Hi. My name is Dr. Lois Ramondetta and I am a professor at The University of Texas MD Anderson Cancer Center. This is Part II of Management of Local Regional Advanced and Recurrent Cervix Cancer.

In this presentation we will be discussing appropriate application of surgery and radiation in patients with recurrent cervix cancer. We will become acquainted with chemotherapy and targeted agent treatments and response rates in women with recurrent or advanced cervix cancer. And we will also discuss the concept of basic supportive care in the treatment of women with recurrent and advanced cervix cancer.

One of the difficulties in cervix cancer treatment is what to do in the setting of recurrence? In Part I, I discussed patients who recurred without having gotten prior radiation therapy. And in those cases chemoradiation therapy for recurrence is appropriate. However, when you have a patient who has recurrence in the pelvis in a previously radiated field this is a much more difficult circumstance.

In very specific small number of cases with a very small central recurrence you could consider doing a radical hysterectomy. Unfortunately, these patients are --- are only rarely caught with a very small lesion and in a radiated field doing surgery especially radial surgery, complications are common. There have been a number of studies that looked at whether or not we could do a radical hysterectomy in a radiated field. Dr. Coleman in 1994, Dr. Rutledge in 1994, and Maneo in 1999. And these original stage tumors were IB to IIIBs but the complication rates were as high as 75% and their survival, five year survival, was limited to 24% in those with more advanced initial disease.

The more common thing to do with somebody who has an isolated central recurrence is to consider total pelvic exenteration. And although these can be done partially, meaning just the bladder and the vagina and the uterus; or just the colon, and the vagina, and the uterus. Most commonly they’re done as a total pelvic exenteration where both the bladder, the vagina, and the rectum are all removed together and the patient has two permanent ostomies. In order to find the appropriate patients they must be scanned and examined to be --- to determine that there is only disease in the central location. These are the only patients who have an option for cure.

In a case series looking at 1957 through 2010 that was recently published actually in two case series that were published both in 2012 and 2013 we looked at factors that were associated with a negative overall survival in pelvic exenteration patients. One of the main reasons to do this is this is such a complicated surgery with such co --- high levels of complications and effect on the patient’s quality of life that we only want to do it if we’re going to have a significant improvement in overall survival and hopefully cure. So how can we identify those patients who are not going to benefit from this life changing surgery? What we’ve found in both our study at MD Anderson and additional studies is that patients who had positive margins on their pelvic exenteration specimen, lymphovascular space invasion on their specimen, positive pelvic lymph nodes that were undetected at the time of presurgical radiologic workup, and perineural invasion all
played a role. In a multivariate analysis positive pelvic lymph nodes, lymphovascular space in invasion all retained a significant impact on overall survival. The combined data revealed that there were 4.5% intraoperative deaths but 35% only 35% were alive at five years. So we need to get better at maybe our radiologic techniques or our intraoperative techniques need to get better at determining who is going to actually benefit from this life changing procedure.

As I said one of this is extremely life changing. Patients have two ostomies in most cases and we have some wonderful support services available at MD Anderson for these patients but I on on this screen are two sites where you can see videos of patients whose ac physicians who performed the procedure in order to do some preoperative counseling for your patients.

So what do you do for those patients who may not be the best candidate for a pelvic exenteration? Perhaps you’re going to remove the specimen the exenterated specimen but you’re concerned that you may have a close margin. Is there a role for intraoperative radiation therapy or IORT? It’s done typically as single fraction in the operation room specialized operation rooms with the radiation therapist working in conjunction with the surgeon and typically electron therapy. A frozen section is used to determine the margins and usually 10-12 Gy are given at to R0 and 15 Gy for R1; meaning you can either have no visible disease or possibly a rind that may be a visible tumor. There is no benefit in gross residual disease. These patients have already been radiated maximally externally and unfortunately you raise your complication rate not just a complication from the pelvic exenteration but by adding intraop radiation you increase the risk of nerve injury, ureteral stricture, and GI toxicity.

So for those patients who are not eligible for an exenterative surgery or intraop radiation with an exenterative surgery, what options do we have? And really cisplatin given at 50 mg per m² per day 1 q 3 weeks had been the standard for a number of years. What we saw is that higher doses of cisplatin led to similar survivals although there was no direct comparison between cisplatin and carboplatin. Combination regimens seem to be more toxic than single agents but did not adversely affect quality of life. And then there was improved response rates to those who had recurrences outside the pelvic field perhaps in their lung or periaortic lymph nodes as compared to those who had disease only within their pelvis.

What the main point of everything I’ll talk to you about over the next few minutes are are that the response rates within the pelvic field the radiation field are extremely low. Cisplatin-based combinations do have significant toxicities. Outcomes are poor and we really need to do research and enroll patients in clinical trials in order to find new cytotoxic and biologic agents in order to better improve this overall survival.

So NCCN recommends for first line chemotherapy as you can see the new standard and I’ll get into the details of these. Cisplatin, paclitaxel, and bevacizumab is the new
standard. Bevacizumab now being FDA approved for the use of recurrent and advanced cervix cancer. Another option are cisplatin and paclitaxel and we'll talk about why you might leave the bevacizumab out. Another option is topotecan, paclitaxel, and bevacizumab; carboplatin and paclitaxel; cisplatin and topotecan; topotecan and paclitaxel; and cisplatin and gemcitabine. You could also consider single agent first-line therapy; however, the response rates are much lower.

This is a --- a --- a queue in the GOG, the Gynecologic Oncology Group, which is our group of gynecologic oncologists, radiation oncologists, and medical oncologists that get together twice a year to discuss the best applications of new agents and --- and the design of clinical trials. And in this particular queue in the GOG, patients are enrolled where they've had recurrent disease but they have not had any prior therapy. This has been done for years. And what you'll see is that the response rates --- really the best response rate was with cisplatin and paclitaxel and the others fall far behind ranging from 12-30%.

When you have a winner let's say in these trials, a cisplatin [and] paclitaxel; or cisplatin and vinorelbine; a cisplatin and irinotecan—a --- a phase 3 trial is designed in order to compare the standard which might be cisplatin single agent to cisplatin and paclitaxel.

And that's where these really key phase 3 trials for cervix cancer are --- are --- come into play. So GOG early trials with cisplatin versus cisplatin plus multiple agents that were compared both in GOG 110, 149, 169 and 179 and the really --- the --- the key trials that bring us to where we are today is cisplatin versus cisplatin and paclitaxel in GOG 169 and cisplatin versus cisplatin and topotecan in GOG 179. What you can see is that there appears to be an improvement at least between cisplatin and cisplatin and paclitaxel from 8.8 to 9.7 months for overall survival. This was not significant, of note, and cisplatin versus cisplatin plus topotecan. And in this particular phase 3 trial there did appear to be an overall survival benefit of about three months. And so what was determined from this is that we really need to decide what is going to be our standard arm? What is going to be the standard of care, the two drugs that we're going to use from this point moving forward as we learn about new molecularly targeted agents that we can add to our standard arm?

And that's where the GOG 204 study came from. This was a four arm randomized phase 3 trial and what you s --- what we did was we took patients who had stage IVB from the start so already had distant disease or recurrent disease after primary chemoradiation therapy and looked at whether or not they did better with paclitaxel and cisplatin; vinorelbine and cisplatin; gemcitabine and cisplatin; and topotecan and cisplatin. This was actually a very difficult trial to accrue to. I accrued many patients to this trial and it was difficult to explain to patients that there was a one in four chance that they would potentially lose their hair because it was only in one arm that they were going to lose their hair. But we accrued well and we di ---
what we found is that paclitaxel and cisplatin still won out at 29%. It was a non-inferiority trial and what we found was all three other arms were not superior to paclitaxel and cisplatin in overall survival. And there was a trend in response rate, progression-free survival, and overall survival that favored paclitaxel and cisplatin although it wasn’t designed to actually show superiority. So it was a really non-inferiority. There was comparable toxicity except for obviously hair loss but also leucopenia, neutropenia, and infection.

And here is a Kaplan-Meyer curve showing survival in the vertical axis and time on study in months on the horizontal axis and showing that the cisplatin and paclitaxel seemed to come above and beyond the other dual-agent arms. So with this trial cisplatin and paclitaxel became our standard arm as we move forward for additional treatments. But remember that cisplatin has multiple toxicities that can make it very hard on patients including nausea and vomiting, increasing neuropathy especially in patients who have already received cisplatin. And so there was a question –

whether or not we could use something maybe a little bit less toxic, less effect on quality of life like carboplatin. And luckily the --- the Japanese Oncology Group, the JCOG, did a trial 0505 a multicenter trial that showed a comparison of paclitaxel and cisplatin versus paclitaxel and carboplatin and essentially they showed that it was relatively comparable.

So here we have Taxol and cisplatin versus Taxol plus fa --- carboplatin and essentially no difference in overall survival and so many of us have converted to using carboplatin instead of Taxol in our recurrent patients.

What we really needed to know is: in those patients who had response rates as --- of --- of in the mid 20% range who were the really poor responders? Who were the people who really aren’t going to do well who may really benefit from something else?

And there was a study published in 2010 by Moore et al., and what we --- what he showed is when he went back to the 204 data he showed that there seemed to be a decreased response rate in certain African American patients who had a low performance status, who had disease in the pelvis rather than disease outside the radiated field, who had prior sensitizing radiation, and who had recurrences that occurred in less than a year versus those who had a longer progression-free survival.

And he grouped those patients into what we call the high-risk group, the mid-risk group, and the low-risk group and really showed that patients who had 4 or 5 of these risk factors present had an overall response rate of only 14% and a progression-free survival of only 3 months, and an overall survival of 5 months compared to those who had only one factor present, where their response was as high as 43%, the progression-free survival was 7 months and the overall survival was almost a year. And so could we really identify these patients and either not provide any additional therapy by really being very clear with them that their chance of benefiting from possibly a f --- a --- a
toxic chemotherapy regimen that can affect their quality of life would not be a benefit to them.

So where are we now?

GOG phase III was really --- I'm sorry --- phase II study in the GOG really showed some interesting data using bevacizumab. And what it showed, looking at just a few patients who had had one to two priors, so these are patients who've already recurred once or twice after their chemoradiation treatment that giving bevacizumab as a single agent for 15 mg per kilogram q 3 weeks showed that there was a 20 --- almost 24% progression-free survival of 6 months with 10% partial response rate. And this was really unusual for us in this population where we hadn't seen extended overall survival at all and so to see a progression-free survival of 6 months really made everybody's ears perk up and pay attention to this new drug.

And --- And this made sense because even those of who are doing only colposcopy know that when we're looking at a cervix some of the first signs we see of a --- of an early cervix cancer are angiogenic changes and n --- neovascular growth. So you can see right here this is a colposcopy and you can even see the new blood vessels, the atypical blood vessels growing. And you can see the --- the intratumoral microvessel density increasing and we're starting to think that maybe bevacizumab makes sense. It --- It actually affects the new blood vessel growth that's feeding some of these cancers.

And thus came GOG 240 which was the 204 replacement. So we had found that the cisplatin and paclitaxel was our new standard arm at least --- or carboplatin in some cases but in this case to be standard we used cisplatin. That if use paclitaxel and cisplatin could we show that adding bevacizumab to this combination would improve survival? But remember there were those patients in the Moore criteria who did worse if they had had prior treatment with chemoradiation and --- and what we thought is maybe those patients who had gotten cisplatin before would not benefit as much from getting additional cisplatin here and thus came this arm 3 and 4 where cisplatin was dropped from the recurrence arm. Paclitaxel and topotecan were given here and paclitaxel, topotecan, and bevacizumab in this section.

This was actually a great study that accrued relatively quickly. And in February of 2012 the interim data was analyzed and it showed that that non-platinum doublet, that Taxol and topotecanarm --- paclitaxel and topotecan arm did not do as well as those who were getting the cisplatin and ta --- paclitaxel arm even in the case of those who’ve gotten prior cisplatin. And so letters were sent to physicians and to patients saying if you're responding continue on the paclitaxel and to --- topotecan but it --- from --- from this point on that arm was going to be dropped from the GOG 240. And we would be left with the --- the paclitaxel plus cisplatin plus or minus bevacizumab.

When the study completed accrual we saw some very interesting data. Patients treated with chemotherapy alone had a median survival of 13.3 months while those who received chemotherapy plus bevacizumab had an improved overall survival of 17
months. The survival difference was statistically significant; however, the patients with bevacizumab experienced more side effects and time was going to be needed to really determine was the extended overall survival worth the side effects that you might see with bevacizumab?

Here is a Kaplan-Meyer survival curve again with the vertical axis showing portion --- proportion surviving and the horizontal axis showing months on study; and showing a significant improvement for those patients who received bevacizumab in the blue versus those who only received the --- the chemotherapy.

This is progression-free survival showing something similarly that you had an 8.2 month progression-free survival for the people who received chemotherapy plus bevacizumab in the blue and then in the red the cisplatin --- I’m sorry --- the chemotherapy alone without bevacizumab in the red.

So the side effects, what were they? And you can see in this first column chemotherapy alone and in the second column chemotherapy plus bevacizumab and this is all --- all patients including those who had the s --- the arm without cisplatin that you saw an increased GI fistula rate, an increased GU fistula rate, increase in hypertension often requiring medication, increase in neutropenia, and an increase in thromboembolism. And so I had mentioned before when we looked at the NCCN guidelines that in some cases not giving bevacizumab in that first recurrent setting is appropriate. And for instance those patients who have tumor that’s verging on invasion into the colon or the bladder are those patients who you really need to be very clear with them that --- that bevaciz --- that the addition of bevacizumab in the recurrent setting has a high rate of fistula. They may get a fistula anyway with the cisplatin as --- if the tumor responds; however, the rate is definitely increased by adding bevacizumab and, thus, it becomes a discussion between the physician and the patient as to whether or not adding bevacizumab is appropriate.

Further, the question was whether or not the functional assessment of --- of cancer surveys revealed that there was a worse ov --- quality of life? And this is the --- the functional assessment of --- of cancer index TOI which is looking at the physical and the functional aspect of the FACT plus the cervical cancer specific subscale. And --- and the reason it does that is it really pulls out the emotional and supportive care aspect of FACT which seems to re --- remain relatively consistent and it --- and looking just as functional and physical assessment and cervix specific assessment of quality of life. What we saw is that patient receive a --- receiving bezciz --- bevacizumab reported 1-2 -- 1.2 points lower on average on their FACT cervix TOI but not statistically significant, only 0.3 P value.

So in conclusion on GOG 240 bevacizumab treatment is associated with a higher level of adverse events, 3-8% rate of known bevacizumab-associated adverse events but the overall survival did not --- was not associated with an assessment of quality of life scale reduction and that the first tar --- this was the first targeted agent in --- in a decade or more to show improved overall survival.
So where do we go from here? Well bevacizumab is very expensive and the question is are we giving the right dose? Could we give less? Could we give it at a different frequency? So cost-effective studies need to be done. Other classes of anti-angiogenic agents may be appropriate at this point inclusi --- including drugs like pazopanib which is an oral anti-angiogenic agent or sorafenib. As well there are many other options like non-VEGF-dependent targets like vascular dependent --- disrupting agents, Wee-1 checkpoint inhibitors, notch gamma secretase inhibitors, and combined angiogenesis and E7-based immunotherapy. And this last point is the --- is one of the main targets of --- of our efforts to eradicate cervix cancer at MD Anderson.

So what are the choices for second-line recurrences?

Well the first thing to really know at this point is that of all the GOG trials that have been done for second and third-line recurrences the response rates --- I’m sorry --- the overall survival rates are typically less than thr --- than 10 months, proportion of progression-free survival and the to --- the months on study. And you can see that most patients are deceased within a year. And that’s something to make very clear with the patient’s that as you embark on new treatments it’s important that you do no harm and that if there’s a --- a definite benefit for the patient, great performance status, low level of toxicity then it is reasonable to consider trying targeted agents but trial --- trying agents off-study are a little bit more difficult and definitely require honest conversations with patients.

So in GOG 127 this is that queue where they’ve had prior cytotoxic agents so these are patients who got their chemoradiation, got their GOG 240 winner, and then recurred after this. And in all these patients you can see that the response rate is really disappointedly low ranging from 0% response rate to 14% response rate. And remember these are very short-lived responses, sometimes as little as three to four months.

Here’s another example of GOG 127 chemotherapy queue gemcitabine and cisplatin, a double-agent, which is a really toxic combination in patients who’ve received a lot of prior chemotherapy so a lot of fatigue and side effects, potentially worsening neuropathy. Fortunately, sometimes you can --- you can substitute the carboplatin for the cisplatin but for many of these patients this will be their third exposure to a platinum-based agent, pemetrexed, 15% response rate published recently and abraxane to those patients who hadn’t received prior taxine recently published with a 29% response rate. Again, the response rates may look more significant but the side effects are --- are greater and the response rates are short-lived.

This was a study that was published recently looking at a new formulation of paclitaxel lasting a little bit longer, kind of a slow release form, with a phase I --- II group looking at recurrent more than one prior recurrence --- failed first one --- first-line cytotoxic drug treatment. And it was given 125 mg/m² IV over 30 minutes on day 1, day 8, and 15, every 28 days so one week off. And then progression-free survival was 5 months. Overall survival pretty impressive at 9 months compared to what I’d shown you before in
those older GOG trials where most patients that were deceased within a year. 28% of these patients had a partial response and 42% had stable disease.

In the 227 queue these patients are looking at --- these trials are looking at non-cytotoxic agents so new molecularly targeted agents following patients who’ve recurred at least twice before. These are tough trials because they are usually treating patients who recurred in a radiated field, chance of response rate is really low, and one of the fears is that by use --- by --- by enrolling patients in these trials that the chance of --- of recognizing an active drug is low because the --- the cancer is within a radiated field and it’s already growing through two prior treatment regimens and the chance of hurting the patient with side effects is high. And so you really have to have a good discussion with the patients as you enroll them on these trials. But how was success defined at this point? We looked for greater than two patients alive in a progression-free interval within a range of 19-25 enrolled patients or greater than three out of the 26 patients. And thus far bevacizumab is the old --- only agent that has demonstrated interesting activity out of this queue.

So here is more information from that queue, that non-cytotoxic second-line recurrences. Bevacizumab was at 24% that we went over before but other drugs that have been tried are erlotinib with 0% response rate, cetuximab, 0% response rate. This is an interesting study using a --- a virus and a immune --- immunotargeting and it looks like it’s interesting enough to have gone on to its second phase. And brivanib was only open for --- it’s an oral anti-angiogenic agent and it was only open for half of its Phase II trial. We don’t have those results yet but we suspect that the response rate was --- was very low.

So what does the NCCN recommend for first-line chemotherapy agents? We talked about before cisplatin, paclitaxel, and bevacizumab versus dropping the bevacizumab. Other single agents: cisplatin alone, carboplatin alone, paclitaxel. And for second-line combination therapy, let’s say you have a patient who got paclitaxel and cisplatin as a first-line recurrence, you could consider doing bevacizumab com --- in combination with the --- one of the other second-line agents, dox --- docetaxel alone, 5-FU, gemcitabine, or a number of other agents again requiring a very good discussion that none of these have led to cure and that quality of life is most important.

There are many explorations ongoing now looking at VEGF pathways other than anti-VEGF antibodies like bevacizumab. Here you see kind of an anti-VEGF antibody bevacizumab but you also have the soluble VEGF receptors which is called the VEGF TRAP. You have anti-VEGFR antibodies.

But there are also multiple other pathways within. So here you see, I mentioned pazopanib here, which addresses multiple VEGFRs 1, 2 and 3, cediranib, as well as the way down here to mTOR inhibitors and other drugs that will affect angiogenesis, vasculogenesis, and hyperpermeability of the vessels. And so a lot of these trials are ongoing now. None of them have taken a lead over bevacizumab but we hope over the next few years that we’ll see advances. And --- and so I really encourage physicians to
consider enrolling their patients with a current cervix cancer on clinical trials rather than giving them some of those drugs that had the very low response rates in --- with survival rates less than a year. It’s really important that we make progress in this area so if you have opportunities to enroll the patient in a trial and refer them to a center where they can go on a trial as long as it doesn’t take them away from their --- their family for too long it’s --- it’s useful to do.

This is an example of one of those mTOR inhibitors I showed you in that last pathway. Temsirolimus is an mTOR inhibitor, 25 mg IV weekly and a 4 week cycle. And 37 patients were evaluable for toxicity, 58% had stable disease. The 6 month progression-free interval was 28%, the progression-free survival was almost 4 months, and there was mild-to-moderate toxicity.

And then is the brivanib study that I mentioned before that it opened as a phase II in the GOG. It’s an oral tyrosine kinase inhibitor working at two anti-angiogenesis points. The primary outcome is objective response and whether the patient had --- what percentage of patients had a progression-free survival for at least six months? And it really didn’t move on to its second phase as we await those results in the near future to find out what the response rate was but suspect this --- this isn’t a drug that will be moving into further trials.

Phase II erlotinib is an epidermal growth factor TKI. Erlotinib was given at 150 mg PO daily until progressive disease or adverse effects. 28 were enrolled, 25 were evaluable, and there were no objective responses.

This is pazopanib which was compared to lapatinib oral antigenic agents --- agents. And you can see that pazopanib kind of won out as a --- a medium progression-free survival of 18 weeks and I --- and I note that we are now looking at response rates and progression-free survival in weeks and it --- and --- rather than months and then lapatinib 17 weeks and --- and this was a significant improvement. So pazopanib actually has moved on to additional trials. There is one that’s about to open at MD Anderson now and we --- we hope that the idea of being able to give an anti-angiogenic inhibitor --- [I'm sorry] --- an anti-angiogenic agent orally will be a benefit to the patients.

Other exciting news in the future is where therapeutic vaccination for human papilloma disease --- papillomavirus disease can be applied. Remember that the three FDA approved HPV vaccines are only used for prevention and so none of them can be helpful to give to patients after they’ve already been exposed to the HPV virus. And so these are very different types of trials looking at what we can do to try to affect patients who have already developed an HPV-related cancer. And interestingly we are looking at can we do, what we’re calling basket trials, where we look at multiple different cancers caused by HPV. For instance, oropharyngeal, penile, anile --- a --- anal, and --- and potentially vaginal or vulvar cancer in addition to cervix and group these patients together to look at vaccine trials. What can we do? Can we develop a more reactive adjuvant meaning something that stimulates the immune system to be more aware of --- of HPV-related changes? Can we look at trial designs? Choice of patient cohorts in
which to determine immunogenicity in effect? Can we look at immune monitor --- monitoring to determine lesional prognostic endpoints meaning biopsying the tumor before and afterwards to see if we’re making differences in the microenvironment of --- of the tumor. So be on the lookout. This is a wonderful review article in Lancet 2009 that reviews some of the --- the options for therapeutic vaccination for HPV-related disease.

So again peptide-based vaccines: can we target the E6 and E7 protein that really comes after the HPV virus has integrated itself into the --- the host’s DNA? Can we use different types of live or recombinant virus vectors like the listeria virus that I mentioned before in the GOG 265 that has moved onto its second arm of the trial? We expect good things from --- from this --- from this result to really see if we can make a difference and --- and improve progression-free survival for those patients. Adenoviruses have been used. Vaccina which is a large enveloped virus belonging to the pox var --- poxvirus family are also being explored. Other vaccine-like trials, some being done at the NCI and hopefully soon here are dendritic cell-based vaccines and whole tumor cell vaccines.

What does the NCCN recommend for these patients who have multiple sites of recurrence or unresectable, not eligible for the curative potential of an exenterative surgery? They recommend chemotherapy or best supportive care and really what I want to make an emphasis on now is that best supportive care should really be a part of all of these patients’ trials as we move forward with recurrent disease.

The ASCO has mentioned some quality improvement indicators that I think are --- are really ones that we should all strive to achieve with our patients with any metastatic recurrent cancer as ASCO guidelines recommended that all patients who have recurrent disease and high cancer burden should be referred to a palliative care physician. Or if you feel able to address even these minimal quality improvement techniques I --- I --- I think it’s absolutely necessary and possibly important to be enrolled --- incorporated into clinical trials. Some of these are simple. Have we assessed for pain when we initially see the patient? Has the pain been quantified? It is moderate-to-severe pain and --- and was action taken? If she was prescribed a narcotic was she counseled about constipation? Was there an emotional well-being status? Did you do a --- a sense of despair for the patient or distress and was each one of those points addressed or did you refer to someone who could’ve addressed them? For instance, a social worker, a case manager or even a chaplain or --- or therapist. So these are actually on the ASCO website and I highly recommend incorporating these few questions into visits with --- with patients.

Other things that we’ll be looking at in the future is whether or not we should be looking to see whether the treatment that had not improved overall survival in these patients improves --- improves overall survival over just adding best supportive care. Or should we always include best supportive care and def --- and --- and obviously define best supportive care for these trials? Could we do something where we look at a second-line agent plus best supportive care versus placebo plus best supportive care? Because as
as I’ve shown before in the second-line setting there has been no improvement in overall survival and has never been compared to best supportive care which in some studies, specifically the study in lung cancer patients by Jennifer Temmel showed that there was an improvement in overall survival for those patients who were sent early to best supportive care providers. We need to determine what this means. What is best supportive care? What is the minimum best supportive care that we provide for these patients and have we documented those points that I made previously?

Can we look at better endpoints? We’ve been designing all our endpoints to look at overall survival, progression-free survival, response rate. But if we’re not going to get to overall survival and we’re only looking at whether or not we shrink the tumor a small amount, does that matter if the patient’s pain didn’t improve? Does it matter if her symptoms didn’t improve? Could we be thinking a little bit bigger as we design these trials? And the GCIG, the international group of people who enroll in gynecologic cancer trials are getting together actually soon to discuss how to incorporate best supportive care into our trials as we move forward.

So, in summary, recurrent cervical cancer in a radiated field is only curable if there are no distant mets or it’s an isolated central metastasis. One other circumstance where there might be a curative technique is an isolated lung metastasis that could be removed when there is no disease anywhere else. Exenterative surgery has a 5 year overall survival as low as 30-40%. And how can we identify these patients better so that the other 60% don’t undergo this life changing surgery? Platinum-based chemotherapy is the standard with response rates in the 22-36% response rate. Bevacizumab significantly improved overall survival when given in combination with cisplatin and paclitaxel and is now considered standard of care for appropriate patients. And focused effort should be made for us to 1) enroll in clinical trials and to understand treatment risk versus benefit through well-designed clinical trials if cure is not an achievable outcome.

I would like to thank you for listening and refer you to our professional education website and encourage your feedback about this lecture or any others that you’ve listened to. Thank you.