

ADVANCED PROSTATE CANCER/HIGH GLEASON SCORE AT DIAGNOSIS?

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The following are recommendations that are important BEFORE considering whether radiation or surgery should be administered. They should be used to establish baseline markers in developing a strategy of treatment. Both radiation and surgery should be held in abeyance with high Gleason Score patients until it is determined whether or not their cancer has migrated beyond the gland. Gleason Scores of 4 + 3/7, 8, 9, and 10 are considered high range. Gleason Score 4 + 3 cancers are associated with a three-fold increase in lethal prostate cancer compared with 3 + 4 cancers. Radiation and surgery are often suggested to “debulk” the amount of cancer that would still require other treatment options, but there are specialists who consider surgery an aggravation of the prostate gland that, when administered to a patient with extensive tumor presence and the likelihood of extension beyond the gland, could result in more harm than good. And, there is a recent study that external beam radiation therapy, even for localized prostate cancer (PC), is linked to bladder, lung and colorectal cancer. For the latter, review the following URLs:

<http://www.medicalnewstoday.com/articles/107505.php>

http://professional.cancerconsultants.com/conference_main.aspx?id=42169

<http://tinyurl.com/ykgdrog>

<http://tinyurl.com/ygkbzky>

With diagnosis of advanced/high Gleason Score PC, you should consider bringing in a Medical Oncologist along with your Urologist to oversee your care. One or the other should be testing your PAP, CGA, NSE, and CEA levels to determine PC aggressiveness, and preferably before starting any treatment method. These tests and what they may indicate are explained in the "PAP, CGA..." URL here:

<http://tinyurl.com/6xq3p7>. Testing should also include a Chemistry

Panel/Complete Blood Count (CBC). Also, check fasting prolactin level since prolactin SENSITIZES the AR (androgen receptor) and also inhibits Dopamine thus favoring angiogenesis. If the fasting prolactin is 5.0 or higher, start Dostinex (cabergoline) at 0.5 mg three times per week. A month later recheck the prolactin level. These tests along with a most current PSA and Testosterone (T) level then provide the necessary baseline markers to develop treatment strategy. Here are specific recommendations in this regard provided to a patient with several biopsies

results (primarily of Gleason Scores of 4,4 but also of 4,3 with tertiary presence of Grade 5) by internationally renowned Medical Oncologist Stephen Strum, specializing specifically in research and treatment of advanced prostate cancer since 1983:

“<Stephen Strum, MD>

This is high volume PC of an aggressive histologic type (mostly GS (4,4) & (4,3) along with PNI (perineural invasion) which is a risk factor for EPE (extra-prostatic extension) along with the fact that EPE was actually seen. This is not the kind of clinical situation that I would be thinking about doing a local procedure without first obtaining sophisticated staging studies to determine the extent of the disease. And, most probably, these biopsy findings are consistent with systemic spread of PC to bone and/or nodes. Thus, the burden of proof on any physician evaluating you is to rule out the presence of non-confined PC. Such studies in this context would include, in my opinion, the following prior to any local procedure:

1. PAP, CGA (Chromogranin A), NSE (Neuron Specific Enolase), CEA (Carcinoembryonic Antigen) blood tests in light of the high Gleason score. See page 64 of The Primer on Prostate Cancer by Strum & Pogliano for discussion of these other blood test biomarkers.
2. Of course DRE (digital rectal exam) but also findings of TRUSP (transrectal ultrasound of the prostate) in relation to involvement of capsule and seminal vesicle.
3. 3T MRI of the prostate but this would need to be done either before the biopsies due to artifact caused by biopsy induced bleeding or 2 months after the TRUSP with biopsies.
4. Evaluation of bone and nodes using MRI of the axial skeleton (spine, pelvis, long bones) and ideally Combidex (only available in Holland) (**MY NOTE: COMBIDEX, UNFORTUNATELY, IS NO LONGER AVAILABLE**). In your case most docs would order CT pelvis and abdomen and nuclear medicine bone scan. If the latter two tests were negative for metastatic disease I would want the former two tests because the latter two are so insensitive (many false negatives).
5. Assessment of bone resorption since abnormalities more often found in patients with systemic spread of PC. This would include DpD (deoxypyridinoline) urine test along with a blood bone resorption test such as b-CTX (C-Terminal

Telopeptide, b-Crosslaps) or amino-terminal procollagen propeptides of type I collagen (PINP). Also, bone density using quantitative computerized tomography (QCT) and definitely NOT using DEXA which will falsely elevate bone density if osteoarthritis or vascular calcium deposits which almost every man over the age of 60 will have.”

Once these tests have been administered, and while determining a treatment option, I believe you should then be prescribed androgen deprivation therapy (ADT) that include an antiandrogen (Casodex or its generic bicalutamide, flutamide/Eulexin, or nilutamide/Nilandron), and LHRH agonist (Lupron, Zoladex, Eligard, Trelstar, or the antagonist Degarelix), AND a 5AR inhibitor (dutasteride/Avodart preferred, or alternatively finasteride/Proscar) ASAP. Medical Oncologist Strum comments: “I personally have been involved with ADT (androgen deprivation therapy) since 1983 and was one of the first investigators for ADT in the world, working as a co-investigator with Fernand Labrie. I would be using a 5ARI (5-alpha reductase inhibitor) such as Avodart in conjunction with the above agents. I also would have checked a prolactin blood level and if 5 or higher would lower it with a drug such as Dostinex. In addition, it is critical to obtain serum testosterone levels to assure that there has been sufficient androgen deprivation (AD) achieved by the therapy being used. Given that ADT causes bone loss by activating osteoclasts, I would be using Zometa + a comprehensive bone supplement immediately.” The comprehensive bone supplement Dr. Strum most often recommends is Jarrow’s Ultra Bone Up; possibly available at health food stores, but also available at www.lef.org. Be certain that your physician starts you on an antiandrogen first (bicalutamide/Casodex 50mg one tablet daily most usually now prescribed) to prevent a side effect that could otherwise occur known as "flare" and explained here: <http://www.ustoowichita.org/pdf/Flare.pdf>, AND a 5Alpha Reductase (5AR) inhibitor (dutasteride/Avodart 0.5mg one capsule daily my choice) to inhibit T conversion to dihydrotestosterone (DHT) to begin a week prior to administration of the first LHRH agonist injection (most likely Lupron but many also using Zoladex Eligard, or Trelstar) and to be continued while also prescribed the LHRH agonist. The reasoning for this sequence of medication administration and the specific performance of each medication is explained in the “ADT Therapy” URL here: <http://tinyurl.com/6qvwc7>. (If the LHRH antagonist Degarelix is prescribed, the antiandrogen can begin with the first injection of this medication, since its action has been found to not cause a “flare” reaction). In the prescribing of Lupron, Dr. Strum, recommends that the initial injection be at only 7.5mg (or the lowest dosage depending on the LHRH medication employed) that is effective for 28 days be first employed and that at about 3 weeks, a blood draw administered to determine that

this therapy is working with your PSA level having drastically dropped into the ultrasensitive levels and your testosterone level also dropping significantly. This provides the indication that your cancer remains androgen "dependent" and this therapy will work. This 7.5mg injection then continues for another 28 days until your PSA drops to $<0.05\text{ng/ml}$ and your testosterone to $\leq 20\text{ng/dl}$ which indicates the ADT is working appropriately. (If this is not occurring, then your cancer may be androgen independent and requires an entirely new strategy for treatment). If the PSA and T levels have dropped as indicated, the injection can change to either the 22.5mg 84-day effective or 30mg 112-day effective doses with further blood draws done at approximately either 70-77 days (for the 84-day injection) or 98-105 days (for the 112-day injection) later prior to a next "check-up" appointment. I personally do not advocate implant of a 6-month or 12-month LHRH agonist. I doubt that the medication actually remains fully efficient for the entire six or twelve months. I am even suspect that the so-called "4-month" (actually 112-days) injection is fully effective for that length of time (just a personal opinion). And at the blood draws after a few months on ADT3, testing for DHT level should also be included with the PSA and T checks, since the 5AR inhibitor should have brought the DHT level down to $<3.0\text{ng/dl}$. This is all explained in the attached. Also, a thorough explanation with supporting references of the importance of a 5Alpha Reductase (5AR) inhibitor (dutasteride/Avodart (my preference) or finasteride/Proscar) as part of triple androgen/hormonal blockade (ADT3) can be reviewed here: <http://tinyurl.com/58hpk7>. Read "ADT Side Effects") for explanation of the side effects that might occur with ADT and how to combat those effects here: <http://tinyurl.com/5snxzx>. Also to be considered to image cancer volume and location would be Color Doppler Ultrasound (CDU) as well as endorectal MRI with spectroscopy (eMRIS). eMRIS would be appropriate to look at the prostate capsule, seminal vesicles and surrounding regional lymph nodes. If there are indications of metastasis despite no solid evidence, a series of chemotherapy with weekly docetaxel/Taxotere (that could be accompanied by carboplatin, an estradiol like estramustine/Emcyt, or other estrogen) to accompany androgen deprivation therapy could also be considered as part of an all out attack to stop continued development and hopefully eradicate the cancer. As a PC friend with Gleason 10 suggested, men with advanced prostate cancer should put on war paint, gather all their ammunition, and attack from every direction with everything available.

You should also be given bone mineral density (BMD) imaging with preferably a Quantitative Computerized Tomography (QCT) imaging, or at least a Dual-Energy X-ray Absorptiometry (DEXA) imaging (this is different than the bone scan checking for metastasis). A good idea is to also have your bone integrity checked

with a Ppyrilinks-D Dpd deoxy pyridinylene urine test and/or b-CTX (C-Terminal Telopeptide, b-Crosslaps). These tests are important because very often at diagnosis with prostate cancer, men are also experiencing osteopenia or osteoporosis. And particularly if bone metastases is considered possible or known, then beginning the bisphosphonate Zometa for bone protection. And particularly with starting on androgen deprivation, this testing should be part of developing base marks for the strategy of treatment. The reasoning for "QCT BMD Imaging vs DEXA BMD Imaging" is explained here:

<http://tinyurl.com/6kx7fj>. If it is determined that osteopenia or osteoporosis is developing or just to protect bone from metastases the prescribing of bisphosphonates is being discussed, a description of "Bisphosphonates & Dental Considerations" is described here:

<http://tinyurl.com/6ygr3e>.

Also, a lengthy compilation of information regarding "Diet and Supplement Considerations in our Fight Against Prostate Cancer" can be reviewed here:

<http://tinyurl.com/6obsym>.

Those with high grade prostate cancer at diagnosis and considering either surgery or radiation that would be more so to debulk the amount of cancer, should take the below suggestion to their physician as well as find and discuss with a Medical Oncologist prior to any plans for surgery or radiation to discuss pre-surgery/pre-radiation treatment with chemotherapy agents docetaxel/Taxotere and mitoxantrone for the possibility of a better chance of recurrence free survival.

See: <http://www.ncbi.nlm.nih.gov/pubmed/20143429> **Cancer 2010 Feb 8 {Epub ahead of print}**

Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer.

[Garzotto M](#), [Higano CS](#), [O'Brien C](#), [Rademacher BL](#), [Janeba N](#), [Fazli L](#), [Lange PH](#), [Lieberman S](#), [Beer TM](#).

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BACKGROUND:: A study was conducted to determine the 5-year recurrence-free survival in patients with high-risk prostate cancer after neoadjuvant combination chemotherapy followed by surgery. Secondary endpoints included safety, pathologic effects of chemotherapy, and predictors of disease recurrence.

METHODS:: Fifty-seven patients were enrolled in a phase 1/2 study of weekly docetaxel 35 mg/m² and escalating mitoxantrone to 4 mg/m² before prostatectomy. Patients were treated with 16 weeks of chemotherapy administered weekly on a 3 of every 4 week schedule. A tissue microarray, constructed from the prostatectomy specimens, served to facilitate the exploratory evaluation of biomarkers. The primary endpoint was recurrence-free survival. Disease recurrence was defined as a confirmed serum prostate-specific antigen (PSA) >0.4 ng/mL.

RESULTS:: Of the 57 patients, 54 received 4 cycles of docetaxel and mitoxantrone before radical prostatectomy. Grade 4 toxicities were limited to leukopenia, neutropenia, and hyperglycemia. Serum testosterone levels remained stable after chemotherapy. Negative surgical margins were attained in 67% of cases. Lymph node involvement was detected in 18.5% of cases. With a median follow-up of 63 months, 27 of 57 (47.4%) patients recurred. The Kaplan-Meier recurrence-free survival at 2 years was 65.5% (95% confidence interval [CI], 53.0%-78.0%) and was 49.8% at 5 years (95% CI, 35.5%-64.1%). Pretreatment serum PSA, lymph node involvement, and postchemotherapy tissue vascular endothelial growth factor expression were independent predictors of early recurrence. **CONCLUSIONS:**

Preoperative chemotherapy with docetaxel and mitoxantrone is feasible.

Approximately half of the high-risk patients remain free of disease recurrence at 5 years, and clinical and molecular predictors of early recurrence were identified.

Cancer 2010. (c) 2010 American Cancer Society.

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Finally, a list of "Books" that every man diagnosed with prostate cancer should consider adding to his home library can be reviewed here:

<http://www.ustoowichita.org/pdf/BOOKS.pdf> .

I don't mean to overwhelm you with this information but more to make you aware that these tests and treatment methods are important and your physicians should be considering them while developing an appropriate strategy for your future treatment. If he/she discounts these tests, you might consider moving to Urologists and Medical Oncologists who understand their value. Visit the Prostate Cancer Research Institute (PCRI) website www.pcri.org and particularly this link direct to PCRI Papers, then use the index on the left of the webpage to access further information:

<http://www.prostate-cancer.org/pcricms/node/16>

Then make note of the recommended treatment for prostate cancer provided by expert/experienced physicians who specialize in research and treatment of our insidious disease at all levels of diagnosis.

There are three Medical Oncologists who are often spoken of by many patients and colleagues as having special expertise in the treatment of advanced prostate cancer. Please take the time to read of them:

<http://www.ustoowichita.org/pdf/MEDICAL%20ONCOLOGIST%20BOB%20LEIBOWITZ.pdf>

or try: <http://tinyurl.com/qof3c8>

<http://www.ustoowichita.org/pdf/MEDICAL%20ONCOLOGIST%20CHARLES%20E%20MYERS.pdf>

or try: <http://tinyurl.com/phsgld>

<http://www.ustoowichita.org/pdf/MEDICAL%20ONCOLOGIST%20STEPHEN%20B%20STRUM,%20M.D.,%20FACP.pdf>

or try: <http://tinyurl.com/o85ncg>

The foregoing and other Medical Oncologists known to have experience in the treatment of advanced prostate cancer are listed here:

<http://www.ustoowichita.org/pdf/Medical%20Oncologists%20for%20Advanced%20Prostate%20Cancer.pdf>

or try <http://tinyurl.com/pbxj2v>

If you have questions or concerns, I am always as close as the other end of your computer to help address them. To know more about my background, advocacy, and mentoring regarding prostate cancer, please click on the URL in the Chapter Website "Observations" line of my signature block, below.

Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. **The comments or recommendations I make are not intended to be the procedure for you to now follow; rather, they are to be reviewed along with the comments or recommendations of others for your own further research, study, and discussion with the physician providing your prostate cancer care to come to your own, personal conclusion.**

"What you leave behind is not what is engraved in stone monuments, but what is woven into the lives of others."

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Biography: <http://www.ustoowichita.org/leaders.cfm?content=bio&id=1>

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Chapter Website "Observations": <http://www.ustoowichita.org/observations.cfm>