



American Head and Neck Society - Journal Club

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[Matted nodes as a predictor of distant metastasis in advanced-stage III/IV oropharyngeal squamous cell carcinoma](#)

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*from **Head & Neck**, February 2016*

Treatment failure from distant metastasis in patient with oropharynx cancer is on the rise, especially in the era of HPV+ tumors. A possible marker of distant metastasis may be matted nodes (defined as 3 nodes abutting one another with loss of intervening fat plane that is replaced with radiologic evidence of extracapsular spread [ECS]) seen on staging CT scan. The 3 year DSS for patients with matted nodes was 58% vs 97% for non matted (p=.0001).

This was all well done study. Looking at long term outcomes from a relatively homogeneous group of patients. They did a nice job showing the effect of matted nodes on survival was independent of multiple other factors including HPV status, smoking status, nodal stage, and ECS. Future consideration of patient characteristics including matted node status will be important in helping selected patients for deescalation of therapy.

[Cetuximab Activity in Dysplastic Lesions of the Upper Aerodigestive Tract](#)

Zubair Khan, Joel B. Epstein, Shanthi Marur, M. Boyd Gillespie, Lawrence Feldman, Hua-Ling Tsai, Zhe Zhang, Hao Wang, James Sciubba, Robert Ferris, Jennifer R. Grandis, Michael Gibson, Wayne Koch, Ralph Tufano, William Westra, Nancy Tsottles, Hiroyuki Ozawa, Christine Chung, Joseph A. Califano

*from **Oral Oncology**, February 2016*



Description of the study

This is a small prospective phase II clinical trial to evaluate whether cetuximab can be used to treat high-risk pre-malignant lesions. Patients that met the inclusion criteria were randomized to cetuximab (for two months) or observation. After 2 months, the patients that were observed had the opportunity to crossover and be treated with cetuximab.

Inclusion criteria

1. Molecular markers of pre-malignancy (loss of heterozygosity (LOH) at one of three loci)
2. High-grade pre-malignant lesions (defined as moderate/severe dysplasia or CIS), but were too extensive to undergo surgical resection
3. High-grade pre-malignant lesions after curative therapy for HNSCC

Primary outcome - Objective change in histology grade

Secondary outcome - Subjective assessment (how the lesion looked + histology grade)

Results:

- Nineteen patients were randomized in the study - 17 completed therapy (2 had treatment toxicity). 12 patients were in the treatment arm, 5 in the observation group
- There was a decrease in the grade of dysplasia in 60% of the cetuximab group.
- There were 4 patients in the treatment group that had complete resolution of dysplasia
- None of the patients in the observation group had complete resolution of their dysplasia, however 40% did have some improvement with time alone.
- In a smaller subset of the 19 patients post-treatment tests of LOH for the 3 loci were tested. In 63% of the treated patients there was a change in LOH.
- Two of the 3 patients that chose to crossover following the 2 month study, had complete resolution of the dysplasia

Strengths

There are limited studies that address chemoprevention for pre-malignant lesions. This is a randomized prospective study with a single chemotherapy. There is a molecular validation of pre-malignancy in at least half of the patients with LOH. Patients were not lost to follow-up. Most importantly there were a number of patients that had complete resolution during the 2 month time period in response to cetuximab.

Limitations

- Underpowered study with a small sample size as study did not meet accrual goals of 60 patients
 - The eligible population was mixed and included patients treated with HNSCC who may have been radiated and/or given other chemotherapeutics.
 - Methods did not clearly outline whether the pathologists were blinded to outcome or group allocation
 - Regarding the two patients that withdrew, secondary to toxicity, there's no description of the actual side effect and they were not included as part of an intention to treat analysis.
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Relation Between the Level of Lymph Node Metastasis and Survival in Locally Advanced Head and Neck Squamous Cell Carcinoma

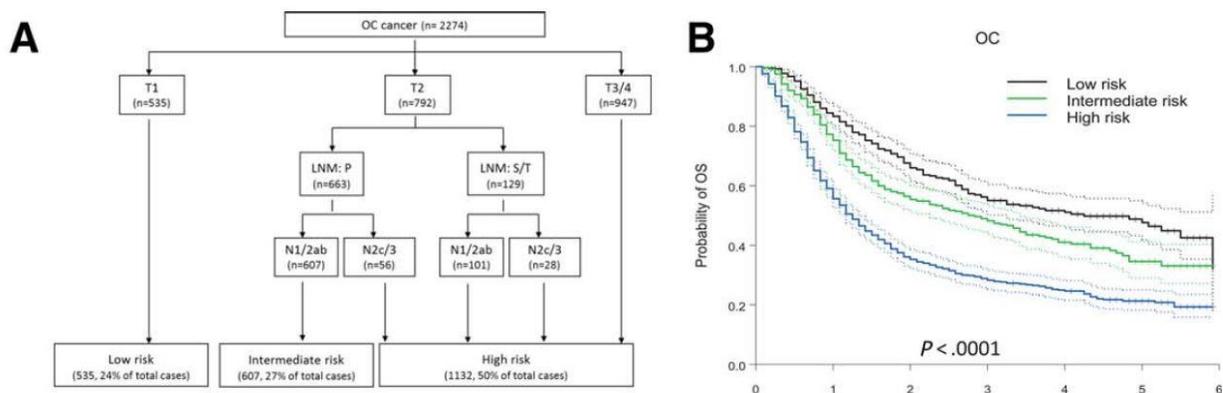
Yan Xing, MD, PhD; Jianjun Zhang, MD, PhD2; Heather Lin, PhD; Kathryn A. Gold, MD; Erich M. Sturgis, MD; Adam S. Garden, MD; J. Jack Lee, PhD, MS, DDS; and William N. William Jr., MD

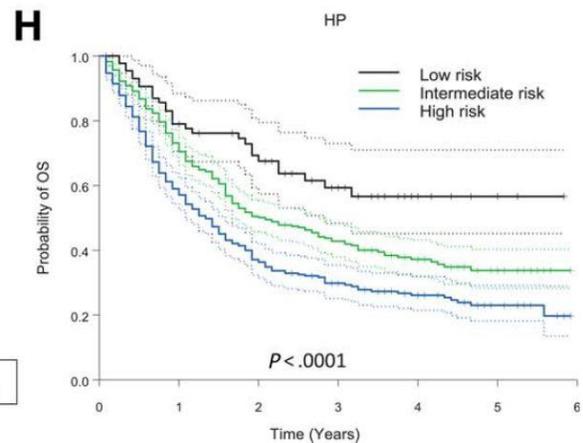
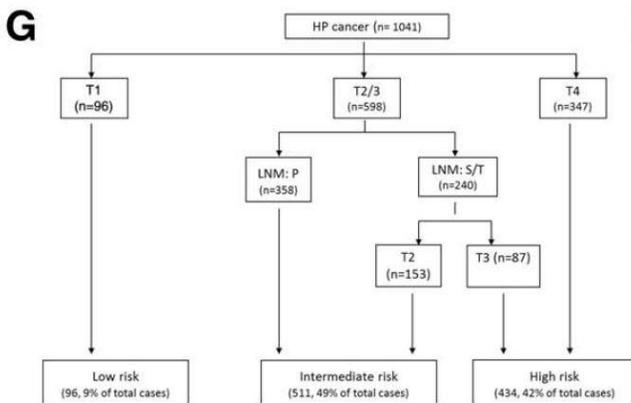
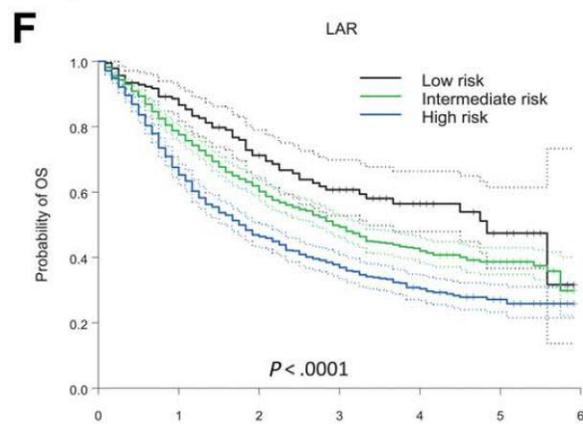
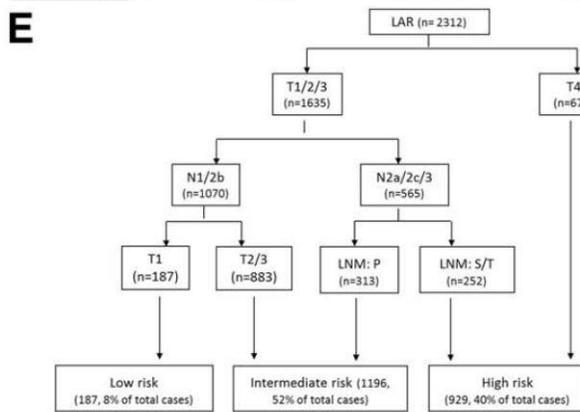
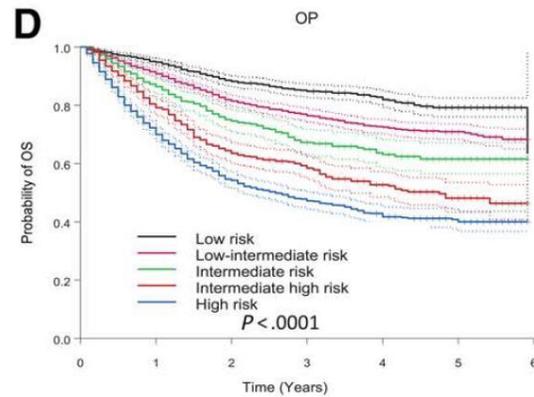
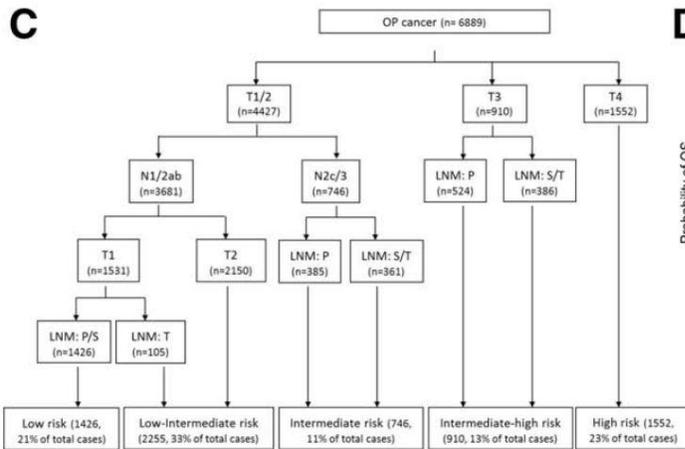
This study queries the SEER database evaluating the prognostic value of the level of lymph node metastasis (LNM) in HNSCC. The authors analyzed 14,499 patients with oral cavity (n=2463), oropharynx (n=8567), larynx (n=2332), and hypopharynx (n=1137) tumors. LNM was then stratified into primary secondary or tertiary as seen in table one.

TABLE 1. Level of Lymph Node Metastasis Based on the Frequency of Involvement

Drainage	Oral Cavity	Oropharynx	Larynx	Hypopharynx
Primary	1, 2, 3 (84%)	2, 3 (60%)	2, 3 (57%)	2, 3 (57%)
Secondary	4 (10%)	1, 4 (30%)	1, 4 (32%)	1, 4 (30%)
Tertiary	5 (6%)	5 (10%)	5 (11%)	5 (13%)

Survival impact and Kaplan-Meier curves were compared between AJCC N classification and LNM level. Survival impact and Kaplan-Meier curves were also compared between AJCC N2 subclassification and the level of LNM patients with N2 disease. In both instances, the authors argue that there is a more clear separation of the curves when analyzed by LNM level raising the hypothesis that the level of LNM may be more accurate predictor of survival than the AJCC N classification. Finally, recursive-partitioning analysis was performed and site specific risk classifications were shown in an algorithm. This chart indicates risk of death categories of low risk, intermediate risk and high risk patients utilizing AJCC T stage, AJCC N stage and LNM levels.





Strengths

- SEER database allows for use of a large sample size
- 4 subsites evaluated
- Interesting construction of a new prediction tool that may provide more accurate prognostic value than current staging system

Weakness

- Short followup time
- Use of SEER database has inherent weaknesses including lack of HPV data (likely skewing the OP curves), lack of quality control of data, lack of information on patterns of failure, lack of specifics on treatment modality, lack of details on features noted in pathology report



Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial

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from The Journal of Clinical Oncology, February 16, 2016

Although a few recent trials have finished accrual, to date a randomized trial comparing radiotherapy (RT) with concomitant cisplatin (CDDP) versus concomitant cetuximab (CTX) as first-line treatment of locally advanced squamous cell carcinoma of the head and neck has not reported results. Magrini et al enrolled eligible patients and randomly assigned in a 1:1 ratio to receive either CDDP 40 mg/m² once per week or CTX 400 mg/m² as loading dose followed by CTX 250 mg/m² once per week concomitant to RT. For primary end points, they used treatment compliance (as defined as number of days of treatment discontinuation) and drug dosage reduction. The acute toxicity rate was also used and defined according to the National Cancer Institute Common Toxicity Criteria. Efficacy end points were local recurrence-free survival, metastasis-free survival, cancer-specific survival, and overall survival.

The study was discontinued early because of slow accrual after the enrollment of 70 patients. RT discontinuation for more than 10 days occurred in 13% of patients given CTX and 0% given CDDP ($P=.05$). Drug dosage reduction occurred in 34% given CTX and 53% given CDDP (difference not significant). Toxicity profiles differed between the two arms, with hematologic, renal, and GI toxicities more frequent in the CDDP arm, and cutaneous toxicity and the need for nutritional support more frequent in the CTX arm. Serious adverse events related to treatment, including four versus one toxic deaths, were higher in the CTX arm (19% v 3%, $P=.044$). Locoregional control, patterns of failure, and survival were similar between the treatment arms. The authors concluded that CTX concomitant to RT lowered compliance and increased acute toxicity rates and that efficacy outcome were similar in both arms. These results raise the issue of appropriately selecting patients with HNSCC who can benefit from concurrent CTX with RT.

Strengths

- prospective randomized controlled trial of an important question that incorporated all head and neck subsites
- Compared CTX to the less toxic weekly cisplatin dosing
- Focus both on efficacy and toxicity, which is important in the era of HPV and de-escalation protocols and because CTX is often thought of as a less toxic alternative to platinum-based CRT.

Limitations

- Poor accrual small subset of patients leading to the study being underpowered (i.e. One- and two-year local control rates were 64% and 53% in the cetuximab arm and 84% and 80% in the cisplatin arm; a 20% difference which was not significant ($p=0.073$))
- No HPV or p16 testing performed; convolutes both survival and compliance outcomes
- Poor compliance rates compared to historical data (only 28% and 20% completed CTX and CDDP regimens, respectively) and high rates of complication (19% rate of severe or fatal complication in CTX arm)



A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma

Brito JP, Ito Y, Miyauchi A, Tuttle RM.

from Thyroid, January 26, 2016

Since the vast majority of subclinical thyroid cancer foci in patients with papillary microcarcinoma (PMC) progress either slowly or not at all, it is critical to reevaluate the traditional management approach, which routinely recommends immediate thyroid surgery for all biopsy proven PTCs. This is particularly important, since thyroid surgery can result in clinically significant morbidity.

This article describes a risk-stratified clinical decision-making framework that was developed by the thyroid cancer disease management team at Memorial Sloan Kettering Cancer Center as the lessons learned from Kuma Hospital in Japan were applied to a cohort of patients with probable or proven papillary microcarcinoma (PMC) who were being evaluated for an active surveillance management approach in the United States.

A risk-stratified approach to the evaluation of patients being considered for active surveillance requires an evaluation of three interrelated but distinct domains:

- Tumor/neck US characteristics: factors considered here include the size of the primary tumor, the location of the tumor within the thyroid gland, molecular profile, and the status of the cervical lymph nodes.
- Patient characteristics: factors considered here include the age of the patient, child-bearing potential, family history of thyroid cancer, the willingness of the patient to defer immediate surgery, and compliance with follow-up.
- Medical team characteristics: factors considered here include the availability and experience of the multidisciplinary team, the quality of neck ultrasonography, and the experience of the clinician treating thyroid cancer.

The findings within each of these three domains allow the patient to be classified into one of three categories that express the suitability of an active surveillance management approach:

- Ideal candidate: the classic ideal patient would be an older patient with a probable or proven solitary PMC with well-defined nodule margins, not adjacent to the thyroid capsule and confined to the thyroid parenchyma.
- Appropriate candidate: these patients may be younger, have multifocal disease, disease that is adjacent to the thyroid capsule at noncritical locations, a potentially more aggressive molecular phenotype, or have other ultrasonographic findings that are likely to make follow-up more difficult (thyroiditis, nonspecific lymphadenopathy, or other benign-appearing nodules).
- Inappropriate candidate: these patients have tumors in critical subcapsular locations (adjacent to the recurrent laryngeal nerve or trachea), have evidence of spread outside the thyroid by either direct extension or metastases, or have evidence of disease progression on serial examinations.

Data from Kuma Hospital convincingly show that patients who are ideal candidates for active surveillance will demonstrate a <1–2% rate of disease progression. Furthermore, salvage therapy is very effective at the time of disease progression, with no significant morbidity or mortality associated with a delayed management approach.



Compared with ideal patients, patients classified as being appropriate candidates have a higher risk of disease progression (e.g., middle-aged patients), child-bearing potential with or without immediate plans for pregnancy, or have specific characteristics that will make it more difficult to follow with observation (e.g., less than high-quality neck ultrasonography, potential of tumor multifocally in patients with a strong family history of thyroid cancer), subcapsular location not adjacent to critical structures (e.g., trachea or recurrent laryngeal nerve), a potentially more aggressive molecular phenotype, or ill-defined nodule margins. While a disease progression rate of approximately 10% is expected in this cohort, treatment offered at the time of disease progression will still be very effective and associated with excellent clinical outcomes when these patients are followed carefully by an experienced management team.

An observation approach in inappropriate patients is contraindicated because thyroid surgery (with or without radioactive iodine ablation) has been demonstrated to be beneficial, because minor disease progression could lead to significant morbidity, or because a high rate of disease progression is expected.

Strengths: Important topic given our increasing appreciation for the indolent nature of this entity the majority of patients afflicted. The authors have significant experience in managing and following patients with this disease.

Limitations: The evidence that supports this study is limited and was reported in a prior publication by one of the authors of this paper (ref 5). This was a single institution observational study of 340 patients who underwent observation of their PMC with comparison of their oncologic outcomes to 1,055 patients who underwent immediate surgery.