



Question and Answer Session after Adjuvant Therapy for Head/Neck Cancer: Focus on Chemotherapy, by Dr. Ezra Cohen

Dr. Weiss: Dr. Cohen thank you for that. That was a truly impressive and comprehensive plain English summary of a pretty complex field -- so thank you for that.

I'll take the privilege to ask the first question, if I may.

You showed the Bernier combined analysis, addressing the question of who should have chemotherapy added to their adjuvant radiation therapy, and you showed that it was clear that for the patients with extra capsular extension or positive margins that patient benefit. There were a number of other risk factors that were looked at by the respective groups, and I know that some consider for multiple high risk factors in a very functional patient that they talk about doing adjuvant chemo/rads in that setting. In your practice, where do you draw the line here? Do you talk about adjuvant chemo/rads for patients with other factors that make you think they're at higher risk for recurrence? And when you do decide to proceed, what do you use?

Dr. Cohen: Yeah. You bring up a lot of good points. First of all, I think you have to consider the patient and what they're able to tolerate. So you mentioned in a patient that has good performance status or is able to tolerate it and it really, although that is a gestalt in sense and we get a feel of it, but it's really an important thing to keep in mind. So let's talk about that patient that you feel can tolerate the addition of chemotherapy. At our center and I think many people share this opinion, we're actually fairly liberal about the addition of chemotherapy and our reasoning is twofold. First of all this is a curative setting and this is why it comes back it's important to remember that survey that I showed you in terms of what patients desires are; that this is a curative setting and our best chance to cure this disease is going to be our first chance.

And then the other thing to keep in mind is that yes, chemotherapy does add toxicity but that toxicity for the most part manageable, it's going to be acute toxicity that is going to get better and what you want at the end of the day is to try to cure as many patients as possible. So with those two things in mind and keeping in mind that the EORTC, the European trial enrolled patients with peri-neural invasion, with lympho-vascular invasion and was on the face of it a positive study. We've decided that we should be fairly liberal in who we include to get the addition of chemotherapy and so patients even with a single risk factor, even with peri neural invasion or lympho-vascular invasion, at our center and certainly patients with 2 or more lymph nodes at our center will almost always have chemotherapy added to the radiation.

And we use the EORTC trial to support that opinion. Now there are many people that are more conservative than that and this is controversial I don't think there's any right or wrong. And we'll say well only patients with positive margins and only patients with extra capsular invasion should get chemotherapy so there is a

bit of variation in terms of how these patients are treated. But again we tend to be a little bit more liberal with the addition of chemotherapy in this patient subset.

Dr. West: As somebody who is not in an academic center with a very dedicated head and neck cancer program. is this kind of approach one that is feasible broadly in a multi-center setting without the kind of support that you have at these specialized programs, or is this really or is the level of attention and aggressiveness such that this kind of work is more feasible pursued at the more narrow centers that really specialize in this work and have a dedicated multidisciplinary team for it?

Dr. Cohen: I think it depends on what facilities and resources you have at your center. I think for the most part, this type of treatment, the addition of, be it cisplatin or there are some variations there as well, but let's take cisplatin, because that's the one that's at least validated by clinical trials; the addition of cisplatin is actually very feasible in a non specialized or non dedicated center.

The surgery is probably the bigger issue. That is, the surgery that some of these patients require can be quite complex. They can sometimes involve reconstruction that is not available at many centers; so the surgery is one issue. And that -- I would advocate that most patients be treated at a specialized center. In terms of the radiation and the addition of chemotherapy, I would say that this is feasible at most centers, and that most centers, even if they don't have a dedicated head and neck team, most centers would be able to do this. So I think it's something most people could carry out.

Dr. West: Also, I was impressed when you highlighted that there are perhaps subsets of patients who are more likely to be the beneficiaries of the integration of systemic therapy, chemotherapy in the post operative setting; and it was not the patients with many lymph nodes. Can you speak to whether you would perceive that the chemotherapy is adding more in distant control or local management, because you might think that chemotherapy or any other systemic therapy could provide a radiosensitizing benefit for local control, but also could help to eradicate micrometastatic disease that would translate to distant disease. Are we seeing that it is more effective in one setting than another?

Dr. Cohen: Yeah, it's an interesting question. It's one that we still are trying to answer, to be quite honest, but what we did not see in these studies is a difference in distant failure. In other words, what the data is telling us is that the addition of cisplatin helped control local disease -- in the RTOG trial that was, in fact, the primary end point -- but didn't have a great effect or appreciable effect on distant failure. And you're quite right, that despite the fact that there were a significant number of patients that were enrolled with two or more lymph nodes -- so the implication there is that those patients are at higher risk for distant failure -- the addition of cisplatin did not seem to affect at least that end point.

Now, that could be for a number of reasons. First, distant failure was not the primary end point of the study, and there may have been centers that were looking more intensively or less intensively at this end point than others. Second, the chemotherapy -- that is, single agent cisplatin -- may not have been effective enough to eradicate distant disease. Third, in the post-operative setting, one could hypothesize that you've already lost the battle against distant disease in the

time that it took to perform and recover from surgery --although I think that that's less likely. And then fourth, related to the second point, we may need in this setting to really combat distant failure similar to what others have advocated in non surgical patients is a block of chemotherapy delivered without radiation; so multiple chemotherapy agents given at full doses for a short period of time, in an effort to eradicate distant disease.

Interestingly, both the groups from MD Anderson and University of Chicago have recently published on this. This idea of surgery followed by a block of chemotherapy without radiation and then followed by chemotherapy/radiation, and although these were not randomized studies, the rates of distant failure appear to be quite promising, suggesting that there may be merit to this approach. But right now, to answer your question Jack, right now the addition of chemotherapy is really designed to improve local control.

And let's keep in mind that head and neck cancer, and what I didn't say in the talk, it is really a local disease, it's loco-regional disease, so that really becomes paramount. If we don't control local/regional disease, the sobering fact is that we don't have to worry about distant failure, because patients will die of loco-regional progression. So the idea, or the emphasis on local regional control is an important one -- it's one done with an important purpose, and that is because loco-regional control is so significant in this disease.

Dr. Weiss: I'd like to ask you a follow up question to my first on if I may. I work at a center that is very surgically oriented, so we ask the question of the addition of chemotherapy to adjuvant radiation perhaps a little more often than other major centers and so I'm very interested to hear, in these patients without those two strict criteria who have other indications to consider adding chemotherapy to the radiation, are you always using high dose cisplatin or are you tempted to scale back to something a little less toxic but perhaps a little less proven when you add chemotherapy for those patients.

Dr. Cohen: Yeah, it's a fair question, and you might think that, "Well, if they have a less high risk factor, so a risk factor that doesn't put them in the highest risk, but a moderate risk, could one then use moderately aggressive therapy versus a highly aggressive therapy?", and in truth we don't know. The studies haven't been done to address that. I can tell you, in our practice, we are not doing that. When we make a decision to add chemotherapy based on, let's say, less well recognized risk factors we add the same chemotherapy with the thought that if we're doing it, we should do it with regimens that are recognized in this setting.

There may be other and there are other approaches that are emerging, we talked about the EGFR inhibitors and in fact an EGFR inhibitor with radiation may be an approach to undertake in certain patients that may not be as high risk, and certainly again coming back to the patient factors that one has to consider, in that not all patients can tolerate cytotoxic chemotherapy, but I think your question was related to the patient who could tolerate it.

Dr. Weiss: Well, thank you for that.