Thank you Dr. Johnston, good morning. I’m pleased to present the grand rounds for the University of Pittsburgh, the Division of Head and Neck Surgery, and the topic for this morning’s lecture is focused on an area of current controversy in head and neck surgery, in head and neck oncology related to the optimal management of intermediate stage larynx cancer, and I will define that, but I wanted to be the first to set the stage for 2011 since we’re almost there.

I think the story really begins back in the early ‘90s with the publication of a randomized clinical trial from, this is known as the VA Larynx Study. This was a randomized trial comparing the standard of care in the ‘80s, ‘70s and ‘80s really, of a total laryngectomy, that’s what is denoted by surgery, followed by radiotherapy. And the patients were randomized to receive chemo, chemotherapy and if they had a sufficient response go on to radiation therapy in the effort to preserve the larynx, the voice box. And this was the, the genesis of the organ preservation era over the course of the 1990s. In the results here this was a landmark study because the results were such that overall survival was equivalent between the two arms, and about half, slightly less than half of patients were able to keep their voice box and so this was the overall message from this trial was that nonsurgical therapy could retain the voice box and preserve the organ.

And I’d like to point out that over the course of the ‘90s head and neck surgeons played an active role in the multidisciplinary tumor groups because we demonstrated what’s known as equipoise. This has a number of definitions, but I think relevant here in terms of patient care and medical ethics is that surgeons were able to step back, avoid performing their traditional role as the surgeon,
removing the voice box which was infiltrated by cancer in the hopes of providing a benefit for their patients in the context of a therapeutic clinical trial. And this is actually manifested by a paper by a Dr. Hoffman at Iowa and you can see this dotted curve decreasing, the rates of surgery decreasing over the course of the mid-1980s, over 15 or so years up to 2001. And you can see that radiation and chemotherapy were increasing over that timeframe consistent with the results of that VA trial.

Now the next landmark study which sets the stage for why I selected this I would say controversial topic of intermediate stage larynx cancer was the intergroup trial from the radiation therapy oncology group, 9111 trial, which was published as you can see here in 2003. And this study established that combined chemotherapy with radiation therapy was a standard treatment for the intermediate and advanced stage larynx cancer, and fundamental to this trial and the reason why I say that this sets the stage for our discussion is that it assumed that total laryngectomy as described in the VA study was the only surgical alternative to patients entered on this trial. Now the results were impressive, this is the larynx preservation rates, and you can see that the concomitant or concurrent chemotherapy with radiation therapy was the take home message and appeared to be the optimal regimen whereas the VA study regimen, chemotherapy followed by radiation was less impressive in both of these, and the addition of chemotherapy was better than radiation alone.

The problem really arose when we followed these patients a bit longer, and I think as the rationale for revisiting intermediate stage larynx cancer and what is the optimal management I’d like to point out that not just the two year data, which I just showed you which demonstrated that concomitant
radiation was better, or concomitant chemotherapy was better than the induction therapy, but if you followed these patients over time the 5 year data now suggests that the laryngectomy free survival was equivalent. And if you look at the same time frame, the 5 years for overall survival interestingly now the chemotherapy before radiation induction looks like overall survival is actually better. And this appears to be in fact widening over 5, 6 and 8 years. Now this has not yet been published, this was abstract form from 2006, it has continued to be presented however by the first author of the 9111 study and so these data come from the abstract presented at this meeting.

And so when we look at the 2 year data and 5 year data I think that one has to conclude that we are not exactly sure what is the optimal sequencing of nonsurgical therapy and so we need to look at the success of the nonsurgical therapy over that timeframe in the Hoffman paper. I mentioned to you that surgery has declined and chemoradiation had increased, and so Dr. Hoffman compared using the SEER database, this was from about 150,000 cases of larynx cancer, and if you compare the survival from the mid-1980s, ’85 to ’90, with survival for larynx cancer in the mid-’90s, years ’94 to ’96, you can see the white bar is lower at essentially every stage of larynx cancer. And so survival was declining concomitant with the decrease in surgical therapy and increase in trying to sort out how to use chemotherapy and radiation. And so this raised some concerns and I think as, as surgeons in the multidisciplinary group led us to reevaluate the role of surgery and fundamentally what is the appropriate surgery for these patients?
And so when we reevaluate these trials we need to understand that they were asking nonsurgical questions, when to use chemo with radiation or before it? Fundamental to this trial was the assumption that all patients needed a total laryngectomy and that’s important because as I’ll show you from that 9111 trial demographics, many of these patients are of the intermediate stage, meaning not early T1 cancers, not advanced T4 cancers, but intermediate T2s and T3s without cartilage or involvement of the base of tongue, and so many of these patients, two-thirds perhaps three-fourths were potentially candidates for some surgical procedure other than a total laryngectomy.

In addition Dr. Mactay a couple of years ago evaluated the acute and long term toxicities and this was a 2 or 3 clinical trials, one of the trials within this paper was the 9111 trial, and you can see the severe and late toxicities were quite significant and other authors have indicated that a partial laryngeal surgery is not available after radiotherapy and so this potentially misses an opportunity personalize the treatment from a surgical standpoint if a total laryngectomy is not necessary.

So here’s the data, depending on how you interpret here is the T stage, T2, T3 combined here and you can see essentially 90% of this study were T2 and T3 tumors with the majority being N0 or N1. And so relatively intermediate stage tumors, T4 tumors were excluded from this trial as were T1s. And so this was a trial of intermediate stage cancer, the assumption being that a total laryngectomy was the only surgical option in order to get on the study. And so again this equipoise over the ‘90s led surgeons to say well, why not give it a try? Let’s see if we can preserve the larynx with a nonsurgical therapy and this was perceived as an organ preservation strategy would be less radical
than a total laryngectomy and the hope was that something other than a total laryngectomy could be used perhaps if that didn’t work.

When you look further at this study, however, the most aggressive chemo/radiation arm these patients could not swallow well for the first year or two, in fact not swallowing more than liquids was a significantly higher rate. When surgery had to be performed after this aggressive chemo and radiation the surgery was more complicated and required the addition of flap reconstruction in nonradiated tissues to resurface and reconstruct the, the swallowing apparatus. In addition, as you know, radiation can only in general be given once, and so second primary cancers now have limited therapeutic options. In the 9111 trial laryngectomy had to be performed in 5% of cases where there was no disease, no cancer just because the organ had been destroyed by the healing of the cancer being treated by chemo/radiation. And now I’d like to address this concept of whether inclusion on the 9111 trial which was relevant in the 1990s is still relevant in 2010 and ’11, and whether a total laryngectomy is truly required for intermediate stage larynx cancers.

One final bit of rationale for reevaluating surgical therapy is that the assumption, this equipoise, the surgeon stepping back, waiting for the chemo/radiation and then coming in in salvage setting to do the total laryngectomy unfortunately leads some patients not to be curable and be unresectable after that recurrence of disease. And it turned out that in that setting the most common cause of the patient’s demise is local and regional, and so this should be something that surgery could actually
plan an important role. The chemo/radiation regimen is, is very aggressive and the fistula rates were quite high, as I pointed out.

I’d also like to put one last piece of evidence in there for this reevaluation, which is that patients who have early stage larynx cancer and are given radiation when that doesn’t work these patients who are initially candidates for a conservation surgical procedure require now a total laryngectomy after radiation, indicating that salvage treatment after radiation is simply not as satisfactory as we thought in the ‘90s.

And if you look at survival, this has really not improved and in some subgroups, in our health disparities we note actually decreased survival from larynx cancer. Obviously overall survival is the key motivation for us to help our patients.

(inaudible)

This is the same patient after radiation, and you can see that after radiation the pallor, the fibrosis, the difficulty that this patient has with swallowing and this larynx is completely stenosed and frozen. Minor salivary tissue is destroyed and so you can see that that sort of an approach in many patients is not satisfactory. And so in terms of reevaluating surgery for these intermediate cases we performed a review of our surgical therapy for intermediate stage T2 and T3 larynx cancers over the course of the past 8 or 10 years, and you can see as we add up the total number of these cases the
ones that we were able to perform a partial laryngeal surgery accounted for approximately 1/3 of these. And I would say that this provides not only the rationale but the role for a head/neck surgical approach that is less than total laryngectomy in a sizable fraction of these patients allowing us to, to perform a procedure that may have sufficient outcomes to utilize. Now the decision to manage larynx cancer really is critically dependent on a 3-dimensional concept of the tumor and this has been known for quite some time and I think is really along the ways how a head and neck surgeon can contribute to the multidisciplinary team.

For instance, staging in these clinical studies is generally not as accurate as when we perform surgery and so often there is a staging drift that can only be accurate when we remove the larynx because the surgery can demonstrate whether there was periglottic space involvement or breach of the oncologic barriers at the thyrohyoid membrane, the thyroid cartilage, the conus elasticus that show a spread extralaryngeal and give us an idea of the true and accurate stage of these cancers. Furthermore the function of the voice box creating a laryngeal natural speech is dependent in large part on how much of the larynx has to be removed in the vibratory surface as shown here.

What the surgeon needs to realize is that the 3-dimensional anatomy is something that we can assess through our angled instruments and rigid endoscopy, and I think over the course of the ‘90s this fell a bit by the wayside as we began to avoid the surgical approaches then I think we did a less good job on the multidisciplinary evaluation by performing endoscopic staging and evaluation and patients often went directly to chemo and radiation, and you can see how the head/neck staging process that
the surgeon provides can give us much more information and at the same time we realize that the functional evaluation of the larynx was really critical and this required the fiberoptic examinations and a number of speech and language therapy collaborations over the course of the ‘90s which helped us to assess the function.

Now endoscopic surgery of the voice box is not new, you can see that our forefathers here, Jackson, Yako and Strong were using endoscopic approaches to the larynx for decades, even in the late ‘60s this began. And they found that fast rehabilitation, and avoidance of airway management could be done and they utilized the laser through the endoscope to remove a tumor like this, and one needs to understand that taking the patient for a biopsy to the operating room is in fact a therapeutic opportunity which we traditionally associated with very early cancers but as I’ll give you some examples, can be applied to intermediate stage larynx cancer.

Now we use a carbon dioxide laser through the endoscope because it has features which are very suitable and allows it to be a cutting instrument, not to ablate cancer but actually to remove it and avoid collateral damage for the majority of situations and allow margins to be assessed by the pathologist. You can see the absorption length characteristics which are favorable for carbon dioxide.

One of the downsides is that in general this is a coaxial of line of sight limitation where coming around the fiberoptic is in development and is not currently in wide spread use but there are some
new lasers that are assisting us in improving our endoscopic approaches, which then would be very useful for the intermediate stage cancers. But in general with exposure techniques, a number of endoscopes available to us, the larynx can be visualized to enable endoscopic laryngeal surgery. There are some contraindications as shown here, and experience head/neck surgeon and endoscopist has to be aware of these and use those angled instruments to select that 1/3 of the intermediate stage cancers, which are then available or candidates for avoidance of the aggressive chemo and radiation which can have side effects.

You can see that one of the advantages of an endoscopic approach as opposed to applying radiation where both vocal cords would then be radiated is that we can preserve the vibratory surface of the uninvolved vocal folds by treating only the side that’s affected and this heals in a suitable fashion that the contralateral vocal fold vibration can be retained.

We can become a bit more extensive assessing the lateral margins in a way that often times we are unable to do in the office by following these patients and get deep periglottic space clearance, even for bulky T2 lesions and you can see these actually heal quite well in this situation.

Now I want to describe the cases that I just mentioned to you so that we can look a little more carefully at what the results were on these individuals who underwent a either transoral laser microsurgery or another partial laryngeal surgery called a super-cricoid partial laryngectomy and we reviewed these cases with sufficient follow-up to assess oncologic outcome. I’ve combined these
both because as you’ll see the staging is in large part T2 and T3 cancers, intermediate stage disease
that would have been involved in this 9111 trial and did not require a total laryngectomy. And as
you can see the oncologic outcome is actually quite favorable in these patients. You can see not
only disease free but overall survival is sufficient to merit, although we cannot obviously directly
compare these patients, certainly we can say in 2010, 2011 they did not require a total laryngectomy
and still have good oncologic outcome.

And so I’ll describe these, but in general the CO2 laser microsurgery here we use more often for the
super-glottic tumors, I showed you one example but often my experience is with glottic cancers, you
end up with a breathy voice and the glottic gap, although we do collaborate with our voice center
and the medialization techniques are quite useful for these patients, in general as I’ll show you, we
use the super-cricoid for those glottic cancers.

Here is the patients that I’m describing in the transoral laser microsurgery, you can see the majority
of these are stage 2 and 3, and this comprises most of those. Now one of the problems with the
staging system is that it’s a very poor predictor of what the surgical approach would be. And so the
European Laryngological Association has recently put together a better staging system which I
won’t go into but I simply point it out since I think surgeons need to be a bit more careful in
describing what the stage and the geographic location within the larynx for these cancers is because
that really then guides the surgical procedure required and then the function of the larynx
posttreatment.
In this group, because many of them had super-glottic cancers we did detect metastasis, I would also point out that in a group that has T2 N0 super-glottic cancer the addition of radiation is often skipped by our colleagues, and so as the surgeon here we can identify metastasis and utilize adjuvant therapy when metastasis is found, and so the converse here is that 65% of patients avoided any additional therapy and were treated purely endoscopically. We almost never place a tracheostomy tube and this came out very early, we did have some patients, all patients were fed with a nasogastric tube and a gastrostomy tube was only performed early on, but these could all be removed in these individuals.

We used some clinical assessments of swallowing, the FOSS scale which basically the normal swallowing is shown at a 0 and poor swallowing at a 5, and you can see that in general we don’t have a significant decrease postoperatively in the swallowing function. Similarly with the transoral microsurgery group the preoperative versus the postoperative voice is quite acceptable, perhaps a slight decrease in selected patients who have some glottic involvement.

I’d like to reinforce that when we perform a partial laryngeal surgery that we need to recognize and these are contributions from the University of Pittsburgh manuscript that indicated bilateral neck dissections provide better regional control than a unilateral neck dissection, and that recurrence is decreased significantly. And so when we perform surgery for super-glottic cancer that a bilateral neck dissection is part of the treatment program at the University of Pittsburgh as supported by these data.
Now this is not specific to the University of Pittsburgh, in fact as published in 2007 there are several other centers and a large number of patients indicating that this is in fact a generalized approach at selected center with sufficient expertise, and you can see that the results seen by these other groups are similar to ours and the side effects and the gastrostomy tube dependence are quite manageable, quite similar although this is not obviously directly comparable to the clinical studies I proposed and described, this does indicate that this is a generalized approach which is, is part of the standard treatment and should be part of multidisciplinary management of intermediate stage disease.

I want to show some direct results of these cases that I described and indicate that in some cases although our preference is to perform an unblocked resection as the German’s Professor Steiner and others have indicated, on some situations division of the tumor can actually assess the depth of invasion and large tumors such as this that involve the entire epiglottis but do not involve the, the vocal folds and have preepiglottic space involvement can be assessed at their deepest extent by obtaining direct tumor control in the preepiglottic space and avoiding injury to the vocal folds and leading to a good voice. I’ll show you one patient, this is the same patient that I’ve just shown the still figures, and you can see that the vocal folds function nicely, aryepiglottic folds are regenerated with granulation and there is no epiglottis, and this patient as you can see has quite good function.

Here is another example, similarly you can see this is a little bit earlier than the previous one, still a little bit of edematous arytenoids but in general quite good function and these patients speak and
swallow essentially normally with a single outpatient procedure. Occasionally we keep them overnight, usually that depends on how they do on our preoperative assessment. Now those cases where it’s a midline epiglottic cancer can be more straightforward, on occasion we are confronted with one of these infrahyoid super-glottic cancers, you can see the left vocal fold here which is a better up close view, this is stages as a T3 N0 with impairment of the right vocal fold and right larynx, this is a classic case that would have been told in the 9111 trial that would have required a total laryngectomy, and you can see our angled instruments can assess the larynx and make sure that we can adequate resect this cancer.

Now at 2 ½ years postoperatively, you can hear his voice, he eats anything he wants and has a good voice despite how abnormal perhaps to the eye the larynx looks and we were able to retain as much of the epiglottis as we could and I think that this allows us to guide the surgery by the location of the tumor as opposed to a generic treatment with chemo/radiation or with a total laryngectomy.

I’d like to discuss our experience with the super-cricoid laryngectomy. This is also useful for intermediate stage cancers as primary treatment and occasionally in the recurrent setting although this result as with others are less, we are less enthusiastic about these. We prefer patients who have no clinical evidence of metastasis although they may have microscopic disease, so that we can potentially avoid the need for radiotherapy and generally these are fit patients who can undergo an open surgical procedure. In this surgery the thyroid cartilage is removed and the hyoid bone is closed at the cricoid, and the effort is made to retain the epiglottis for improved function. This is a
very good oncologic procedure, you can see the entire thyroid cartilage removed and the cancer is completely excised with good oncologic margins.

Here is an example of a patient where the periglottic space is infiltrated by this T2 N0 squamous carcinoma of the right vocal fold, there is no super-glottic or subglottic extension, you can see the cricoid cartilage is clear. And our experience with these cases which this series stopped in 2008 you can see in large part were glottic cancers. Some of these patients had attempted laser surgery and could not have adequate control, but in large part these again are intermediate stage cancers of the voice box. So we now can see the T2 T3 laryngeal cancers that comprised this subset. Most of these patients, 2/3 could retain the epiglottis, in some situations, not quite half, we had to remove part of the arytenoid or the complete arytenoid. The results are better when you can retain both, and I’ll show you some videos, and we perform staging neck dissections in order to hopefully avoid the need for radiotherapy and we were successful in about 80% of these patients avoiding any further adjuvant therapy. Eventually some of these patients did require a total laryngectomy, either due to recurrent disease or a function in one patient, and so the larynx preservation rate was over 80%.

Similarly our swallowing function was a little worse as you can see here from the preoperative stage, this is an open procedure, and so the postoperative swallowing results are a little bit worse than the transoral procedure could yield. Likewise the voice results, although many of these patients have poor voice because they come in with a cancer of the voice box, of the glottic larynx. We actually do make this worse in some situations, although this is quite a serviceable voice and many of these
patients go back to work and live normal speaking lives. You can see a case here with mobile vocal folds, and this is the same patient now 5 months postoperatively, hopefully this projects well and you can see we’ve kept both arytenoids, the recurrent laryngeal nerves are intact and functional, and here’s an example of a case where we had to remove the right arytenoid or part of it and you can see the voice is formed by the arytenoid mucosa vibrating against the epiglottis in the airway, speaking and swallowing and is quite good.

Now the things that we need to recognize with partial laryngeal surgery is to select the appropriate patients, and so I think in the multidisciplinary team we collaborate with our swallowing center, our speech and language therapists and the physicians in our voice center and swallowing center to assess these patients preoperatively and postoperatively. And it does require a motivated patient. And so this is the role in the tumor conference is to really personalize therapy for the patient who is capable of undergoing a procedure that requires some postoperative motivation and laryngeal rehabilitation. On occasion, as I pointed out, in the order of 25 to 30% we do use radiotherapy and this leads to some edematous laryngeal structures and we need to also recognize that these patients have abnormal landmarks which can affect future procedures such as endotracheal intubation and so this is important when you perform these procedures.

But the advantages of such an approach is that you can perform an organ preservation surgery and often this is a single procedure as opposed to a chemo/radiation approach which takes often a couple months of daily treatment and these procedures can be repeatable, as I pointed out, some of the laser
patients can undergo a super-cricoid and you always retain the ability to undergo radiation or chemotherapy and so this approach does not burn any bridges whereas the converse is unsatisfactory and often we cannot surgically salvage some of these patients with a partial procedure.

And then ultimately the pathologic staging is more accurate, telling us the true stage of the disease, helping us to then apply more aggressive therapy when that’s necessary. I’ll just show you one example here of a patient who did undergo radiation after endoscopic super-glottic laryngectomy, he had bilateral metastasis with ________ and required a chemo/radiation. And you can see the larynx generally functions well although there is some random ________ speaks well. And so this is the point of not eliminating future approaches, oncologic approaches.

Some disadvantages are that we often take these patients back a month or 6 weeks later to do the neck dissections and accurately stage the neck, and this is a second anesthetic because we need to address the potential for metastasis and then in about 30% of the cases still use radiation and chemotherapy. But I would suggest that this is really more of a personalized approach using adjuvant therapy only in patients who require it and excluding 2/3 of the patients. And this does stake some specialized training in multidisciplinary tumor conferences, selecting the right patient and having a surgeon capable of offering this to the patient.

So we need to recognize the potential for these complications in the transoral approaches. We’ve not had any catastrophic bleeding here but in other large studies this rate is approximately 3%.
Essentially all of these patients aspirate in the early postoperative period and some of them can have a voice that is not as strong and often times our voice center at UPMC helps us to strengthen their voice and get them back as they would to their normal activities. As with radiation therapy, a partial laryngeal surgery at the anterior commissure leads to an increased rate of recurrence, and so we need to be aware of the sites of recurrence and potentially at the anterior commissure the risk of web formation, but again these can be improved with modern voice techniques as in Pittsburgh that we’re able to employ.

So in summary I think as opposed to the 1990s now in 2010 and ’11 we have a number of new options that we can utilize in combination. These were all available individually but I think now are being in the mainstream of treatment of intermediate stage laryngeal cancer and potentially robotic surgery may come along in the next several years for super-glottic cancers. I think in the nonsurgical phase this is similar to how induction chemotherapy has come and gone and we are trying to understand what the role of these nonsurgical approaches is but in the meantime we realize we do not need to perform a total laryngectomy on many patients and can offer in a multidisciplinary setting a, a organ preservation surgery. And I think that I’d like to point out that collaboration with the radiotherapists, medical oncologists and head and neck surgeons in the tumor board is something characteristic of the way we approach it at the University of Pittsburgh, and we have to find a way to assess not in these individual single site experiences such as I’ve shown you but more prospectively with our colleagues in the working groups so that we can focus not just on the survival but on the function of the larynx when we approach these intermediate stage cancers.
So decision making generally relates to the patient and the tumor status. Is the patient of sufficient activity level and robust in terms of their age and the tumor is one that could be potentially amenable to a surgical approach which avoids a total laryngectomy. And this is often the case. As I mentioned for glottic cancers, there are a couple of options, the super-cricoid or a vertical partial laryngectomy, or the laser which is a transoral approach and is desirable in large measure over an open procedure. And I think as many individuals are trying to assess the neck with less than these open neck dissections, we may find now at the time that the super-glottic cancer is removed that a sentinel lymph node biopsy intraoperatively may allow us to stage the neck immediately and avoid this open neck incision which would be even more preferable for our patients.

And so the goal here is the equipoise of each member of the tumor conference to look at the patient and try to determine what is the optimal oncologic outcome as well as the functional outcome. And now what we do is to try to discuss within our team each patient and those features to make the best decision and offer that to the patient, and obviously incorporate them in the decision making also.

I want to acknowledge that the way that this is successful at UPMC is through a large number of individuals in the multidisciplinary tumor conference, it’s not just the treating physicians, the oncologic physicians, it’s also our colleagues that assist in assessment of function, assessment of tumor staging and radiographic and pathologic approaches. Thank you.