CURRENT CONCEPTS

IN

HEAD AND NECK SURGERY

November 5 & 6, 2011

~ Toronto ~

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Saturday November 5, 2011

Session I – Larynx Cancer Presentations

Current Concept in Head and Neck Surgery November 5 and 6, 2011
MaRS Discovery District Auditorium,
101 College Street, Lower Level
Toronto, Ontario

"Options for Improving Outcome in Laryngeal Cancer"

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Professor of Radiation Oncology and Otolaryngology / Head and Neck Surgery
University of Toronto

Historically the management of laryngeal cancer has been confounded by geographically-based and specialty related attitudes regarding the management of patients with all stages of the disease. Interestingly surgical and radiation oncologists have held very similar views in some jurisdictions about the best approach for most stages of disease. However in others, significant diversity has existed with separation in attitude to treatment that appears highly correlated with the specialty of the practitioners who manage these cases. This was most dramatically evident in the locally advanced settings (T3 and T4 disease), notwithstanding absence of any difference in survival of patients in population-based comparisons of jurisdictions with opposing views about the use of larynx preserving management strategies. Evidence underpinning these observations will be outlined to illustrate methods by which alternative approaches to management can be seen to prevail in different jurisdictions. Some commentary on the historic evolution of laryngeal preservation in the Toronto area will also be provided. In more recent decades most geographic regions have also established robust protocols to avoid total laryngectomy and preserve laryngeal function wherever possible. The key clinical trials that brought about this change will be summarized and especially the VA Laryngeal Cancer Study Group and the RTOG 91-11 trials. In the contemporary era however, there remain ongoing challenges in formulating change in management. In early disease settings, conduct of clinical trials is very problematic in part because of ongoing beliefs among practitioners about the role of modality based approaches, as well as the ability to design clinical trials with sufficient statistical power to address relevant questions that usually require non-inferiority design. The paucity of events for the early disease remains daunting in designing such trials and for addressing accrual. Nevertheless, approaches have "borrowed" from management strategies used in more advanced settings and in particular altered fractionation approaches and the use of more conformal dose delivery methods such as IMRT appear to offer potential advantages for even early disease patients. Evidence and challenges in addressing these areas will be provided, including a detailed discussion regarding radiotherapy quality when implementing such approaches. The latter will also include comparison between centres in the province of Ontario, Canada regarding the treatment of early larynx cancers. Newer strategies will also be addressed for the more advanced disease settings where laryngeal preservation remains the predominant concern among practitioners. This discussion will address some issues relating to choice of patients suitable for these approaches, the methods of assessment of

patients enrolled on laryngeal preservation trials, the end-points to be used in such trials, and the need to include translational research in the design of trials. More recent trial approaches will be summarized including the use of TPF induction chemotherapy for larynx preservation championed by the GORTEC group in France, and the recent preliminary results of the TREMPLIN trial employing sequential biotherapy by the same group. Finally long awaited results of an experience of T4 laryngeal cancer from the University of Chicago will be shown to illustrate the real potential for laryngeal preservation even in such tumors if treatment is judicially intensified.

Notes

Speech and Swallowing: Functional Assessment and Outcomes

Patients treated for head and neck cancer will experience changes in speech and swallowing function as a consequence of the selected treatment modality whether it is surgery that removes the organ or a conservation procedure that spares it. Combinations of chemotherapy and radiation for organ preservation are well documented alternatives to ablative surgery for intermediate and advanced stage disease but there are few studies that have objectively addressed and compared the issue of preservation of function across treated patient populations. The goals of any cancer treatment must be first and foremost to eradicate the tumor and cure the disease but also to ensure that respiration, deglutition, speech, phonation, and cosmesis are maintained while complications and problems are minimized so that the greatest patient satisfaction is achieved. Thus, cure, functional preservation, and the ability to return to an acceptable quality of life are at the current forefront of treatment selection for patients with malignancies of the head and neck.

General principles of speech and swallowing tell us that the keys to successful functional outcomes include preservation of both anatomy and physiology to maintain the ability to eat, drink and speak by mouth. Data clearly identify the critical importance of the range of motion of the tongue, pharyngeal motility, and unrestricted laryngeal mobility to ensure safe swallowing and intelligible speech.

Experience has shown that organ preservation is not synonymous with functional preservation nor is the potential for functional preservation synonymous with functional recovery. When organ preservation protocols fail, the patient often becomes dependent on a tracheostomy tube to maintain the airway and a gastrostomy tube to maintain nutrition. Given the current advances in rehabilitative and restorative technology, it is sometimes the case that complete surgical resection produces better functional outcomes and superior quality of life than those that spare but cripple the organ, as is the case for some patients with advanced cancer of the larynx. Postoperatively, perceptual and acoustic measurements of voice quality will show a wide range of results and although descriptively useful for comparative purposes, they do not always accurately reflect patient satisfaction and adequacy for daily communication needs. Often, patients are quite accepting of an abnormal sounding voice in lieu of no voice at all. Alternatively, patients who have undergone total laryngectomy and tracheoesophageal (TE) voice restoration often demonstrate better ability to speak and swallow, and greater satisfaction than some patients in whom a dysfunctional larynx has relegated them tracheostomy and G-tube dependent.

Rehabilitation following total laryngectomy has continued to evolve over the course of the last 5-10 years. Primarily, alaryngeal voice restoration has shown the most dramatic change in the areas of reconstructive alternatives and prosthetic technology. Surgical resections that include both the larynx and the pharynx managed with reconstructive options such as those that use the anterolateral thigh flap (ALT) show a higher level of functional success for both speech and swallowing than the functional outcomes

demonstrated in patients who have been reconstructed with other alternatives such as organ transposition. Our research has shown a 90% success rate for fluent TE speech production and return to oral alimentation without significant effect from radiation therapy or surgical defect in appropriately selected patients who have been reconstructed with an ALT flap. Experience has shown that TE voice restoration is not always simple, particularly, in patients with involved medical histories and complex surgical reconstructions. Not every patient is a candidate for TE voice restoration nor is a single prosthesis the best choice for all patients. We have found that ultimate TE speech success requires careful thinking, thorough evaluation, and strong multidisciplinary collaboration.

Baseline examination of speech and swallowing function should be performed for all patients who have or are at risk for post-treatment dysfunction. Pretreatment evaluation of speech and swallowing function should always begin with a comprehensive clinical evaluation that may or may not indicate a need for additional instrumental evaluations using videofluoroscopy or flexible endoscopy, or laryngeal videostroboscopy. However, the results of baseline examination help identify other variables such as the occurrence of silent aspiration or a mobile but stiff, non-vibratory vocal fold that otherwise might be overlooked to the "naked eye" but becomes critical to decisions regarding patient candidacy for organ-sparing protocols or the need for pretreatment G-tube placement. At our institution, PEG tubes are placed for therapeutic indications, never prophylactically. Our recent analysis showed that PEG tube placement may be avoided in up to 40% of patients with advanced oropharyngeal or hypopharyngeal tumors based on thorough swallowing examination by the speech pathology team. Furthermore, our data showed that the ability to place the PEG tube, if necessary, during treatment without a delay or interruption in treatment makes prophylactic placement of G-tubes hard to justify.

It is important to remember that swallowing physiology cannot be reliably inferred from subjective reports. In some cases, patients report no problems swallowing, while in fact, they are silently, without coughing or any other indication, aspirating what they swallow. The only way to reliably evaluate swallowing physiology is to perform an objective, instrumental, examination. The most common of these examinations are the modified barium swallow (MBS) study, and the flexible endoscopic evaluation of swallowing (FEES). These examinations allow the clinician to diagnose the dysphagia etiology and match the appropriate intervention to the swallowing disorder. Data have shown that appropriate swallowing rehabilitation can eliminate aspiration, reduce the risk for pneumonia, and successfully return over 80% of select patients who aspirate to oral intake even years after treatment.

Alternatively, voice production is best assessed using videostroboscopic imaging of the vocal folds to analyze patterns of movement to make differential etiologic determinations of pathology and voice disorders. One can distinguish between the asymmetries of vibration and vocal fold stiffness associated with laryngeal hyperfunction from those associated with papilloma, scar tissue, vocal fold paralysis, and laryngeal carcinoma. The overall presentation in patients with true vocal fold cancer is one of mass effect. Large exophytic masses are easily visible within the glottis; however, early tumors may be

identified by the change in the vibratory wave that is generated during abductor and adductor movements of the vocal folds. As such, laryngeal videostroboscopy has become a key diagnostic tool in head and neck clinics to assess both vocal fold pathology and function.

When radiation therapy is performed, either as a definitive treatment or as an adjunct to other treatment modalities, the functional effect may be significant. The adverse impact of radiation can result in long-term alterations in speech, voice, and swallowing that may increase in severity even years after the completion of radiation therapy. In general, radiation has a greater effect on swallowing than it does on speech, and the addition of chemotherapy can make the problems worse because of the intensifying effects. Most swallowing problems result from scarring or fibrosis that occur following radiation therapy. Fibrosis reduces mastication, tongue movements, pharyngeal motility, and airway protection. Patients should be encouraged to swallow throughout the course of their radiation or chemoradiation therapy as tolerated. Even brief NPO intervals have been shown to reduce swallowing function and should be avoided as much as possible. Precise planning for radiation therapy coupled with early therapeutic regimens of swallowing exercises that are designed to strengthen musculature, increase the precision of movements, and maintain range of motion provide the best prevention of long-term swallowing dysfunction in patients who have been irradiated for head and neck cancer. In a recent analysis performed at MD Anderson Cancer Center of 603 patients with oropharyngeal cancer and 56 with hypopharyngeal tumors, adherence to swallowing exercises was significantly associated with G-tube dependence and removal ($p<0.05$). Patients who regularly performed swallowing exercises prescribed by the speech pathologist, experienced quicker return to oral alimentation and removal of their PEG tube compared with patients who did not perform the exercises routinely. Therefore, it is important that therapy start early, preferably at the initiation of treatment and continue throughout the course of treatment. In some cases, therapeutic regimens may need to continue well past the end of radiation to counter the late effects.

In conclusion, critical evaluation of the functional consequences of selected treatment modalities will allow more accurate comparison of outcomes as they relate to current treatment alternatives for patients with head and neck cancer. Treatment regimens that are prospectively designed and implemented are the best methods for avoiding long-term complications. Appropriate and timely use of instrumental evaluations with adherence to prescribed speech and swallowing exercise regimens optimize functional outcomes and help preserve an acceptable quality of life for patients with head and neck cancer. Early referral to expert speech pathologists for pretreatment baseline examination of speech and swallowing function should be the norm for any patient with head and neck cancer with or at risk for post-treatment functional sequelae.

Notes

Session I

Panel Discussion – Management of Laryngeal Carcinoma

No material

Notes

Saturday November 5, 2011

Session II – Skin Cancer Presentations

Notes

Current Concepts in Head and Neck Surgery
Toronto, ON
November 5, 2011

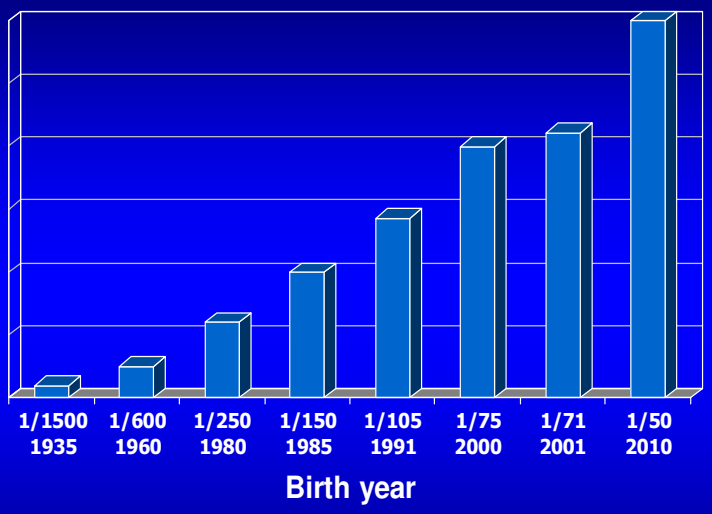
The Local Regional Surgical Management of Head & Neck Cutaneous Melanoma

Dennis H. Kraus, MD
Attending Surgeon, Memorial Sloan- Kettering Cancer Center
Professor, Cornell University Medical Center

Learning Objectives

- **Accurately stage a patient presenting with primary cutaneous melanoma in the head and neck**
- **Surgically manage the primary of a cutaneous head and neck melanoma**
- **Describe nuances of lymphoscintigraphy and sentinel node biopsy in cutaneous head and neck melanoma**

- The incidence of melanoma is increasing at a rate faster than any other cancer (101.5% between 1970-1990)
- Seventh most common cancer
- Occurs in younger individuals
  - Most common cancer in women ages 25-29

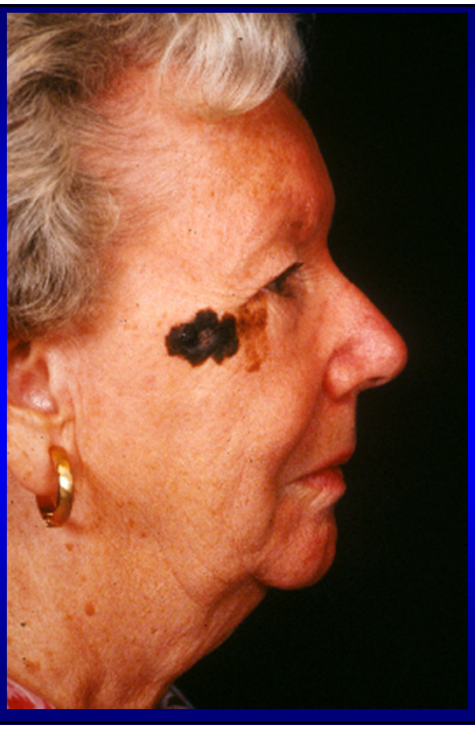


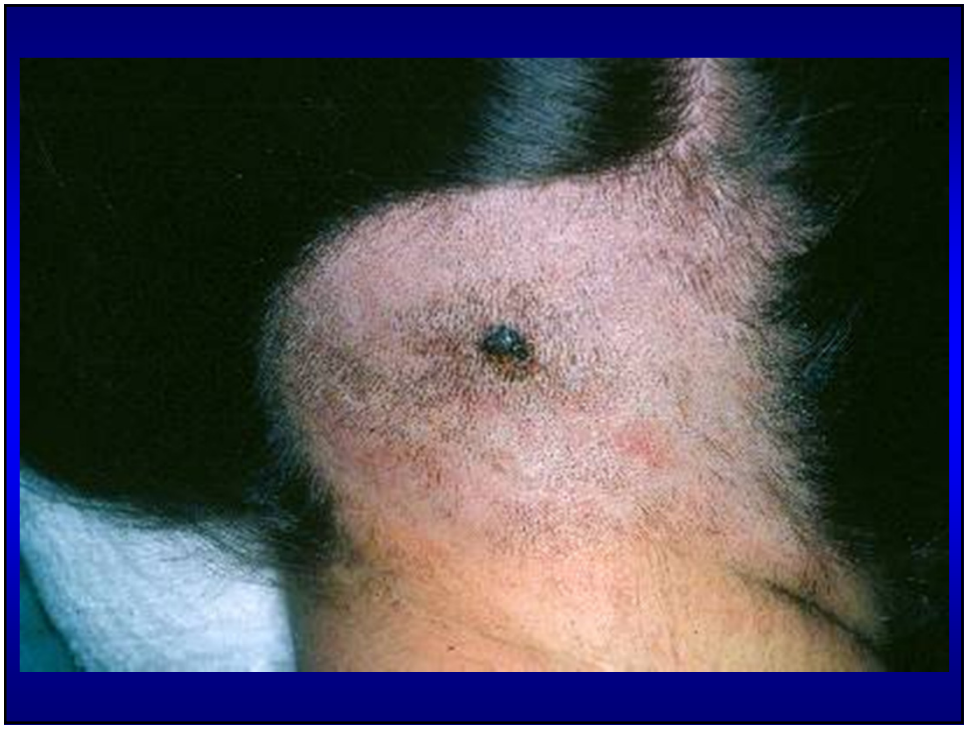
1/65 born in 2004 will develop invasive melanoma

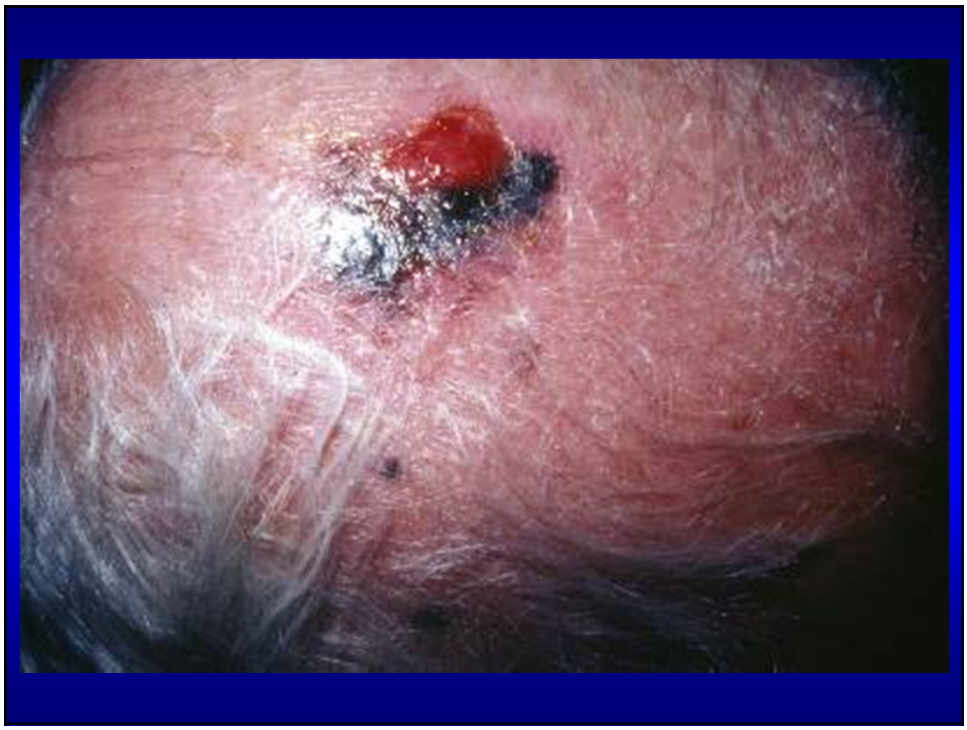
Melanoma Presentation

At the time of detection:

- **85% localized disease**
- **10-13% regional disease**
- **2-5% metastatic disease**







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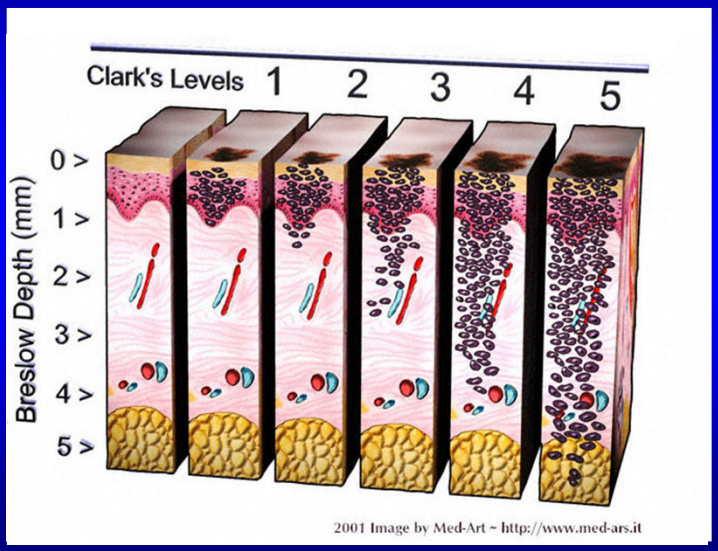
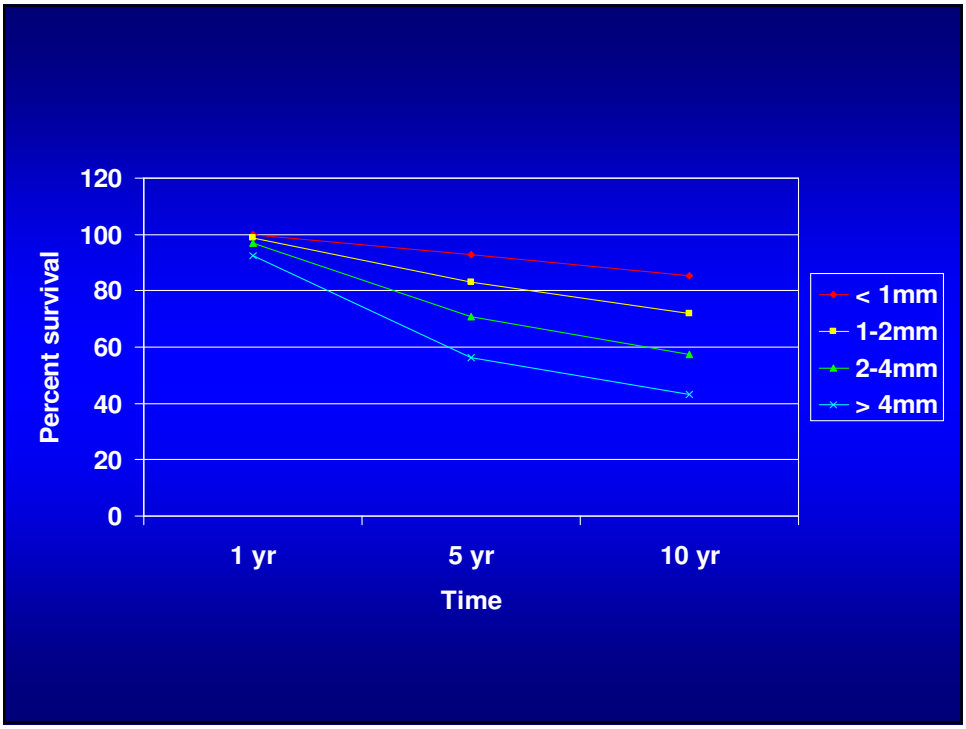




T Stage

- Tx, T_0, T_{is}
- T1 less than 1.0mm
  - T1a level II/III, no ulceration
  - T1b level IV/V, with ulceration
- T2 1.01-2.00mm
- T3 2.01-4.00mm
- T4 >4.0mm
  - A without ulceration
  - B with ulceration

Stage Grouping

Stage 0	Tis	N0	M0
Stage1A	T1a	N0	M0
Stage1B	T1b,T2a	N0	M0
Stage 2A	T2b, T3a	N0	M0
Stage 2B	T3b, T4a	N0	M0
Stage 2C	T4b	N0	M0
Stage 3	Any T	Any N	M0
Stage 4	Any T	Any N	M1

Wide Local Excision

Goals:

- Complete tumor removal to achieve durable local control
- Remove normal appearing surrounding skin with lymphatics that may harbor tumor cells
- Preserve form and function

Wide Local Excision

Local recurrence affected by:

- Thickness
- Presence of ulceration
- Mitotic index
- Location
- Surgical margins

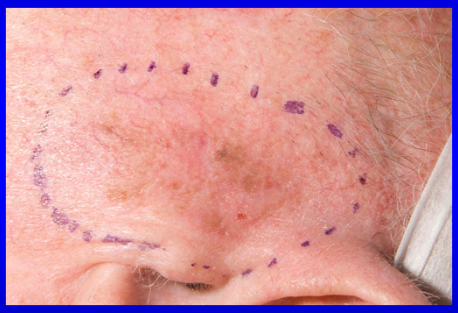
Local Recurrence Rates

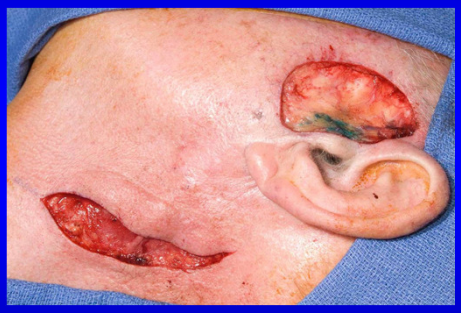
Extremity	1.1 %
Trunk	3.1 %
Distal extremity	5.3 %
Head & Neck	9.4 %

Balch CM et al. Ann Surg Oncol 2001

Recommended Margins

Tumor Thickness	Excision Margin
In situ	0.5 cm
≤ 2.0 mm	1.0 cm
> 2.0 mm	2.0 cm





Surgical Margin Control

- Intra-operative frozen section analysis be difficult, especially in chronically sun-exposed skin
- Delayed reconstruction for permanent margins analysis

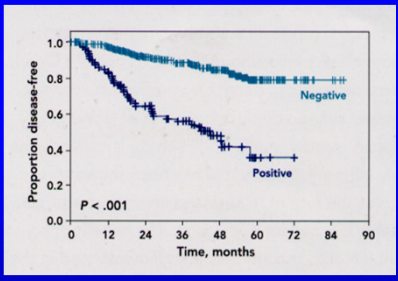
Deep Margin of Excision

- Most tumors are confined to the skin
  - Include skin and subcutaneous fat
- Tumors extending to subcutaneous tissues
  - Underlying structures should be taken *en-bloc*
  - Structures closer in the head & neck

Why do Sentinel Lymph Node Biopsies?

- For prognosis and staging

SLN status is the most powerful independent prognostic factor predicting survival

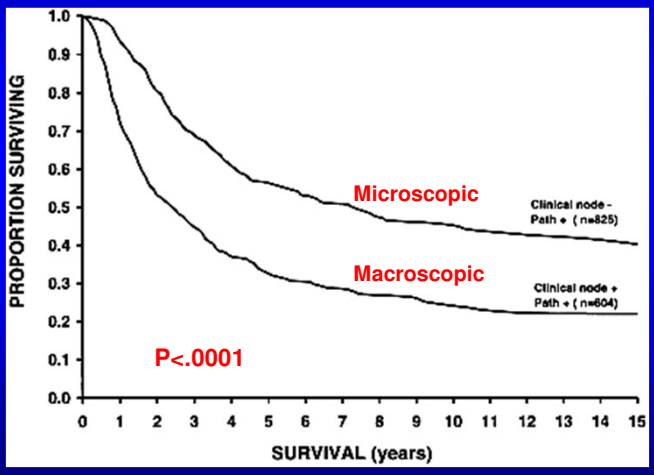


Disease-free survival stratified by SLN status

Gershenwald et al., Multi-Institutional Melanoma Lymphatic Mapping Experience: The Prognostic Value of Sentinel Lymph Node Status in 612 Stage I and II Melanoma Patients. *J Clin Oncol*. 1999.

Survival curves:1,429 patients with lymph node metastases

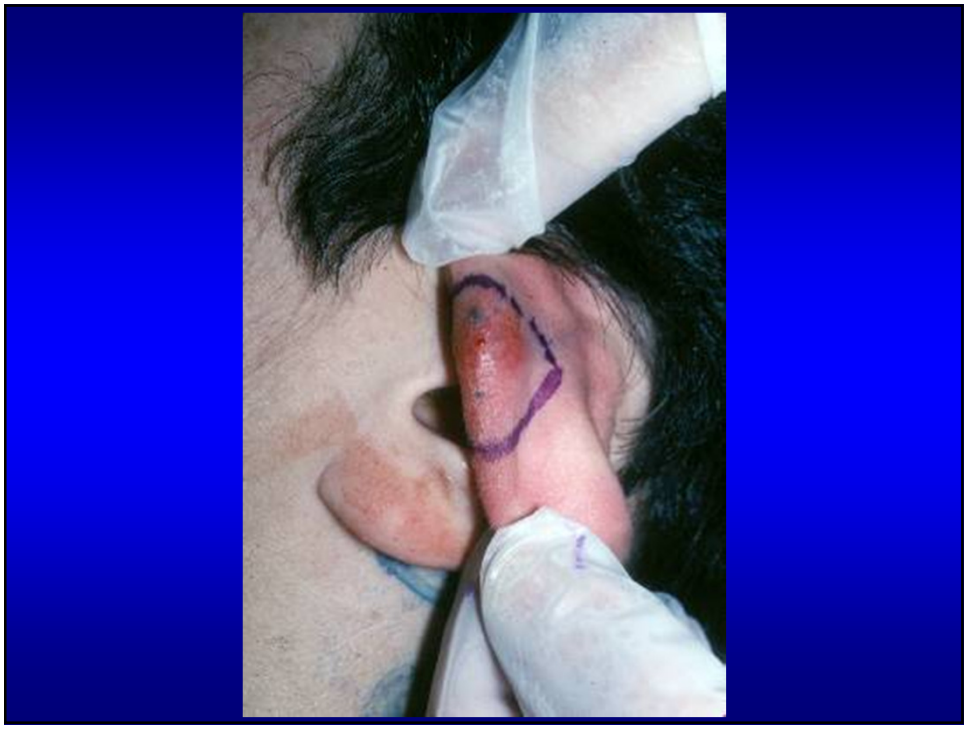
Subgrouped by presenting clinical staging. Survival rates calculated from onset of the primary melanoma diagnosis

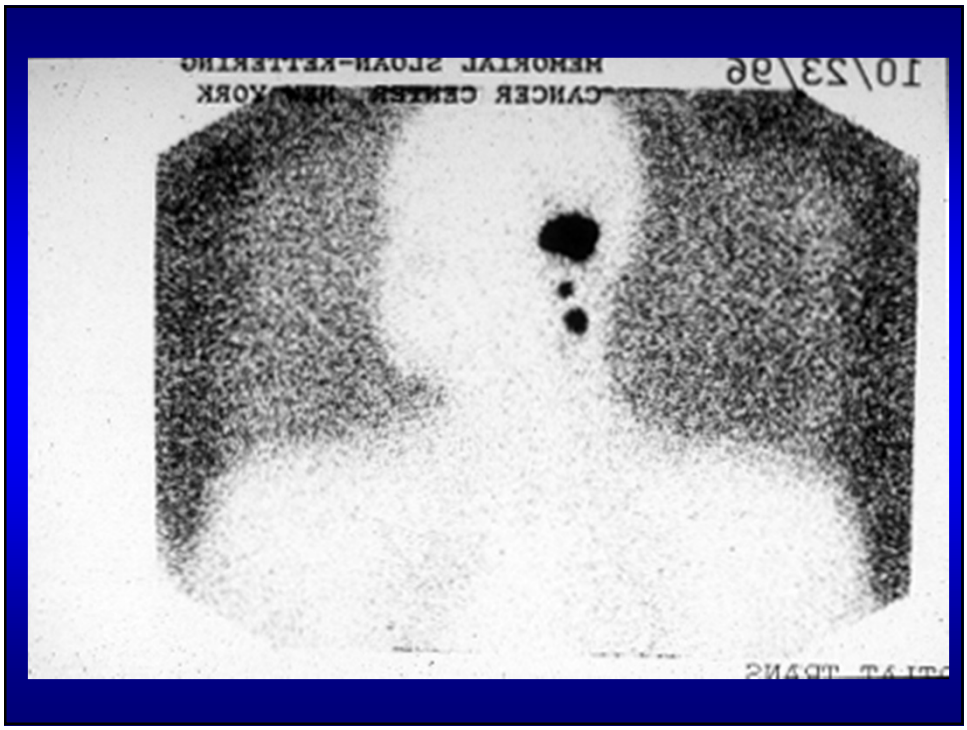


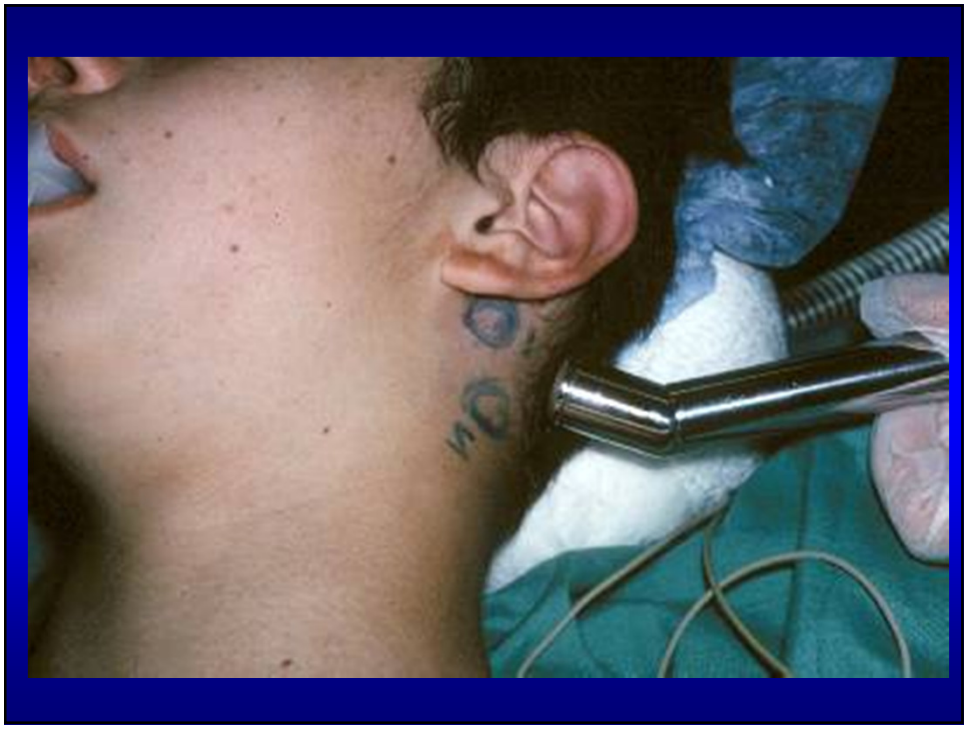
Balch C., et. al. Prognostic Factors Analysis of 17,600 Melanoma Patients: Validation of the American Joint Committee on Cancer Melanoma Staging System. J Clin Oncol 2001;19:3622-34

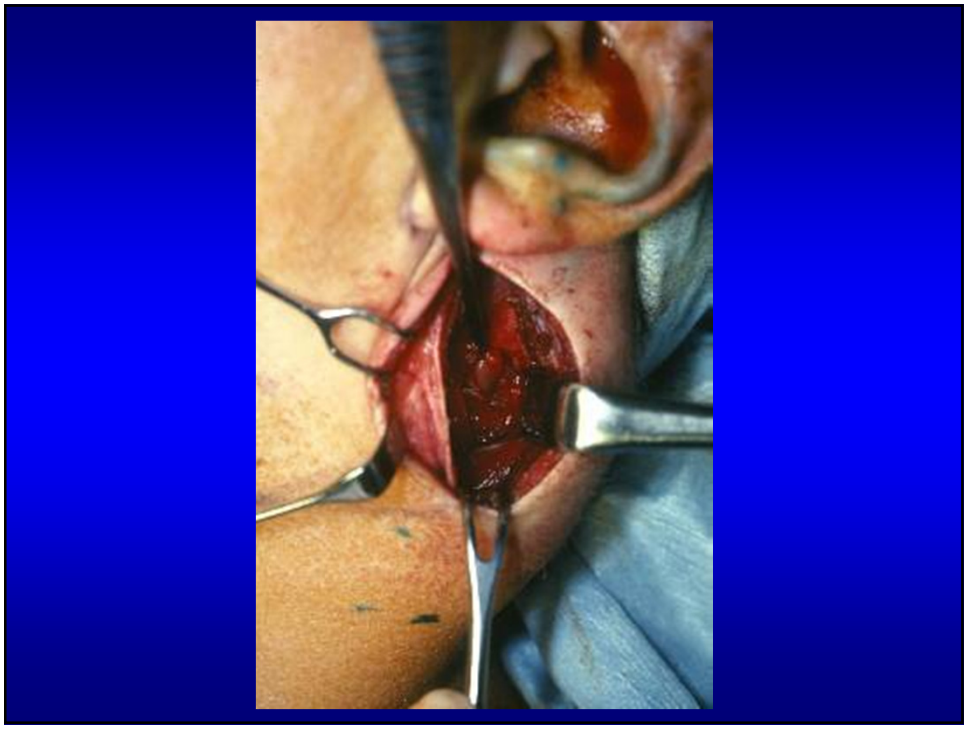
Lymphoscintigraphy

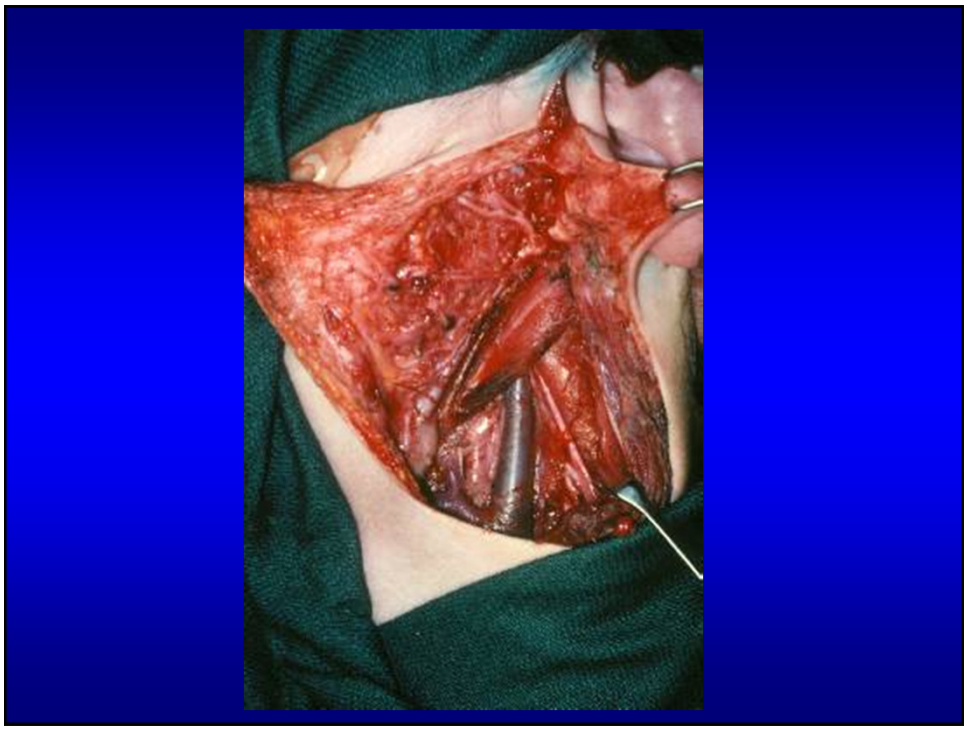
- **Each primary skin site has a unique nodal drainage**
- **Lymphoscintigraphy can accurately predict the regional nodal basin**
- **The unique initial draining node, the sentinel node, can be identified using this technique**
- **The status of the node is highly predictive of the entire nodal basin**

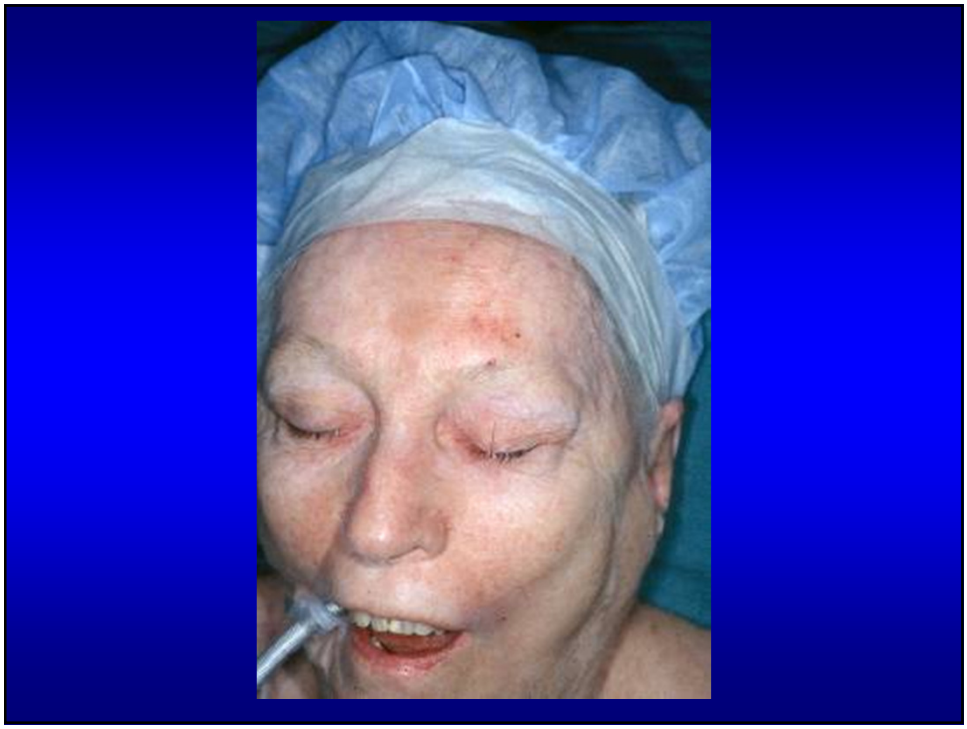


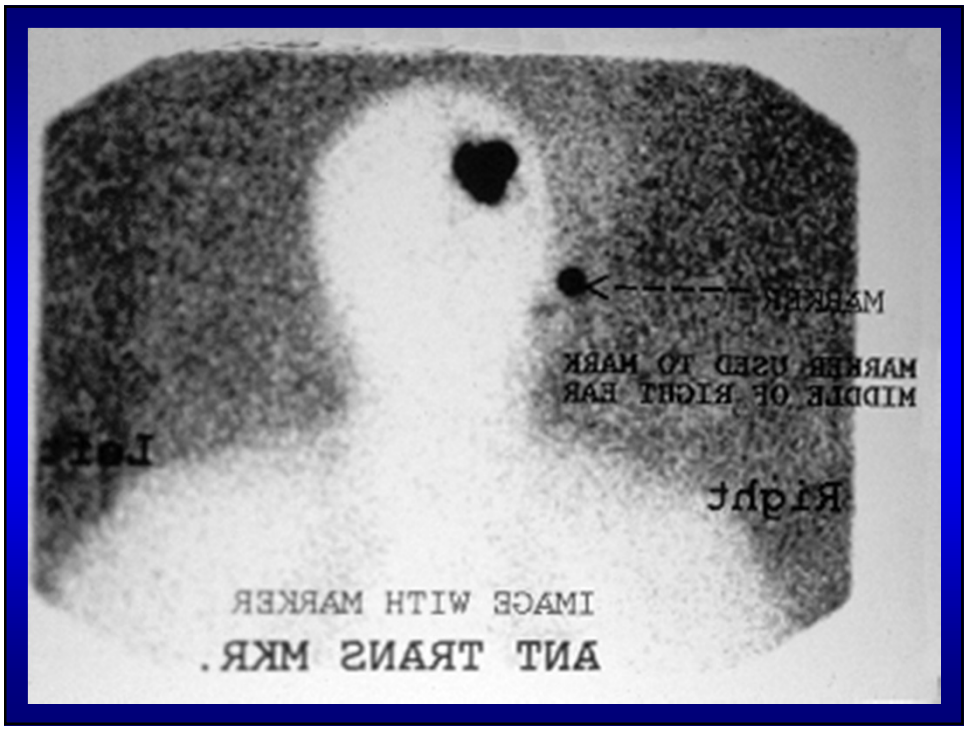








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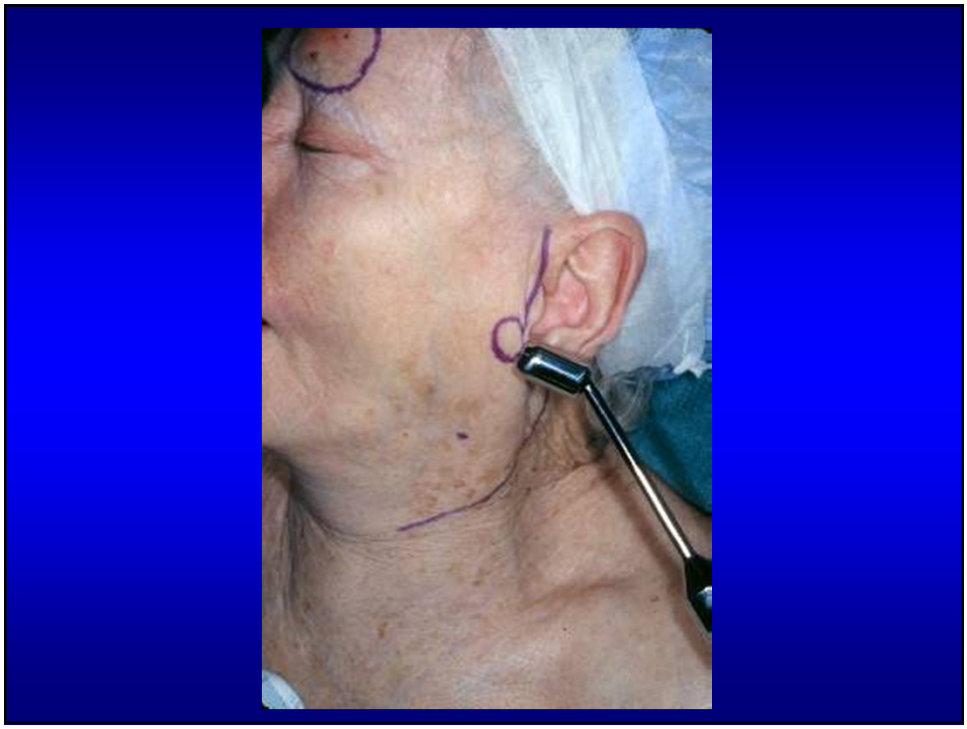
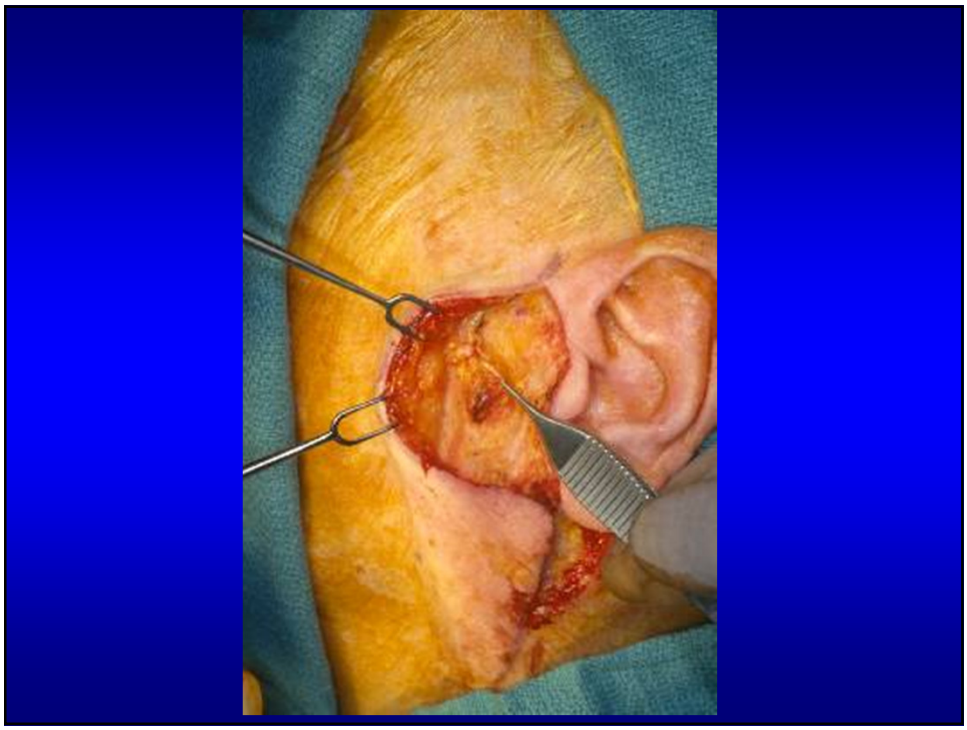


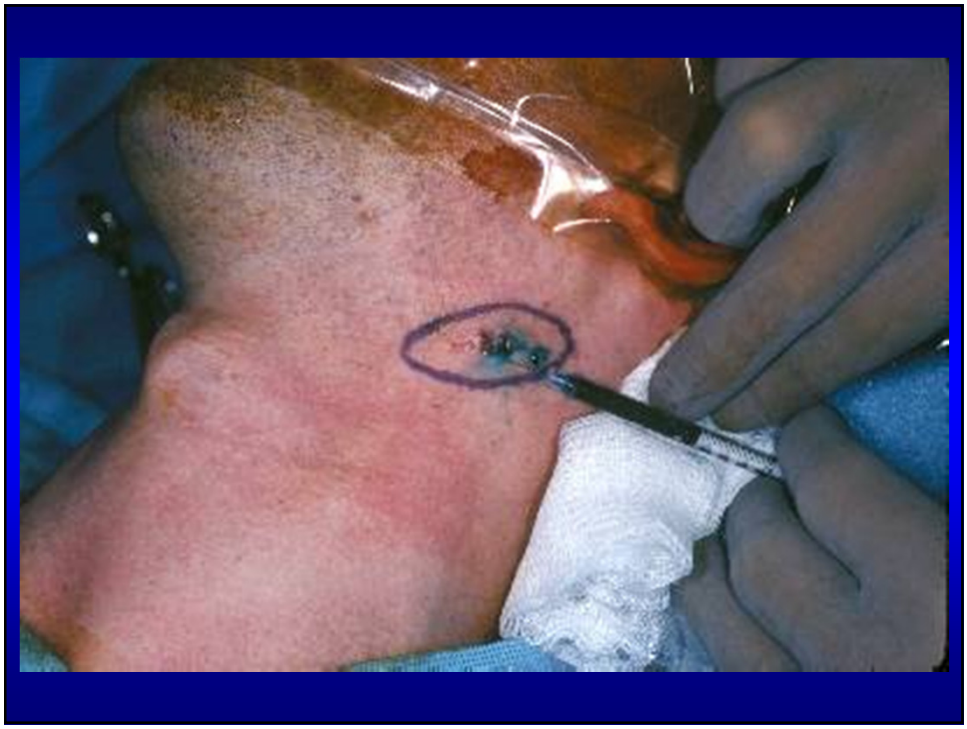


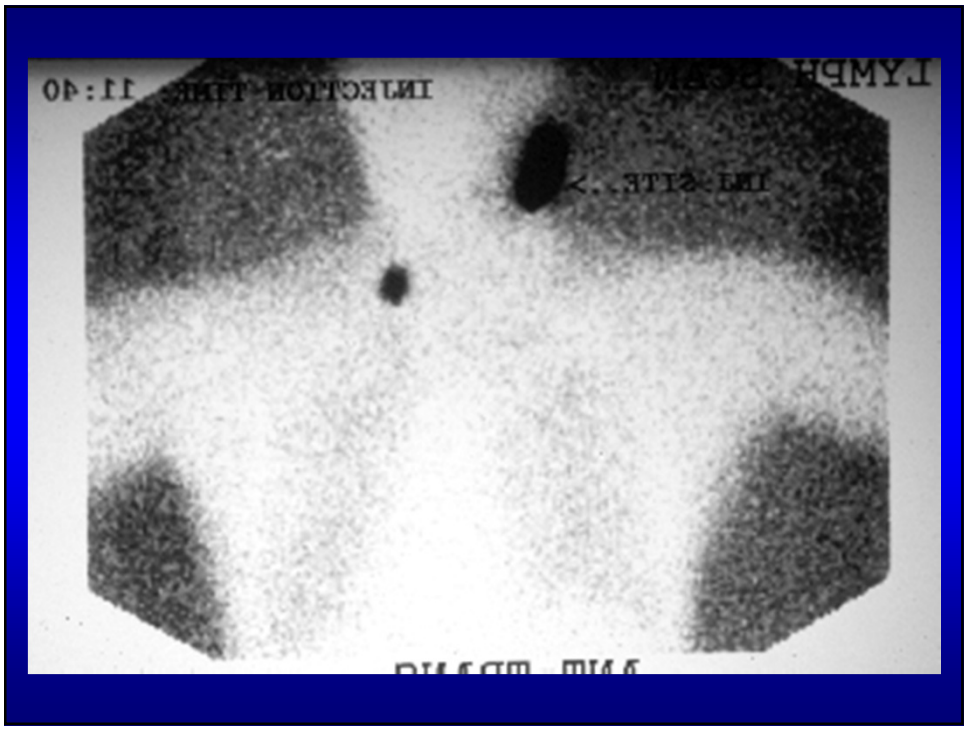
Sentinel Lymph Node Biopsy for Cutaneous Head and Neck Melanoma
Mapping the Parotid Gland

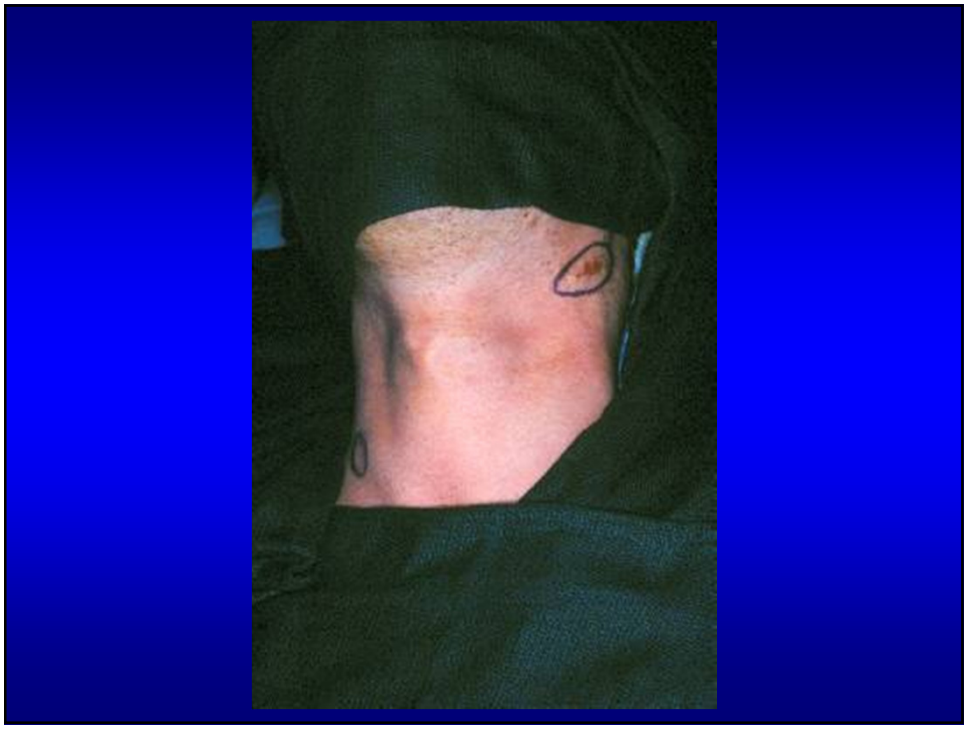
Results: Facial Nerve Function

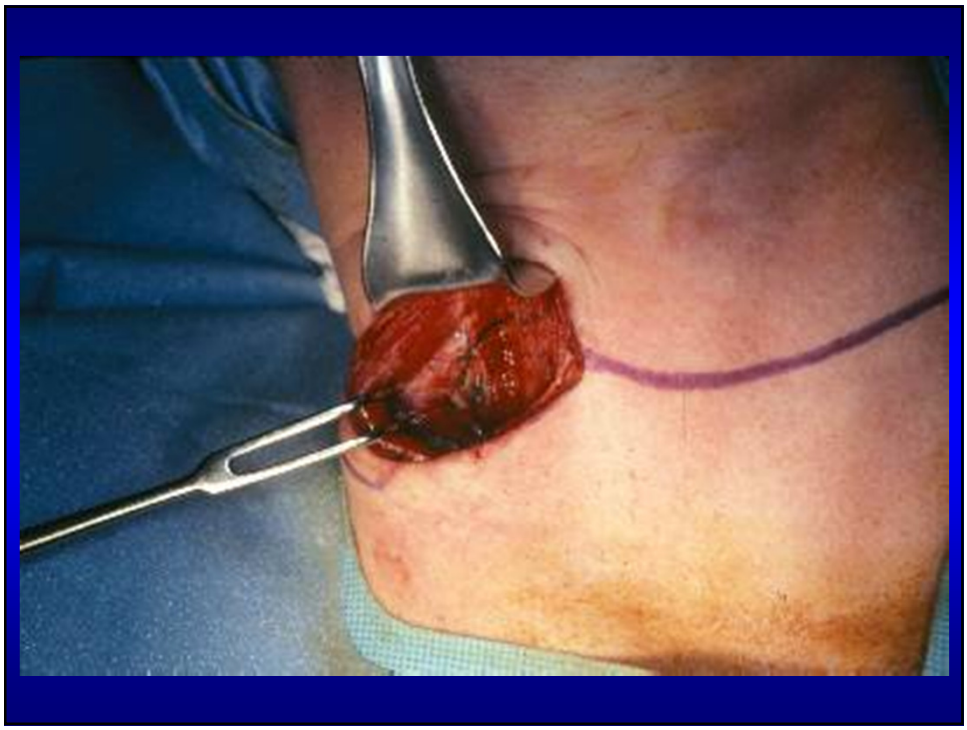
Procedure	Facial nerve affected	Facial nerve function	Postoperative visit (%)*		
			1st	2nd	3rd
Intraparotid LN Biopsy (n=37)	Mandibular branch (n=2)	Normal	94	97	100
		Paresis	6	3	0
		Paralysis	0	0	0
Parotidectomy (n=16)	All branches affected (n=5)	Normal	70	94	100
		Paresis	24	6	0
		Paralysis	6	0	0
Periparotid LN biopsy (n=19)	None	Not affected	100% normal		
TOTAL	Injury: 7 (10%)	Normal function:	90	97	100

*Postop visits: 1st=first 2 wks, 2nd=3 months, 3rd=6 months









Descriptive Statistics for the Cohort

- Total patients having SLNB at MSKCC between 1996-2007: 236
- Range of follow up: 0-124 months
  - Average follow up 43 months; median 37 months
- Sentinel Lymph Node statistics
  - 217 cases where a SLN was found
  - 19 (8%) cases failed to ID a SLN by both the lymphoscintigram or intraoperative gamma probe.
  - 27 positive SLN by frozen section and IHC.
    - 13 (48%) of these were only positive on immunohistochemistry and/ or /permanent pathology.

Results

Sensitivity & Specificity

- There was nodal recurrence in 15 of the 171 patients who had a negative SLNB
  - Sensitivity: 64%
  - Specificity: 100%
  - Negative predictive value: 93%
  - Positive predictive value: 100%

Study	# of Patients	Positive SLNB (%)	Regional Recurrence	Total Positive	False Negative Rate ‡	Follow Up
MSKCC	234	28 (12.0)	12	40	30.00%	37 mos. (median)
Sydney Cancer Centre[9]	136	14 (10.3)	11	25	44.00%	34 mos. (mean)
MD Anderson[10]	113	23 (20.4)	5	30	23.30%	34 mos. (Median)
U. of Michigan[11]	80	14 (17.5)	3	17	17.60%	25 mos. (median)
Sunbelt Melanoma[12]	287	43 (16.1)	6	49	12.20%	15.5 mos.

‡ The false negative rate is equal to the regional recurrence divided by the true positives (positive SLN and regional recurrences).

† While 5 patients recurred in the regional lymphatics, two other patients in a prospective trial had a negative SLNB but a contemporaneous lymphadenectomy revealed a positive lymph node.

Survival Analysis-Univariate

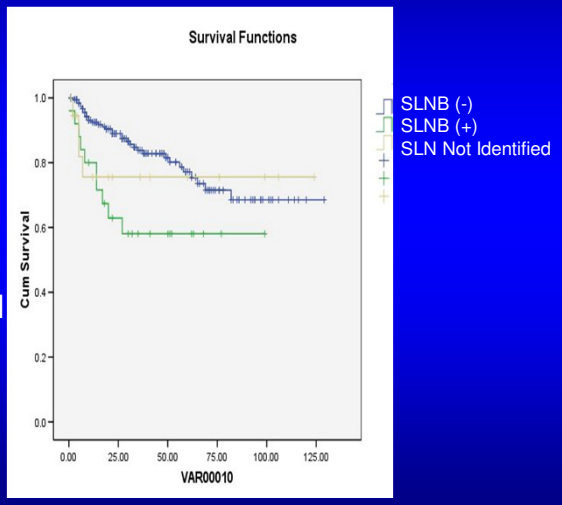
Disease Free Survival

Stratified by Sentinel Lymph Node Status

SLNB negative
- **3 yr: 84%**
- **5 yr: 77%**

SLNB positive
- **3 yr: 58%**

No SLN identified
- **3 Yr: 75%**



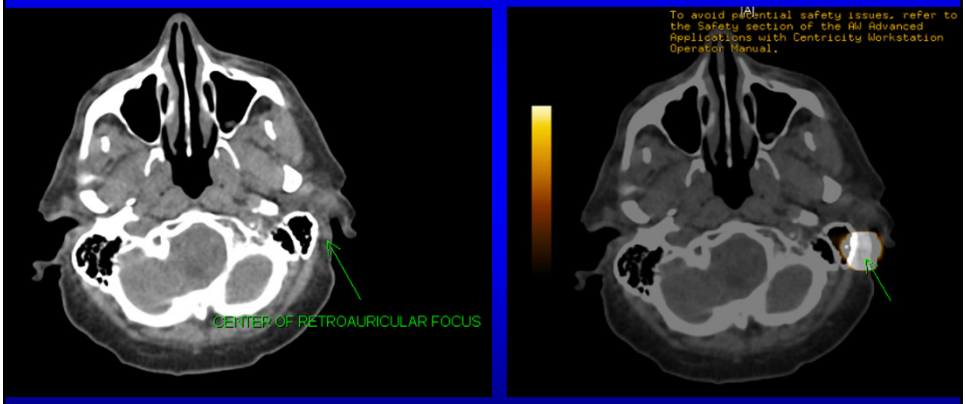
Survival Analysis-Multivariate

COX Regression Analysis of Survival

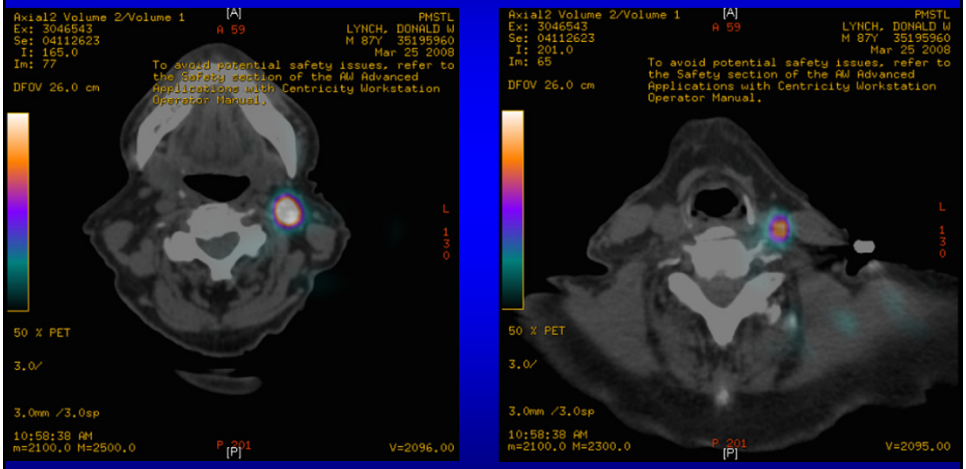
The only two covariates which were statistically significant were:

- **Sentinel Lymph Node Positivity**
- **Melanoma Ulceration**

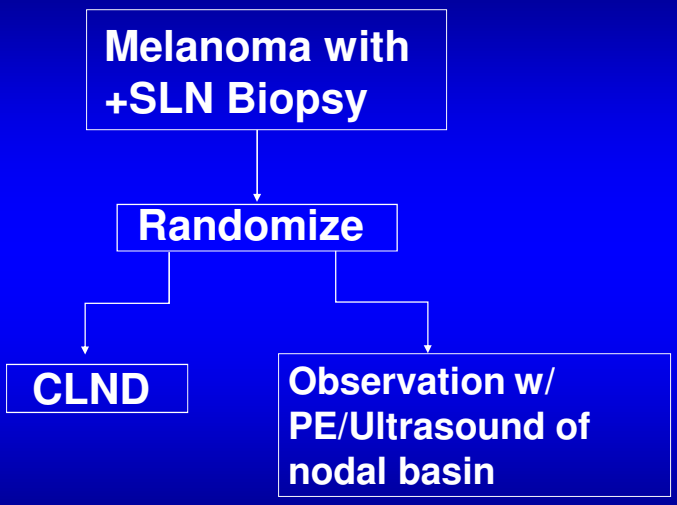
SPECT- CT Sentinel Node Biopsy Lymphoscintigraphy



SPECT- CT Sentinel Node Biopsy Lymphoscintigraphy



MSLT-II



Primary endpoint: DSS

Summary

- Early diagnosis offers best chance of cure
- Aggressive surgical management of the primary role of lymphoscintigraphy evolving
- Optimal, adjuvant therapy remains elusive

Notes

Innovations in the Medical Management of Malignant Melanoma

From being a malignancy with limited therapeutic options for several decades the medical treatment of melanoma has undergone great change within the last 2 years. The realization that melanoma is amenable to both immune based therapies and targeted therapies has lead to a resurgence in the interest in melanoma worldwide from both academic and pharma investigators. The presentation will review the recent advances with vemurafenib and ipilimumab, concentrating on the response characteristics and side effects. Other targeted drugs relevant to mucousal head and neck melanoma such as c-kit inhibitors and their utility will also be commented on. The future of melanoma therapies will also be explored, and the role of combination therapies discussed

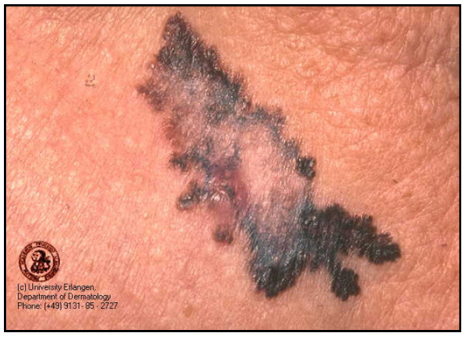
Anthony Joshua

Notes

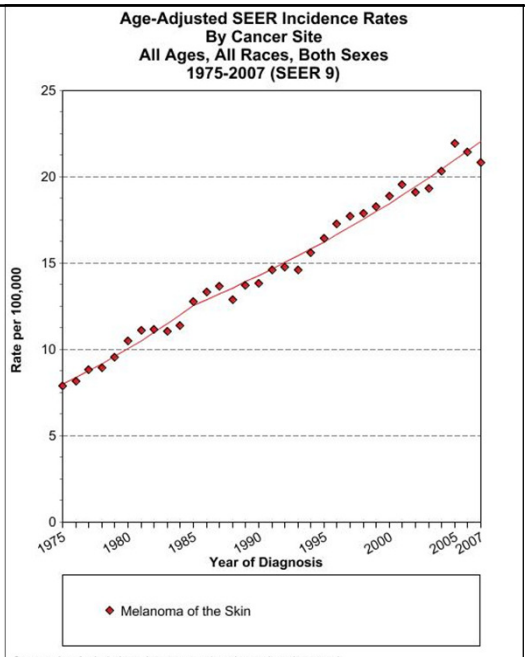
Innovations in the Medical Management of Malignant Melanoma

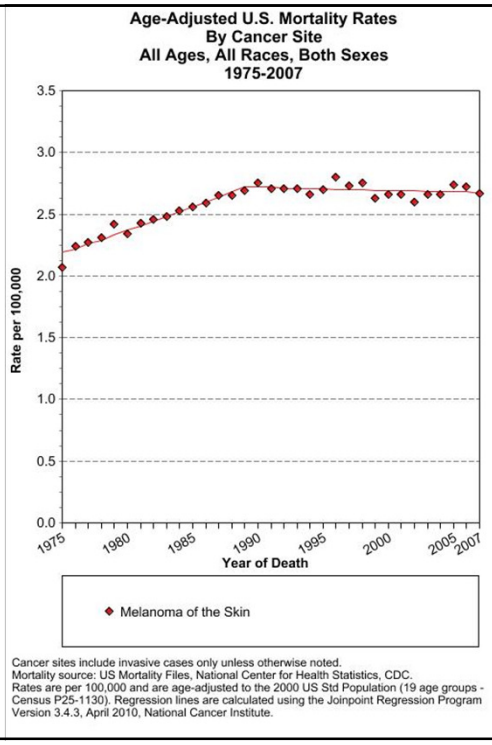
Anthony Joshua
BSc (Med) MBBS PhD
Department of Medical Oncology
Princess Margaret Hospital
Toronto, Ontario, CANADA

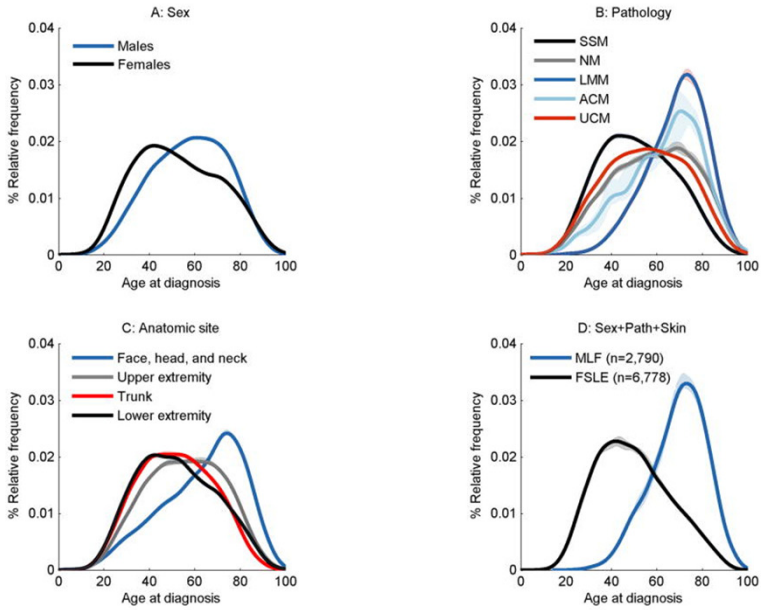
Melanoma



- Lifetime risk ~1/75 in the Canadian population
- Related to ethnic origin, family history, sun exposure
- High potential of metastasis
- Fatality rate is ~20%


Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975-2007 (SEER 9)
Rate per 100,000
25
20
15
10
5
0
1975
1980
1985
1990
1995
2000
2005
2007
Year of Diagnosis
Melanoma of the Skin
Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute.


Age-Adjusted U.S. Mortality Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975-2007
Rate per 100,000
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1975
1980
1985
1990
1995
2000
2005
2007
Year of Death
Melanoma of the Skin
Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute.



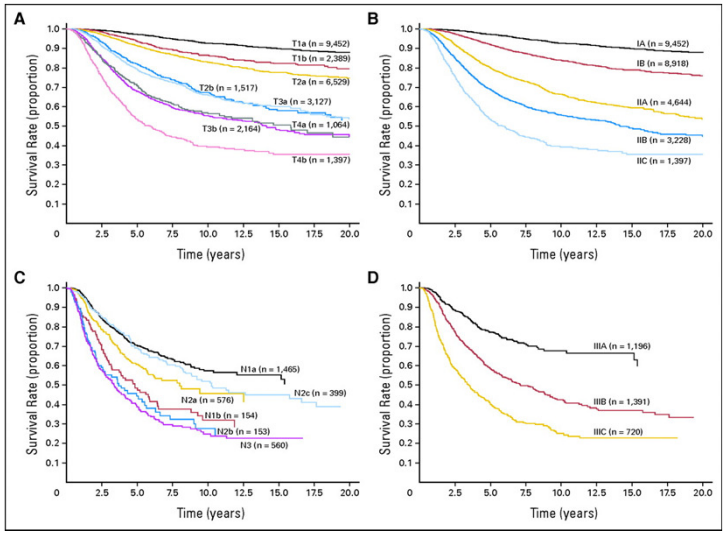
Anderson *et al* Cancer 2009

Prognostic features in melanoma AJCC 2010

- Thickness of the primary lesion, in mm
- Ulceration
- Mitotic rate
- Involvement of regional lymph nodes
- Distant metastases

6

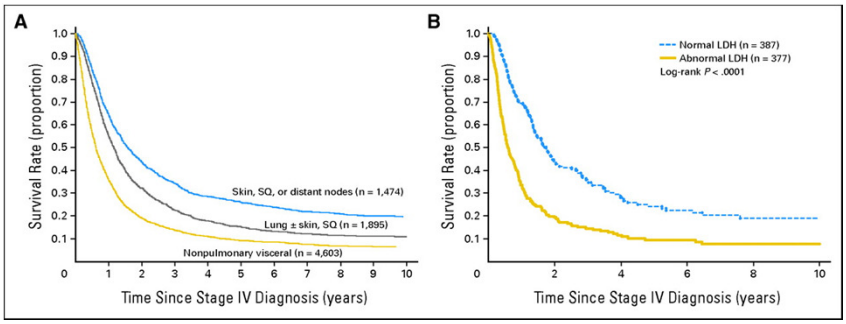
Survival curves from the American Joint Committee on Cancer Melanoma Staging Database comparing (A) the different T categories and (B) the stage groupings for stages I and II melanoma.



Balch C M et al. JCO 2009;27:6199-6206

JOURNAL OF CLINICAL ONCOLOGY

Survival curves of 7,635 patients with metastatic melanomas at distant sites (stage IV) subgrouped by (A) the site of metastatic disease and (B) serum lactose dehydrogenase (LDH) levels.



Balch C M et al. JCO 2009;27:6199-6206

JOURNAL OF CLINICAL ONCOLOGY

Treatment of melanoma

- Dependent on the stage
- Stage I-II (no spread)
  - Surgical excision of lesion
- Stage III (local nodes)
  - Surgical excision of tumor and nodes ± Interferon
- Stage IV (metastases)
  - Chemotherapy ± radiation, surgery
  - Immunotherapy
  - Targeted agents

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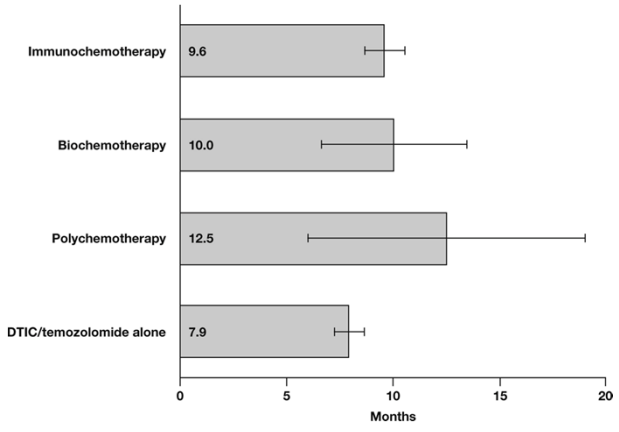
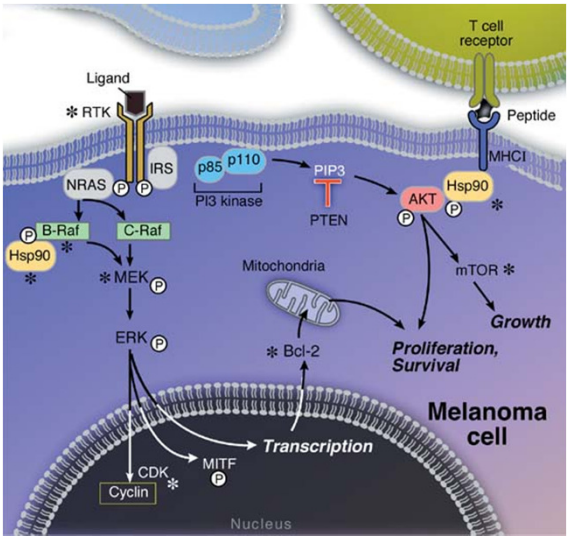
Overall survival of patients treated with different therapies for melanoma

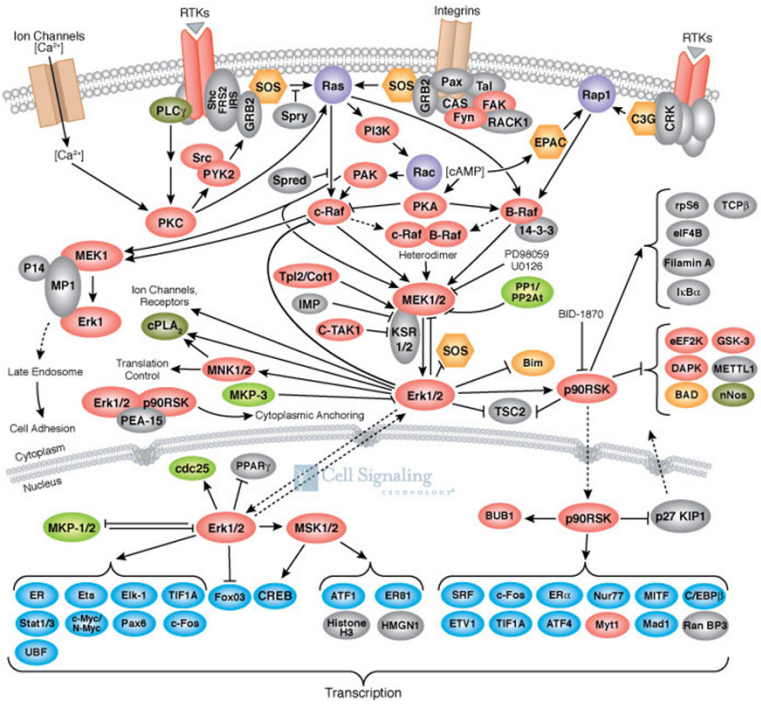


Current Classification

- **BRAF(+)s**
- **BRAF(-)**
- Everything else (NRAS, c-kit, MEK, AKT, GNAQ/11, etc)

MAP Kinase pathway





Pivotal phase 3 trial

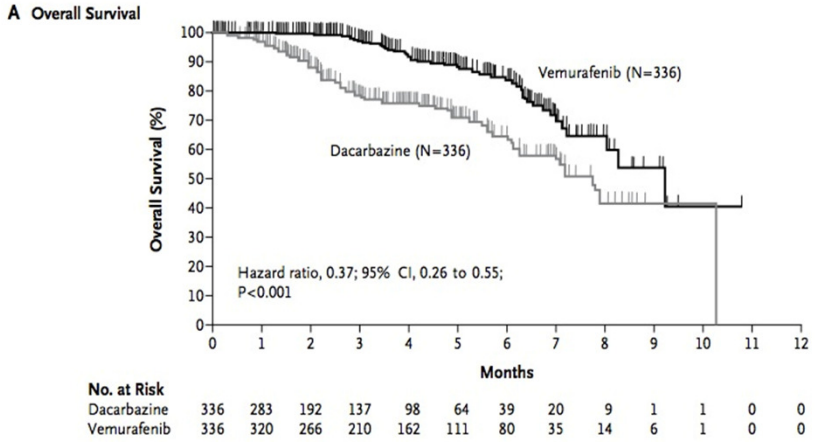
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

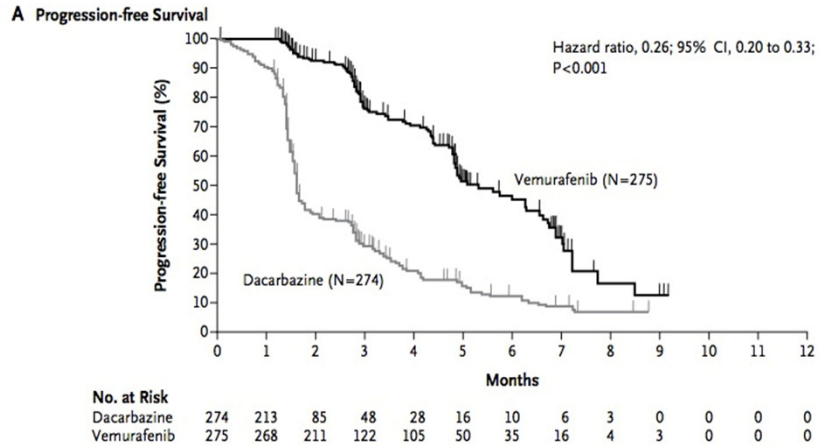
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

Overall survival



Progression Free Survival



Best tumour response

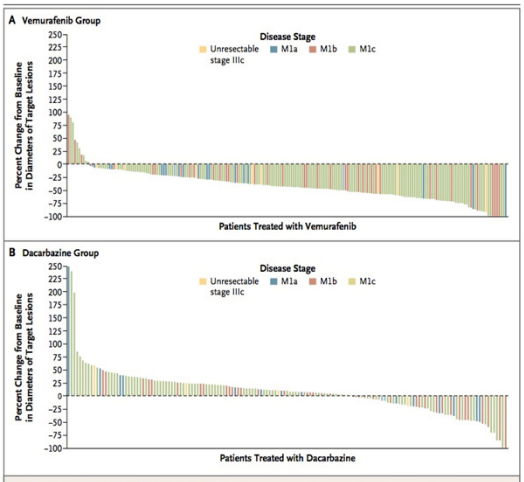
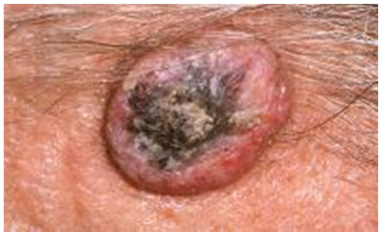
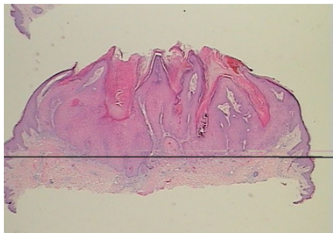


Figure 3. Best Tumor Response for Each Patient.

Data regarding the best tumor response are shown for 209 patients in the vemurafenib group (Panel A) and 158 patients in the dacarbazine group (Panel B) who were registered at least 14 weeks before the clinical cutoff date on December 30, 2009, and who had undergone at least one tumor assessment after treatment. Each bar represents data for an individual patient. Colors indicate the tumor substage for each patient. The percent change from baseline in the sum of the diameters of the target lesions is shown on the y axis. Negative values indicate tumor shrinkage.

Cutaneous SCC – Keratoacanthoma (KA) Subtype





- Characteristics of KA subtype
- Raised button-like, central crater
- Well-differentiated neoplasm with low probability of invasion/metastasis
- Can grow rapidly; may involute and regress
- Typically treated by excision
- Observed with other agents (e.g., sorafenib)

KA in the Phase I RG7204 Trial

- Occurred on sun-exposed skin
- Did not result in treatment discontinuation

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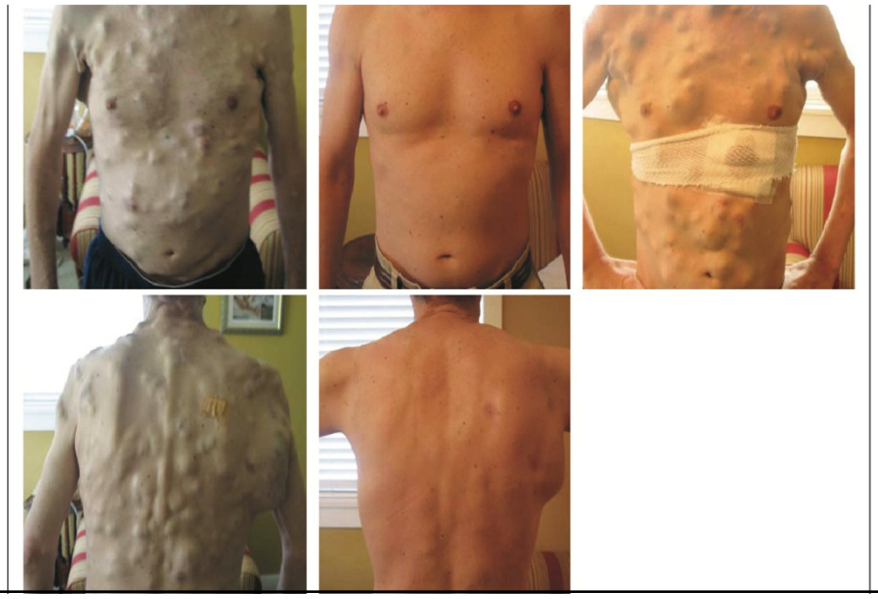
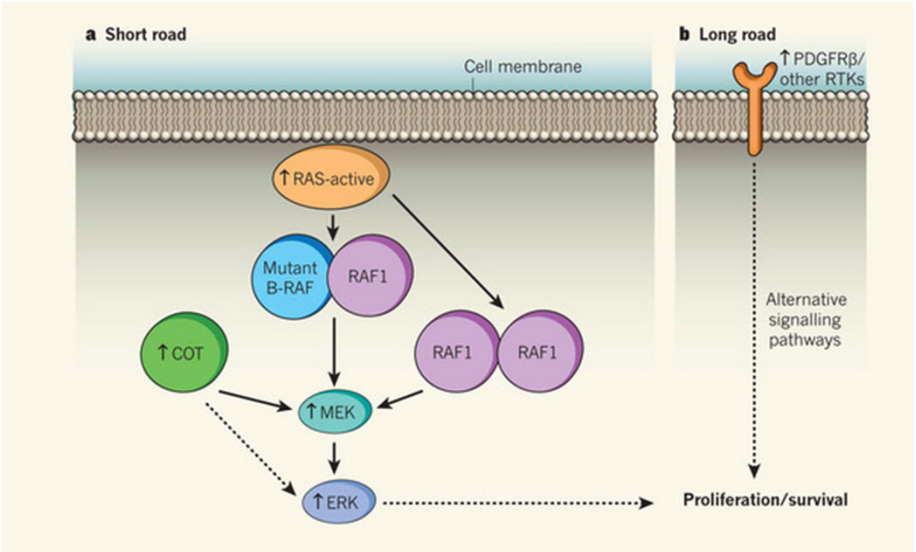
Resistance

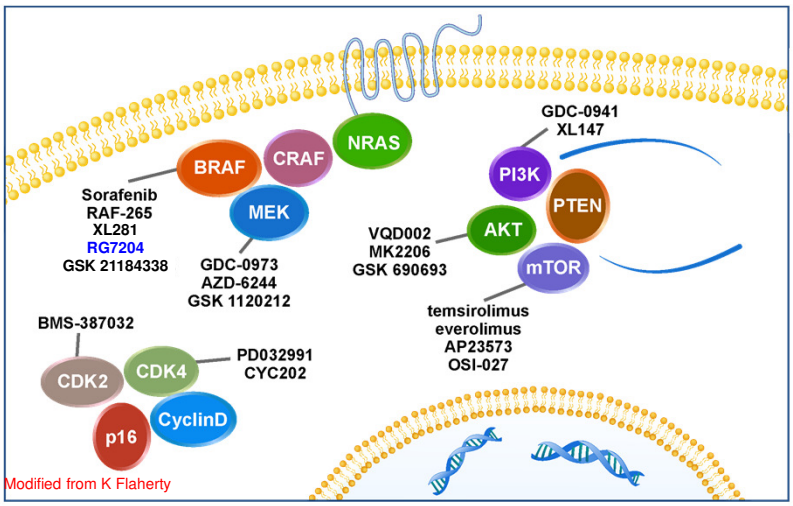


Mechanisms of BRAFi resistance

Solit and Sawyers, *Nature* 2010



The Future of Targeted Therapy for Melanoma



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Head and Neck Mucousal Melanomas

- Most commonly nasal cavity
- Generally poor prognosis
  - Largest review, (962 pts), 3 year survival rate 39%, 5 year survival rate of 17% (Manolidis et al., 1997). Little evidence much has changed.
- Impression that they are more chemosensitive to carboplatin/paclitaxel
- Mutations and or copy number increases in c-kit are found in ~30% of early series of mucousal melanomas, however mutations may be the only clinically targetable findings

22

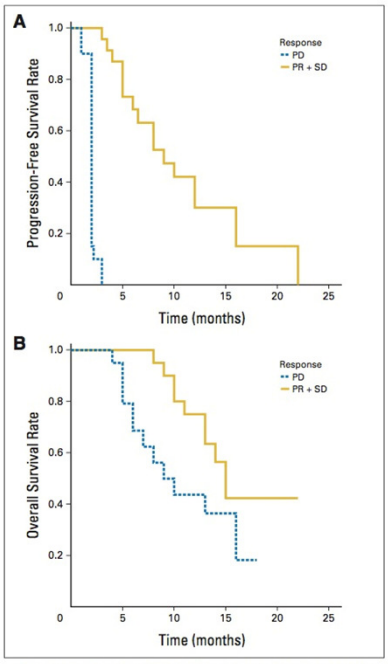

Fig 2. Correlation of response to progression-free survival or overall survival. Solid yellow line indicates partial response (PR) plus stable disease (SD; n = 23), and dotted blue line indicates progression of disease (PD; n = 20).

- Guo et al., JCO, 2011;
  - 43 patients, median PFS of 3.5 months
  - Rate of total disease control was 53.5%: 10 patients (23.3%) had PR and 13 patients (30.2%) had SD
  - 18 patients (41.9%) demonstrated regression of tumor mass.
  - Notably, nine of the 10 PRs were observed in patients with mutations in exons 11 or 13.
  - The 1-year overall survival (OS) rate was 51.0%.
- Other responses to sorafenib, sunitinib, dasatinib reported

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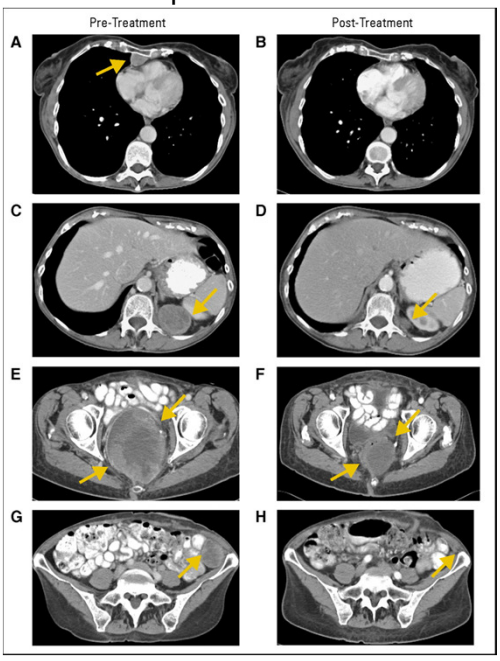
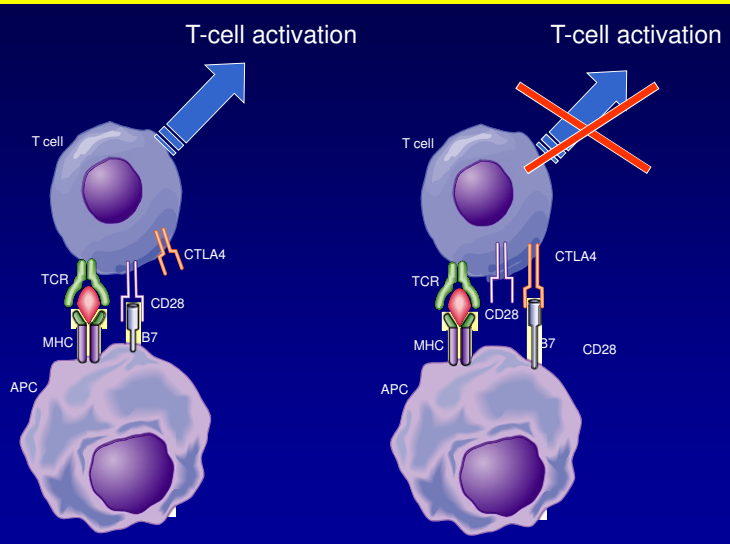
Response to Imatinib



Hodi, F. S. et al. J Clin Oncol; 26:2046-2051 2008

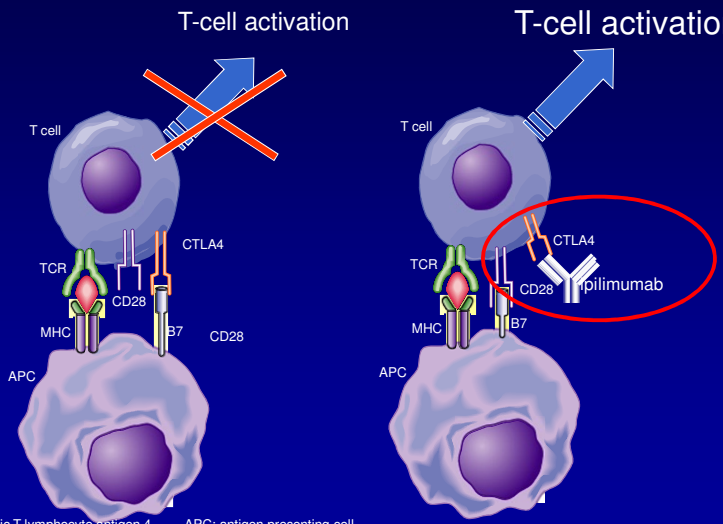
Natural T-cell Braking System From CTLA4



Adapted from Lebbé et al. ESMO 2008

25

Restoring Signaling

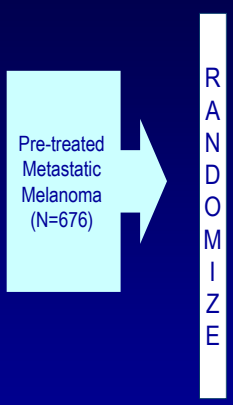


CTLA4: cytotoxic T lymphocyte antigen 4 APC: antigen presenting cell
TCR: T cell receptor MHC: major histocompatability complex

Adapted from Lebbé et al. ESMO 2008

26

Ipilimumab: Pivotal Phase 3 Trial (Study MD020)



Ipilimumab + gp100
N=403

Ipilimumab + placebo
N=137

gp100 + placebo
N=136

Primary Endpoint = overall survival
2ndary Endpoints:
- best overall risk reduction (BORR):
- Duration of response
- PFS

gp100: glycoprotein 100
Hodi FS, *et al: N Engl J Med* 2010; 363(8):711-23.
Also presented at ASCO 2010 (Plenary Session, Abstract #4)

27

Ipilimumab: Pivotal Phase 3 Trial Baseline Demographics

Variable	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)	Total (N=676)
Mean age — yr	55.6	56.8	57.4	56.2
Sex — no. (%)				
Male	247 (61.3)	81 (59.1)	73 (53.7)	401 (59.3)
Female	156 (38.7)	56 (40.9)	63 (46.3)	275 (40.7)
ECOG performance status — no. (%)†				
0	232 (57.6)	72 (52.6)	70 (51.5)	374 (55.3)
1	166 (41.2)	64 (46.7)	61 (44.9)	291 (43.0)
2	4 (1.0)	1 (0.7)	4 (2.9)	9 (1.3)
3	1 (0.2)	0	0	1 (0.1)
Unknown	0	0	1 (0.7)	1 (0.1)
M stage — no. (%)‡				
M0	5 (1.2)	1 (0.7)	4 (2.9)	10 (1.5)
M1a	37 (9.2)	14 (10.2)	11 (8.1)	62 (9.2)
M1b	76 (18.9)	22 (16.1)	23 (16.9)	121 (17.9)
M1c	285 (70.7)	100 (73.0)	98 (72.1)	483 (71.4)

ECOG = Eastern Cooperative Oncology Group
Hodi FS, *et al: N Engl J Med* 2010; 363(8):711-23.
Also presented at ASCO 2010 (Plenary Session, Abstract #4)

28

Ipilimumab: Pivotal Phase 3 Trial Baseline Demographics (con't)

Variable	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)	Total (N=676)
Lactate dehydrogenase level — no. (%)				
≤Upper limit of the normal range	252 (62.5)	84 (61.3)	81 (59.6)	417 (61.7)
>Upper limit of the normal range	149 (37.0)	53 (38.7)	52 (38.2)	254 (37.6)
Unknown	2 (0.5)	0	3 (2.2)	5 (0.7)
CNS metastases at baseline — no. (%)	46 (11.4)	15 (10.9)	21 (15.4)	82 (12.1)
Received study drug	42 (10.4)	15 (10.9)	20 (14.7)	77 (11.4)
Had had previous treatment for CNS metastases	39 (9.7)	15 (10.9)	19 (14.0)	73 (10.8)
Previous systemic therapy for metastatic disease — no. (%)	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Previous interleukin-2 therapy — no. (%)	89 (22.1)	32 (23.4)	33 (24.3)	154 (22.8)

CNS = central nervous system
Hodi FS, *et al: N Engl J Med* 2010; 363(8):711-23.
Also presented at ASCO 2010 (Plenary Session, Abstract #4)

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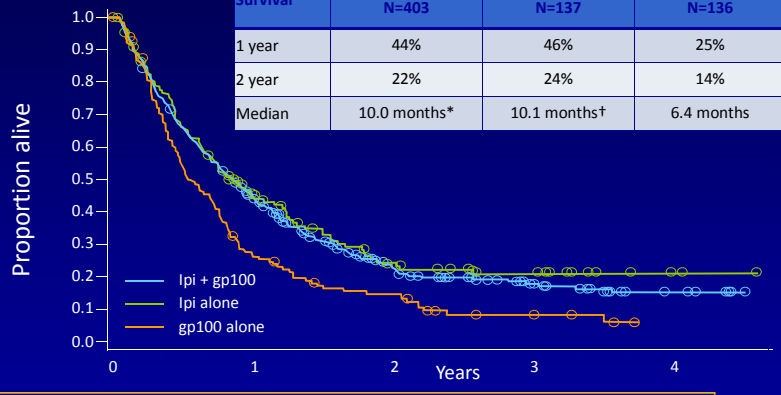
Overall Survival With Ipilimumab in Pivotal Phase 3 Trial

Survival	Ipi + gp100 N=403	Ipi + placebo N=137	gp100 + placebo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%
Median	10.0 months*	10.1 months†	6.4 months



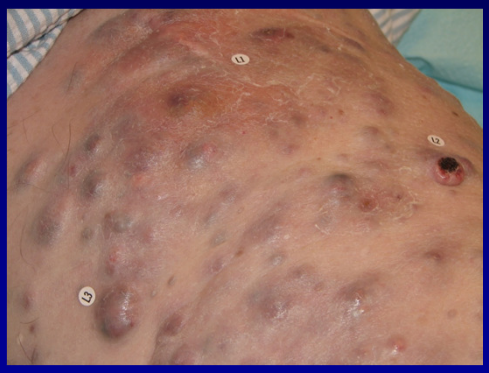
Only trial to show a survival advantage in metastatic melanoma

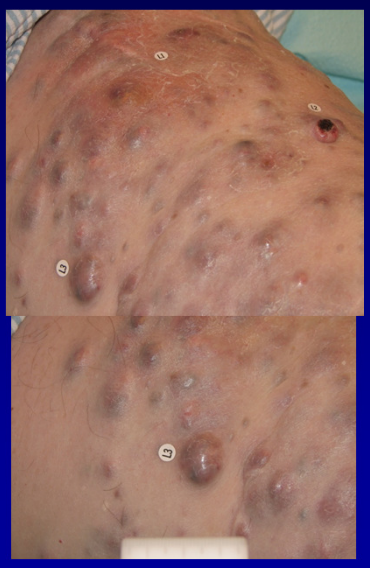
n = 676 patients with unresectable stage III or IV melanoma
*p<0.001 vs. gp100 + placebo; †p=0.003 vs. gp100 + placebo

Hodi FS, *et al: N Engl J Med* 2010; 363(8):711-23.
Also presented at ASCO 2010 (Plenary Session, Abstract #4).

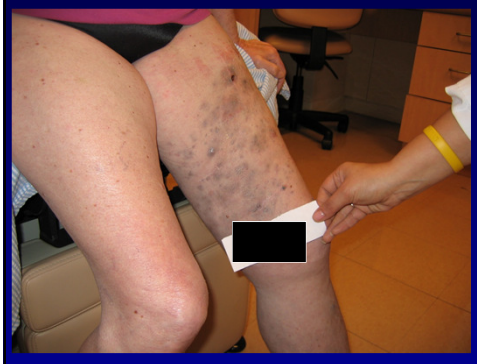
30

Pretreatment

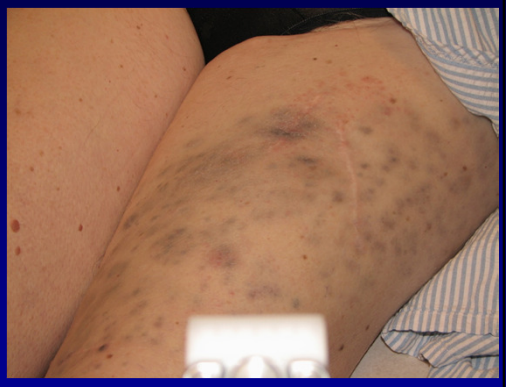


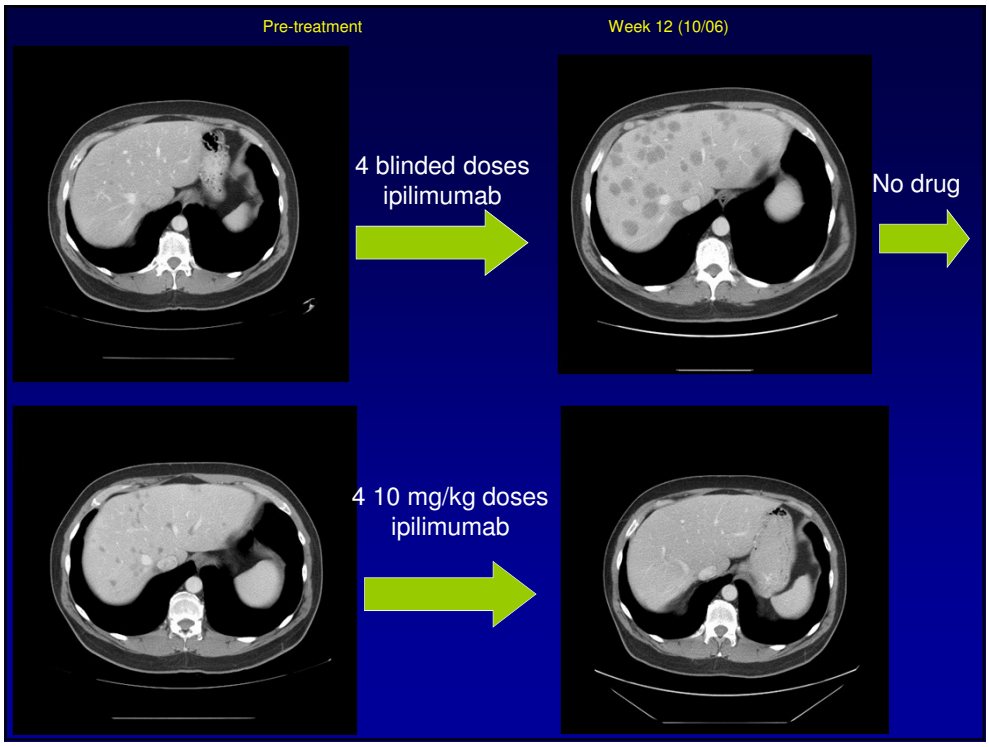


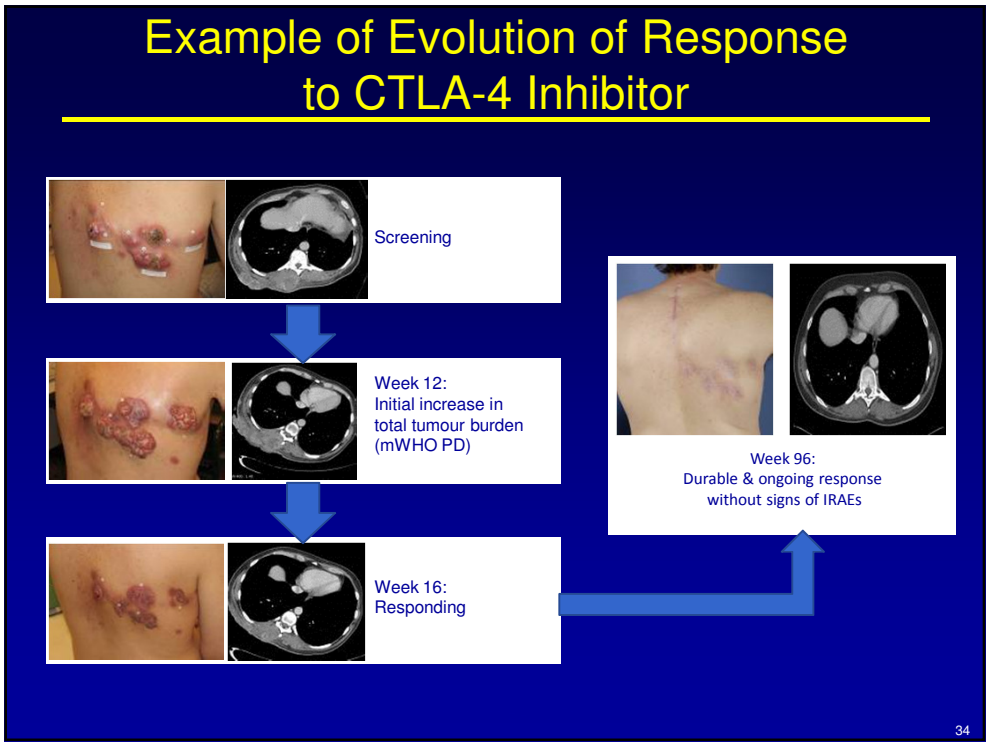
Week 7



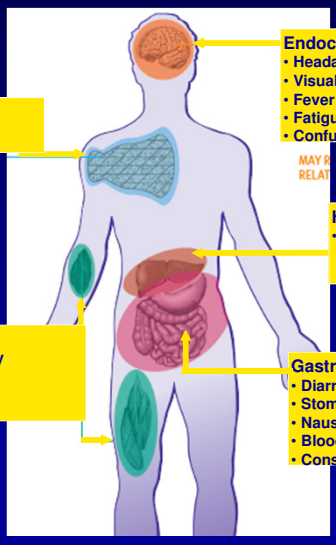
Week 12




Pre-treatment
Week 12 (10/06)
4 blinded doses ipilimumab
No drug
4 10 mg/kg doses ipilimumab


Example of Evolution of Response to CTLA-4 Inhibitor
Screening
Week 12: Initial increase in total tumour burden (mWHO PD)
Week 16: Responding
Week 96: Durable & ongoing response without signs of IRAEs
34

irSEs Observed With Immune and Targeted Agents



Endocrine
- Headache
- Visual changes
- Fever
- Fatigue/weakness
- Confusion

Skin
- Skin rash or pruritus

Hepatic
- Abnormal LFTs (eg, AST, ALT, total bilirubin)

Neurologic
- Sensory or motor neuropathy
- Muscle weakness
- Fatigue
- Difficulty waking up

Gastrointestinal (GI)
- Diarrhea
- Stomach pain
- Nausea/vomiting/pain
- Blood in stool
- Constipation

If not vigilant, may result in more serious immune-related side effects.

ALT = alanine aminotransferase ,
AST = aspartate aminotransferase,
LFT s= liver function tests

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Immune therapies going forward

- Combination with B-RAF inhibitors
- PD-1
- Tumor Infiltrating Lymphocytes

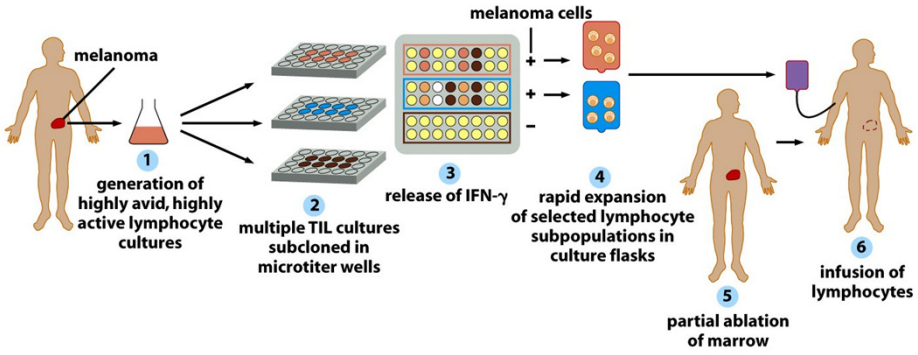
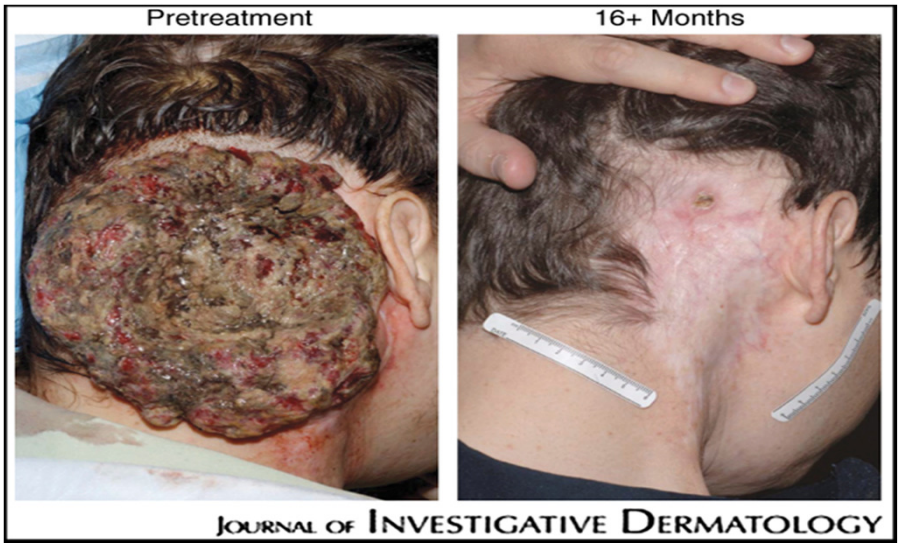


Figure 15.44a *The Biology of Cancer* (© Garland Science 2007)



Cancer Therapy: Clinical
See commentary by Heslop, p. 4189

Clinical Cancer Research

Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy

Steven A. Rosenberg[1], James C. Yang[1], Richard M. Sherry[1], Udai S. Kammula[1], Marybeth S. Hughes[1], Giao Q. Phan[1], Deborah E. Citrin[2], Nicholas P. Restifo[1], Paul F. Robbins[1], John R. Wunderlich[1], Kathleen E. Morton[1], Carolyn M. Laurencot[1], Seth M. Steinberg[3], Donald E. White[1], and Mark E. Dudley[1]

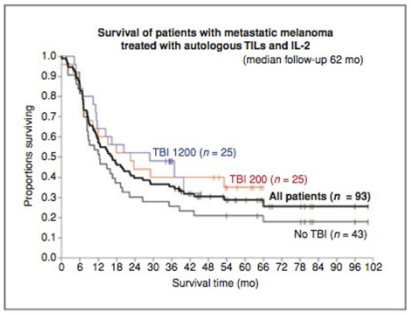


Figure 1. Overall survival of patients receiving TILs with the chemotherapy preparative regimen alone (no TBI) or plus 2 or 12 Gy TBI.

Table 1. Cell transfer therapy

Treatment	n (%) of patients (duration in mo)			OR (%)
	Total	PR	CR	
No TBI	43	16 (37) 84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2	5 (12) 82+, 81+, 79+, 78+, 64+	21 (49)
200 TBI	25	8 (32) 14, 9, 6, 6, 5, 4, 3, 3	5 (20) 68+, 64+, 60+, 57+, 54+	13 (52)
1,200 TBI	25	8 (32) 21, 13, 7, 6, 6, 5, 3, 2	10 (40) 48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19	18 (72)
Total	93	32 (34)	20 (22)	52 (56)

NOTE: Data updated as of August 1, 2010.

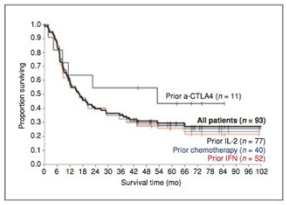


Figure 2. Overall survival of patients receiving cell transfer based on prior treatment received.

With special thanks to:

- Melanoma nursing staff - Nancy Gregorio
- Clinical trials nurse - Bian Zhang
- Fellow - Craig Gedye
- David Hogg
- Ian Quirt
- ...and all our patients

Notes

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Management of Aggressive Nonmelanoma Skin Cancer

Randal S. Weber, M.D.

Current Concepts
Toronto, Canada
2011

Overview

- Epidemiology
- Definition of "Aggressive" NMSC
- Case Discussion
  - Prognostic features
  - Patient evaluation
  - Staging
  - Principles of management
- Reconstructive challenges

Nonmelanoma Skin Cancer

- Basal cell carcinoma
  - Superficial
  - Nodular
  - Infiltrative
  - Micronodular
- Heterogeneous malignancies
- Merkel cell carcinoma
- Adnexal carcinoma
  - Eccrine carcinoma
  - Apocrine carcinoma
- Squamous cell carcinoma
  - Well-, mod-, poorly-diff
  - Verrucous
  - Spindle cell
  - Desmoplastic
  - Basosquamous
  - Clear cell

NMSC Epidemiology

- Rising incidence[1]
  - 1.0-1.3M new cases/year
  - Increasing 2-3% per year
  - Expected to double in 20 yrs
- True incidence difficult to track
  - Not reported in cancer registry
  - Up to 3.5M new lesions in 2006
  - Affecting 2.1M patients[3]
- Lifetime risk of NMSC
  - 25-33% BCC
  - 7-11% SCC
- Demographics
  - Decreasing age at diagnosis
  - Male:Female ratio = 3-4 : 1
  - BCC:SCC ratio = 4 : 1
- Global public health concern
  - 5x all other cancers in Australia
  - 1170 cases/ 100,000 people[2]

1) Alam M et al, *New Engl J Med* 2001
2) Staples MP et al, *MJA* 2006
3) Rogers HW et al, *Arch Dermatol* 2010

Costs of NMSC

- Mortality: ~2,000 per year
- Significant morbidity
  - 16% increase in procedures (2002-2006)[1]
  - 13M non-Hispanic whites estimated to have had 1 NMSC in 2007[2]
- Rising expenditures
- Direct costs (2005) = $1.423B[3]
  - 5th most expensive cancer (Medicare claims data)
  - 4.5% of Medicare cancer costs
  - 0.7% of Medicare budget[4]
- Indirect costs (2005) = $959M

1) Rogers HW et al, *Arch Dermatol* 2010
2) Stern RS. *Arch Dermatol* 2010
3) The Lewin Group, 2005
4) Housman TS et al, *J Am Acad Dermatol* 2003

Baseline Facts

- 80% of NMSC is basal cell carcinoma
- 80% of lesions occur on the head and neck
- Infrequent cause of mortality
  - Does not generate much fear or attention
  - 1200-2500 deaths per year
  - *MORBIDITY CAN BE SIGNIFICANT!*

Clayman GL et al, *J Clin Oncol* 2005

UV Exposure

- Dominant risk factor
- UVA and UVB tumorigenesis
  - P53 pyrimidine dimer formation
  - Loss of *Fas-Fas* ligand interaction
- Exposure variance*
  - Intense, intermittent (BCC)
  - Chronic (SCC)
- Elevation of risk
  - Sunbathing
  - Artificial tanning beds
  - Ozone depletion

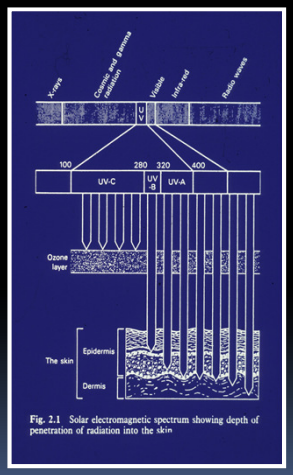
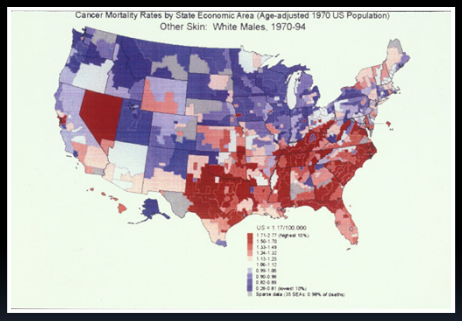


Fig. 2.1 Solar electromagnetic spectrum showing depth of penetration of radiation into the skin

*Zak-Prelich M et al. *Dermatol Surg* 2004

Environmental Risk Factors



- UV exposure
  - 10% ozone thinning - 300K cases[1]
- Latitude of habitation
  - 2x risk per 8-10 degrees
  - Ozone or lifestyle or both?
  - 1300/100,000 rate of SCC in Townsville, Australia[2]
- Radiation exposure
  - Childhood cancer survivors
  - Nuclear reactors/weapons
- Chemical exposure
  - Arsenic
  - Coal tar
  - Polycyclic aromatic hydrocarbons

1) WHO ultraviolet radiation and the INTERSUN programme

2) Buettner PG, Raasch BA. *Int J Cancer* 1998

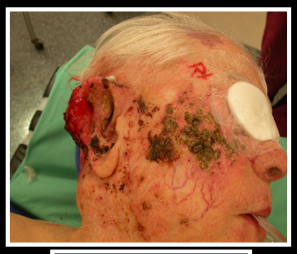
Patient Risk Factors

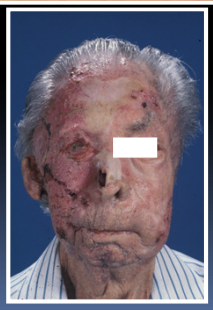
- Skin, hair, eye color
- Immunosuppression
- Genetic conditions
  - Basal cell nevus syndrome
  - Xeroderma pigmentosum
  - Albinism
- Previous skin cancers
- HPV (Beta-genotype 5,8)*
- Pre-existing lesions
  - Actinic keratosis
    - 6-10% cumulative risk
    - 0.025-20% risk per year
  - Bowen's disease
  - Epidermodysplasia verruciformis

*Asgari MM et al, *J Invest Dermatol* 2008

Immunosuppression

- Significant increase in incidence
  - SCC predominates
  - BCC:SCC ratio switched
- Transplant patients
  - Cardiac (45% SCC by 10 years)[1]
  - Renal (81% NMSC by 20 years)[2]
  - Liver
- Chronic lymphocytic leukemia
- Non-Hodgkin's lymphoma
- AIDS
  - Less impact on BCC incidence[3]

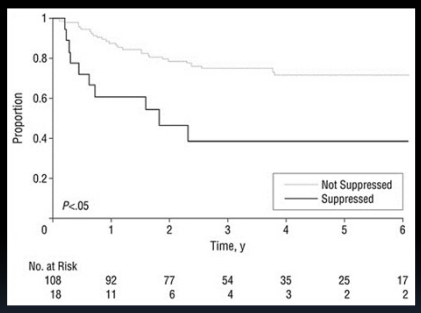




1) Berg D et al. *J Am Acad Dermatol* 2002
2) Ramsey HM et al. *Br J Dermatol* 2002
3) Wilkins K et al. *J Am Acad Dermatol* 2006

Post-Transplant Immunosuppression

- 18-250x increased risk of NMSC
  - Lesions appear after 2-4 years
  - Risk increases over time
- Aggressive behavior
  - Early local recurrence
  - Lymphatic metastases
  - Distant metastases
- *Extremely challenging!*
  - Screening
  - Early intervention



Veness MJ et al, *Cancer* 1999

Immunosuppression

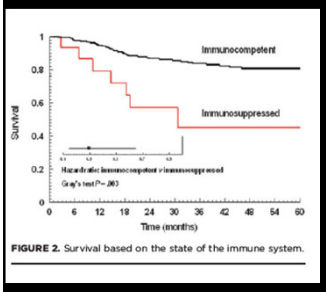
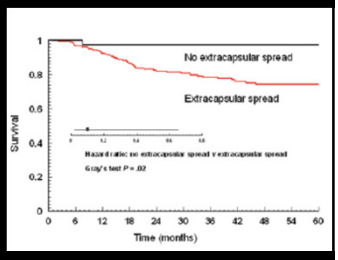


FIGURE 2. Survival based on the state of the immune system.



I M
T Immunosuppression Treatment Extracapsular Spread Margin Status
E

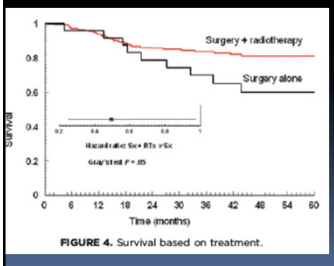


FIGURE 4. Survival based on treatment.

18-250x increased risk
Lesions appear after 2-4 years
Risk increases over time

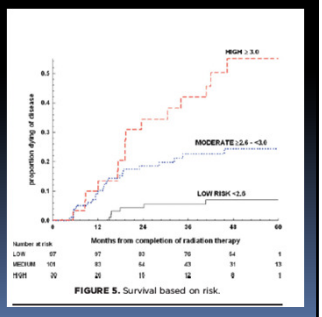


FIGURE 5. Survival based on risk.

Palme et al: 2003

Aggressive NMSC

Table 8–1. Features of Aggressive Nonmelanoma Skin Cancer and Risk Factors for Regional Metastases

Clinical Features	Pathologic Features	Risk Factors
Recurrent lesions	Poor differentiation	Recurrent lesion
Regional metastases	Histology	Size >2.0 cm
Size >2 cm	Desmoplastic SCC	Invasion into subcutaneous tissues
Rapid growth	Spindle cell SCC	Poor differentiation
Location	Basosquamous carcinoma	Pre-existing scar
Central H-zone of the face	Infiltrative BCC	Ear or lip location
		Perineural invasion
		Lymphovascular invasion
		Inflammation

From Weber RS, Moore BA, eds. *Cutaneous Malignancy of the Head and Neck: A Multidisciplinary Approach*. San Diego: Plural, 2011.

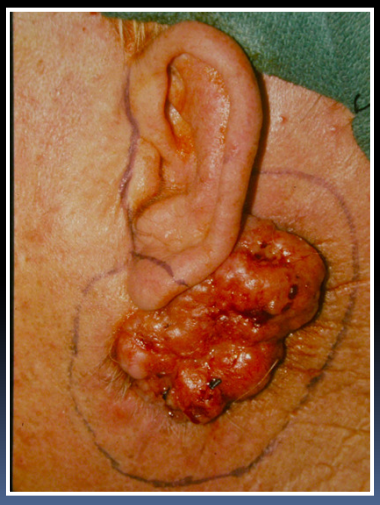
Staging of NMSC

Table 8–2. 2010 AJCC Staging TNM Classification for Cutaneous Squamous and Basal Cell Carcinoma (excludes eyelid skin)

Primary Tumor (T)	Regional Lymph Nodes (N)
TX Primary tumor cannot be assessed	NX Regional lymph nodes cannot be assessed
T0 No evidence of primary tumor	N0 No regional lymph node metastases
Tis Carcinoma in situ	N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
T1 Tumor 2 cm in greatest dimension with less than two high-risk features*	N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
T2 Tumor greater than 2 cm in greatest dimension or tumor any size with two or more high-risk features	N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
T3 Tumor with invasion of maxilla, mandible, orbit, or temporal bone	N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
T4 Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of the skull base	N3 Metastasis in a lymph node, more than 6 cm in greatest dimension
*High-risk features Depth/invasion >2 mm thickness Clark level IV or greater Perineural invasion Anatomic Site Primary site ear or nonhair-bearing lip Differentiation Poorly differentiated or undifferentiated	

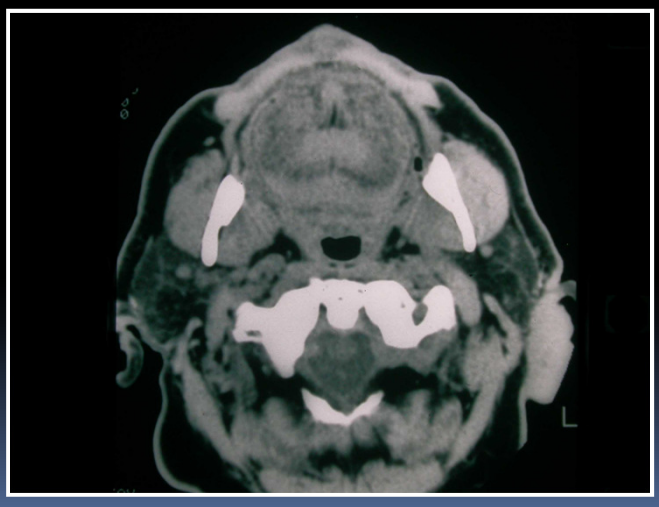
Distant Metastasis (M)	Staging			
M0 No distant metastases	Stage 0	Tis N0 M0	Stage IV	T1 N2 M0
M1 Distant metastases	Stage I	T1 N0 M0		T2 N2 M0
	Stage II	T2 N0 M0		T3 N2 M0
	Stage III	T3 N0 M0		T Any N3 M0
		T1 N1 M0		T4 N Any M0
		T2 N1 M0		T Any N Any M1
		T3 N1 M0		

Patient #1

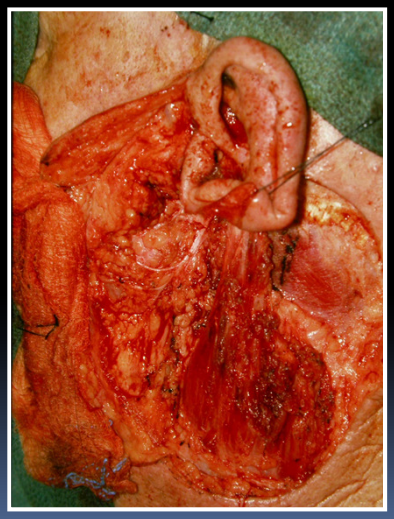


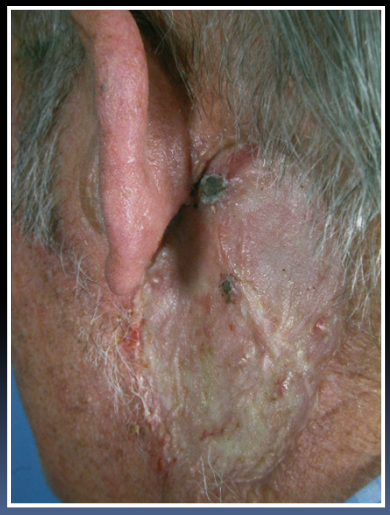
- 62 year-old male
  - Neglected BCC
- Workup
  - Anatomic imaging?
  - Management
    - Technique?
    - Margins?
    - Parotidectomy?
    - Neck dissection?

CT to Assess 3rd Dimension

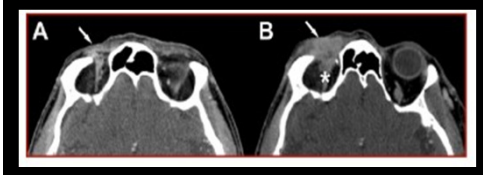


Surgical Management: Parotidectomy with resection of Skin, SCM, reconstruction STSG

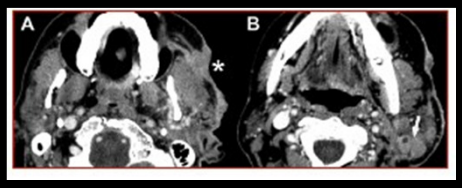




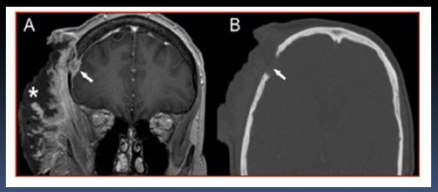
Benefits of Anatomic Imaging



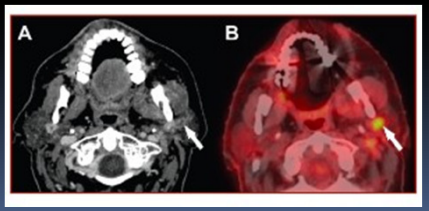
Depth of invasion, PNI



Depth of invasion, Nodal involvement



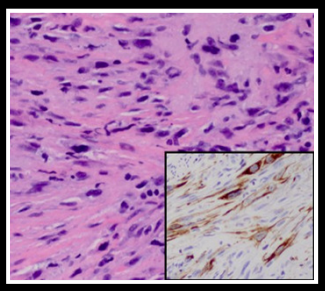
Bone erosion, intracranial disease

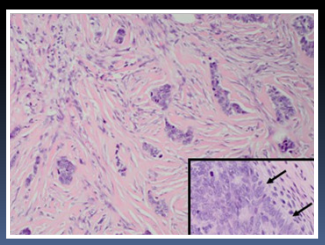


Staging

Aggressive Histopathology

- Squamous cell carcinoma
  - Poorly/undifferentiated
  - Spindle cell
  - Desmoplastic
  - Basosquamous
- Basal cell carcinoma
  - Infiltrative
  - Micronodular





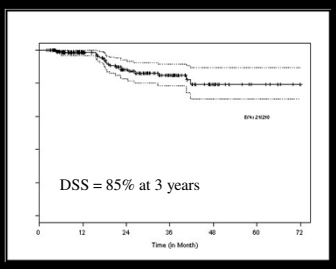
Images Courtesy Jonathon L. Curry, M.D.

Lesion Dimensions

- Tumor size > 2 cm
  - 30-68% vs. 9-13% rate of regional metastases in SCC[1,2]
  - Lesions as small as 1.5 cm may metastasize
- Depth may be more important for nodal mets[3-5]
  - Tumor thickness > 4-6 mm
  - Clark level IV-V
  - Extracutaneous involvement

1) Cherpelis BS et al. *Dermatol Surg* 2002
2) Rowe DE et al. *J Am Acad Dermatol* 1992
3) Kraus DH et al. *Arch Otolaryngol Head Neck Surg* 1998
4) Veness MJ et al. *Cancer* 2006

Aggressive Phenotype



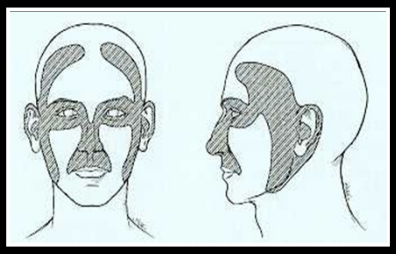
- Prospective database of 210 cutaneous SCC patients
- Features associated with decreased survival
  - Recurrent lesion at presentation (p=0.05)
  - Deep invasion (p=0.009)
  - Perineural invasion (p=0.002)
  - Lesion size ≥ 4cm (p=0.0003)
  - Depth of invasion ≥ 7mm (p=0.05)

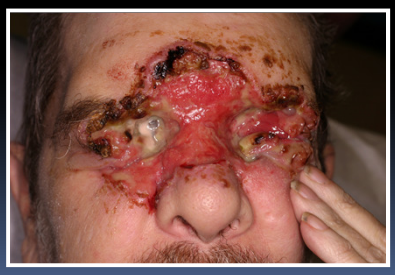
3-Year DSS drops from 100% to 70% if one of these elements is present

Clayman GL et al. *J Clin Oncol* 2005

Location

- Central H-Zone of the Face
  - Site of aggressive lesions
  - Local recurrence
  - Nodal metastases
- What makes this unique?
  - Location of fusion planes
    - Early deep invasion
    - Late superficial spread
  - Higher density of nerves
  - Close apposition of skin to deeper structures
  - More glands
  - Surgeon reticence?





Panje WR. *Laryngoscope* 1979

Treatment Options

- Surgical
  - Electrodissection and curettage
  - Cryotherapy
  - En bloc excision
  - Mohs Micrographic Surgery
- Medical
  - Topical therapy
  - Systemic therapy
- Radiation therapy
- Chemotherapy?

Multidisciplinary Care

Multidisciplinary Evaluation

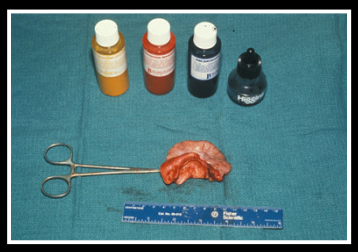
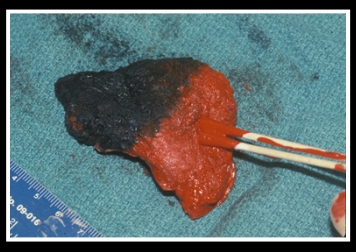
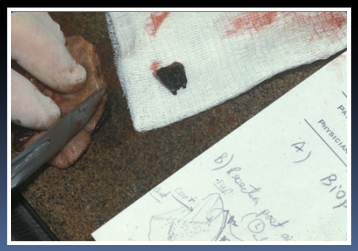
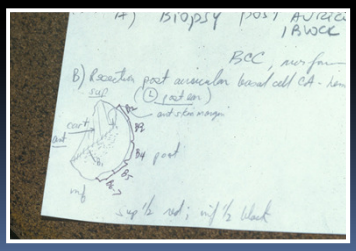
- Head and Neck Surgeon
- Mohs Micrographic Surgeon
- Reconstructive Surgeon
- Radiation Oncologist
- Medical Oncologist
- Dermatologist
- Prosthodontist

Prior to definitive treatment

Traditional Surgical Management

- Foundations
  - En bloc resection
  - Margins vary with size, histology, and prior treatment
  - May orient prior to final removal
  - **FROZEN SECTION CONTROL**
- Minimum margins for untreated lesions
  - Nodular BCC: 4 mm
  - Infiltrative BCC: ≥ 5 mm
  - Primary SCC: 5mm
- Minimum margins for recurrent or aggressive lesions
  - BCC: >= 5mm
  - SCC: 1-2cm

Meticulous Mapping for Frozen Section Margin Control

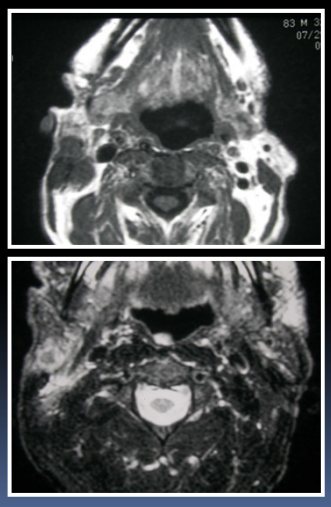





Pathology Templates: Communication is Paramount

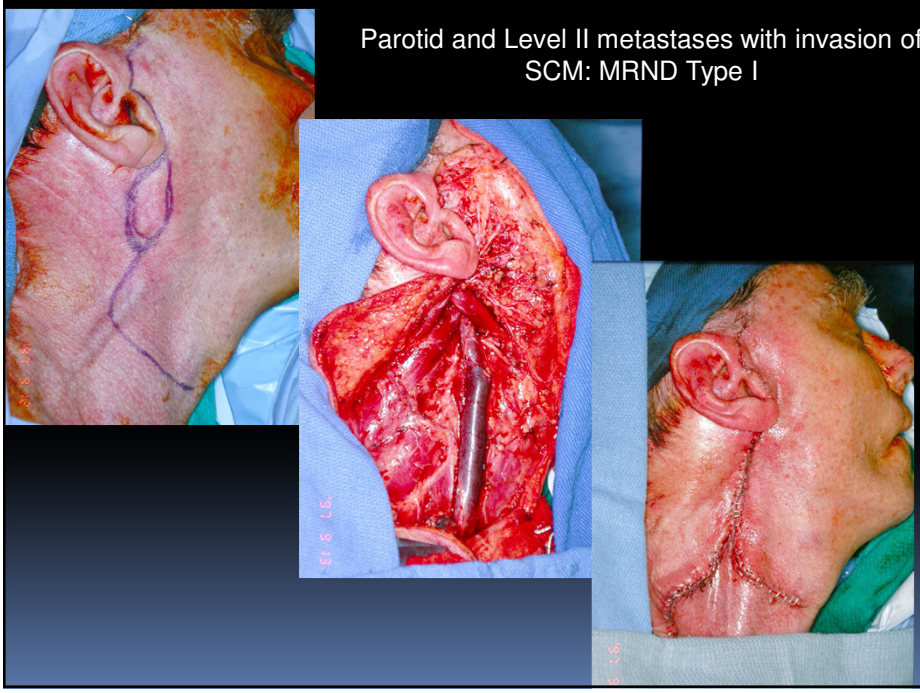
- Margin status
  - Positive
  - Negative
  - Close (< 2mm)
- Perineural invasion
- Tumor thickness
- Depth of invasion
- Lymphatic/vascular invasion
- Positive nodes
  - Number and level
  - Extracapsular spread

Patient #2

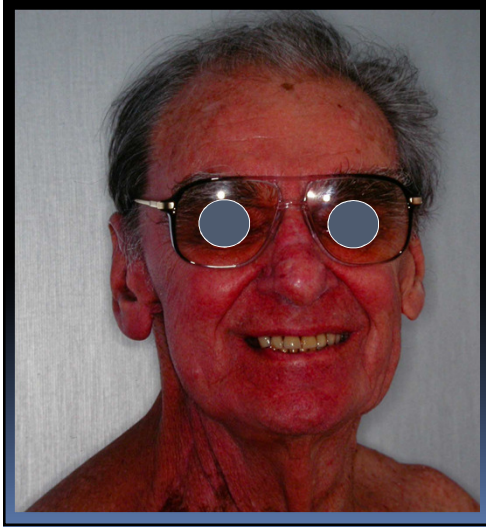
- 70 year-old male
  - Prior postauricular SCC
  - WLE 12 months prior
  - Upper neck mass x 1 mo
- Workup
  - Imaging
  - FNA
- Management
  - Parotid
  - Neck dissection
  - Radiation/CRT?

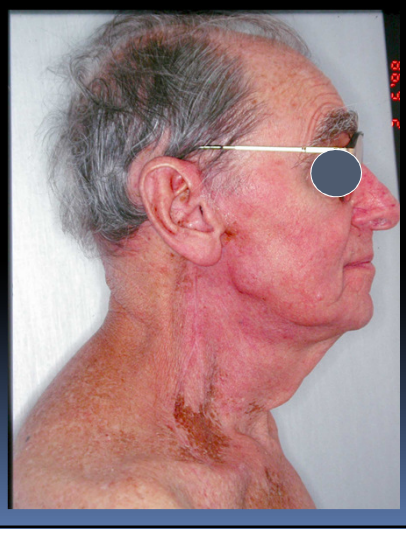


Parotid and Level II metastases with invasion of SCM: MRND Type I



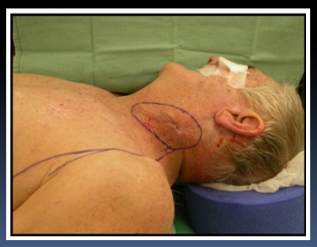
Normal VIIth nerve function postoperatively.
Comprehensive postoperative irradiation to the parotid and neck.

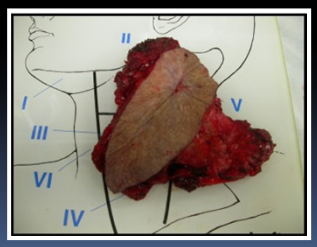




Lymph Node Metastases

- Reported incidence 0.1-21%[1] → 5% most common
- Delayed appearance
  - 10-19 months after treatment for primary
  - Nearly all metastases evident by 3 years
  - Elicit cutaneous SCC history in patients with "unknown" primary

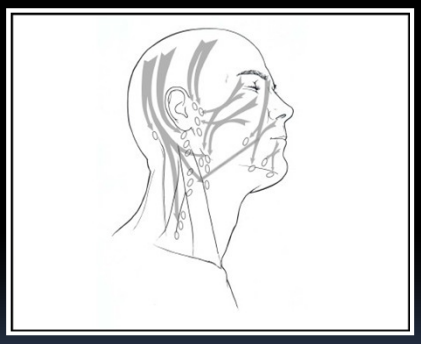




Moore BA et al. *Laryngoscope* 2005

Lymphatic Drainage Patterns

- Midface/lip lesions
  - Bilateral perifacial nodes*
  - Bilateral upper neck
  - Parotid spread uncommon
- Periorbital/cheek lesions
  - Parotid and upper neck
  - External jugular nodes
- Auricular/temporal lesions
  - Parotid and upper neck
  - External jugular nodes
- Postauricular lesions
  - Posterolateral neck
  - External jugular nodes



Netterville JL et al. *Head Neck* 1998

Why is the Parotid Important?

- First echelon of lymphatic drainage
  - Lateral face, periauricular region
  - Periorbital region, temporal scalp
- Anatomy
  - >20 intraglandular lymph follicles or aggregations
  - Rich supply of paraglandular nodes
  - Few nodes located deep to retromandibular vein
- Tumor cells may then pass to Levels II-V
- Metastatic SCC is #1 parotid malignancy in Australia
- O'Brien pioneered "P" stage

Conley J. *Arch Surg* 1963
Jackson I et al. *Am J Surg* 1981

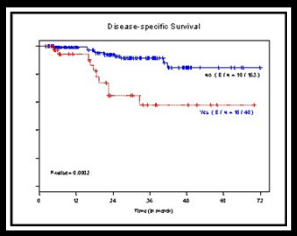
Lymph Node Metastases

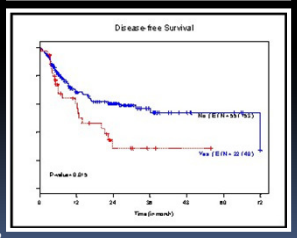
- Location of nodal metastases
  - 35% limited to parotid
  - 30% limited to cervical nodes
  - 35% involved both
- 42% of cervical mets were occult
  - Reported rates up to 35%[1]
  - Overall 52% pathologic neck mets when parotid is (+)
- Associated pathologic features[2]
  - Recurrent lesions (p=0.002)
  - Lymphovascular invasion (p=<0.0001)
  - Inflammation (p=0.01)
  - Poorly differentiated histology (p=0.001)
  - Deep invasion (p=0.0001)
  - Perineural invasion (p=0.005)
  - Depth of invasion
  - Size of lesion

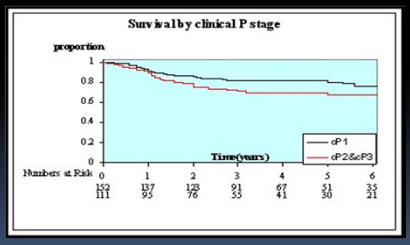
1) O'Brien CJ et al. *Head Neck* 2001
2) Moore BA et al, *Laryngoscope* 2005

Prognostic Import of Nodal Metastases

- Different patterns of failure
  - P(+) regionally[1]
  - N(+) distantly[3]
  - LN(-) locally[3]
- Survival worsens w/ burden[2]







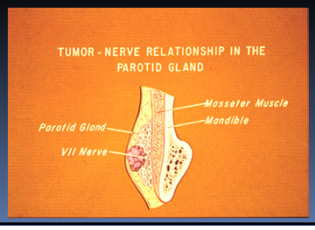
1) O'Brien CJ et al. *Head Neck* 2002
2) Palme C et al. *Arch Otolaryngol Head Neck Surg* 2003
3) Moore BA et al, *Laryngoscope* 2005

Indications for Surgical Treatment of Nodal Basins

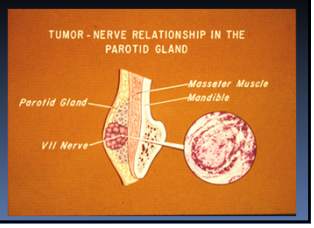
- Clinical evidence of nodal metastases
- Direct invasion of the parotid gland or fascia
- Identification facial nerve branches required to excise primary
- Recurrent lesions in tissues adjacent to the parotid
- Size > 2cm, invasion beyond the subcutaneous fat
- Immune compromise
- Direct extension of an EAC primary thru fissures of Santorini
- Need for exposure of recipient vessels for free tissue transfer
- Potential application of sentinel lymph node biopsy
  - Perineural invasion, lymphovascular invasion in primary
  - Aggressive histology

Extent of Nodal Basin Dissection

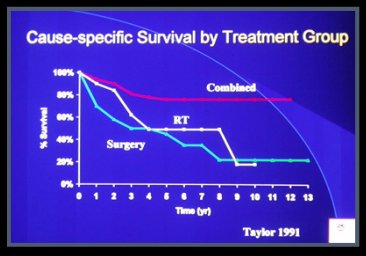
- Based on primary location, prior treatment
- Selective neck dissection performed in 80%
  - Levels II + III, often with Level I ~ 50%
  - Posterolateral, comprehensive (I-IV), MRND
  - MRND more likely if previously radiated
- Superficial parotidectomy in 70%
  - Facial nerve preserved (unless nonfunctional, PNI, no plane)



Moore BA et al, *Laryngoscope* 2005



Adjuvant RT is Imperative



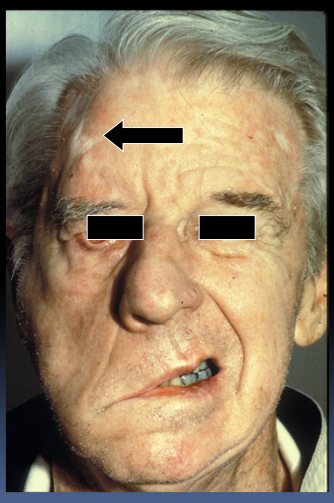
- Multimodal therapy improves outcomes
  - Surgery + RT > RT or surgery alone
  - Adjuvant CRT currently being evaluated (TTROG)

Management of Nodal Metastases

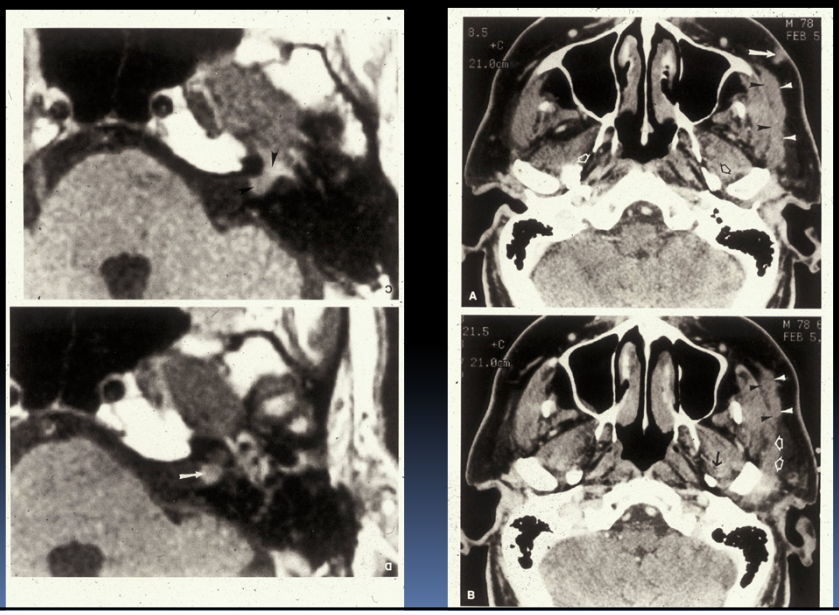
- Appropriate nodal basin dissection
- Adjuvant radiotherapy (chemoradiotherapy?)
  - Improved regional control and survival with combined Rx
  - Numerous studies demonstrate improved DSS, LRC
- Aggressive approach maximizes locoregional control
  - 17.5% locoregional failure in our cohort
  - Historical failure in up to 52% of cases
- **Remember the external jugular vein nodes!!!**

Patient #3

- 72 year-old male
  - Right temple SCC
  - MMS 8 mos prior
- Facial pain and paralysis
  - Dx tic doloreaux
  - Dx Bell's palsy
- Workup
  - Imaging (CT or MRI)?
  - Treatment
  - Surgery
    - What to do with CN VII?
  - RT

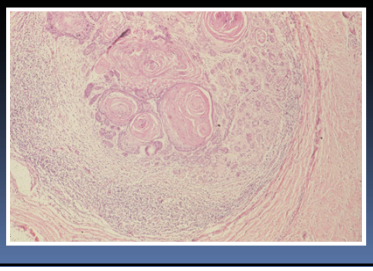


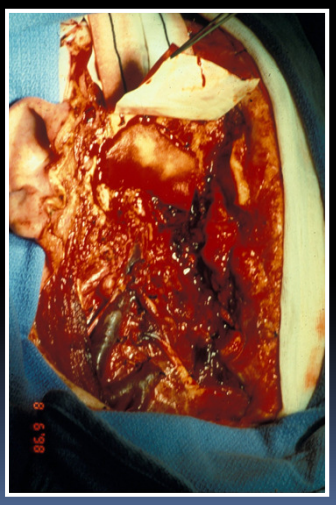
MRI demonstrates significant involvement of the VIIth nerve



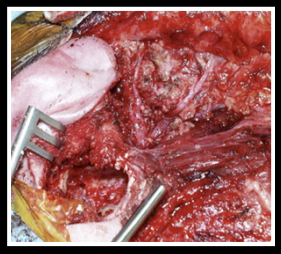
Surgical Management

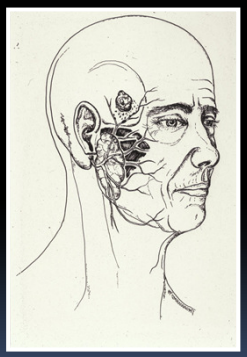
- Radical parotidectomy
- Facial nerve sacrifice
- Lateral temporal bone resection
- Neck dissection
- Free flap reconstruction





Perineural Invasion

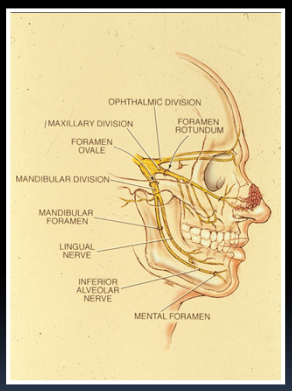




- First described in 19th century by Cruveilheur
- Clinical import noted by Ballantyne in 1963
  - Squamous cell carcinoma
  - Adenoid cystic carcinoma
  - Mucoepidermoid carcinoma
- Reported incidence 2-31%
- 0.1-1% of recurrent BCC are neurotropic

Signs & Symptoms

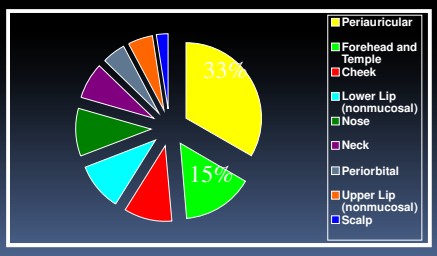
- Formication
- Pain
  - Burning, stinging, lancinating
- Dysesthesia/anesthesia
- Diplopia, facial paralysis
- Historic data
  - V2 most commonly affected
  - Most (60%) asymptomatic
- Significance threshold?
  - Peripheral vs named
  - Symptomatic, radiographically apparent is too late



Goepfert H et al. *Am J Surg* 1984

Perineural Invasion

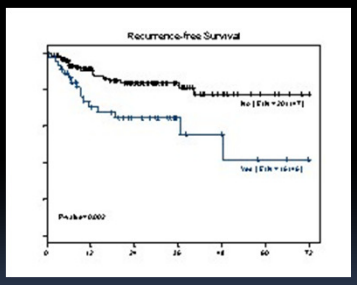
- 193 patients with CSCC of the head & neck
  - Perineural invasion identified in 31%
  - 26.1% of PNI+ patients died of disease (vs. 5.4% PNI-)
- 32.6% were symptomatic at presentation
  - Pain or dysesthesias most common
  - CN V > CN VII > CN VI
  - 15% radiographically apparent



Moore B et al. *Abstracts of the 6th International Conference on Head and Neck Cancer* 2004

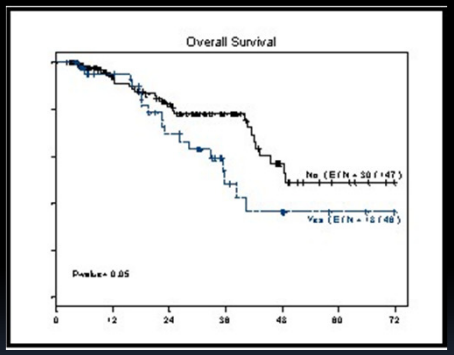
Perineural Invasion

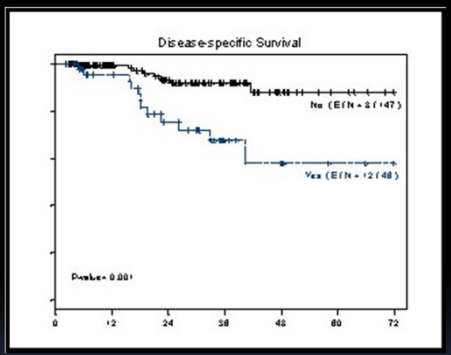
- Associated pathologic findings[1]
  - Recurrent lesions at presentation (p=0.014)
  - Lymphatic/vascular invasion (p=<0.002)
  - Ulceration (p=0.0006)
  - Positive margin (p=0.046)
  - Inflammation (p=<0.0001)
  - Deep invasion (p=0.007)
  - Nodal metastases (p=0.007)
  - Depth of lesion
  - Size of lesion
- Historic outcomes[2]
  - 47% vs. 7.3% local failure
  - 35% vs. 15% regional lymph node metastases
  - 15% vs. 3.3% distant metastases



1) Moore B et al. *Abstracts of the 6th International Conference on Head and Neck Cancer* 2004
2) Goepfert H et al. *Am J Surg* 1984

Impact of PNI on Survival





Moore B et al. *Abstracts of the 6th International Conference on Head and Neck Cancer* 2004

PNI Management

- Maintain high index of suspicion
  - Forehead and temple
  - Periauricular region
- Histologic evaluation of nerve branches
- Retrograde dissection of involved major nerves
- Adjuvant procedures
  - Mastoidectomy, maxillectomy, mandibulectomy
  - Orbital exploration or exenteration
- Adjuvant radiation
  - Follow course of the main nerve to skull base

Surgical Management of the Involved Facial Nerve

- Complete parotidectomy
- Resection of involved branch(es)
- Proximal and distal frozen section control
  - Mastoidectomy when necessary
  - Applies to CN V as well
- Cable graft nerve
  - Except when paralyzed preoperatively
  - Early static intervention

Indications for Adjuvant Radiation Therapy

- Large, recurrent tumors (especially > 4 cm)
- Close or positive margins
- Aggressive histology
  - Spindle cell SCC
  - Poorly differentiated SCC
- Perineural invasion
- Multiple positive nodes
- Extracapsular spread

Notes

Session II

Panel Discussion – Skin Cancer

No material

Notes

Saturday November 5, 2011

Session III – Oral & Oropharyngeal Cancer Presentations

Notes

Surgical Approaches to the Management of Oral Cancer

Danny J. Enepekides MD, FRCS(C)
Assistant Professor of Head and Neck Surgery
University of Toronto

Objectives

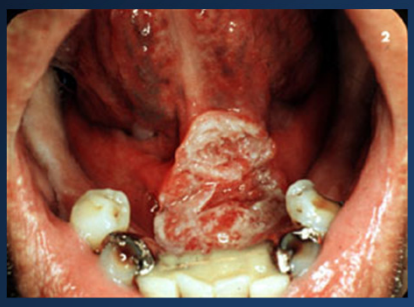
1. To review the emerging trends in oral cancer.
2. To be knowledgeable about the surgical approaches to oral cancer and the importance of negative surgical margins.
3. To review the indications for elective neck dissection in clinically N0 patients.
4. To understand the appropriate extent of neck dissection for N0 and N+ disease.
5. To review the indications for adjuvant therapy.

Abstract

The incidence of smoking related head and neck cancer, oral cancer included, is decreasing. Unlike tumors of the oropharynx, HPV infection does not seem to be an important etiologic factor for squmaous cell carcinoma of the oral cavity. The mainstay of therapy for this group of cancers remains surgery. Primary radiation or chemoradiation therapy is generally reserved for inoperable disease or patients medically unfit for ablative surgery. Surgical approaches to the oral cavity continue to evolve with the addition of robotic and transoral laser techniques. The approaches can be categorized as transoral, transmandibular, and transcervical. The approach used should allow for complete resection to negative margins while minimizing morbidity. Current microvascular reconstructive techniques maximize functional results and permit the ablative surgeon to be as appropriately aggressive as necessary. Elective neck dissection is indicated for all T2 – T4 N0 tumors as well as T1N0 cancers with a tumor thickness > 4mm. In the N+ patient, less than comprehensive neck dissection is appropriate except for those patients with N2b disease. Indications for adjuvant radiotherapy include close surgical margins, 1-2 positive nodes without extracapsular spread, and perineural invasion while chemoradiotherapy is reserved for high-risk tumors.

Notes

Surgical Approaches to the Management of Oral Cancer



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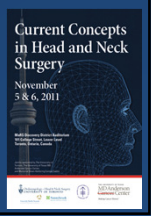
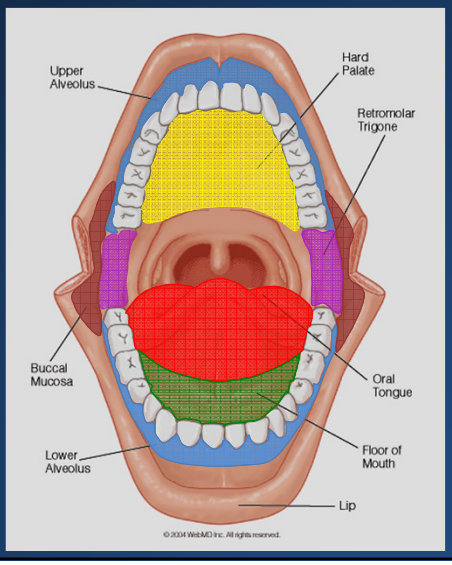
Sunnybrook
HEALTH SCIENCES CENTRE



The Oral Cavity

Subsites

a. Oral Tongue
b. Floor of Mouth
c. Gingiva
d. Hard Palate
e. Retromolar Trigone
f. Buccal Mucosa
g. Lips



Oral Carcinoma : *Trends in Incidence*

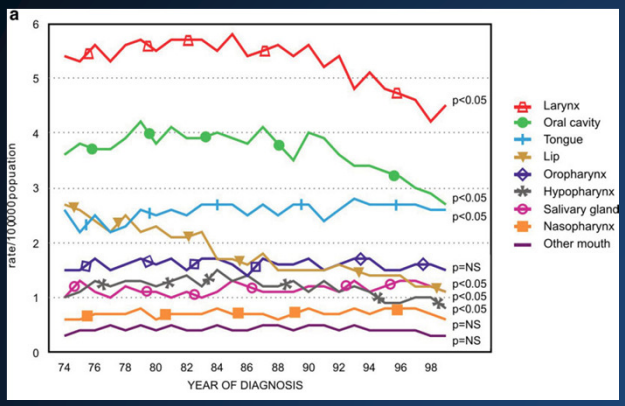
Table 1: Oral Cancer, Total Number of Cases by Gender and Age

Total number of US oral cancer cases and percent of population, by selected characteristics, 2004
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute
U.S. 2006 cancer prevalence counts are based on 2006 cancer prevalence proportions from the SEER 9 registries (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta) and 1/1/2006.

	Gender	All Ages	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 plus
Total Number	Male	157,250	23	492	1318	3276	14,407	37,003	40,095	60,638
	Female	87,223	101	501	1668	3489	8222	15,686	18,110	39,446
Percent of Total Population	Male	0.0732	not enough data	0.0018	0.0050	0.0144	0.0548	0.1667	0.2775	0.6367
	Female	0.0372	0.0004	0.0022	0.0066	0.0142	0.0289	0.0607	0.1009	0.2926

Increasing incidence with age

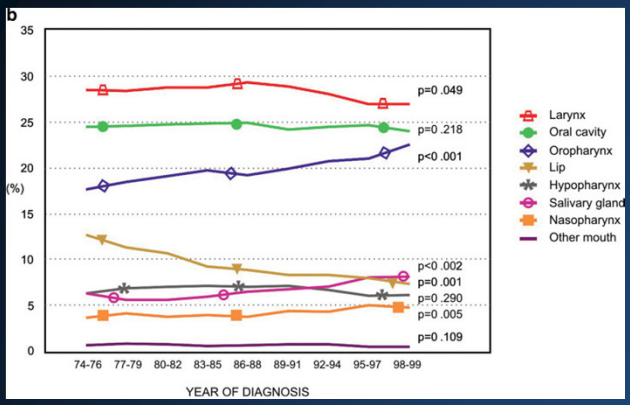
Oral Carcinoma : *Trends in Incidence*



Overall decrease in smoking related cancers.

Carvalho AL, et al. Int. J. Cancer: 114, 806–816 (2005)

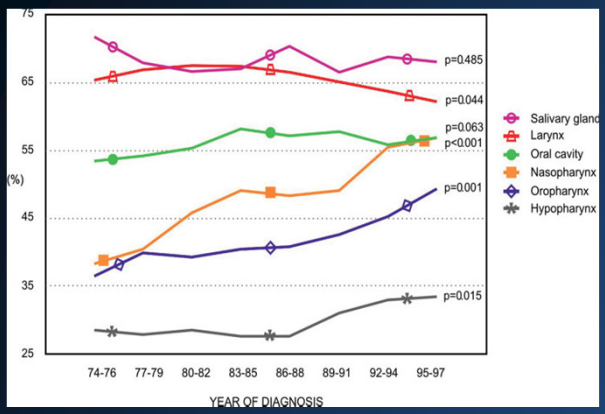
Oral Carcinoma : *Trends in Incidence*



Overall, oral cavity represents ~25% of all head and neck cancers.

Carvalho AL, et al. Int. J. Cancer: 114, 806–816 (2005)

Oral Carcinoma : *Trends in Survival*

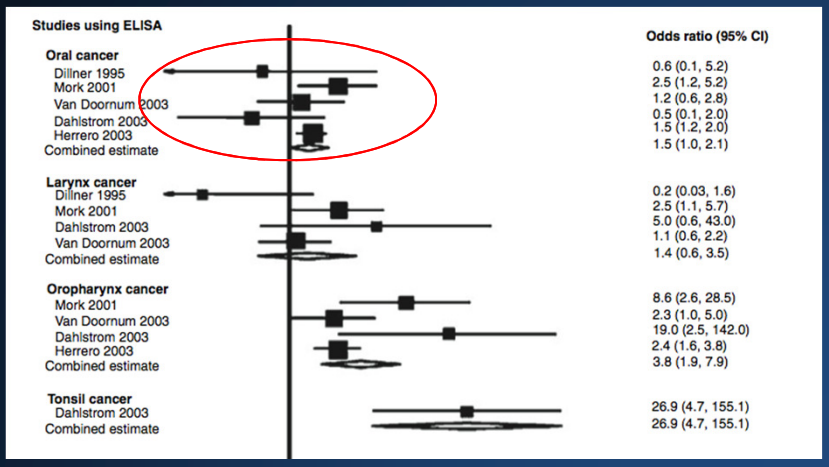


Overall, 5-year survival has changed little in oral cavity carcinoma.

Carvalho AL, et al. Int. J. Cancer: 114, 806–816 (2005)

Oral Carcinoma : *Trends in Survival*

HPV and Oral Cancer



Clinical Otolaryngology 2006; 31:259-266.

Oral Carcinoma : *Treatment Principles*

Stage I/II → Single modality therapy

Stage III/IV → Multimodality therapy

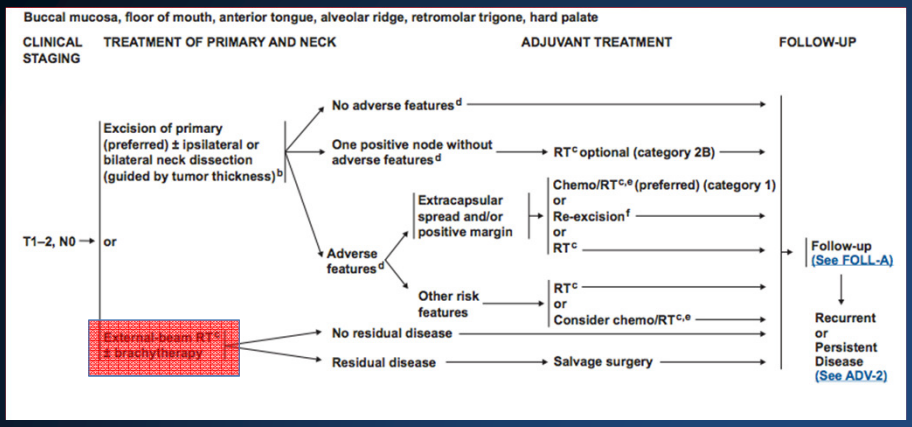
Treatment Options

Surgery

Radiotherapy

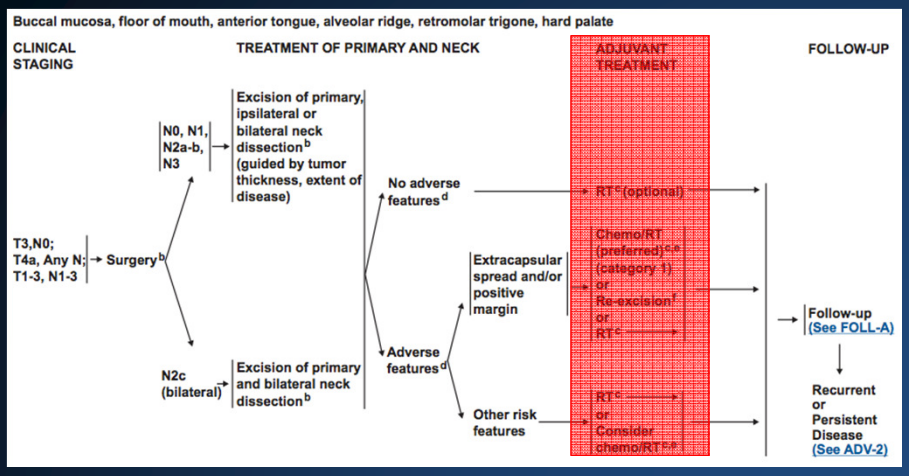
Chemoradiotherapy

Oral Carcinoma : *Treatment Principles*



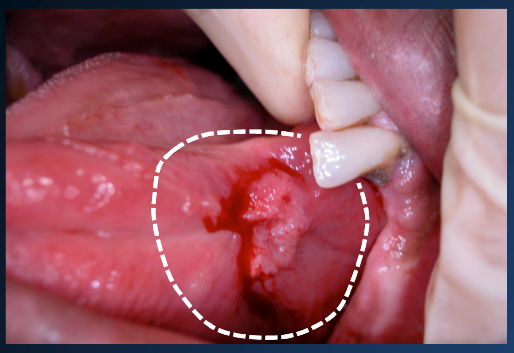
National Comprehensive Cancer Network®

Oral Carcinoma : *Treatment Principles*



National Comprehensive Cancer Network®

Oral Carcinoma : *Surgical Management*



Complete surgical resection to negative margins is key to the successful surgical management of oral cancer.

Intraoperative frozen section margin analysis

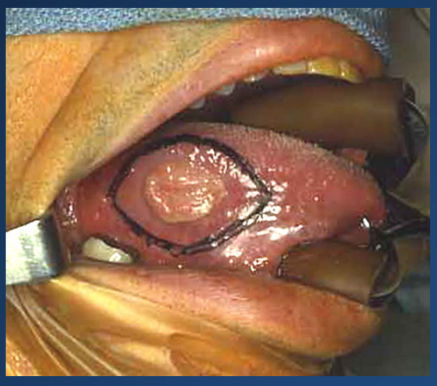
Adjuncts

- Vital staining
- Loss of fluorescence
- Laser induced auto-fluorescence

Oral Carcinoma : *Surgical Management*

Surgical Approaches

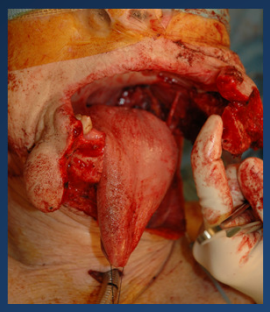
a. Transoral
b. Transmandibular
c. Transcervical

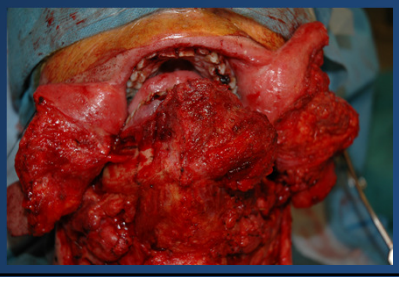


Oral Carcinoma : *Surgical Management*

Surgical Approaches

a. Transoral
b. Transmandibular
c. Transcervical

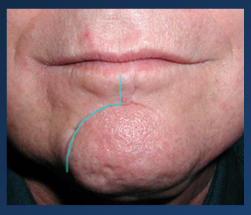


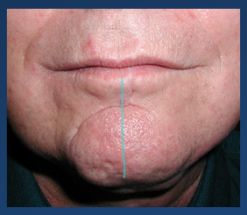


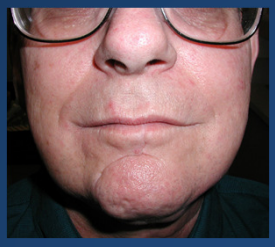
Oral Carcinoma : *Surgical Management*

Surgical Approaches

a. Transoral
b. Transmandibular
c. Transcervical





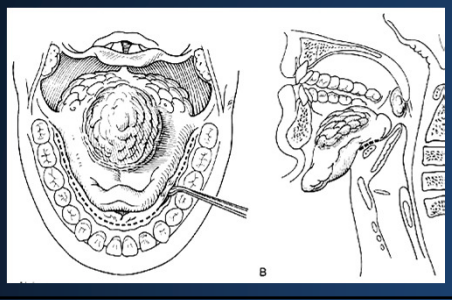


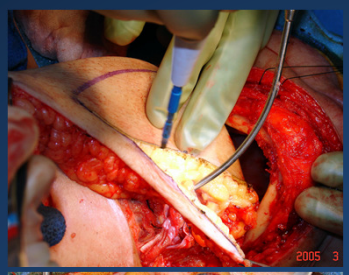
Rapidis et al J Oral Maxillofac Surg 2001

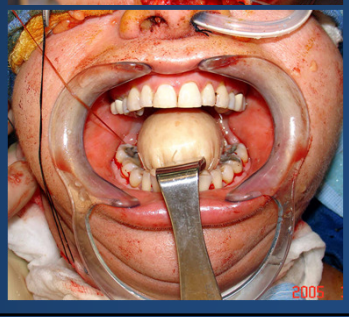
Oral Carcinoma : *Surgical Management*

Surgical Approaches

a. Transoral
b. Transmandibular
c. Transcervical







Oral Carcinoma : *Surgical Management*

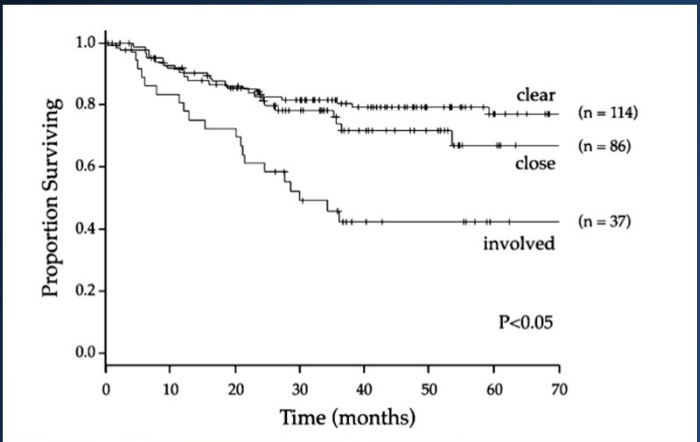
Surgical Approaches

a. Transoral
b. Transmandibular
c. Transcervical

The approach utilized should be the least morbid that permits **complete** resection of the primary and must always take precedence to any reconstructive concerns.

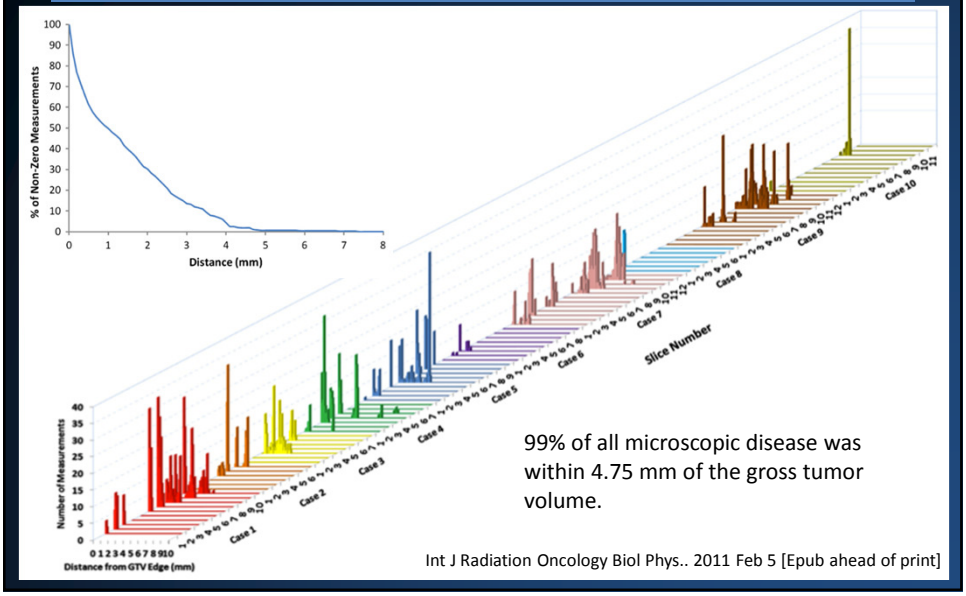
Oral Carcinoma : *Surgical Management*

Margin Status



British Journal of Oral and Maxillofacial Surgery (2003) **41,** 224–231

Oral Carcinoma : *Surgical Management*

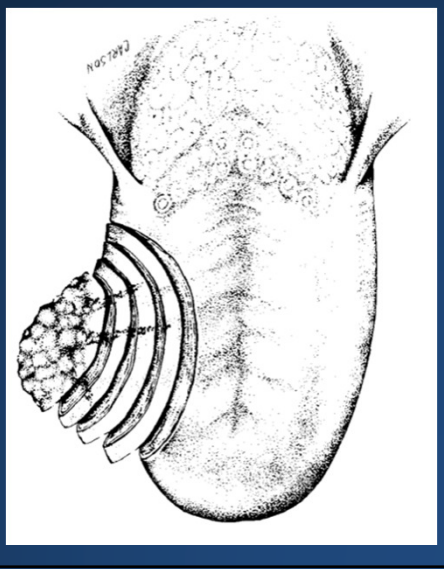


99% of all microscopic disease was within 4.75 mm of the gross tumor volume.

Int J Radiation Oncology Biol Phys.. 2011 Feb 5 [Epub ahead of print]

Oral Carcinoma : *Surgical Management*

Does microscopic tumor cut-through matter and is it an indication for adjuvant treatment?



Oral Carcinoma : *Surgical Management*

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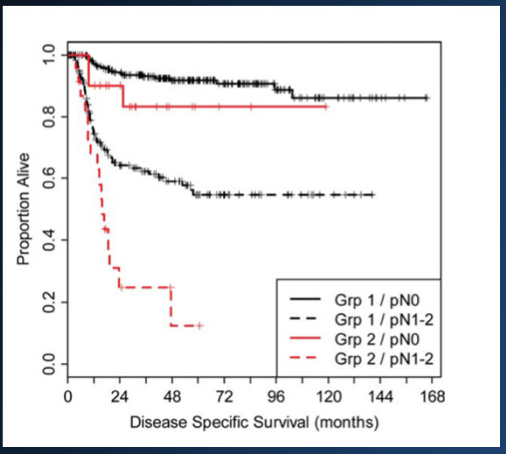
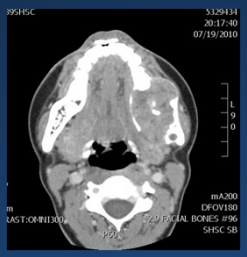


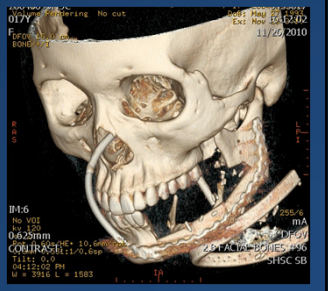
Grp 1 – No cut-through

Grp 2 –Cut-through

Head & Neck 32: 1444-1451,2010

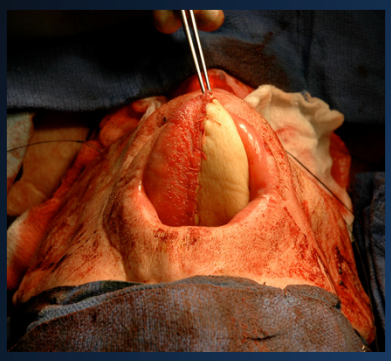
Oral Carcinoma : *Surgical Management*

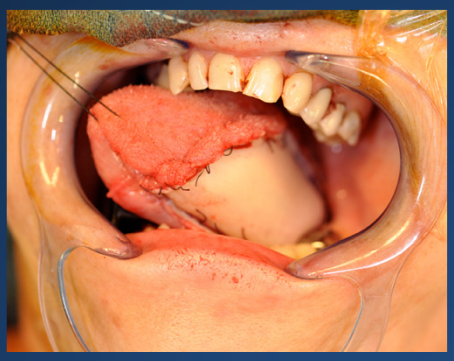




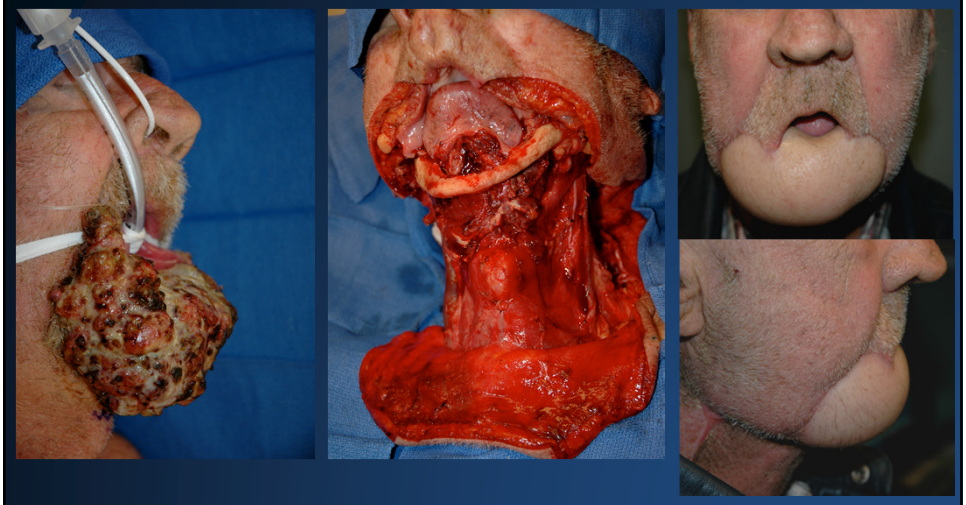
"The Oncologic Step Stool"

Oral Carcinoma : *Surgical Management*

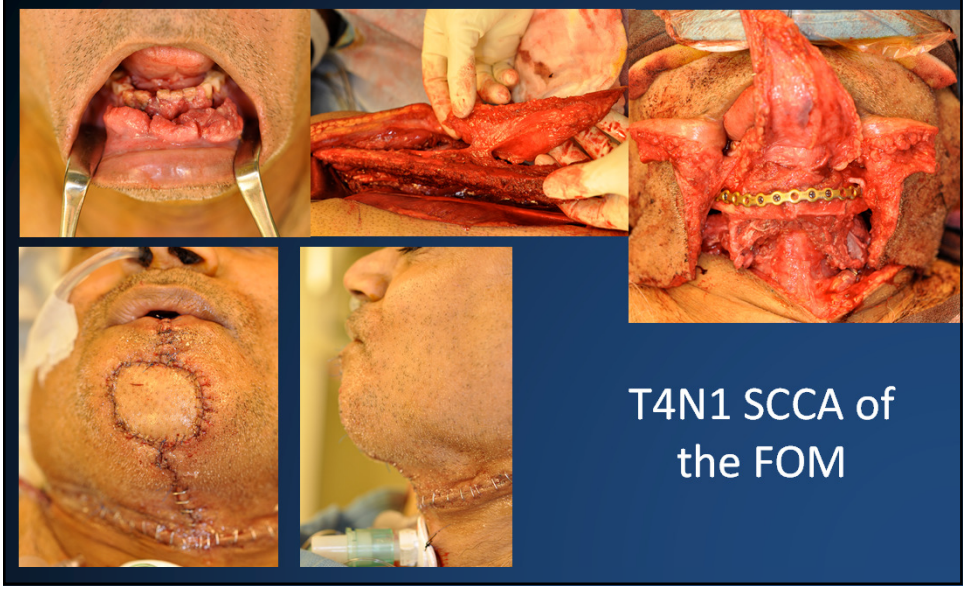




Oral Carcinoma : *Surgical Management*



Oral Carcinoma : *Surgical Management*



T4N1 SCCA of the FOM

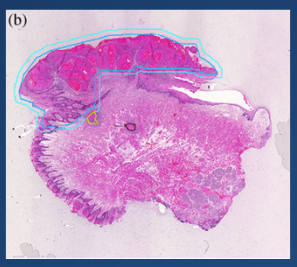
Oral Carcinoma : *Surgical Management of the Neck*

The N0 Neck : Elective Neck Dissection

T2 – T4 N0 Tumors

T1 N0 Tumors with depth of invasion of >4mm

Oral Oncolog 39(4): 386-390, 2003



Oral Carcinoma : *Surgical Management of the Neck*

The N0 Neck – Is the routine dissection of levels IIB or IV necessary?

Risk of level IIb disease in the cN0 neck is <5%.[1]

Rate of recurrence in undissected level IV is approximately 2%.[2]

1. *Arch Otolaryngol Head Neck Surg. 2004;130:1088-1091*
2. *Laryngoscope (2001),111(6):1088-1090*

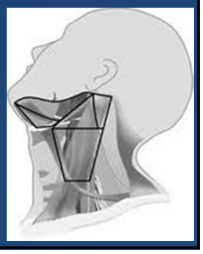
Oral Carcinoma : *Surgical Management of the Neck*

Table 2. Ipsilateral Regional Recurrence in Selective Neck Dissection and Radical/Modified Radical Neck Dissection

Pathological Neck Stage	No. No Radiotherapy	Radiotherapy	Total
Selective Neck Dissection			
pN0	4/99	1/15	**5/114**
pN1	2/24	0/23	**2/47**
pN2b	0/3	5/27	**5/30**
pN2c	0	0/4	**0/4**
Total, No. (%)	**6/126** (4.8)	**6/69** (8.7)	**12/195** (6.2)
Radical/Modified Radical Neck Dissection			
pN0	0/3	0/2	**0/5**
pN1	0/1	0/2	**0/3**
pN2b	0	0/15	**0/15**
pN2c	0	1/2	**1/2**
Total, No. (%)	**0/4**	**1/21** (4.8)	**1/25** (4.0)

Arch Otolaryngol Head Neck Surg. 2005;131:874-878

Is SND as effective as MRND for cN0 neck?



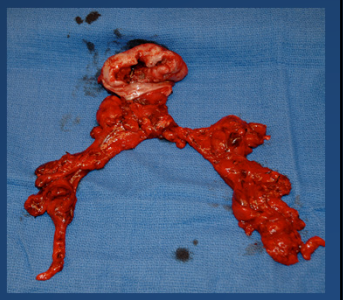
Oral Carcinoma : *Surgical Management of the Neck*

Table 3. Ipsilateral Regional Recurrence in Selective Neck Dissection for Clinically N0 and N+ Necks

Pathological Neck Stage	No. No Radiotherapy	Radiotherapy	Total
Clinically N0 Necks			
pN0	3/88	1/13	**4/101**
pN1	2/20	0/13	**2/33**
pN2b	0/2	1/12	**1/14**
pN2c	0	0/2	**0/2**
Total, No. (%)	**5/110** (4.5)	**2/40** (5.0)	**7/150** (4.7)
Clinically N+ Necks			
pN0	1/11	0/2	**1/13**
pN1	0/4	0/10	**0/14**
pN2b	0/1	4/15	**4/16**
pN2c	0	0/2	**0/2**
Total, No. (%)	**1/16** (6.3)	**4/29** (13.8)	**5/45** (11.1)

Arch Otolaryngol Head Neck Surg. 2005;131:874-878

Is SND as effective as MRND for the cN+ neck?



Oral Carcinoma : *Adjuvant therapy*

Outcome end points	EORTC Trial 2931 5-year estimates	RTOG Trial 9501 2-year estimates
Disease-free survival	47% versus 36% (p = .04)[a]	54% versus 45% (p = .04)[a]
Overall survival	53% versus 40% (p = .02)[a]	64% versus 57% (p = .19)[a]
Local-regional failure rates	17% versus 31% (p = .007)[a]	18% versus 28% (p = .01)[a]
Grade 3+ acute toxicity	p = .008/p = .28[a, b]	77% versus 34% (p <.0001)[a]
Late toxicity	38% versus 41% (p = .25)[b]	21% versus 17% (p = .29)[a]
Impact on distant metastases	p = .61	p = .46
Second primary tumors	p = .83	NA

[a]Chemoradiation versus radiotherapy arm values

[b]Functional/objective acute reactions

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; NA = Data not available; RTOG = Radiation Therapy Oncology Group

Table 2. Comparative analysis of criteria of selection related to risk factors in EORTC trial 22931 and RTOG trial 9501

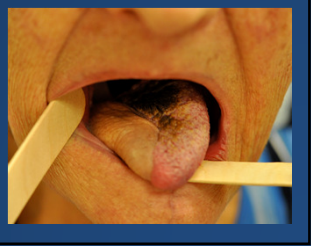
EORTC 22931 only	EORTC 22931 and RTOG 9501	RTOG 9501 only
Stage III/IV disease	Surgical margins microscopically involved	Two or more positive lymph nodes
Positive lymph nodes at levels IV or V in patients with tumors arising from oropharynx or oral cavity	Extracapsular extension in positive lymph nodes	
Vascular embolisms		
Perineural infiltration		

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group

The Oncologist 2005;10:215–224

Oral Carcinoma : *Summary*

- Oral Cancer remains a surgical disease.
- Complete surgical resection is essential in order to maximize loco-regional control and survival.
- Modern reconstructive techniques should be employed to maximize functional outcomes.



Oral Carcinoma : *Summary*

- Elective neck dissection should be performed in all T2-T4 tumors and given strong consideration in thick (>4mm) T1 primaries.
- Comprehensive neck dissection is indicated for management of N2b disease.
- Adjuvant chemoradiation therapy is reserved for high risk patients.

Notes

Erich M. Sturgis, M.D., M.P.H.
Professor, Department of Head & Neck Surgery
and Department of Epidemiology
The University of Texas-M.D. Anderson Cancer Center

The Emerging Epidemic of HPV-Associated Oropharyngeal Cancer: Outcomes and Clinical Implications

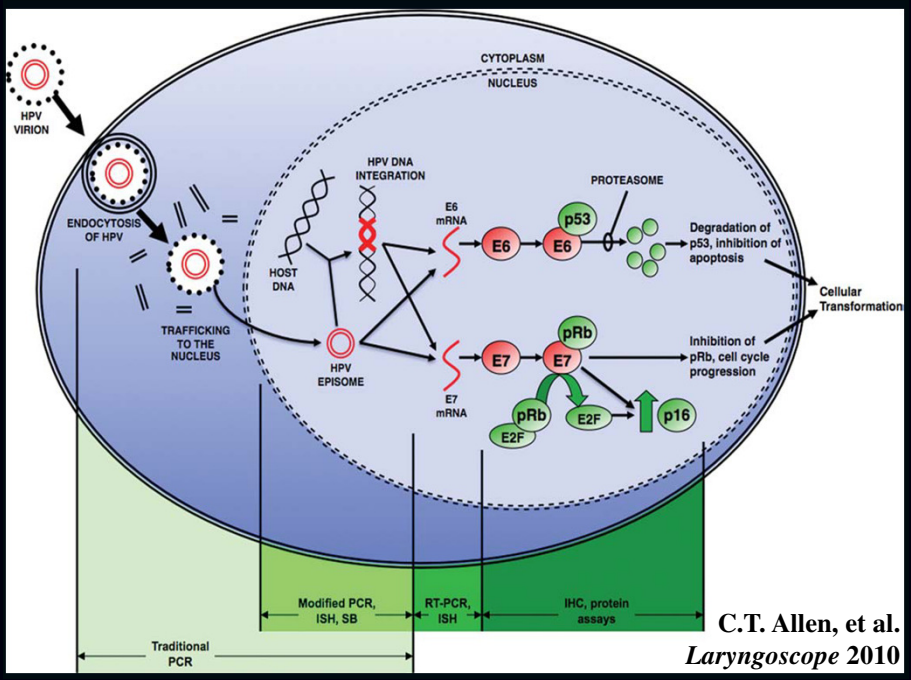
This presentation will review the typical clinical presentation of human papillomavirus (HPV)-associated oropharyngeal cancer and in relation to the changing incidence of head & neck cancer in the U.S. The retrospective data suggesting a better prognosis for HPV-associated oropharyngeal cancer than HPV-negative cancer will be reviewed. The prospective clinical trials which have supported these findings will also be reviewed. Finally, future trials and potential areas for study will be discussed.

Notes

HPV-Associated Oropharyngeal Cancer:
The Clinical Implications

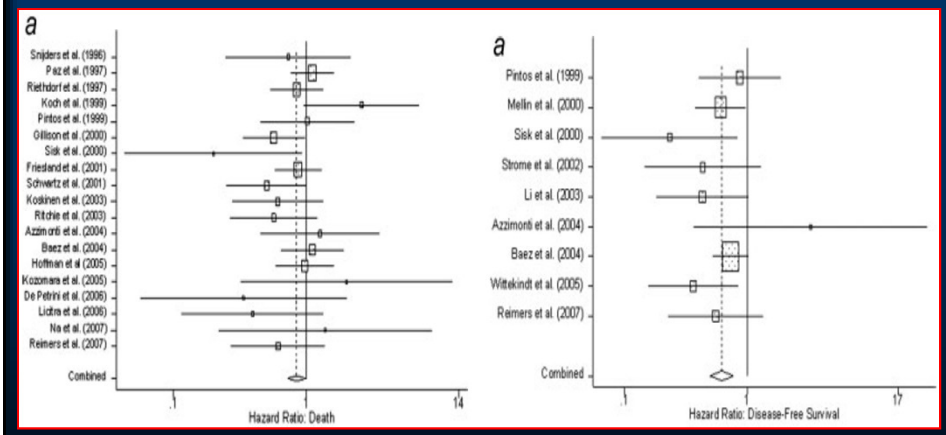
Erich M. Sturgis, M.D., M.P.H.
Professor of Surgery
Department of Head and Neck Surgery
Department of Epidemiology

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

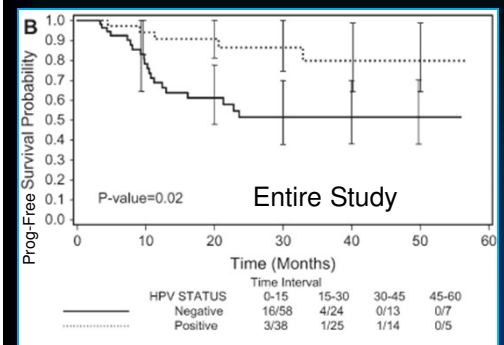


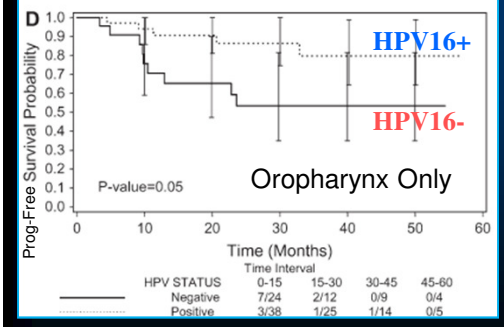
C.T. Allen, et al.
Laryngoscope 2010

Meta-Analysis of Overall & Disease-Free Survival Associated with HPV status



Ragin CC, Int J Cancer 2007

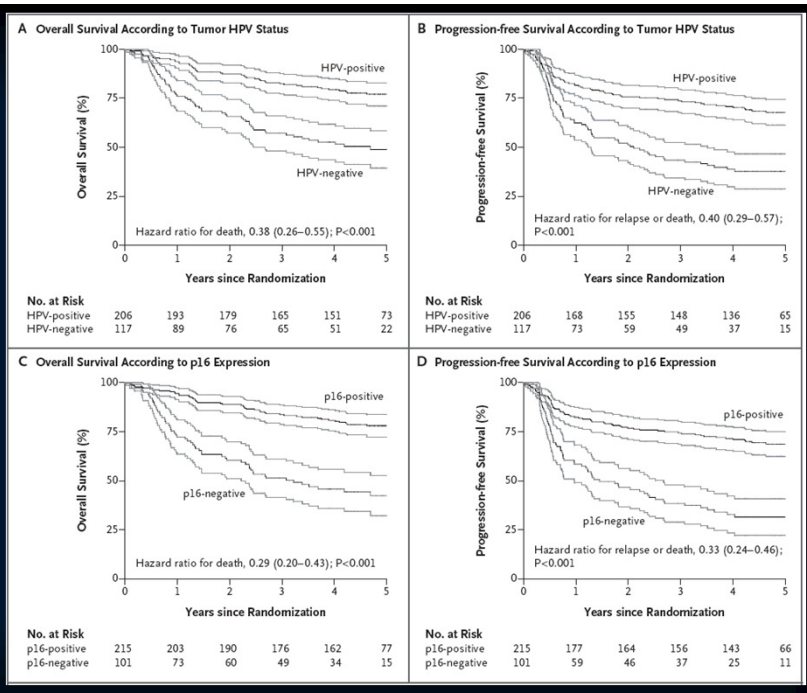




Prog-free & Overall Survival
Oropharynx patients (N=62)
Txd on Phase II Clinical Trial

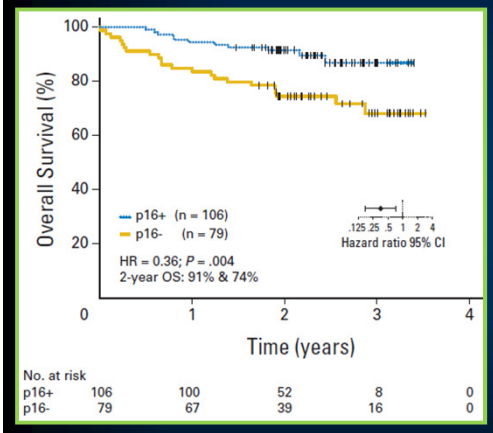
Fakhry C, et al.
JNCI 2008;100:261-9

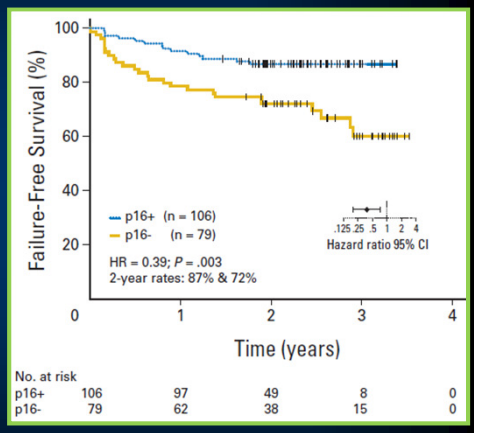
RTOG 0129 Phase III



Ang et al., *NEJM*, July 1, 2010; 363:24-35

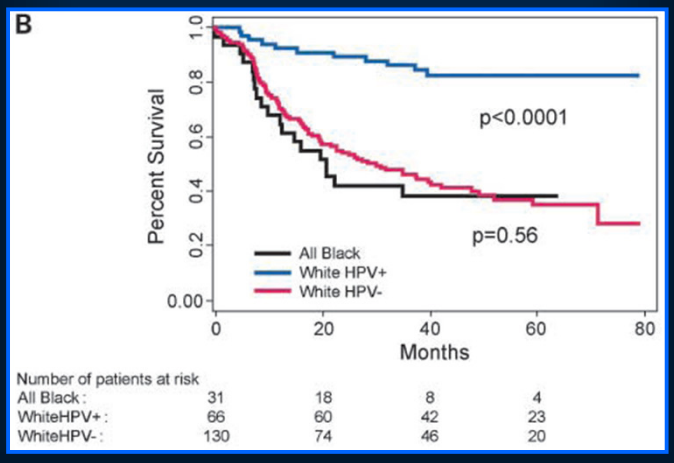
TROG Phase III Trial





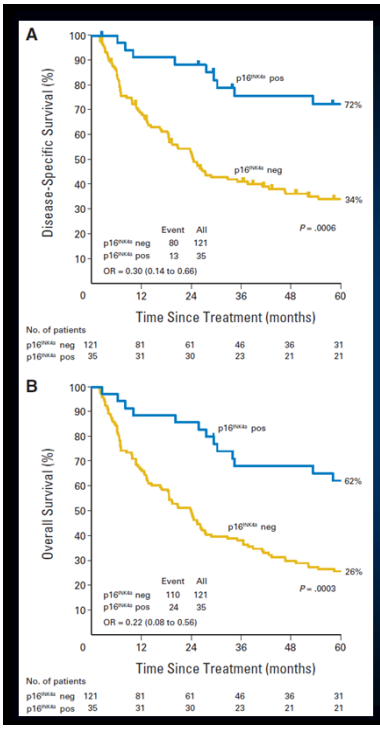
Rischin D et al. JCO 2010.

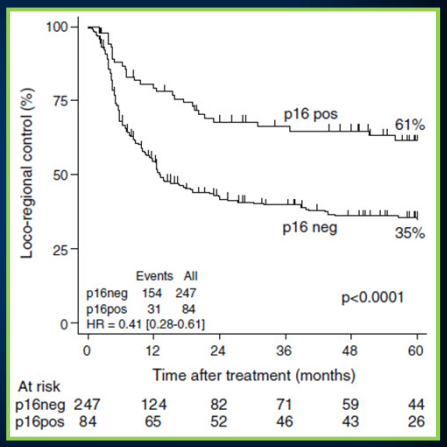
TAX324 Phase III Trial



Settle K et al. Ca Prev Res 2009.

DAHANCA Phase III Trial





Lassen P et al. Radiother Oncol 2010.
Lassen P et al. JCO 2009.

Clinical Directions & Questions

- Revised staging system
- Better definition "HPV-driven" vs. "HPV-assoc"
- Less morbid local-regional treatment (selection)
  - Induction CTX + Targeted tx (immuno approaches?)
  - Lower (dramatically?) XRT doses
  - Robotic/Transoral surgery?
- Better screening for DM, recurrence, or 2nd prim.

Survival (Smoking Status)

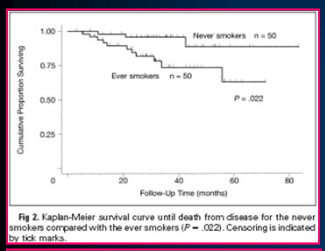


Fig 2. Kaplan-Meier survival curve until death from disease for the never smokers compared with the ever smokers ($P = .022$). Censoring is indicated by tick marks.

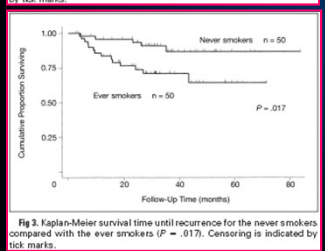
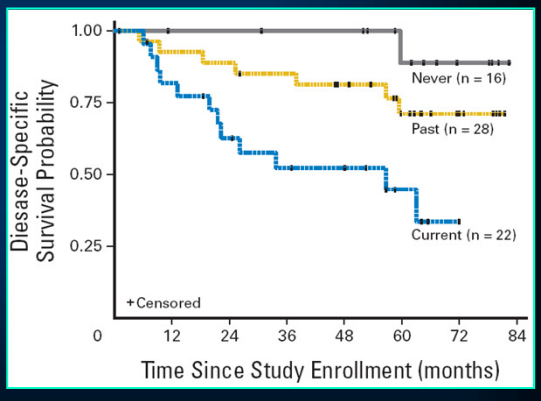


Fig 3. Kaplan-Meier survival time until recurrence for the never smokers compared with the ever smokers ($P = .017$). Censoring is indicated by tick marks.

EMS Pytynia K, JCO 2004



Worden FP, JCO 2008

VOLUME 22 · NUMBER 19 · OCTOBER 1 2004
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Matched-Pair Analysis of Survival of Never Smokers and Ever Smokers With Squamous Cell Carcinoma of the Head and Neck

Kristen B. Pytynia, Jonathan R. Grant, Carol J. Etzel, Dianna B. Roberts, Qingyi Wei, and Erich M. Sturgis

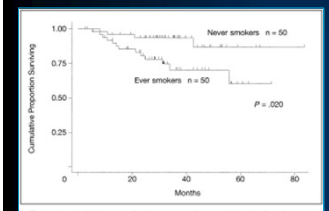
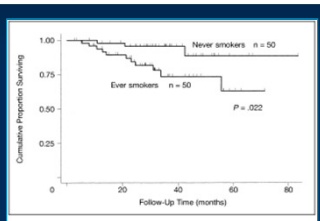


Fig 1. Kaplan-Meier survival curve until overall death for the never smokers compared with the ever smokers (P = .020). Censoring is indicated by tick marks.



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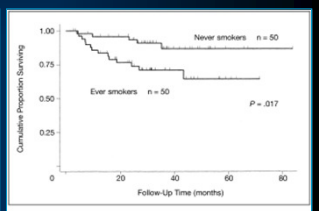


Fig 3. Kaplan-Meier survival time until recurrence for the never smokers compared with the ever smokers (P = .017). Censoring is indicated by tick marks.

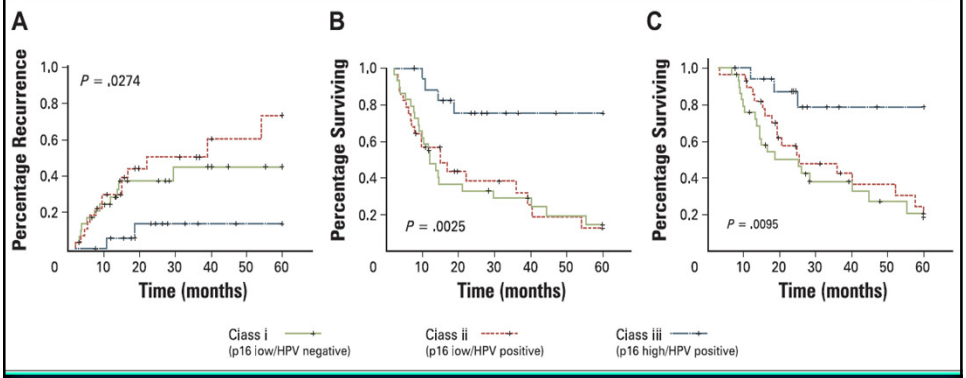
Table 3. Risk Associated With Ever Smoking

	Risk, Ever Smokers to Never Smokers			Risk After Regression for Cancer Associated Symptom Index and Alcohol Use		
Matched Pair Analysis	Risk	*P*	95% CI	Risk	*P*	95% CI
Death, all causes	3.50	.029	1.14 to 10.77	3.04	.062	0.94 to 9.80
Death, owing to disease	3.98	.034	1.11 to 14.33	3.29	.078	0.87 to 12.36
Recurrence	3.29	.023	1.18 to 9.14	2.73	.061	0.96 to 7.80

Journal of Clinical Oncology 2004; 22(19):3981-3988.

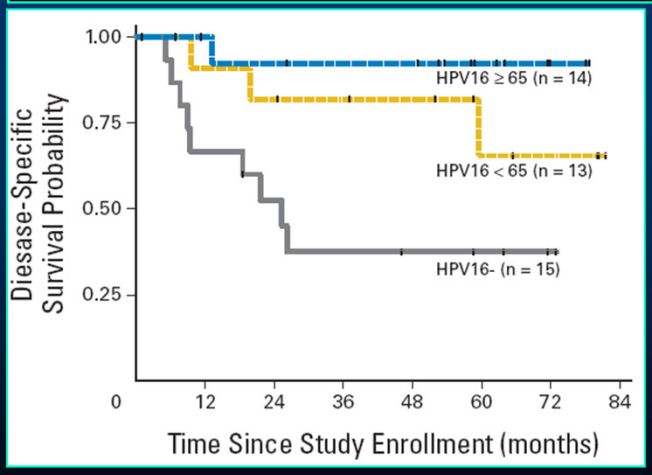
EMS

Joint Effects of HPV and p16 Status



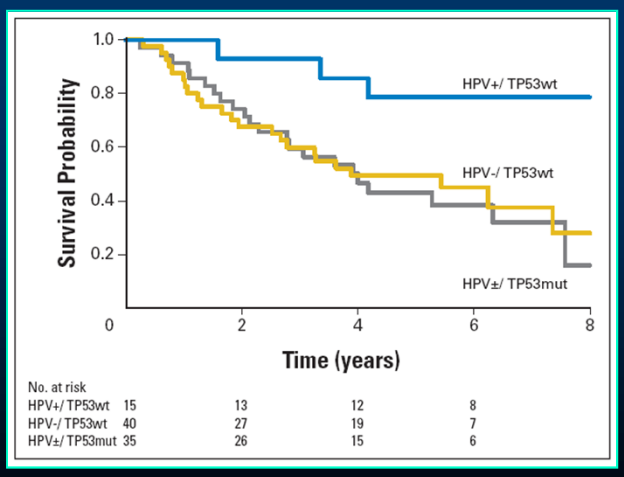
Weinberger PM, et al. *JCO* 2006

Survival (HPV16 copy number)



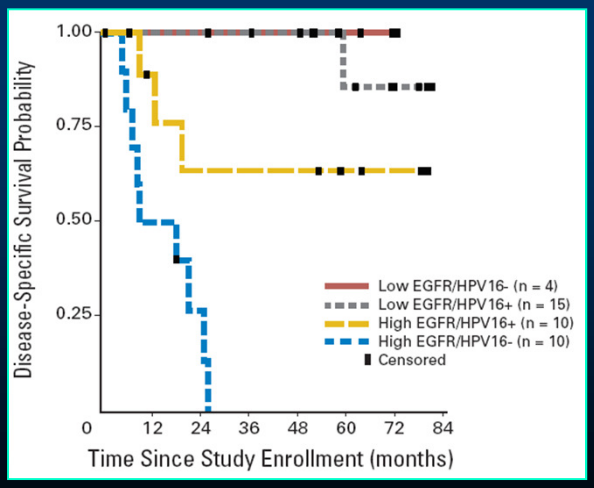
Worden FP, JCO 2008

Joint Effects (p53 mut & HPV)



Licitra LJ, JCO 2006

Joint Effects (EGFR and HPV)



Kumar B, JCO 2008

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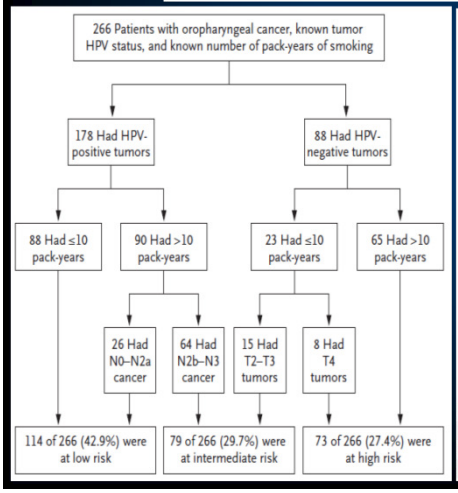
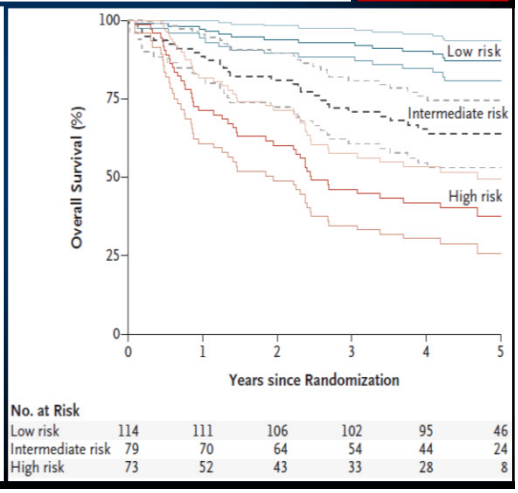
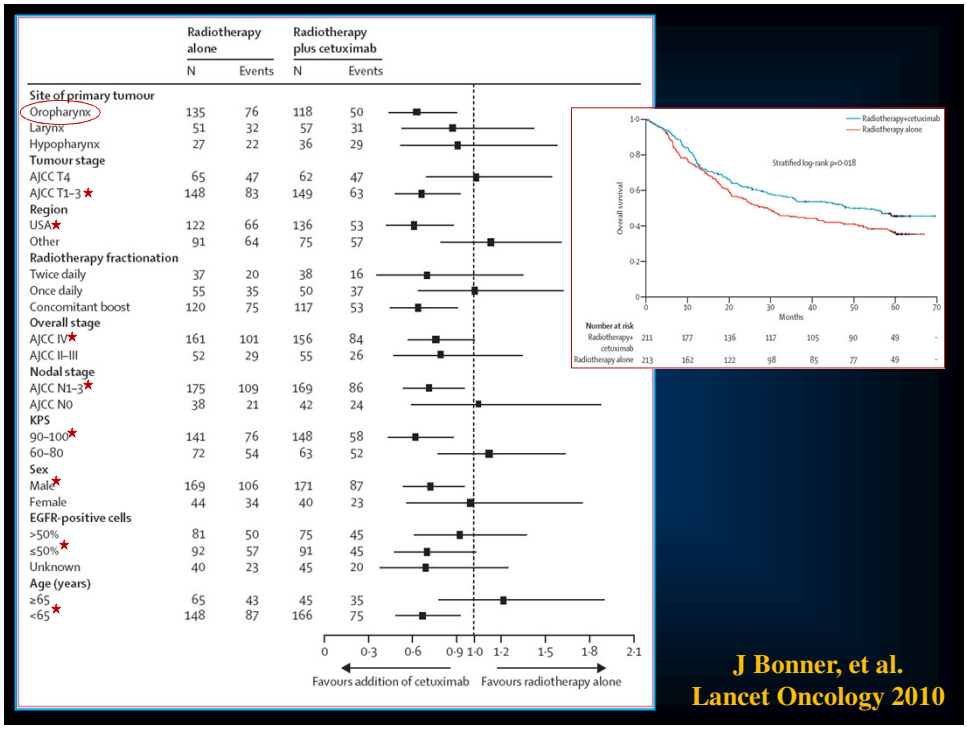
NEJM, July 1, 2010; 363:24-35





No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8



J Bonner, et al.
Lancet Oncology 2010

ECOG Phase II Trial

Induction: Cycles 1-3

Paclitaxel 90 mg/m^2 Days 1,8,15
Cisplatin 75 mg/m^2 Day 1
Cetuximab[2] 250 mg/m^2 Days 1,8,15
Every 21 days for 3 cycles

Evaluate for response

Response CR
Concurrent therapy[3]: 6 weeks

Low dose IMRT, 54 Gy/27 fractions, 5 days a week for 5 weeks and 2 days plus cetuximab 250 mg/m^2 weekly for 6 weeks

Response PR or SD
Concurrent therapy[3]: 7 weeks

Standard dose IMRT 69.3 Gy/33 fractions 5 days a week for 6 weeks and 3 days plus cetuximab 250 mg/m^2 weekly for 7 weeks

RTOG Phase III Trial

			T Stage:		
R		S	1. T1-2	R	
E		T	2. T3-4	A	Arm 1 (Control):
G	p16 +	R	N Stage:	N	Accelerated IMRT, 70Gy for 6 wks
I	Oropharynx	A	1. N0-2a	D	+highdose DDP(100mg/m^2) Dys 1&22
S		T	2. N2b-3	O	(Total: 200 mg/m^2)
T		I	Zubrod	M	
E		F	Perf. Status:	I	Arm 2:
R		Y	1. 0	Z	Accelerated IMRT, 70Gy for 6 wks
			2. 1	E	+8 doses cetuximab
			Smoking Hx:		(400 mg loading pre-IMRT,
			1. ≤ 10 pk-yrs		250 mg weekly during IMRT,
			2. > 10 pk-yrs		and for 1 week after IMRT)

REALISTIC Phase I Trial

ADXS11-001 (Advaxis corp.)
Bioengineered *Listeria monocytogenes*
Secretes HPV-16 E& fused to Listeriolysin O

PI: Mr. Terry Jones
Locations: Liverpool, Royal Marsden, & Cardiff

45 Incident Oropharyngeal Ca Patients (27 -> 18)
6wks post Standard Tx: 3 vaccinations q4wks

PHASE III INDUCTION TRIAL for all sites
TPF-C vs. PCC-C
HPV to be documented
XRT alone is possible after.

PHASE II INDUCTION TPF TRIAL for HPV+ OP
P.I. David Schwartz, M.D. (Hofstra University)
Reduced dose xrt for C.R. at the primary

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Variable	HPV-Positive (N=206)	HPV-Negative (N=117)	P Value†
Overall survival at 3 yr — % (95% CI)	82.4 (77.2–87.6)	57.1 (48.1–66.1)	<0.001
Cause of death — no. of patients/total no. (%)			0.67
Primary cancer	25/50 (50.0)	29/58 (50.0)	
Second primary tumor	4/50 (8.0)	8/58 (13.8)	
Protocol treatment	1/50 (2.0)	0/58	
Nonprotocol treatment	1/50 (2.0)	1/58 (1.7)	
Cause unrelated to cancer or treatment	10/50 (20.0)	8/58 (13.8)	
Unknown	9/50 (18.0)	12/58 (20.7)	
Progression-free survival at 3 yr — % (95% CI)	73.7 (67.7–79.8)	43.4 (34.4–52.4)	<0.001
Local–regional relapse at 3 yr — % (95% CI)	13.6 (8.9–18.3)	35.1 (26.4–43.8)	<0.001
Distant metastasis at 3 yr — % (95% CI)	8.7 (4.9–12.6)	14.6 (8.1–21.1)	0.23
Type of first treatment failure — no. of patients/total no. (%)			0.55
Local–regional disease	26/66 (39.4)	33/72 (45.8)	
Distant metastasis	21/66 (31.8)	17/72 (23.6)	
Death, no documented progression	19/66 (28.8)	22/72 (30.6)	
Second primary tumor at 3 yr — % (95% CI)	5.9 (2.6–9.1)	14.6 (8.1–21.0)	0.02

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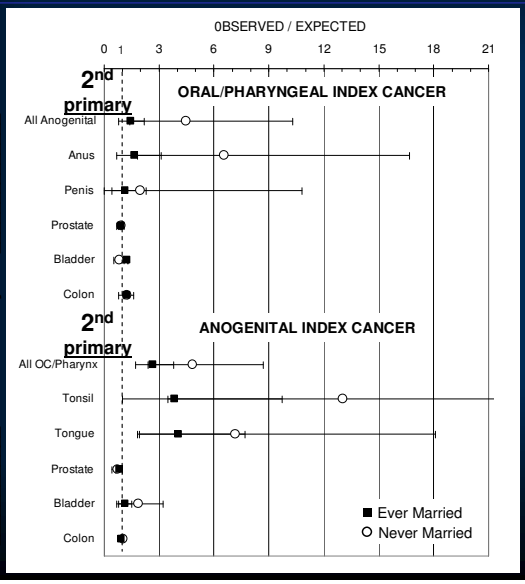
Second primary tumor at 3 yr — % (95% CI)	5.9 (2.6–9.1)	14.6 (8.1–21.0)	0.02
Site of second primary tumor — no. of patients/total no. (%)			0.91
Head and neck	5/19 (26.3)	5/21 (23.8)	
Lung	8/19 (42.1)	9/21 (42.9)	
Prostate	2/19 (10.5)	2/21 (9.5)	
Colon	0/19	1/21 (4.8)	
Rectum	0/19	1/21 (4.8)	
Kidney	0/19	1/21 (4.8)	
Breast	0/19	1/21 (4.8)	
Skin	3/19 (15.8)	1/21 (4.8)	
Unknown	1/19 (5.3)	0/21	

Second Primary Cancers in Men Segregated by Marrital Status
SEER Database



• Sikora & Sturgis, *Arch Oto-HNS*, 2009

Conclusions

- HPV + do better.
- “HPV driven” is real - never smoker, etc.
- Staging system needs modification.
- Tx refinement is needed to maximize function.
- Distant metastases is major problem.
- Second primary is less of a problem.

Thank You

esturgis@mdanderson.org

Session III – 1:40pm Presentation

Not available at time of printing

Notes

De-escalation of Treatment in Oropharynx Cancer:
What are the options?

Dr. John Kim

Following the identification of human papilloma virus-associated (HPV+) oropharyngeal cancer, the understanding and clinical characterization of this disease entity have increased dramatically over the past decade. There are now several reports demonstrating that HPV+ oropharynx cancer has a much better prognosis than HPV- oropharynx cancer treated with radiation and concurrent chemotherapy. Radiation and concurrent chemotherapy is associated with significant toxicity. Hence, current and future trials are exploring the opportunity to de-escalate therapy in HPV+ oropharynx cancers. This presentation will review the emerging clinical behaviour of HPV+ cancer and the evidence supporting the investigation of de-escalation of therapy in these patients.

Notes

Session III

Panel Discussion– Management of Oral & Oropharyngeal Cancer

No material

Notes

Saturday November 5, 2011

Session IV – Video Session I

Notes