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Q&A with Jay Cooper about 90-03

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This interview was conducted with Sue S. Yom, on 12/23/2013.

SY: Could you describe how the original idea for the study came about?

JC: The study was conceived in an era in which we had figured out how to make the transition from cobalt machines to linear accelerators. We had figured out how to make the transition from hand calculations to computer calculations. We had begun to understand how 3D images, CAT scanners and early MRI scanners could let us see beyond what we were doing in the 2D era. And we began to think about biology in a way that allowed us to apply it to patients, in an era in which people were routinely prescribing different fractionation. We began to feel that we had the physics and technology to test if it really mattered. Remember, linear-quadratic is a theory. People had been mulling over these ideas for nearly 100 years and it just was the right time to put them to a test.

SY: What was the thinking about altered fractionation? Were people pretty sure that it was going to make a difference? Or were there doubts?

JC: I think that there were some people who were more convinced that fractionation mattered, and others who weren't quite as convinced. You certainly had enough data from giants of Radiation Oncology like Rod Million in Florida and C.C. Wang in Boston who wrote eloquently about their results applying hyperfractionated protocols.

SY: Could you talk a little bit about the split-course regimen, because a lot of us coming up now find it difficult to understand, given what we now know about repopulation.

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JC: Another one of the giants of radiation, in the early days of landmark RTOG trials and still very active in Puerto Rico, was Victor Marcial. He was looking for a way to make treatments equally effective, perhaps more effective, with less stress for the patient. Split-course accelerates the time that the patient actually is getting each active phase of treatment and we didn't know if it was deleterious to have a break in between. There was a hope that this was a different way – perhaps a more efficient way – of giving treatment to tumors and allowing normal tissues to heal in the interval.

SY: You've named some pretty prominent figures. How much did the personalities and early pioneers of that era influence the design of the trial?

JC: In the 50's and 60's, patients were largely treated the way that one of the earlier giants said to treat someone. The truth of their pronouncements had as much to do with their personalities or their willingness to analyze their personal results or the fact that they published, than a true randomized trial design. In those days, that was actually was the best we had.

SY: When do you think the concept of randomized trials really did enter radiation oncology? Was it simultaneous with the entry into other specialties or was it later?

JC: I think we were in the forefront. If you go back and look at the first few trials coming out of RTOG, when Simon Kramer was the chair, they did not have all of the sophistication of current trials, but we were looking at advancing science by conducting randomized clinical trials nonetheless. Certainly they began to establish the idea that you would find patients who were brave enough to allow themselves randomly to have their care allocated to different forms of treatment so that at the end any biases would wash out.

SY: So how do those results and conclusions shape your thinking about the use of hyperfractionation? And what about its potentially increased costs?

JC: I think an important part of the hyperfractionated regimen is not so much the acceleration, but rather the use of the small fraction which was designed to be more gentle on normal tissues. As for cost, the cost per fraction is an artifice; it's how we just happen to be practicing in the current era. If hyperfractionation proved to be that much better than everything else, I think cost consideration would become much more secondary.

SY: How do you see the balance between bringing chemotherapy and accelerated regimens together into the clinic?

JC: What makes the 90-03 trial so important for oncologists, not just radiation oncologists, is that it's probably the last major trial we are ever going to do that so clearly tests for different fractionation regimens. In the current era, as you suggest, the effect of things that biologically moderate radiation reactions in normal tissues and tumors, like chemotherapy, or equally the things that moderate it on a physical basis, such as better imaging, better treatment delivery, IMRT and IGRT, make it very hard to know how much the lessons from 90-03 will carry into the future. We've learned, at least to some of our satisfaction, that there

really is a difference at the biologic level of different fractionation regimens, but I don't think it will be the final answer to what's the best way to treat a patient.

SY: The RTOG has used a concomitant boost or purely accelerated schedule, often in combination with chemotherapy.

JC: I've always looked at concomitant boost as a hybrid. When it gets to the point where we thought that you were going to get accelerated repopulation it switches to a twice daily hyperfractionated-like regimen, but with fractions that are bigger than standard hyperfractionation regimens. It's the Toyota Prius of radiation; sometimes it runs once daily, sometimes it runs twice. To some degree you could argue that concomitant boost is a variant of a six-day schedule.

SY: What do you think about the long term report of this trial indicating that there may be some increased damage over the long term from concomitant boost compared to hyperfractionation?

JC: It's an interesting hypothesis. On the other hand, I don't know of any radiation regimen that doesn't take some risk of causing toxicity. You have to look at the current era and say, is it still going to be true with better 3D planning and with better delivery. I don't think 90-03 will be the death of concomitant boost, because you have to put it in the historical precedent of looking at how the radiation was delivered in 90-03.

SY: Do you think there is any future for accelerated split-course fractionation schedules?

JC: That's probably the one arm out of the trial that has seen the end of its usefulness, save for palliation. None of the RTOG split course-trials are as good as non-split trials, but they're not terrible. If you have a patient who's not imminently at risk of dying, but who has metastatic disease and still a substantial burden of tumor in the head and neck region, a split-course regimen is a very good way to treat.

SY: The question is whether we can really take anything out of this trial at this point, given that as you mentioned several times the near-universal nature now of 3D conformal physical tissue sparing and the move now to really advanced forms of intensity-modulated planning.

JC: It would be lovely to think that our physical techniques are going to be so good that we won't have to think about biology. Certainly we see a movement in that direction, certainly we see people doing stereotactic radiosurgery, certainly with current techniques you can to some degree bend the laws of biology. On the other hand, I don't see us becoming so proficient that we will in any time in the near future be able to forget radiation biology. And if radiation biology still is important, then I think the lessons of 90-03 remain important.

SY: The authors of the long term update propose hyperfractionated IMRT, that we could enact forms of altered fractionation to specific parts of the overall clinical target volume. Do you see something like that as an advance or do you see that as logistically or even economically impossible?

JC: It's a way to say, "I know what the biology does based on 90-03. I know what I can do better about the physics based on IMRT and IGRT." What may be a very good question is with the increased complexity, physics time, delivery time, and effort on the patient's part, not to mention the actual physical dollar cost of it, should we consider it seriously. We seem to be at a point in the evolution of medicine that we now have invented very smart drugs and very smart radiation techniques, but they can't be done at the same cost as our old drugs and our old techniques. And I think we are wrestling with: What's the value of human life? How much can we as a society afford? How much should people be allowed to spend? How much better does it have to be to be worth so many dollars more? I think that the authors raise a very good question. But, am I ready to go out tomorrow and start treating people with hyperfractionated IMRT? No.

SY: Do you think that this hypothesis is statistically testable, given the long-term follow up that would be needed and the likely small advantage in a select number of patients?

JC: You've just put in a bias that it's likely to be small. Sadly, I probably agree you. But unless we tried it, we will never know if it is small. I would suggest that we need a big enough difference for it not to be just statistically significant but clinically significant. We need to say, "Wow, that's a big enough difference, that I'm willing to spend X amount more to get that."

SY: I'm going to ask you some questions about hyperfractionation. The first is that, it's not uncommon when you implement a hyperfractionated schedule that patients sometimes miss their second fraction. The other problem with hyperfractionation is that in the era of IMRT, the fraction size to the clinical CTV's could drop very low. Are you comfortable with those ideas?

JC: I think that a facility that treats has an obligation to make sure that it routinely has the staff and equipment to deliver intended treatment reliably. So we need to do our part. But patients also have to do their part. And that means if it's extremely inconvenient or nearly impossible, then they should have the choice not to accept hyperfractionated treatment, even if it's better. I guess I'm of the school that says if you miss one fraction in a total course, terrible things won't happen. It's really only when you on a day-to-day basis continually miss fractions that there's a real problem. Then again, there are few things in life that we all agree upon. And patients should be able to be given enough information to make an informed choice about what they want to do.

SY: What about dropping the clinical elective treatments to such a low fraction size?

JC: I think we don't know the answer to that. Maybe we're getting closer to an era of medicine, where you can take a molecular-level sample and it will tell you, don't worry about the elective nodal treatment because the problem is at the primary, and there will be other samples that will tell us that nodal spread is the important problem, or distant spread is the primary problem.

SY: Those will be much smaller trials.

JC: Wouldn't hurt. One of the realities of all of the trials that we've done is that they are relatively so full of heterogeneity that we've had to accrue larger numbers of patients, which in turn has taken longer times to complete. And in reality, if a trial takes a very long time, by the time you have its answer the question may not be relevant anymore.

SY: In the end, what do you feel was the single greatest challenge in designing and initially implementing 90-03?

JC: I think it was getting people to agree on four clearly different flavors of fractionation. Even though it was fairly clear that what we wanted to do was test the biology, getting everyone to agree on the details of the regimens probably was the greatest challenge in making the trial work.

SY: If you had to design this trial again, is there anything you wish had been able to be settled differently?

JC: I think that like most things that you look back on, I wish we were smarter. I wish I knew we shouldn't have done the split-course arm. It would have saved us a number of patients that we could have had volunteer to be in the other arms and get the trial done more quickly. But in the era in which it was designed, with the equipment that was available, with the expertise we had, I think it did what we wanted it to do. And I think it holds up well today because it was cleanly done. While the implications may be moderated by changes in physics or biologic modifiers in the future, it firmly convinced me, and hopefully others, that there really is a clear difference in fractionation. While it's not proof per se, in my mind it's pretty good "proof" that the linear quadratic theory - our understanding of how one manipulates fractionation - really does work the way that we think it does. And that's important.

SY: Do you think it would be worth having another showdown using modern techniques and potentially chemotherapy or targeted therapy to recapitulate the match between hyperfractionation versus concomitant boost acceleration?

JC: Absolutely. The only question is at what dates and time. I don't know that we're done manipulating biology and physics. I hope we're not. I think that imaging, treatment delivery and immobilization will get better. And every time we have a substantial improvement in any or all of those things, I think that the radiobiologic questions asked in 90-03 need to be asked again.

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