2nd Annual Prostate Cancer Forum
An Educational Initiative

Case Management of the Newly-Diagnosed Patient

Isaac Powell, MD

I. Local Disease

1. Treatment Algorithm

Patients suspected of having prostate cancer should have a PSA and digital rectal exam. If either or both are abnormal, then a biopsy is recommended. If the biopsy is positive, then the question is whether a bone scan and A CT scan should be done. In low-risk prostate cancer, a bone scan and CT scan do not have to be done. Low-risk disease is indicative of a PSA less than 10 and a Gleason Score of 6 or less, and on the rectal exam it is only felt on one side or not felt at all.

In low-risk, early stage cancer, the options for treatment would be active surveillance, radiotherapy plus or minus hormone therapy, radical prostatectomy plus or minus hormone therapy or investigational protocols. If the cancer is locally advanced and is felt on rectal examination, the treatment options are radiotherapy plus or minus hormone therapy and radical prostatectomy plus or minus hormone therapy.

2. Active Surveillance

Active surveillance is a relatively new term. Whereas watchful waiting refers to patients we do not intend to treat, active surveillance refers to patients we do intend to treat but we are not treating immediately. It is primarily for low-risk disease. Depending on the age or comorbidity, we may recommend active surveillance. For men in their forties and early fifties, we would probably not recommend active surveillance because of their life expectancy. Cancer is a dynamic disease, and it does change over time. However, we offer these options to everyone. If the patient is young and chooses to participate in active surveillance, it is his choice. We do twelve biopsies, and if less than three are involved that would be considered a low-risk patient, or less than 50% of any one biopsy would be considered low-risk.

Follow up is a PSA and digital rectal exam every three months for two years and then every six months assuming the PSA remains stable. At one year, we do a twelve-core biopsy and then every three to five years if the PSA is stable up to age 80. If anything changes, we recommend treatment. That would include a doubling time of less than three years or a change in the grade of the disease.

T1 disease is when we do not feel anything on a rectal exam, and T2 is when we feel the cancer but it is less than one-half of the prostate, less than one lobe of the prostate. If one lobe is positive but it's less than half of that one lobe, we describe that as T2a. T1 and T2a are considered low-risk prostate cancer.

3. Surgical Treatment Protocols for Local and Locally-Advanced Prostate Cancer

The surgical treatment options for low-risk prostate cancer include radical retropubic prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, and robotic-assisted laparoscopic prostatectomy. The radical prostatectomy was the most utilized surgical approach, but now the robotic procedure is more commonly done. Understanding the anatomy has decreased the intraoperative complications and surgical time associated with these procedures, and epidural pain control has decreased the length of stay as well as the cost.

4. Radiation Therapy

Radiation therapy is a treatment option for early prostate cancer, and that includes both external beam radiation and seed implant therapy.

5. Cryotherapy

Cryotherapy is ice balls essentially being injected into the prostate cancer using a probe in the rectum with ultrasound-guided placement.

6. Stage T3/T4

Stage T3/T4 is an indication of locally advanced disease. The prostate cancer may have spread to the seminal vesicle. It may have also spread to the bladder or rectum in T4 disease. There also may be a high-grade disease, which would be described as locally advanced disease or very aggressive disease. A PSA of 20 or higher would be described as locally advanced disease if there's no evidence of metastasis that can be seen on bone scan or bone x-ray. Those with a doubling time of a year or greater have a significantly better survival than those who have a doubling time of less than three months. Depending on these factors, we would recommend certain protocols for treatment. Neoadjuvant hormone therapy would be before the surgery, and adjuvant hormone therapy would be after surgery.

7. CALGB

The CALGB protocol is a phase 3 trial in which a patient is treated or offered standard treatment or observation. It is in biopsy-proven prostate cancer again before the radical prostatectomy. The patients in this study have had no prior systemic therapy, and they have a predicted probability of biochemical recurrence at five years after surgery of 60%. The systemic chemotherapy is followed by surgery, and the other arm is surgery alone. The primary endpoint for the study is to determine if early systemic treatment prior to radical prostatectomy would decrease the recurrence rates compared to surgery alone. The secondary outcomes are the safety and tolerability of neoadjuvant hormone therapy and chemotherapy, the impact of neoadjuvant strategies on pathological tumor stage including lymph nodes and surgical margin status, the time to clinically apparent disease recurrence, and overall survival.

8. Patients with Locally Advanced, Aggressive Prostate Cancer

There is a study in patients with a rising PSA, doubling time of less than nine months and a testosterone level greater than 100 nanograms/milliliter. The two arms are hormone therapy and chemotherapy versus hormone therapy alone. Subjects in the group may have no radiographic findings that are clinically suspicious for metastatic disease, but they can have salvaged radiotherapy when appropriate for positive margins. The primary endpoints are progression-free survival in the period of 18 months of therapy and in at least 18 months of follow-up. The secondary endpoint is to evaluate cancer-specific survival and to compare overall survival between the two treatment groups and molecular correlates with clinical outcomes.

9. Patients with Locally Advanced Disease, Radiation Therapy Protocol

Another study is a radiation therapy protocol for men who have T3 disease, negative for nodes and negative for metastases, to look at improved survival and decreased risk of metastases. A total of 431 patients were included in the trial, and they were randomized to adjuvant radiotherapy or observation. The primary study endpoint was metastasis-free survival. The results were statistically significant, and there was a 71% survival in the men who had radiation therapy versus 61% in those who did not. The median follow up was 14 years for those who had treatment versus 12.9. The adjuvant radiation therapy after radical prostatectomy for a man with T3 prostate cancer significantly reduces the risk of metastasis and increases survival.

10. Lymph Node Metastasis

Finally, in a study from 1999 in men who have lymph node metastasis with prostate cancer, the subjects were randomized to an observation group after removing the prostate gland or a treatment group with hormone therapy. There were 16 out of 51 cancer deaths in the observation group and 3 out of 41 in the treatment group, and 42 of 51 had a PSA recurrence in the observation group and 7 of 47 in the treatment group. The study was statistically significant, and we are continuing to treat men with lymph node metastasis after radical prostatectomy with this particular protocol.

11. Conclusion

In conclusion, locally advanced prostate cancer plus early aggressive combination therapy equals long-term survival and possible cure.

Ulka Vaishampayan, MD

I. Metastatic Prostate Cancer

The most common site of spread for prostate cancer is bones, and a lot of times patients will come in with bone pain, which is sometimes mistaken for arthritis. It ends up being related to metastatic disease. This is an incurable condition; it is really a terminal diagnosis. The best you can hope for is to control any symptoms that the patients have and to try to keep the disease in remission for as long as possible so that it doesn't become an issue either symptomatically or affecting their survival. The associated morbidity is significant.

1. Hormone Therapy

Eighty to ninety percent of the patients in this category that you treat with hormone therapy will respond fairly quickly to the treatment, but it lasts on average about two years though in the African American population it tends to give less time, about 10 to 12 months.

The majority of relapse patients will only have a rise in PSA but no obvious evidence of metastatic disease. In that group, it is critical to know when to start them on hormones. They are likely to be on hormone therapy for a longer period of time, and hormone therapy is going to bring with it side effects that are likely to make them feel worse. It is one patient population in which we don't have good evidence or guidelines that indicate when we should start hormone therapy. The only guidelines are from the Department of Defense database, which has looked at this issue retrospectively to try and figure out who the patients were that benefitted from getting hormone therapy early. What they found is that patients with a high Gleason score were the ones who would benefit in terms of long-term survival if you started them on hormone therapy before their PSA hit five. If the PSA doubling time is less than 10 months, that also indicates it is time to put them on hormone therapy rather than waiting until they have metastatic disease.

Another question is whether we should keep hormone therapy going year after year or give them a break and re-start when it is needed. Recently, a study compared continuous versus intermittent, and they found that the eventual outcome is the same. However, the patient can avoid some symptoms of hormone therapy in between by doing intermittent therapy. If the patient is motivated enough to come back for PSA checks every month, it is a valid approach to consider. Physicians need to follow the testosterone level to make sure the therapy is getting to where it is supposed to go and having the desired effect. It has been found that a high dose of Casodex was actually harmful to some patients, and that approach has been abandoned. The LHRH agonists are all pretty similar or interchangeable as long as they get the testosterone down.

Another major question is should we stop treatment when it stops working? The typical convention has been to keep going with therapy even though the PSA continues to go up. There is more and more basic science evidence that is coming out that is showing that the cancer maintains its dependence on hormone therapy so you should keep going with the therapy.

2. Common Complications of Hormone Therapy

Fatigue from hormone therapy is not quite tangible, but men definitely feel a difference the moment you start them on LHRH therapy. They do adjust to the baseline after a while. Hot flashes are not severe except in maybe 10% of the patients. Impotence is a big issue, and it is unfortunately unavoidable because when you suppress the testosterone levels, it does cause a loss of desire to have sex. There are some patients who maintain the desire. Other complications can include osteoporosis, gynecomastia and breast tenderness, mood swings, liver toxicity and diarrhea and/or nausea. Some studies report that even a year or two of hormone therapy is enough to increase the risk of metabolic syndrome. A lot of these symptoms require multi-disciplinary management.

3. Strategies to Address Side Effects of Hormone Therapy

Hormone therapy works by suppressing the male hormone/testosterone levels, and that's what you need to follow to see if the treatment is effective. Ways that patients can fight the side effects include

increasing awareness, staying active, eating a healthy diet, utilizing medicine to address hot flashes, considering intermittent therapy if feasible and monitoring cholesterol and blood sugars periodically.

4. Advanced Prostate Cancer

I recommend that patients take vitamin D and calcium for bone strengthening therapy, and bisphosphonates have been shown to prevent or delay skeletal-related events compared with placebo. Radiation can be used for pain control, and sometimes you can do preventive radiation to prevent gynecomastia. Pain control therapies need to be judiciously managed, and chemotherapy and novel agents should be considered as patients start showing progression on hormone therapy.

5. Dietary Factors

Lycopene has been shown to reduce the risk of development and progression of prostate cancer, can cruciferous vegetables should be eaten at least five servings per week to reduce the risk of developing prostate cancer by 20%. Green tea may have possible protective effects. A large study showed, on the other hand, that too much calcium could increase the risk of metastatic prostate cancer. Caution has to be exercised. A multi-vitamin is recommended, but an overdosage of vitamins can potentially be harmful. Proscar/finasteride, which is used to treat benign prostatic hypertrophy tends to reduce the risk of prostate cancer by 25%. That with medical advice after careful discussion is a medication that is worth considering. Selenium and vitamin E have also been tried in different combinations, but no benefit was seen.

6. Systemic Therapy in Treatment of Prostate Cancer

There comes a time when hormone therapy is likely to stop working though typically in locally advanced prostate cancer the hormone therapy improves the cure rate of whatever local treatment is going to be undertaken. In metastatic disease, you want to control the disease as long as possible and keep the patient away from symptoms. There is a difference in the duration and goals of therapy depending on the stage of the patient's disease.

7. Castrate-Resistant Metastatic Disease

There are a number of treatment options for castrate-resistant metastatic disease, and some of them are very well tolerated and can make a big difference in the lifespan of the patients as well as make them feel better by improving symptoms even after hormone therapy fails.

II. Questions

Participant

Are you familiar with any epidemiologic studies of prostate cancer in Indian men?

Dr. Vaishampayan

The incidence is relatively low. The only studies that I have come across are similar to those in breast cancer where when they moved to the West it seems to slightly increase the incidence. The problem, of course, with those studies is knowing whether they increase the screening by moving to the West. That skews the results.