/36 therapeutic non-operable

Survival Curves Elective Vs. Therapeutic show No Difference

Vendenbrouk et al., Cancer, 1980

Study Design - Prospective Randomized Study

- 70 patients T_1/T_2 N_0 oral tongue
- 40 patients hemiglossectomy watch neck
- 30 patients hemiglossectomy elective RND

Farik et al., Am. J Surg, 1989

- 23/40 Watch and wait +ve nodes 57.5%
  (5 unresectable)

- 30 Elective 10 +ve nodes 33%

- <u>Survival:</u>
  - Elective 63%
  - Therapeutic 52%

Not Significant

(minimal f.u. 12 mo.)

Farik et al., Am. J. Surg., 1989

>4 mm thickness 76% +ve watch and wait
66% +ve END

No significant difference in survival

Farik et al., Am. J Surg, 1989

Study Design - Prospective Randomized Study

- 67 patients stratified by Stage (T1-T2) and randomised to resect or resect + SOHND
- 33 resect only
- 34 resect + SOHND

- 30 patients <4mm thick, 37 >4mm.

Kligerman et al Am. J. Surg. 1994

Study Design - Prospective Randomized Study

- **Resection only**, recurrence 42%, disease free survival 49%
- **Resection + SOHND** recurrence 24%, disease free survival 72%
- Late Stage p = 0.05 and increased tumor thickness p = 0.005 associated with treatment failure

Kligerman et al Am. J. Surg. 1994

Study Design - Prospective Randomized Study

Conclusion

Neck disection remains mandatory in the early stage of oral CA because of better survival rates compared to resection alone and the poor salvage rate. In particular patients with tumor thickness >4mm treated with END had significant benefit on disease free survival.

Kligerman et al Am. J. Surg. 1994

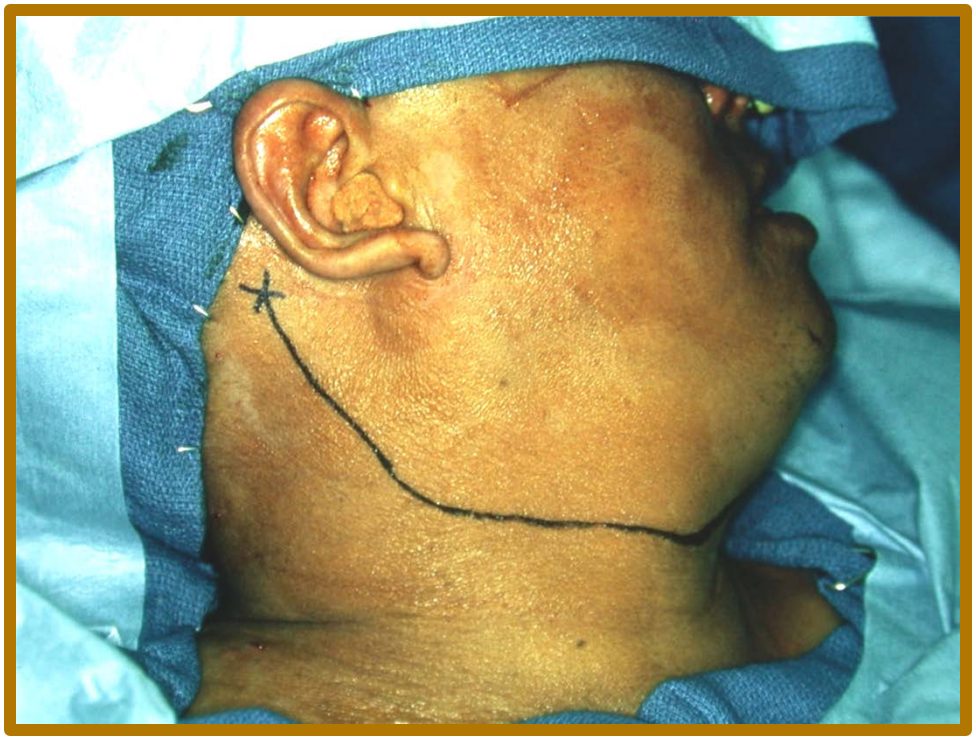
Conclusions N0 Neck

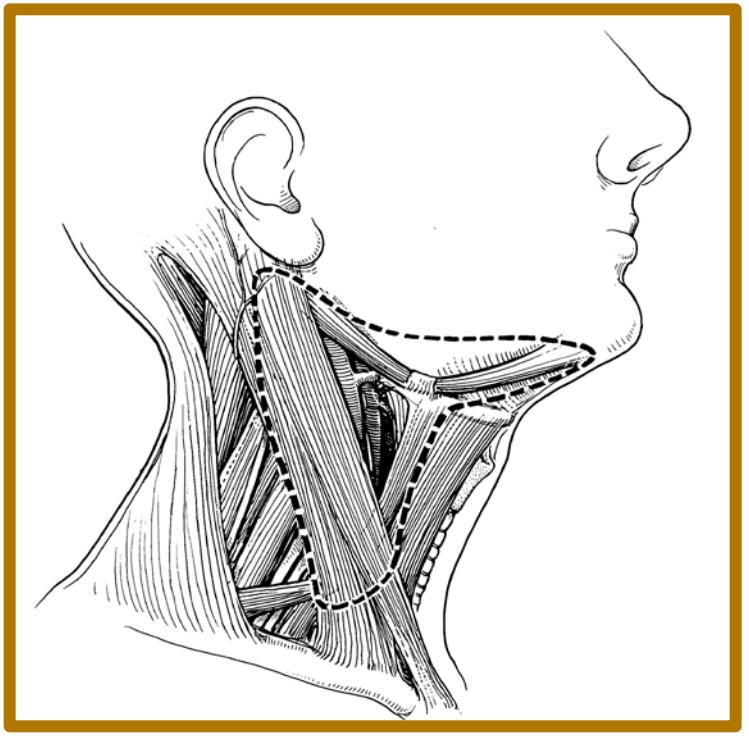
- SOHND for T2,3,4 and T1 thicker than 4mm. or with perineural invasion.
- No need for level IV or submuscular triangle dissection unless suspicious nodes found during the dissection.
- RT + chemotherapy for any node with ECS. ?? RT for 2 or more nodes with microscopic disease.

Elective Neck Dissection - Indications

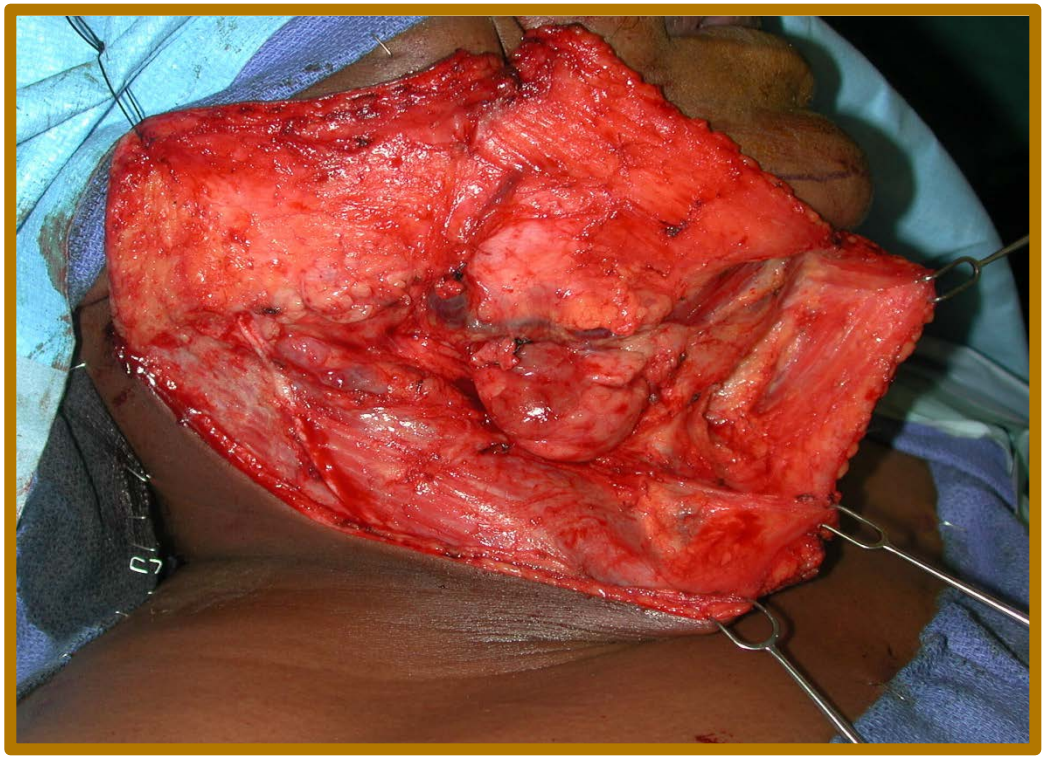
- Depth of invasion
  - 2 – 10 mm
- Tumor size
  - Greater than 2 cm (T2 –T4)
- Need for blood vessel access for vascularized flap reconstruction

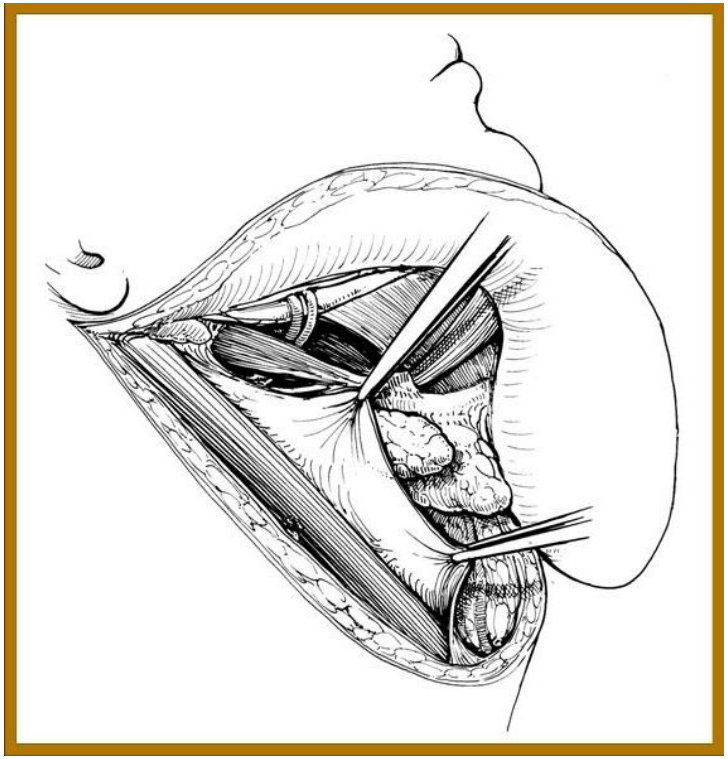
SOHND



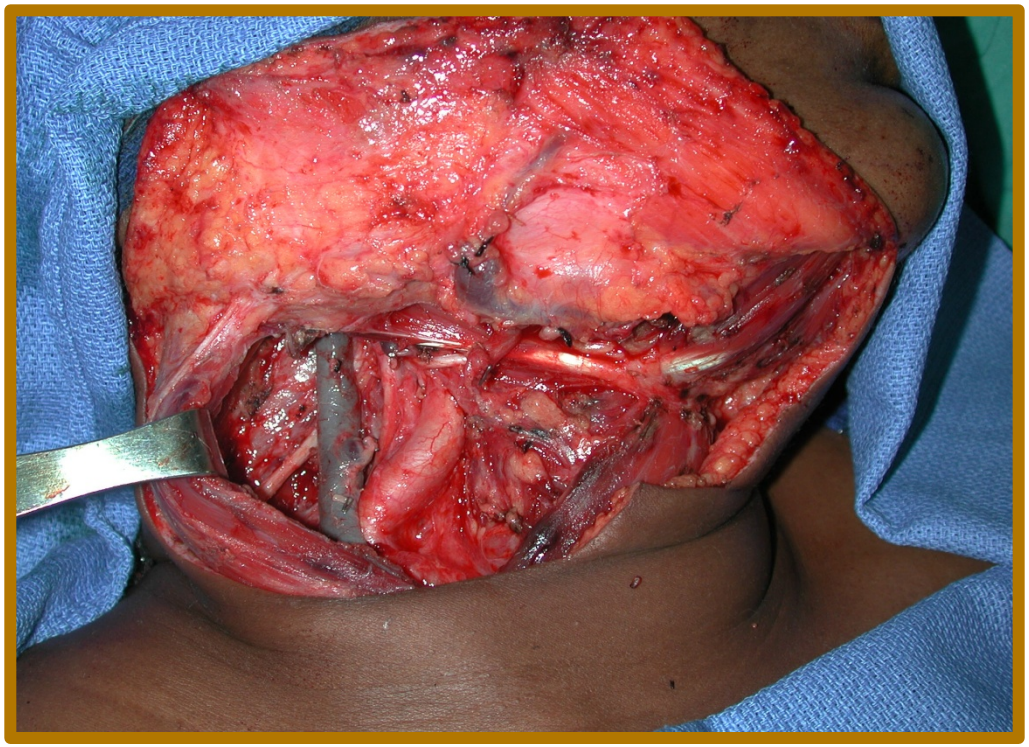


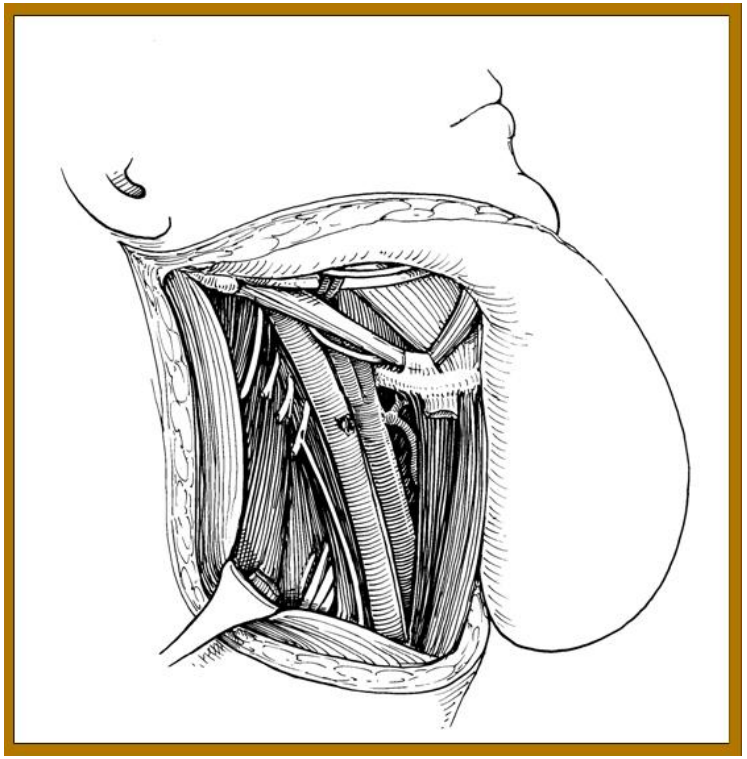
SOHND



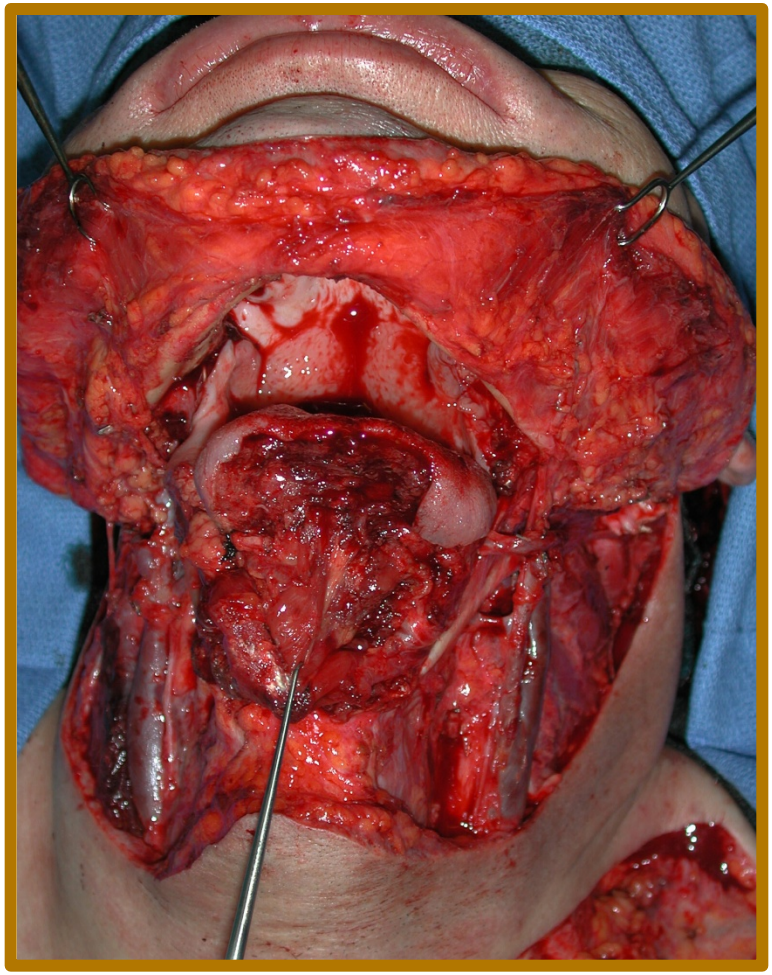


SOHND



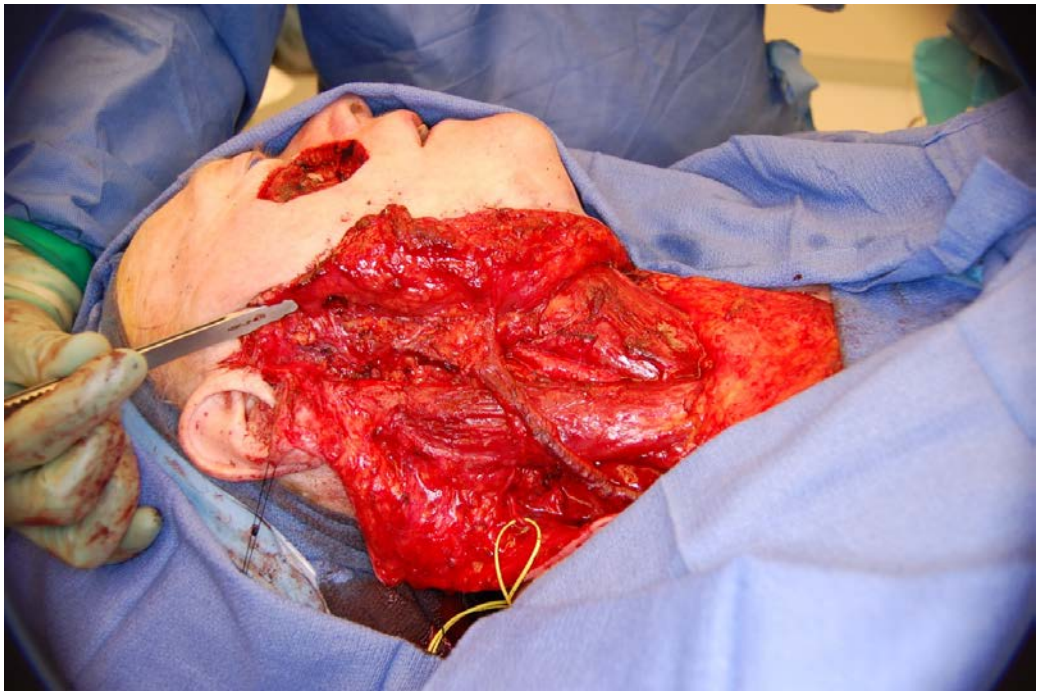


Bilateral SOHND

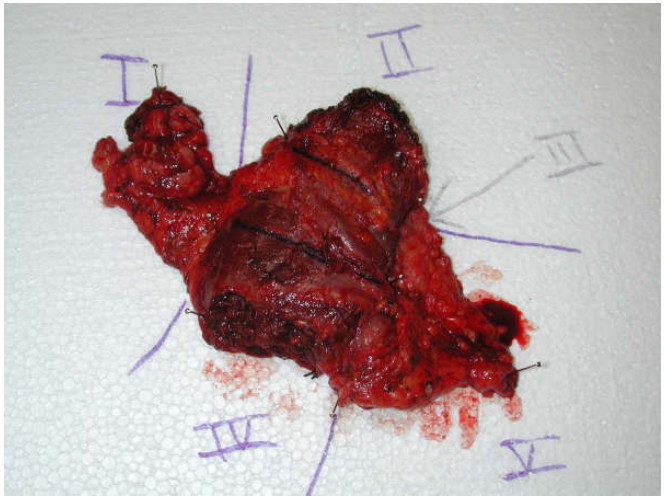


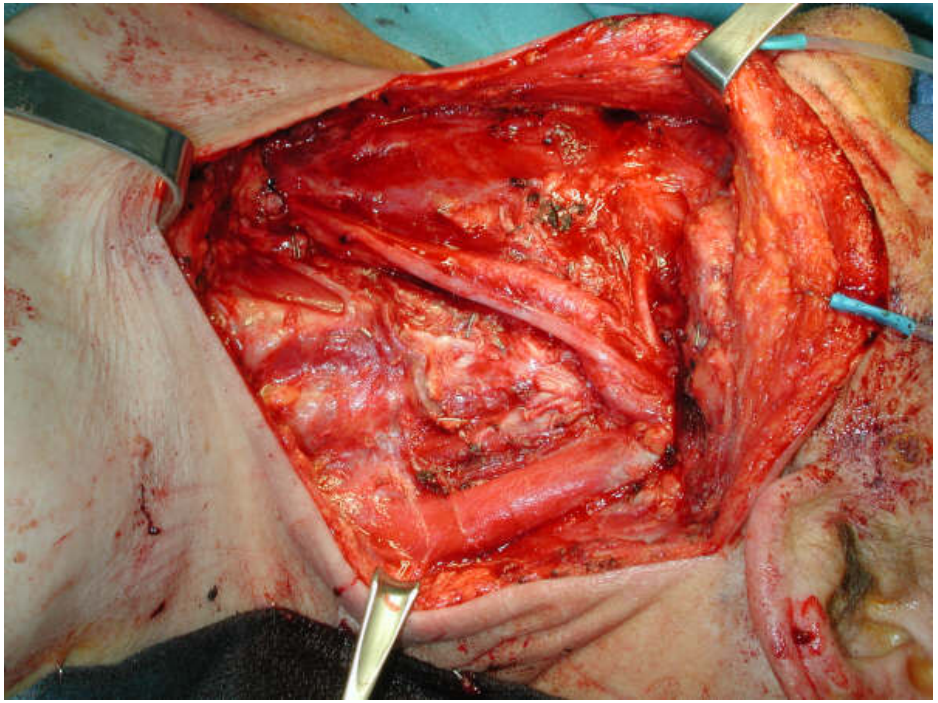
Modified Radical Neck Dissection Levels I – V

- Type I
  - CN XI
- Type II
  - CN XI, Internal Jugular V.
- Type III
  - CN XI, Internal Jugular V., SCM



Radical Neck Dissection





TNM staging – Oral Cancer

- 5 year survival
  - Stage I
    - 75-90%
  - Stage II
    - 70%
  - Stage III
    - 50%
  - Stage IV
    - 30%

Oral Carcinoma – Prognostic Variables

- Stage
- Surgical margins
- Nodal disease
  - Multiple nodes
  - Levels IV/V
  - Extracapsular disease
- Perineural invasion
- Perivascular invasion
- Degree of differentiation

Risk Factors - Distant Metastases

- 3 or more positive lymph nodes
- Extracapsular extension
- Clinically positive nodes

- Most common sites
  - Supraglottis
  - Hypopharynx
  - Tongue

Conclusions N1 Neck

- Classically Modified Radical Neck Dissection is best option but newer studies suggest selective neck dissection may give equal results but should include level IV.
- RT/Chemotherapy if ECS or more than 1 positive node on histopathology.
- If primary is treated with RT treat neck with 65Gy and save MRND/RND for salvage

N2-3 Neck Disease

- Usually ECS, multiple nodes and levels; poor control with single modality treatment.
- RT/Chemo alone provides poor control.
- Radical ND levels I-V with adjuvant RT/Chemotherapy is best.
- Distant metastases in up to 50%

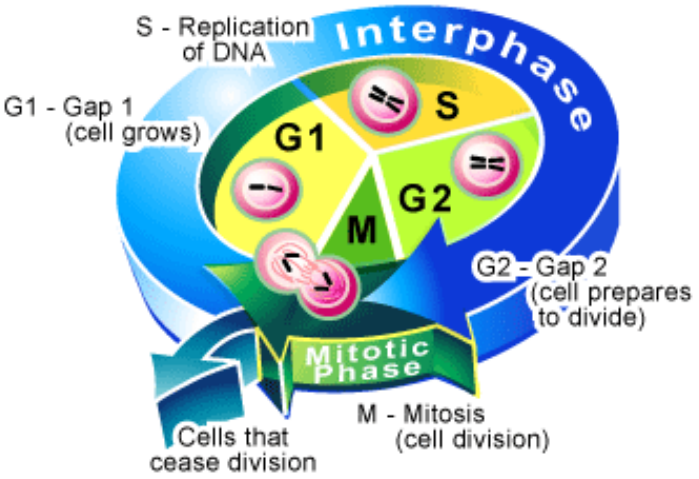
Conclusions N2/3 Neck

- Modified Radical Neck Dissection if possible may need Radical or Extended Radical ND.
- All cases will need RT/Chemotherapy given concomitantly.
- Where there is ECS and multiple levels involved high risk of distant metastases.

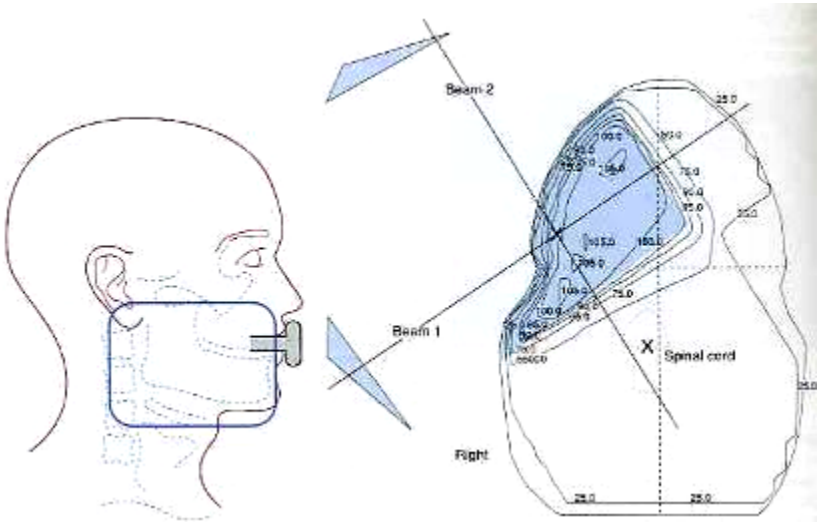
Adjuvant Therapy

Radiotherapy

- Mechanism of action
  - Interacts with atoms and molecules of the cells
  - Produces free radicals
  - Damages DNA
  - Affects all phases of the cell cycle but cells going mitosis are most affected



Radiotherapy



Radiotherapy

- Indications
  - Unable to tolerate surgery
  - Multiple cervical nodes
  - Close/positive surgical margins
  - T3 –T4 size
  - Perineural invasion
  - Perivascular spread

Chemotherapy

- Conventional
  - Platinum based medications
- Growth factor modulators
  - Erbitux (EGFR)
- Role for combined adjuvant therapy with radiation therapy

New England J of Medicine.

May 6th, 2004.

- Post-operative Radiotherapy and Chemotherapy for High Risk Squamous Cell Carcinoma of the Head and Neck.
- Cooper J.S. et al **RTOG 9501**
- Post-operative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer.
- Bernier, J. et al **EORTC 22931**

RTOG 9501

- **<u>Conclusions</u>**
- Concurrent postoperative chemotherapy and RT significantly improves rates of loco-regional control and disease free survival in resected high risk head and neck cancer patients. However, there is a substantial increase in adverse side effects.

EORTC 22931

- **<u>Conclusions</u>**
- Post-operative Chemo/RT with Cisplatinum is more effective than RT alone in advanced H+N Cancer. Does not cause undue number of complications.

NCCN Practice Guidelines in OSCC 2007

- 1 positive node with no adverse factors: **RT optional**
- < 2 minor adverse factors: **RT**
- 1 or both major or > 2 minor adverse factors: **Chemo/RT**

Minor : T3-4, N2-3, Nodes level IV-V, Perineural/Perivascular

Major : Positive margin, ECS.

Tumor Surveillance

- Most recurrences occur locoregionally within 2 years of initial treatment

- Routine Follow-up
  - q1-2 months (first 2 years)
  - q3-4 months (years 3-4)
  - q6 months (year 5)
  - Yearly exam greater than 5 years disease free


THANK
YOU!