Managing Hormone Sensitive, Non-Metastatic Relapse Prostate Cancer

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I will be talking about postoperative radiation therapy following radical prostatectomy. As an introduction, about a third of patients under radical prostatectomy as initial therapy, about a quarter to a third of those will fail surgery over time, and of those, 60-70% will develop metastatic disease within ten years without further treatment. We offer radiation postoperatively in three settings, or two categories of adjuvant treatment or salvage. The main distinction is that adjuvant is typically within 12 weeks of surgery and having an undetectable PSA versus salvage radiotherapy, which is someone who usually has a disease-free interval where PSA is undetectable after prostatectomy, then PSA slowly starts to rise, or salvage could be someone who has a PSA that never went to undetectable. Salvage is those who just have a biochemical recurrence versus those who we actually either feel on exam recurrent tumor, or those in whom we see actual disease on imaging, which are the worst patients.

What is the rationale behind giving adjuvant therapy? A certain group of patients are considered to be at high risk and may have residual disease; there may be a substantial number of cells present before PSA is actually detectable. I will show you which groups are considered high risk. Finally, if we give it in the adjuvant setting, we may have the greatest chance of curing a patient because the cell load will be lowest at that time versus waiting until a rise and then maybe having a higher tumor burden. This rationale has not been very popular in the U.S. Only about 7% utilize adjuvant radiation nationally.

These are the indications; these are the high risk patients, the ones with T3 disease, extracapsular extension or seminal vesicle involvement, T3A or T3B, and those with positive surgical margins.

Here are the three prospective randomized trials that have been published thus far. The SWOG is the oldest, so it has the longest follow-up. The first two trials used older radiation technique; they did not even use 3D but rather 2D planning. The doses that were used were a bit lower versus the more current German trial. There are two European trials here: this is the older trial, 400 patients; ERTC is 1000; and this modern trial has the fewest. These were the indications for adjuvant radiation. The German trial was the only one that required an undetectable PSA, but many actually had undetectable PSA. Primary endpoint for the SWOG trial was metastases-free survival, and for both

the German and ERTC trials, primary endpoint was biochemical relapse-free survival. They met all primary endpoints.

Here are the results. In the German trial, there was about a 20% difference at five years for those who had just surgery versus those, so biochemically, these patients failed; 20% more failed. The ERTC, the trial with 1000 patients was pretty consistent with the German data: the difference is about 20%, so it, too, met its primary endpoint and statistically significant. There was also a statistically significant improvement in local control of about 10%. This was reported at five years; hopefully with ten-year follow-up, we will see some differences in other endpoints such as overall survival. The SWOG trial was initially reported at five years and then updated at ten years; this trial with 400 patients and the longest follow-up showed almost a 30% difference in biochemical control. At ten years, that difference decreased slightly to 25%. Local control: as in the European trial where there was 10% improvement, the SWOG trial showed 20% improvement at five years, which maintained at the ten-year mark.

Even if there is no improvement in cure rate, a 20% difference I think is significant. As I will show later, I do not think we make an impact in their quality of life with side effects, particularly with today's technology, so this could be very meaningful. Looking at other endpoints, here is clinical disease-free survival; this is metastases-free survival; and then overall survival, kind of a gold standard.

The German trial did not report on disease-free survival or metastases-free survival; they did report on overall survival. Metastases-free survival is not different. Disease-free survival shows a 10% difference, roughly what we see in SWOG initially at five years. We know prostate cancer can return. The ten-year data becomes more significant, almost a 20% difference for disease-free survival. When you look at the metastases-free survival, this is what in my opinion is translated to your improvement in overall survival; if we impact local control, we can decrease distant metastases. This is to me really a landmark trial: if we see a difference in overall survival, to me, that would almost make this indisputable that these are the patients we really should be treating.

This slide looks at the role of hormone therapy in the adjuvant setting in a small randomized trial: 100 patients following surgery with positive lymph nodes; half were observed, half were given hormone therapy indefinitely. An improvement was seen in both overall survival and in cancer specific survival of about 30%. These are ongoing studies to look at the role of hormones. It is an unanswered question whether in the adjuvant setting if you add hormone, what benefit would be seen in addition to radiation. I would add hormones only if radiation alone failed. But for positive nodes, I do typically recommend hormonal therapy; their greatest risk is a more distant failure and not local.

We have to determine where the disease is coming from: the bone or somewhere else. Since we do not have a good imaging study, we have to look at studies which have been done, or look at various predictive factors to say which ones we will succeed with. With PSA, half-life is 3.1 days; it will become undetectable at four weeks. Biochemical relapse has been variably defined after salvage.

Factors associated with metastatic disease and death: this works into my thought process when I see a patient to help me decide should I give radiation, or I see someone who is

probably going to fail more distantly. So we look at things such as a persistently elevated PSA after prostatectomy, those patients tend to do worse; shorter interval from surgery to biochemical relapse; shorter doubling time; and high Gleason scores. Mayo also developed a scoring system to help us predict which ones might fail.

Here are some factors which help predict metastatic disease and death. This was a study by Mayo Clinic which came out in 2001 and updated in 2007. For the GPSM tool, G is for Gleason score, P is the pre-op PSA, S is for seminal vesicle, and M is the margin. This study from Rochester analyzed a group of patients who were treated over a three-year period, and demonstrated that if you had a score of ten or greater, you had an increased risk for a biochemical relapse. Subsequently in their study, they showed an increased risk for death. Here is the graph: a higher score meant you had a higher Gleason and worse pathologic features upfront. That is a way to help predict how someone will do post-surgery.

Doubling time has been strongly associated with clinical relapse. Those with a doubling time of less than three months have a short life expectancy; these patients are going to develop metastatic disease. With doubling time of less than 12 months, 50-75% of these patients will have a clinical relapse within ten years; if less than 15 months, 90% are going to actually die from the prostate cancer. We know doubling time is an important feature: if greater than 15 months, only about a third of them will succumb to prostate cancer. Rarely do we see abnormalities, but here are some sites of recurrence. This is important in considering what areas to target; the anastomoses is the highest risk of recurrence.

There is a short list of studies that gave salvage radiation. The two largest studies in the country are, first, one by Stevenson, a multi-institutional study with 1500 patients from Memorial Sloan-Kettering and Cleveland Clinic, and another study from my Chairman at Mayo Clinic Jacksonville with 368 patients, and one of the longest follow-ups. As a group as a whole, at least in terms of being biochemically free, we are going to be successful in about a third of patients. Here are the prognostic factors to determine which patients we will be successful with; these are some factors we talked about.

When a surgeon sends me a patient with rising PSA, these are the two studies which I turn to, the two largest. The Stevenson paper, which was originally published and updated about a year-and-a-half ago, shows a nomogram with factors which they think were important in determining the probability of being successful if you give radiation. They looked at prostatectomy PSA, Gleason score, vesicle involvement, and other factors which help determine which patients will fail, then the points are added up and a six-year probability of being biochemically controlled is calculated. This study told us that 61% of patients in that situation would be biochemically free at four years, versus 48% if less than ten months doubling time. This data is used to counsel the patient on his chances of being successful.

The second study from Mayo Clinic Jacksonville, my Chairman looked at the patients treated at Rochester, Scottsdale, and here, and he went through a variety of factors and identified the three most important factors in predicting success, namely, seminal vesicle involvement, Gleason score, and PSA. I write this out every time I see a patient; I do it right in front of them. Results showed that with a score of zero to one point, you had a

70% chance of being biochemically controlled at five years; this person probably had localized disease. Someone with high PSA and seminal vesicle involvement got a score of five, and only 6% of those patients got retreated at one of the Mayo Clinic sites. When I counsel the patient, I look at both studies to determine whether to recommend salvage radiation. I do recommend radiation for patients who have a 6% chance; the benefit is too low to justify the risk.

Here are side effects long-term: with 5% chance of late complication, does the patient want to take a 1-in-4 chance of maybe being successful in exchange for a 5% risk of damaging the bladder and rectum? We looked at dose response in a salvage setting; we showed a bit higher dose was helpful.

For someone in the salvage setting, if we give salvage radiation plus hormones, does it make a difference? This is the only trial that has been completed; we are still waiting for the results. I was enrolling patients when I was in residency on this trial; they are waiting for the follow-up to mature.

Salvage radiation has been endorsed by a number of societies: NCCN, the European Association of Urology, European Society of Medical Oncology, and the Radiation Oncology Group in Australia and New Zealand. Most believe we should offer these people treatment. Finally, in the salvage setting, this is a worst group of patients in my mind those who have a PSA and we can actually feel disease. These are the various studies, which basically show that the range is a little bit out there, but these numbers here are pretty low; there is probably some patient selection here. They gave adjuvant doses, but I usually go to a higher dose if there is actual gross visible disease. This is not a very well studied population; you can see the number of patients in these studies is low. A national organization called RTOG came out this January with some guidelines on volumes; this will make our data more uniform.

Side effects can be different because these patients had surgery, the blood supply to the various organs, the rectum and bladder are not as good, they may not heal as well after giving radiation. So we have two types of side effects: early side effects, which happen during radiation or within 90 days, and late side effects which happen three months or more after treatment is finished. Some prognostic factors help determine which patients might have problems; if we use modern techniques and are conscientious about volumes and we localize the area we need to treat with technology, we can reduce complications.

Early side effects include dysuria, urgency and frequency, soreness of the rectum, increased daily stools; this therapy is so well tolerated. Most of my patients do not need medicine during their treatment to help with symptoms; they are just kind of bothersome. Prognostic factors for determining early effects includes how much dose gets to the rectum. Late side effects: grade two toxicity is generally less than 20%, including both GU and GI. Many of these side effects are not chronic; severe events like having surgery or even for someone who needs to have a colostomy for rectal injury is much less than 1%. Here are the late side effects: increased stool, soreness of the rectum, blood, mucous discharge, rectal stricture, fecal incontinence; five-year incidence is less than 5%. Severe side effects, or grade three requiring some intervention, is less than 1% for late toxicity.

Turning from late GI to late GU, incidence of grade two is about 10% , bladder neck contracture, urethral stricture, to me, this is the biggest one that you can have; it is hard to

know if this is from surgery or radiation. Many surgical data will show 3-5% urethral strictures, so I do not know how much we add; it is hard to know. Urinary incontinence is comparable to surgery alone and is mild if it occurs. Sexual erectile function did not appear to be affected though this is controversial.

This was a study published earlier this year. This was our experience. Our Mayo Clinic study reported only on late effects. We looked at 308 patients; not all of the 400 patients were evaluable. We looked at GI and GU. Basically, our experience showed that grade two toxicity, which did not require much intervention or medication, was about 7%; serious complication was about 1%; 14 of 18 developed urethral strictures requiring dilatation; 3.4% had worsening urinary control. Looking at GI toxicity, serious complication was 0.3%; only one patient required surgery due to injury to his rectum. This is an overview for late GI toxicity. Our data falls within the range of what else has been reported. We did not have any serious grade three, which is consistent with the rest of the studies that are out there.

In conclusion, adjuvant radiation is for patients with a non-rising PSA within 12 weeks with one of these indications; we have a study showing about 10% improvement in survival; given the low toxicity from treatment, this should be standard, but many urologists will not be sending these patients, they do not believe in the study or have their own experience; salvage therapy is for patients with a rising PSA; and in my opinion, toxicity is very acceptable.

In response to an audience question regarding second malignancy, it usually takes eight years for a blood-borne malignancy like leukemia, and ten years for a solid malignancy, but going to older studies where 2D is used, it is extremely low. These older patients may be more prone to develop second malignancies, and they also receive chemotherapy which can cause malignancies, too. I cannot emphasize enough the value of adjuvant treatment: our toxicity is very low, and we may improve cure rates by 10%. If this trial with 1000 patients shows survival benefit, it would be convincing to most.

In response to an audience question, some patients come in having had bad radiation damage; this probably influences clinician decision as well. Cryo failures present a problem; the only modern study that I found came out of Emory and showed success in controlling 12 of 16 patients. To me, cryo is not standard therapy and the outcomes are not optimal; I am against cryo. Thank you.