LONG TERM OUTCOMES FOR PROSTATE CANCER THERAPY CHOICES

By Peter Grimm, DO

What's the right choice? A man diagnosed with prostate cancer has a bewildering array of choices to make. Should he pursue Active Surveillance only? If he is to receive treatment with intent to cure, which treatment will result in the best chance of 'cure' while minimizing side effects? Medicine does not have a proven answer to the question of which treatment option is 'best', because there is no randomized clinical trial (the standard for proof) that has compared all the treatment options against the others, and a large definitive trial probably will never be possible. Why no randomized trial? Men simply want to be able to choose their own treatment and not be subject to a randomization process, which removes their choice.

What does the evidence indicate is the best for cancer control? While medical science does not have definitive 'proof' of which prostate cancer therapy choice is best, there are hundreds of published clinical trials and clinical reports describing outcomes of the various therapies. The difficulty has been to organize them all in one place and make it understandable. The Prostate Cancer Treatment Center in Seattle formed the Prostate Cancer Results Study Group to review all the modern prostate cancer literature and treatment results. More than twenty-five well known prostate cancer specialists in radiation therapy, urology, pathology and medical oncology joined to form the group with the goal to review results (freedom from rising PSA over time) by treatment method. The group has reviewed all the literature in the past ten years and has established criteria to allow the best articles and results to be compared. By sorting out the studies that met quality guidelines, they have created , in a simple, graphical form, a way to easily compare treatment results. — Read the complete report here – http://www.prostatecancertreatmentcenter.com/ProstateCancer/ProstateCancerResultsStudyGroup.aspx

PROSTATE CANCER TREATMENT OPTIONS		
SURGERY	EXTERNAL BEAM RADIATION (PHOTONS)	PERMANENT RADIOACTIVE SEED IMPLANT
CRYOTHERAPY	TEMPORARY HIGH DOSE RATE SEED IMPLANT	EXTERNAL BEAM RADIATION (PROTONS)

As this work is ongoing, those who would like to be on an update list can contact the study coordinator, Dr. Peter Grimm, at lisa@prostatecancertc.com and request to receive updates as they become available.

(Continued on page 4)

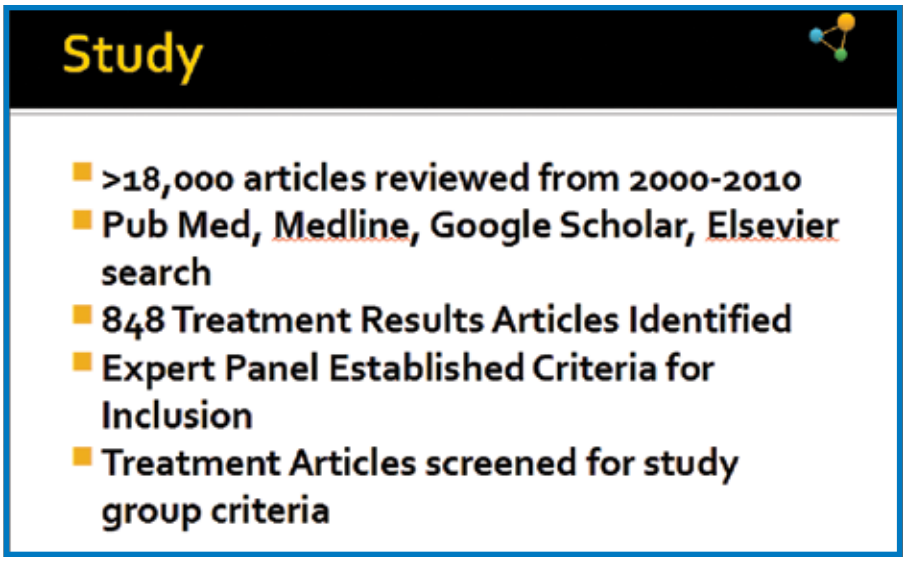
How the Study Was Conducted

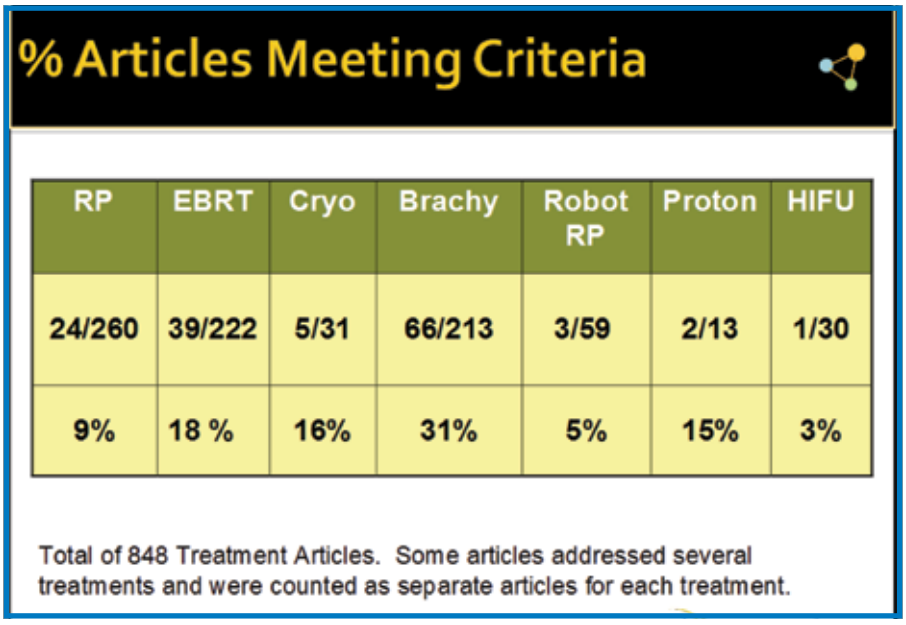
The expert panel agreed that many PCa studies did not allow for easy comparison. For example, most of the surgery studies sorted patients after the surgery into good and bad patient groups. It is logical that one cannot compare a group of "cherry picked" post surgery patients to a group that hasn't been selected out after treatment. The experts agreed that patients should be compared to the same group treated by another treatment (apples to apples) . The standard method of evaluating a treatment is to put a patient into a risk group (low, intermediate or high) based on their pretreatment stage, grade, and PSA. For example, low risk patients treated with surgery can then be reasonably compared to low risk patients treated with brachytherapy or IMRT.

The expert panel agreed unanimously that only studies that allowed comparisons of similar patients would be included in the graphs.

The expert panel established the following other simple criteria for an article to be included in the graphs.Patients had to be stratified into recognizable Pre-Treatment Risk groups: Low, Intermediate, and High Risk by either D'Amico, Zelefsky or NCCN stratification.

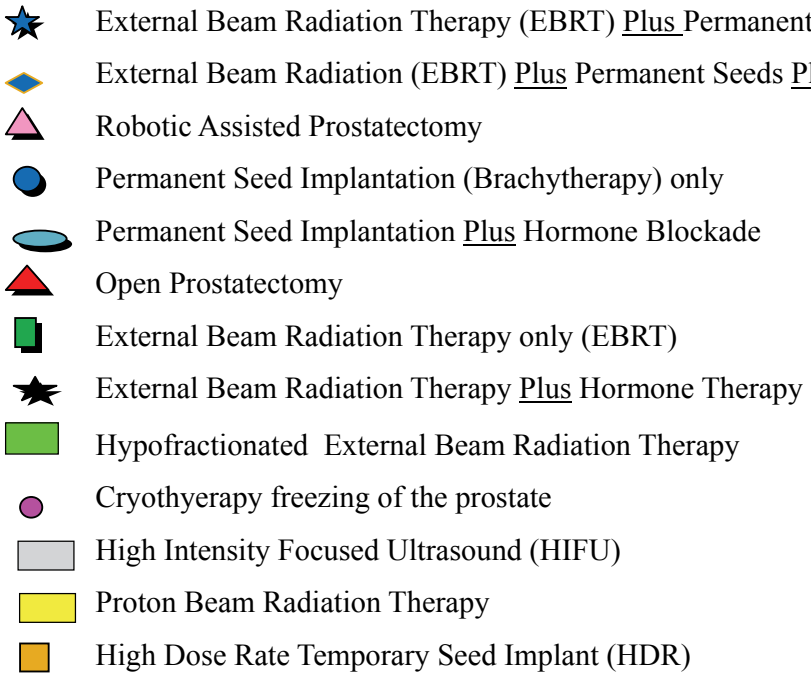
1. A PSA based, standardized endpoint for treatment failure had to be used. (Biologic Relapse Free Survival – BRFS). Note: Radiation, Cryotherapy, and HIFU use the ASTRO or Phoenix definition of PSA failure. Surgery uses PSA >= 0.2 ng/ml as an indicator failure. PSA is the most sensitive tool for measuring results.





2. Once entered, a patient couldn't be eliminated (No exclusions after clinical staging) (For example, the surgery studies couldn't remove positive margin or positive lymph node patient from the study).
3. Only modern, higher-dose radiation studies were accepted (EBRT must be minimum 72 Gy with an IMRT/conformal technique).
4. All Treatment modalities were considered: Seeds, Surgery, IMRT, HIFU, CRYO Protons, HDR.
5. The article must be in a Peer Reviewed Journal.
6. Only studies with larger numbers of men were considered, in order to have good statistical power.
7. Low Risk - Accepted minimum number 100 patients.
8. Intermediate Risk - Accepted minimum number 100 pts.

HOW TO INTERPRET THE SLIDES Each treatment option is given a symbol. Within each symbol is a number corresponding to the article it can from.



- External Beam Radiation Therapy (EBRT) Plus Permanent Seed Implantation
- External Beam Radiation (EBRT) Plus Permanent Seeds Plus Hormone Blockade
- Robotic Assisted Prostatectomy
- Permanent Seed Implantation (Brachytherapy) only
- Permanent Seed Implantation Plus Hormone Blockade
- Open Prostatectomy
- External Beam Radiation Therapy only (EBRT)
- External Beam Radiation Therapy Plus Hormone Therapy
- Hypofractionated External Beam Radiation Therapy
- Cryothyerapy freezing of the prostate
- High Intensity Focused Ultrasound (HIFU)
- Proton Beam Radiation Therapy
- High Dose Rate Temporary Seed Implant (HDR)

In the graphs, the % PSA Progression Free vertical axis at left represents the percentage of men who do not have a consistent rise in their PSA (PSA progression). 100% is best The horizontal axis at the bottom is years from the date of therapy. Longer is better

For example look at the blue dot 27  at top right of the Low Risk PCSG slide.

- Blue dot code means the study was Brachytherapy (permanent seed implant alone)
- The #27 in the blue dot is the article reference number, located in the notes section of the slide (you can get these in the full slide set from lisa@prostatecancertc.com.)
- Blue Dot 27 vertical axis shows that the patients are out 12 years after therapy.
- Blue Dot 27 horizontal axis indicates that 12 years after seed implant, about 97% of men are free of biochemical recurrence.

- **COLORED ELLIPSES**
- The Blue Ellipse is the range of results of the men who got some form of permanent or temporary seeds.
- The Green Ellipse is the range results of men who got External Beam Radiation (IMRT).
- The Red Ellipse is the range of results of men who got surgical prostatectomy.

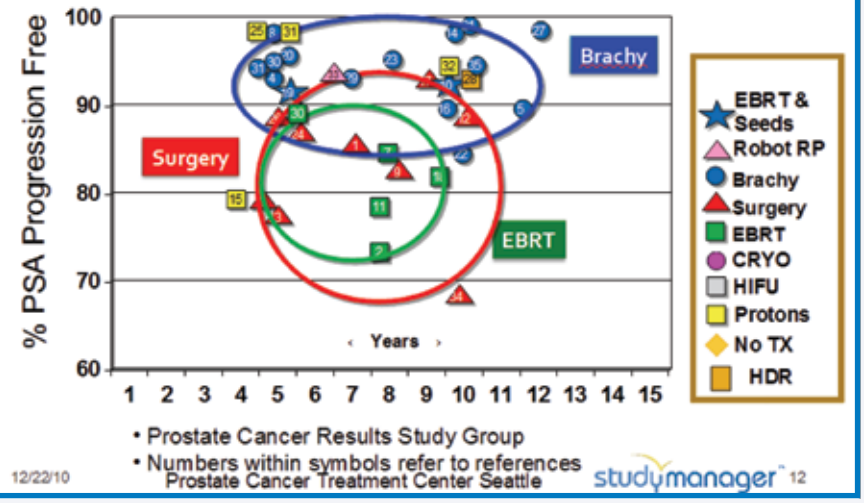
(Continued on page 6)

Primary Reasons for Article Rejection

	Strat. %	BRFS %	Excl. %	<72Gy %	<100pt %	<5yr f/u%	Other %
RP	66	4	8	-	4	14	3
EBRT	35	5	3	21	12	19	5
Brachy	32	4	7	-	18	34	6
Cryo	11	0	4	-	30	52	4
RobRP	76	0	0	-	6	18	0
Proton	44	0	0	-	11	44	0
HIFU	20	0	0	-	28	52	0

*Some articles were rejected for multiple reasons- only primary reason recorded studymanager

Low Risk PCSG Criteria



Low Risk = Stage T1-T2b , Gleason score ≤ 6, PSA < 10

9. High Risk - Accepted minimum number 50 pts.

10. Minimum Median Follow Up: 5 years. *Note:* ALL studies appear to do well within the first 5 years. Therefore the panel required 5- 15 years of follow up to be able to compare the long term success of the treatment.

The Prostate Cancer Results Study Group, to date, has reviewed greater than 18,000 articles published from 2000–2010. These articles came from all available respected medical journals and were reviewed by other experts. From these articles, the 848 Treatment Results Articles were examined to see if they met the group's criteria for comparison.

Only 140/848 (17%) of the articles met all the minimum reporting requirements for inclusion. The most common reasons for rejection were failure to provide risk stratification, too short of follow up, and too few subjects.

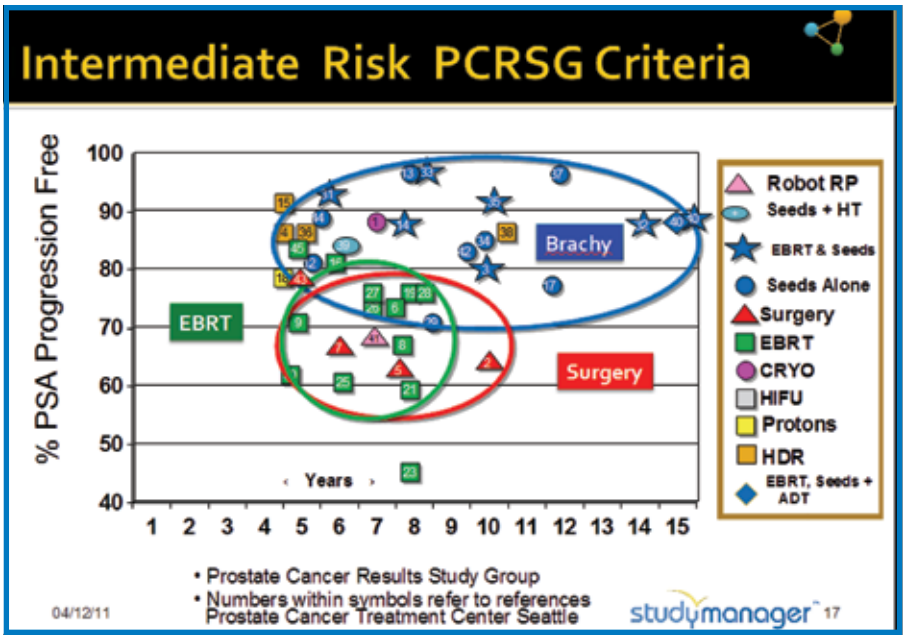
Other than sorting the studies for minimum inclusion criteria, no other factors excluded a study from review.

Low Risk Results

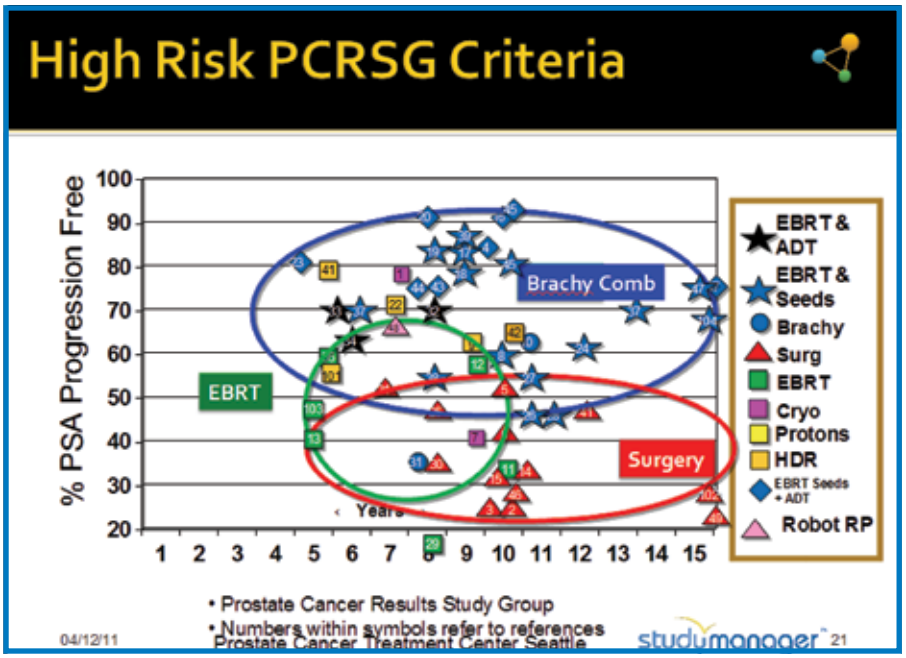
The good news — Most low risk patients' cancers will be controlled by any modality. While brachytherapy appears superior, most patients have low volume disease and will do well with any treatment.

Intermediate Risk Results

In this group, brachytherapy (seed implantation with or without External beam radiation) approaches appear to be superior. Why would this be so? As the disease becomes more advanced the risk of disease beyond the prostate increases. Therefore a surgical approach which treats only the prostate and seminal vesicles, has a predictably higher likelihood of leaving microscopic disease behind. The intermediate group may also require a higher dose of radiation to control the cancer. This may explain why external beam approaches such as IMRT alone, which limit the dose in the gland to approximately 81Gy, may fail more often. Brachytherapy allows much higher dose inside the prostate and does treat 5–10 millimeters around the outside of the gland. Adding IMRT to brachytherapy can address the need for irradiating possible cancer beyond the gland and in lymph nodes.



Intermediate Risk = Any patient not high or low risk



The Slide Above Includes Only Men At High Risk

• PSA >20 • Stage T2c or T3a • Gleason 8, 9, or 10.

High Risk Results

In this group of high risk men, adding hormone blockade to the radiation and giving more radiation with seeds and EBRT (external beam radiation) seems to improve BRFS (PSA Control) An interesting observation is the wide range of reported outcomes for the same treatment modality. For example, in the combined External Beam (EBRT) + Seeds group (star symbol), Study 26 had 45% Biochemical Relapse Free Survival (BRFS) (PSA Control) while Study 39 had about 87% BRFS. An interesting question will be to learn what caused the big difference, and to adopt treatment strategies that make all studies perform more like Study 39. It is likely, because high risk patients have a large range in the amount of disease, that it will be necessary to separate out this group further into low-high risk and a high- high risk groups. The more important take home message from this study is that high risk patients generally need a more aggressive approach of combination treatment to achieve the best result.

(Continued on page 8)

PROSTATE CANCER THERAPY SIDE EFFECTS – QUALITY OF LIFE

Too often, the potential side effects, that may negatively effect quality of life (QOL), are not carefully examined by patients before choosing a particular prostate cancer therapy. All the therapy options have the potential to reduce sexual function, urinary continence, and bowel function.

Imagine what it would be like to never have another erection, to be perpetually wet and have to wear a diaper due to urinary incontinence, or to have daily bowel urgency, pain, and bleeding. Fortunately, only a minority of men experience these severe side effects.

In 2009 Dr. James L. Talcott and colleagues, published an excellent article that compares side effects outcomes for surgery, External Beam radiation, and brachytherapy seed implant, at three years after therapy. Dr. Talcott is an associate professor of Medicine at Harvard Medical School. Download the complete article for free here http://jco.ascopubs.org/content/27/24/3916.full.pdf

They mailed follow-up questionnaires to 522 participating patients at 3, 12, 24, and 36 months after treatment began; follow-up was discontinued after 36 months. Excluding 84 patients who stopped participating before the 36-month questionnaire, 438 patients (84%) with complete follow-up comprised the study population. Patients who dropped out did not statistically significantly differ demographically, clinically, or in baseline QOL scores from those who did not. Reported results include 409 patients who chose the three most common treatment modalities: RP, EBRT and BT.

Dr. Talcott demonstrated that the side effects risk depended on both treatment modality, and on the sexual, urinary, and bowel function at the time of starting therapy. Men with good function have more to lose but do better overall. Also, the good news is that some men with urinary obstructive symptoms may actually see improvement after therapy.

Chen, Clark, Talcott – Prostate Therapy Side Effects Study: Why It Is Important and Different from Other Studies

- Unbiased researchers (It has been shown that doctor reported side effects differ from patient reported side effects. This report is 100% patient reported.)
- Validated QOL questionnaires given prior to and at 3, 12, 24,a nd 36 months after therapy
- Prospective study – consecutively treated men received questionnaires
  - 74 men received Nerve Sparing Radical Prostatectomy (NNSRP)
  - 53 received Non-Nerve Sparing Radical Prostatectomy (NSRP)
  - 190 received External Beam Radiation Therapy (EBRT)
  - 92 received permanent seed implant brachytherapy (BT)
- Study conducted from 1994 through 2000
- Surgical and brachytherapy patients were younger than EBRT patients
- Brachytherapy patients had earlier stage disease.

Editor's Note: Figure A indicates significantly worse sexual function risk than is usually reported elsewhere. This may be due to the definitions used by Dr. Talcott, where the report of NORMAL basically means no loss of any sexual performance at all. Most other articles report that if a man can achieve any sexual performance, he is considered potent. This would include men who only occasionally can achieve an erection sufficient for penetration, and may include men who can achieve some erection only with the aid of drugs like Viagra or the use of vacuum assist aids. Another factor could be the reporting time of three years. Many older men might report some loss of sexual performance after three years, whether they had cancer therapy or not. A final caveat is patient reporting was voluntary, and after 36 months, only 409 out of the original 522 were still participating. We do not know what percentage of the men who dropped out had 'Normal" function, or if it would change the statistics.

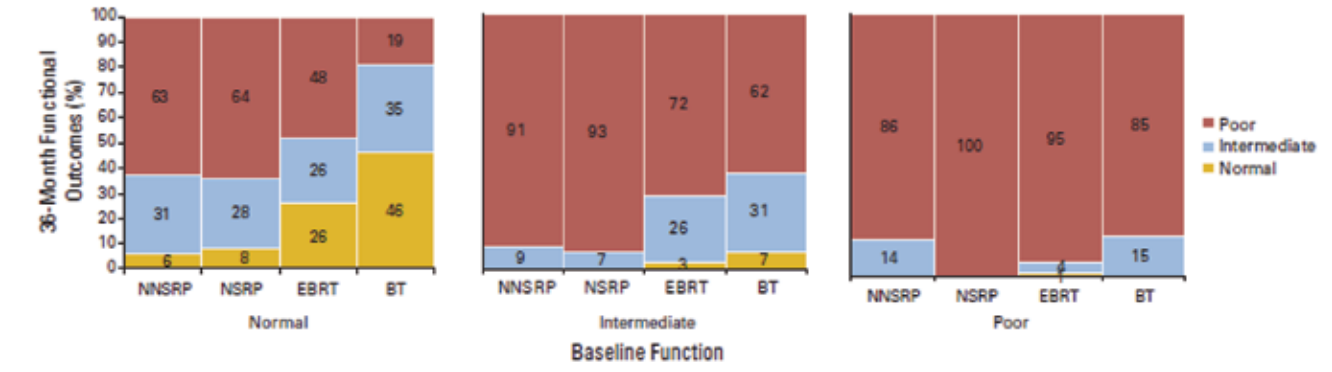
TALCOTT DEFINITION OF SEXUAL PERFORMANCE

Normal – Full erections with little or no difficulty getting and keeping erections. Always able to reach orgasm.

Intermediate – Nearly full or partial erections (penetration only with manual assistance), some difficulty with keeping erections, sometimes able to reach orgasm.

Poor – Incapable of penetration or no erections. A lot of difficulty getting and keeping erections. Not able to reach orgasm, no sexual activity.

Dr. Sanda presented a larger (1201 patients), more recent (2006), long-term study comparing side effects, available for free download here: http://www.nejm.org/doi/pdf/10.1056/NEJMoa074311. Combining data from nine institutions, the results are similar to Talcott, but with slightly different definitions and statistics.



NNSRP = Non Nerve Sparing Radical Prostatectomy
NSRP = Nerve Sparing Radical Prostatectomy
EBRT = External Beam Radiation Therapy
BT = Brachytherapy – permanent radioactive seed implantation

To interpret Graph A, the left graph is for men who had 'Normal' sexual function when starting therapy for prostate cancer. If there was no change in sexual function, the color of all four bars would be the 'Normal' color. We see that only 8 percent of the NSRP had no loss of sexual function at three years.

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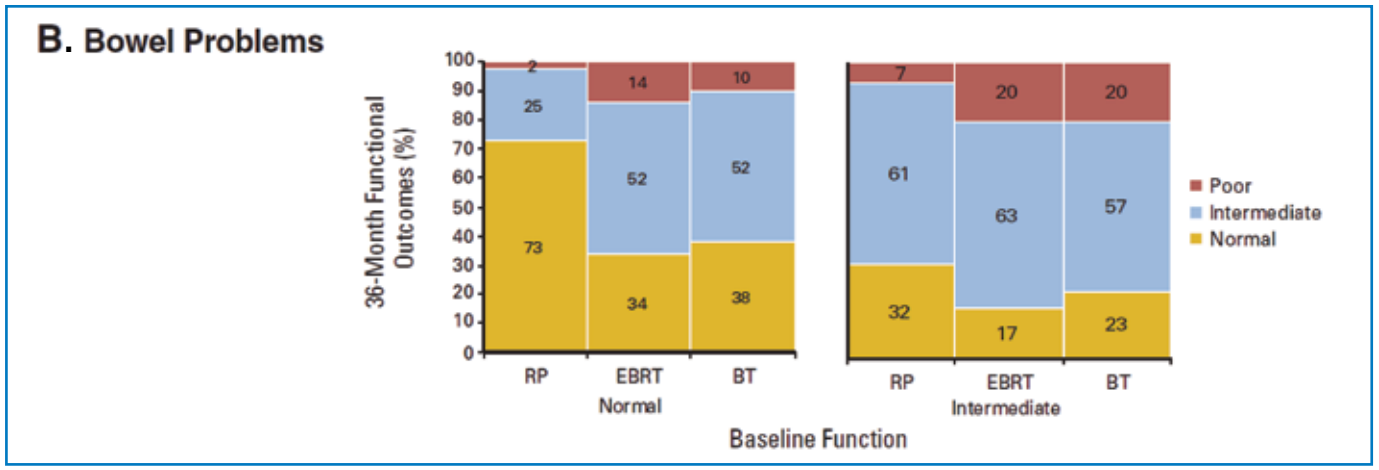
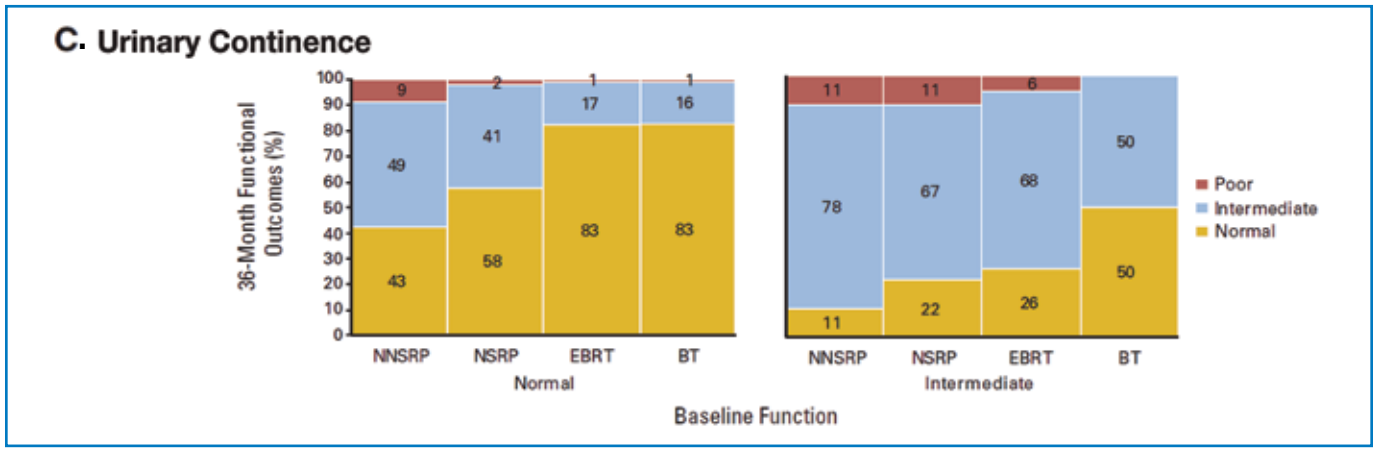


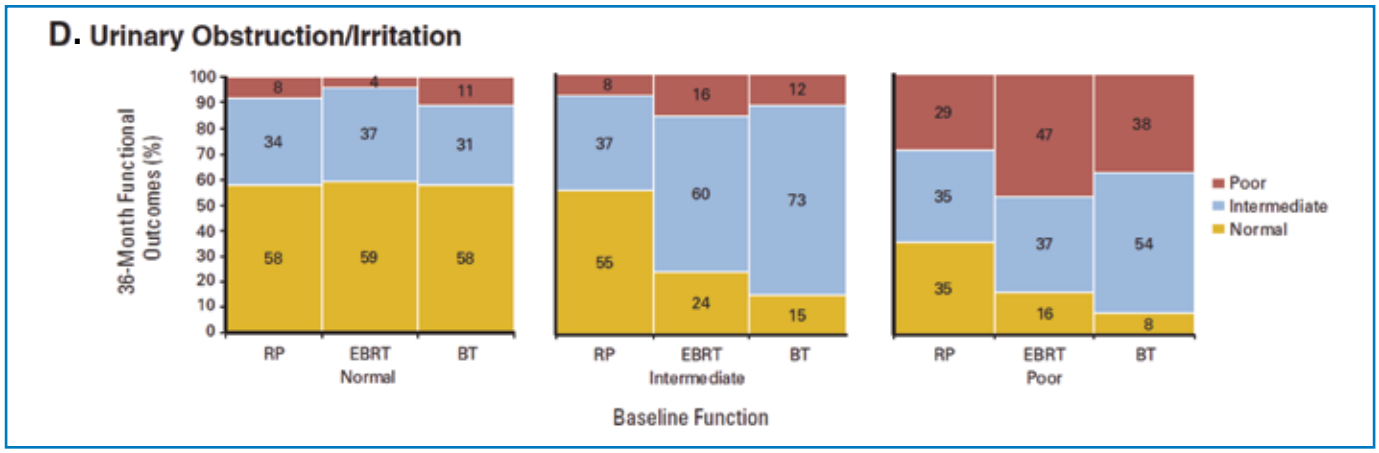
Bowel Problems Definitions

- **Normal** No diarrhea, urgency, abdominal cramping, tenesmus, bleeding, or pain with bowel movements.
- **Intermediate** Occasional (once or twice weekly) diarrhea, urgency, abdominal cramping, tenesmus, or pain with bowel movements. Occasional or fairly frequent (several times a week) bleeding with bowel movements.
- **Poor** Fairly frequent (several times a week), frequent, or very frequent (several times a day) diarrhea, urgency, abdominal cramping, tenesmus, bleeding, or pain with bowel movements. Frequent or very frequent bleeding with bowel movements.



Urinary Continence Definitions

- **Normal** Complete control, no leaking at all
- **Intermediate** Leaking only at certain times occasionally to frequently and no more than a few drops
- **Poor** Little or no control, leaking very frequently (several times per day) more than a few drops



Men rated "POOR" for urinary obstruction prior to therapy, often have improvement.

Urinary Obstruction Definitions

- **Normal** No obstruction or irritation
- **Intermediate** Requiring medication
- **Poor** Requiring surgical intervention

Peter Grimm, DO

Doctor Peter Grimm is the Director of the Prostate Cancer Treatment Center in the Seattle area. In the late 1980's he pioneered, with his partners, low-dose brachytherapy technique known as seed implantation for prostate cancer. He and his pioneering colleagues have treated over 10,000 patients and have trained over 6,000 physicians from around the world in prostate brachytherapy. He developed six U.S. patented devices that have lead to continuous improvements in the equipment widely used in prostate implantation. In 2010 he received the highest award in the Brachytherapy profession, the President award from the American Brachytherapy society for outstanding achievement and contributions.