My task is a little bit challenging this morning but it’s actually a very exciting topic because cancers of the head and neck and throat have evolved substantially, so there is a lot to talk about. And I have a lot of slides, realizing we have time later to delve into some depth but I wanted to give the audience an overview of some of the evolution particularly in the surgical field but where surgery fits in organ preservation and personalizing therapy for patients with cancers generically on the program called the throat, I broke that down into the voice box, the larynx as well as the oropharynx, these are the large sites that require multidisciplinary collaboration. And so I’ll tell you about some of that. These are my disclosures, our departmental motto of course, in the otolaryngology we heal with steel, so we wish the team were doing better but we’ll stick with them.

The key to understand about head and neck cancer is this is really truly not, not just lip service this is a multidisciplinary disease. The patients require it, it often requires multimodality therapy and so trying to figure out what is the most appropriate treatment for patients with cancers of the head and neck, the larynx and the oropharynx crucial organs of speech and swallowing and breathing is really key. And so obviously the major modalities of surgery, radiotherapy and chemotherapy, medical oncology are advantaged on the patient’s behalf by the addition of a number of colleagues in radiology, pathology and expertise in these areas, swallowing therapy; our nursing colleagues, our coordinators on our clinical trials are really crucial to our patient population and so I think what we’ve tried to build at UPMC and the UPMC Cancer Centers is not just a network of buildings but of people for the patient’s benefit.
And so I’ll describe the evolution over the past 20 years in management of head and neck cancer. The major sort of thunderbolt in the field was the VA Larynx trial. Traditionally surgery was the major modality for cancer of the head and neck, the VA Larynx trial demonstrated that larynx preservation in a large proportion of patients could be afforded by nonsurgical therapy, chemo and radiation. And as you can see you don’t need to know which color is which, they are roughly equivalent. Overall – this is overall survival for patients with surgery followed by radiotherapy or induction therapy followed by radiotherapy. We’ll discuss that this is not the exact regimen today and this is not the sort of surgery. This required a total laryngectomy to get on the VA Larynx trial and I’ll make the case to you that many of our larynx cancer patients don’t require a total laryngectomy. But this said that we had a bit of a problem in the field of head and neck cancer which is how to choose surgical therapy versus nonsurgical therapy. We had the benefit of options but that also challenges the patients and the doctors and required us to work together.

So that VA Larynx trial had a follow-up trial comparing different regimens of nonsurgical therapy saying well if overall survival is equivalent with induction chemo followed by radiotherapy let’s try to figure out what the best regimen is. And so in this trial concurrent the message out of this trial published as you can see in 2003, the 91-11 trial tells you it was initiated in 1991, that was when the VA Larynx trial was published and the 91-11 trial was initiated and it took 12 years to come out with the result that concurrent chemotherapy with radiotherapy according to this message, the initial New England Journal paper was the optimal therapy for patients with advanced cancers of the larynx. We are starting with larynx, we’ll talk about oropharynx subsequently.
And the problem for surgeons is that we were and patients were assumed to require a total laryngectomy to get into this trial, and we’ll talk about why that’s important. But what I’d like to take a slight diversion is that data here from Arlene Forastiere three years later in an abstract form show you that the yellow line which was the message I just told you, concomitant chemoradiation is better at 2 years, you can see at 2 years the yellow line is higher than the white line. The white line is that old VA regimen, induction chemo followed by radiotherapy, concomitant chemoradiation seemed better. Now if you start to follow these folks though for 5 years, 3 years after that 2003 report at 5 year now the two seem much more equivalent. And if you actually look not just at laryngectomy free survival, one end point, but overall survival obviously the ultimate end point is is the patient alive, whether they have their larynx or not. to play with their grandkids, to enjoy life, now the induction, the white line, induction followed by radiation not concomitant chemoradiation appears to yield the best overall survival.

So I would suggest that in the past 10 or 20 years the nonsurgical regimen for larynx cancer has evolved and we don’t quite know, is concomitant like the original message of the 91-11 trial suggested, or induction followed by radiotherapy or chemoradiation really the best regimen? And it’s in this situation, in this scenario or this paradox that the surgeons find themselves because in this trial the majority of patients were not really advanced cancers, big bulky cancers that require a total laryngectomy a large fraction of the time, but a lot of them if you look here about 60 to 70% of them were what we call intermediate stage, T2, T3 with relatively low volume neck disease. You can see the percentages here 50% were N0 in the neck, no clinical evidence of metastasis, another quarter were N1. These are patients that we would not really characterize as advanced larynx cancer.
So the surgeons sort of looked at these chemoradiation trials and said well where do we fit? Does every patient require a total laryngectomy if we are going to embark on surgical therapy? And the trials, to get on those trials I just described to you a total laryngectomy was the – had to be the treatment of choice. So as surgeons we realize that surgical therapy had also evolved and a T2, T3 cancer of the larynx without cartilage involvement, without base of tongue involvement was also well suited to organ preserving surgery. And that was the majority of patients on this trial.

We also started to see some of the toxicities of concomitant chemoradiation, swallowing difficulties, xerostomia, dysfunctional larynges, 5% on the 91-11 trial even though they were cured of cancer require a total laryngectomy because of a nonfunctional organ. And partial laryngectomy might be an option upfront but it’s not an option as a salvage setting in the vast majority of cases. After radiotherapy a total laryngectomy now really is mandatory. And we were informed by some more recent data indicating that upfront treatment of a patient potentially a candidate for conservation organ sparing surgery when radiotherapy or chemoradiation didn’t work total laryngectomy was the option required. So we asked ourselves as surgeons where does surgery fit when we know nonsurgical therapy is effective but it’s not perfect?

Then Mitch Machtay published in 2008 in the JCO looking at a series of RTOG trials, one of them as you can see, from the back of the room maybe not, the 91-11 trial I just described and some other RTOG trials that severe late toxicity is actually quite common. So we can cure the patient, we can sterilize the organ of the cancer but we were sometimes left with a very suboptimal functional result
on the part of the patient. And I think in part we recognized that treating cancers of the head and neck with nonsurgical therapy really does require a high volume and experienced folks, which fortunately we have here in Pittsburgh, but when these New England Journal trials come out I think sometimes less experienced folks that may see 1 or 2 larynx cancers think okay well I can treat that as well and we started to see some of the sequelae for the patient. This is just an example of our Swallowing Center which is on the second floor of the Eye & Ear Institute, we work very closely with the Hillman Cancer Center on staffing a Swallowing Center for patients going through chemoradiation for larynx cancer and we see on the head, neck, surgical and swallowing therapy side that just because one preserves the organ, the larynx, doesn’t mean that you’ve preserved the function of the larynx. And you can see, realize this is a little bit difficult or defocused, you can see a stenotic area, scar tissue forming, this sort of very pale xerostomia, thick mucus, all of these things and so we collaborate with the swallowing therapist to try to help patients get through this treatment.

And then about 5 years ago Harry Hoffman in Iowa looked, if you just look in the black lines that’s 1985 to 1990 survival for larynx cancer, and in the white bars is the mid – yeah, ’85 to ’90 in the black, ’94 to ’96 in the white, comparing survival over a 10 year period. And from the back of the room you can see that the white bar, survival in the ‘90s is lower stage for stage than survival in the ‘80s from larynx cancer. What I’m not showing you is what you already know which is that surgery, the total laryngectomy we all want to avoid, and I think I would too if I had advanced larynx cancer, has somehow happened concurrent with a decreased survival of the larynx. Now maybe that’s a tradeoff that’s okay, that to avoid a laryngectomy we’ll take a few percentage point decrease in survival for larynx cancer, but I think we need to think about whether we are under-treating or
under-staging so as I mentioned we now have some new surgical tools, transoral laser surgical resection, maybe not a total laryngectomy, a cancer such as this a T2, potentially T3 cancer can be resected transorally with no requirement for a total laryngectomy. And then a procedure that was popularized in France, had not really been adopted in the U.S. began to take hold called a supracricoid partial laryngectomy so transoral and partial laryngeal surgery as opposed to total laryngectomy became more commonplace, did have some requirements here in terms of the patient’s robustness and vigorousness, anyone who has walked up the hill, the Lothrop Street hill to the Eye & Ear Institute knows that that’s how we decide if you are a candidate for a partial laryngectomy. Back in the ‘80s we had a resident who is now an otolaryngologist who I work with closely, he lives in Johnstown named Dave Rogerson, Dave is a little bit on the heavy side and he smoked, so we said if you can beat Rogerson up 2 flights of stairs you are a candidate for a partial laryngectomy. We had a number of different techniques, but basically age greater than 70, good performance status. But remember here, T2 T3 N0 N1 these are folks on the 91-11 trial that were required to have a total laryngectomy but don’t necessarily need it if you are skilled in these partial laryngeal procedures.

I’m not going to go into the detail of this but it’s a very good oncologic procedure, the entire thyroid cartilage is removed and we reconstruct the hyoid down to the cricoid as you can see here and sometimes we preserve the epiglottis, people do better if you preserve the epiglottis. But the entire specimen, the thyroid cartilage, the entire larynx plus vocal folds plus the periglottic and some of the preepiglottic space is removed. So it’s actually quite a good oncologic procedure although it’s an open procedure for the patient, requires a trach temporarily, a couple of weeks, but you can see cancers like this without subglottic extension with periglottic space invasion are good candidates for
that if the patient is vigorous and at a period of time bilateral vocal folds the epiglottis is retained, the
drynoid cartilage is and the functional unit, the mobile vocal folds are retained and we reconstruct
the larynx and patients can do well in the right hands. And so in these situations we ask to see these
patients with early to intermediate cancers to see if they are a candidate, and we’ve worked out a
great scenario situation in collaboration with Brian and Dwight Heron and so on at the Hillman
where we will fit folks in and just assess them for whether they are a candidate for partial
laryngectomy, and I’ll explain why.

Now nobody likes an external incision, nobody likes a trach, wouldn’t blame them, what can we do
through the mouth with the laser? Well here is a large epiglottic cancer, you can see it does not
involve the vocal folds which are normal, we’ve got a good 8 or 10 mm here, preepiglottic space
involvement so a T3 N1 in this particular case. And here is the postoperative view. I didn’t have
time to get our videos in but you can see mobile vocal folds, there is no epiglottis but the patient has
no pooling, has a pristine looking larynx. When things get a little bit more dicey is when you get –
you have to be more experienced, you can see this cancer is not up here on the tip of the epiglottis
like the last case but is really deeper, infrahyoid, closer to the vocal folds, here is the left vocal fold,
you can see an up close view of the left vocal fold and this tumor is approximating the right side and
so this takes a bit of a more of a skilled endoscopist and laser surgeon, but the postoperative view
from that patient you can see that the right side is more affected, the left side is essentially
untouched, T3 N1 no extra capsular spread, this patient did not require any adjuvant therapy and is 5
or 6 years out now.
So not just anecdotes, surgeons can be I think appropriately criticized for publishing their occasional anecdote. We reported almost 80 patients over this period that had the cancers I just described, those folks were involved in this trial and we published this last year with 3 years of follow-up. You can see the majority of these are T2 T3 N0 N1 as we would otherwise have seen in the 91-11 trial. Our overall survival was quite good, disease free survival similarly as you know these patients have a lot of comorbidities and 75% of the time the key here is if we are going to have an advanced cancer that’s going to require adjuvant therapy what percentage of them can be treated with surgery alone? In this case selecting appropriately in the hands of a surgeon who can perform less than a total laryngectomy we actually can use single modality therapy. When I reviewed all of the T2 T3 larynx cancers we saw this came to about 35ish percent, so a large minority, the other 2/3 went to radiation and chemotherapy but it was that collaboration where a surgeon capable of performing less than a total laryngectomy saw the patient and ¾ of the time selected correctly because we could avoid any further therapy, the other 2/3 were treated with chemoradiation and so we’re trying to personalize therapy appropriate to the patient, the anatomy and the extent of their disease. And what we get here is surgical staging which is usually the most accurate. Some of these patients required a trach for an extended period of time, but none were tracheostomy tube dependent. Similarly G-tube dependence was very low.

We did some surveys in terms of swallowing outcomes, the FOSS scale. The patients came in at diagnosis, the lower score is better so a 0 means you know no effect on their swallowing, a 1 is mild, not to go too much into the scales but you can see there is about a 1 level decrease in the majority of the patients but some of them actually had similar swallowing as they came in with, similarly voice
outcomes were affected mildly but became moderately in I’d say the majority of these patients. Some of them had some dramatic voice changes. I think the surgical therapy one of the downsides is voice. We think potentially surgical therapy leads to potentially better swallowing but certainly worse voice at least based on this review.

Not every T2 T3 cancer is appropriate for upfront surgery therapy or transoral surgery. This patient in particular had what we – had mobile vocal folds, we would stage him as a sort of big T2, had preepiglottic space involvement, but was 80, had had cardiac stents from an MI 6 or 8 months previously, we have to assess not just the tumor but also the patient and so in a case like this the patient went on to chemoradiation and so we try to discuss these at our tumor conference and make the best personalized decision.

So partial laryngectomy is here, many of the trials that have been published have assumed these patients require a total laryngectomy, I’m trying to communicate that that’s not always the case in experienced hands in a high volume center and that we can select out those patients who can do very well with upfront surgical therapy if we are not talking about a total laryngectomy which I think we would all agree should be avoided if possible. Occasionally we have to use radiotherapy or chemoradiation, it’s on the order of 25 to 30%, but this is because we identify extracapsular spread or multiple lymph nodes positive where it was not evident radiographically. And it’s not available everywhere, we have a series – a few surgeons here at the Eye & Ear but the patient would need to come and have us evaluate them. One does need to be aware that surgery has some complications, bleeding is present and we have to monitor these patients. I borrowed this from Carl Snyderman, I
like this because the title of the boat – or the name of the boat is Temporary Insanity II, so there was a I out there somewhere.

All right, let’s move onto the oropharynx. This is another very large subsite, this is for the post-test questions we are going to ask you later to answer this in – to get your CME credit, but to transition to the oropharynx. Here is a patient that we’ve all seen walk in the door, young man, no overt risk factors for head/neck cancer, cystic mass in the neck. You can see it doesn’t really look like a brachial, it’s cleft cyst, you have not just a very thin wall like out here but you have some nodularity. This is a patient we sort of beat it into our Residents and Fellows a neck mass like this in an adult is cancer until proven otherwise, even without a smoking history and we’ll talk about why that is, but these are generally a symptomatic doc, I was going to say he cut himself shaving but it doesn’t look like he shaves all that often.

So here’s our case, we like to say he’s a lawyer, I hope nobody in the audience is a lawyer but a 45 year old lawyer just to really make it an interesting case. We can talk about it on the panel. Healthy, no comorbidities, usually shows up Wayne Cook at Hopkins published that it takes 3 months for an oropharynx cancer patient to get to the appropriate clinician because people get antibiotics, they think it’s a URI. This patient shows a firm and indurated enlarged ipsilateral tonsil, and the neck mass shows that Level II 4 cm node. A needle biopsy is performed and as we do and I think you do as well here HPV testing is performed with P16 immunohistochemistry and in situ hybridization for HPV DNA and the patient gets a appropriate scan, CT or PET CT and is staged as an oropharynx
cancer patient. The problem is what’s the best treatment for a 45 year old individual who has only half of their life gone they’ve got another 50 years to live and the treatment is key.

Well the important thing is why, what is the most appropriate treatment for this patient and recognizing that the disease as we knew it in the ‘80s and ‘90s when we’ve looked at oropharynx cancers and we published this earlier this year the frequency of HPV went from 30% in the ‘80s to 80% in 2011 and 12. So human papilloma virus is increasing the incidence of tonsil invasive tongue cancers as we see it overall decline in the carcinogen or smoking induced cancers, thankfully. But we see many more oropharynx cancers, this is more common in young adults with less smoking history although we still in our HPV positive population here see about 60% smokers, so they are not never smokers but this is the experience at the Eye & Ear, dramatically increased frequency of HPV positivity and so the disease changed causing us as doctors if we are thinking and if we are intelligent on the behalf of the patient causing us to really reconsider what is the most appropriate treatment given the change in demographics and the biology.

So we have two different diseases, we have the traditional head/neck cancer population where carcinogen exposure leads to P53 mutation 60 to 80% of the time and other genetic genomic alterations. Our group published in the Journal of Science two years ago in August 2011 that the mutations, the genetic mutations in the HPV negative were 4-fold higher than the mutations in the HPV positive where this virus cannot knock out these tumor suppressor pathways much more efficiently without requiring all these genomic alterations. So what does the different biology mean for therapy?
The first thing is to tell you just briefly why we use P16 as a surrogate, this is based on the RTOG91 – sorry RTOG0129 trial which was a negative trial just comparing fractionation of radiation schemes. This was published by Maura Gillison and the late Can Ang, a good friend to many of us who died suddenly a few months ago, but Can and Maura looked at HPV DNA positivity as shown here versus P16 immunohistochemistry and showed that the concordance rate was actually quite high. There were some patients who were P16 positive but HPV negative, that seems to be in part because the in situ technique is less sensitive and so we can get rid of a lot of these by more sensitive techniques like PCR but in general we use P16 immunohistochemistry as a surrogate for HPV positivity. And if you look at survival by these two biologically different and demographic subunits the survival is 30% different. In the TAX 324 induction trial that Marshall Posner presented 40% difference in survival in HPV positive versus negative, so we have to treat these as different diseases, no clinical trial prospectively should ever clump in HPV positive and negative cancers. And just to go back, part of it is you can see second primary tumors are 3-fold lower in the HPV positive group.

So what’s the role of the surgeon in this? In the old days we did these crazy morbid surgeries that even the surgeon didn’t feel good at the end of the day having performed for a patient. We now have surgical technology, transoral, laser and as we’ll talk about robotic techniques where we operate on the tumor from the inside out as opposed to the other way around. It required surgeons to be trained and to really utilize our 3-dimensional anatomy, but this brought us to the present day, nonsurgical therapy of tonsil invasive tongue tumors because of that very morbid mandibular split crazy
surgeries that head/neck folks used to do. We moved away from that toward this nonsurgical therapy, it was more organ preserving. And this was because the treatment results, the overall survival was good, we didn’t know in the ‘90s that that was because HPV was increasing and enriching this good prognosis subset. The surgery had morbidity and functional impairments and chemo and radiation seemed to work beautifully on the oropharynx. Again in retrospect as we’ve done HPV typing we’ve understood in part that’s because we are changing the patients in that and minimally invasive surgical options were pretty rare, only at a few centers. I bring this back up again to say that we were treating not just larynx cancers but the majority of clinical trials in the ‘90s, in the 2000s included oropharynx at least half of the patients on the major clinical trials if not 2/3 were oropharynx cancer patients. And so this severe late toxicity for a 45 year old individual with a long life span they are more vulnerable to toxic therapies. The question is do we have any alternatives and do we have any clinical trials not just retrospective studies?

So he Eastern Cooperative Oncology Group in the first HPV specific trial with an attempt to de-intensify therapy with the understanding that the survival is 30 to 40% better for the HPV positive subgroup, and so it’s toxicity and morbidity of therapy that’s the key on the surgical PI on this trial that accrued 90 patients and was reported that one year progression free survival quite good at the ESCO a few months ago. This used biological staging. The patients got induction chemotherapy, this is a typo, it’s Paclitaxel, Cisplatin, Cetuximab and a complete response, a patient with a complete response would get 54 Gy of radiotherapy instead of the traditional 69 to 70 Gy. We asked can we back off on the radiotherapy dose if the tumor demonstrates to us that it appears more curable with induction chemotherapy. The follow on trial is being designed currently but you can see the 1
year PFS was in the 90 to 91% range if you pulled out the T3s and T4s it got even better. As you may or may not know the HPV positive cancers the majority of them are smaller, so T4 HPV positive cancers are quite rare but they did not do as well in this trial.

So along comes the transoral surgical robot. People make fun of this, of course it’s an interesting device. We resisted it, some traditional surgeons resisted it until 4 or 5 years ago. The arms of the robot go through the mouth, the patient is under the drapes here, you can see going into the patient’s mouth and you operate the robot through these joy sticks in a console about 10 or 20 feet away. This required training on the part of the surgeons, it required the surgeon again to learn a new device and evolve ourselves on behalf of our patients to keep up with the technology. And so we did that, we all had to go through training but we realized the benefits of binocular – the endoscopic laser is often monocular because it’s a narrow tube. The beauty of the robot is that you have two hands and you have binocular vision, high resolution magnified optics and you have wristed instruments that is not rigid like our traditional sinus instruments that our other ENT colleagues use in their endonasal surgery, you had 540 degree rotation, and so a number of us down at the Eye & Ear became trained and credentialed in transoral robotic surgery. You can see this cancer at the base of tongue early on.

Published last year was the positive margin rate. There is a lot of data here but all I want you to see here is the rate of positive margins is 5% or less in about 170, sorry 192 patient tumors, so positive margin rate is low. Then we can deliver these patients for potential adjuvant therapy with negative margins to our colleagues. But I was uncomfortable, I’m the Co-Chair of the Head/Neck Committee on the ECOG and was uncomfortable that 6 or 800 robotic surgical cases had been published retrospectively, the classic surgeon we do 50 or 100, we retrospectively review our series and we
write it up and it goes into the old laryngology literature, sometimes called a contradiction in terms. And so I ask the question can we ask a prospective question, can we monitor the efficacy?

And so we developed a trial of transoral robotic surgery that I’ll describe to you trying to ask prospective questions not retrospective, and do this in collaboration with our radiation and medical oncologists. This was an FDA cleared device but it had never been tested or compared to nonsurgical approaches. And I would suggest to you that our lack of understanding of HPV biology in part was contributed to the fact that all of the nonsurgical treated patients just left a void in our tissue banks with vigorous cancer centers like we have down at Hillman to study the disease. We hadn’t had specimens available for our translational scientists to understand why HPV positive versus negative tumors do 30 or 40% better to radiation or chemotherapy. In fact one of the big problems with these genomic studies, one of ours that we published and the NCI is funding one that will come out in the next couple of months, 10 to 15% are HPV positive because we don’t operate on that in general. But as surgeons we needed to learn to generate Level I evidence which our colleagues in medical and radiation oncology had done.

One suggestion that HPV was different came from our review, Jesse Maxwell is going to be one of our head/neck Fellows and we published together earlier this year that extracapsular spread, which we’ve always seen to be a negative prognostic factor for HPV negative cancers with a 25% difference in survival when there is extracapsular spread of the lymph nodes in HPV negative cancers is essentially an irrelevant pathologic biomarker. In HPV positive cancers they do so well you can see at 2 and 3 years 90% survival whether extracapsular spread is present or not. And so we
need to ask for this vulnerable population do we have to intensify by adding chemotherapy as the RTOG 9501 trial suggested we do when extracapsular spread is present? So we designed the ECOG 3311 trial, we had designed a single arm phase II trial and the NCI had a clinical trials planning meeting November of 2011 and we came out of that with suggestions from Dave Brizell and Jonathan Biteler and a number of others to randomize this, to ask the question how low in the adjuvant radiotherapy can we go?

So this is a phase II randomized trial of transoral surgical resection, not just the robot, we are not – we have no conflict of interest with the robot company, you can use the headlight and a bovi, you can use a laser. You have to get a margin negative resection. And these are HPV or P16 positive, advanced stage patients with the vast majority of what walks in the door with HPV positive cancer, T1 T2 N1 through N2b. We had to initiate a surgeon credentialing. Our colleagues at RTOG are outstanding at monitoring the quality of the radiotherapy, they have the ability through phantoms to measure what each site is delivering in terms of radiotherapy dose in their planning, we’ve never done this in the surgical community we just get a new device and start using it. So we’ve built a surgeon credentialing website as part of this trial. At UPMC the clinical trial was IRB approved yesterday and so I will be the first surgeon hopefully that gets credentialed, which is a little weird to be the PI. I hope that I get credentialed. We stratify by stage and smoking status, we require 20 cases, the number is a little fuzzy as to what the appropriate number is but we selected 20 cases and I have to submit 10 operative notes and path reports for credentialing to a committee. I’m coming down the home stretch here but I want you to see the ECOG trial. These patients have as I mentioned not just HPV positive disease but have baseline functional and quality of life assessments.
They will all undergo transoral surgical resection with a neck dissection. Low risk patients that are
down staged about 10% of the time we actually find that those clinically N1 nodes are not pathologic
and these patients can be observed. So we are de-intensifying therapy in return for adding a surgical
procedure.

Jump down to the Arm D, high risk patients who a surgeon could not obtain negative margins, who
had extensive extracapsular spread or 5 or more metastatic lymph nodes based on the 10 year update
from J. Cooper on the RTOG 9501 trial, these high risk patients go to standard adjuvant high risk
therapy with radiotherapy and concomitant Cisplatin. The majority of patients we estimate 70% of
the trial will be in this intermediate group, will have clear margins or 2 to 3 mm close margins, have
microscopic extracapsular spread which I showed you does not confer a negative prognostic value in
HPV positive like it did for HPV negative, have sort of intermediate levels of positive nodes,
lymphvascular invasion, paraneural invasion and these folks will get randomized to traditional
adjuvant 60 Gy versus low dose 50 Gy therapy in the hope that at the end of this if we can show
equivalent outcomes with surgery followed by 50 Gy that a randomized phase III trial would be this
regimen, surgery followed by 50 Gy radiotherapy as compared, randomized to our traditional
concomitant chemoradiation, and whether that would be Cisplatin radiation or Erbitux radiation is
the subject of the 1016 trial which is ongoing.

And so we’ve assumed an 85% 2 year progression free survival which is the number that the
nonsurgical trials have achieved, so we have stopping rules not just for positive margins, recurrence
and bleeding but we have stopping rules if our therapy is not effective and this is one of the first
times that the surgeons have suggested themselves – subjected themselves to cooperative group trials and had NCI funding to do it.

So oropharynx cancer has been rising, 5% per year for the past 20 years, this is essentially all attributable to HPV positivity. Survival is outstanding, causing us to sort of reinterpret the trial results from the past 10 or 29 years and look in terms of the long term toxicities in this younger HPV population, reevaluating our therapeutic approach given that transoral surgery is not only feasible and safe but it’s being done at many centers around the country and we need to study it. So we have these trials that are ongoing and we hope we can use them to personalize therapy for the patients.

Here is our group. Here is our future for head/neck cancer, for any of you that tried to download that new operating system update, maybe not very funny. Is there time for questions? Panel, fantastic, thank you.