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Contents

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QUALITY OF LIFE: "What Are the Side Effects of Your Treatment, Doctor?" - Second Edition

A patient's choice among treatment options is increasingly determined by consideration of unwanted side effects. Lead off statements from two recent articles on heath-related quality of life (QOL) issues underscore this point. One stated, "Given the lack of unequivocal survival data clearly favoring one treatment over another for localized prostate cancer, patients strongly consider quality-of-life effects when choosing treatment for this common malignancy" - Dr. David Penson in "Quality of Life After Therapy for Localized Prostate Cancer" in The Cancer Journal, Sep/Oct, 2007. And, another - "The primary treatments for clinically localized cancer confer equivalent cancer control, but disparate side effects" - Dr. Litwin, in "Quality of life after surgery, external beam irradiation, or brachytherapy for early stage prostate cancer, Cancer, June 1, 2007. This putative equivalence of outcome among the three major modes of primary therapy highlights the need for an accurate assessment of therapy related urinary, bowel, and sexual dysfunction. Candidates for primary therapy need well founded information so they can translate their preferences into their best choice of a treatment modality.

The most reliable QOL information arises from studies that incorporate essential methodological and data elements. The number of subjects must be sufficient to support claims of statistical significance, and the reports of individual symptoms ***must*** come from **patient-centered validated questionnaires**. (Reporting from doctors is notoriously inaccurate.) The best data will include a patient's assessment of his baseline pre-treatment status in the various domains of interest followed by interval assessments

over a period of two or more years. Patients' ages, PSA levels, Gleason scores, and T-stages should be well matched among treatment types. The data collection period should be as current as possible to insure that contemporary radiation doses were used; and for RP patients, optimal information would detail whether nerve-sparing technique was employed. Single institution reports, although informative, may be biased by special criteria for patient selection and may reflect special expertise not evenly shared by the overall clinical community.

One of the best recent articles that fulfilled these all these criteria is the report in CANCER by Litwin et al. referenced above. Additional coverage of this topic in the excellent article by Talcot and D'Amico, JCO Nov. 2003, was reviewed in the first edition of "What Are The Side Effects Of Your Treatment, Doctor?" (October 2005) in the PCa Commentary, indexed in the archives under "Quality of Life Issues." Their findings remain relevant and their presentation of data in tabular form makes the comparisons easy to grasp.

First, the generalizations based on many review articles - a tricky prospect when the devil lies so much in the details. Health-related QOL assessments conventionally divide this subject into therapy consequences in three main domains of interest.

Urinary symptoms - usually divided into 1), obstructive and irritative voiding dysfunction - frequently referred to as "bother; and 2), urinary control (incontinence, often measured by the number of pads required).

Urinary obstruction and irritation: Brachytherapy (BT) commonly results in initial irritative dysuria, due to radiation effect on the urethra. This symptom subsides over a year, remaining significant in a very few patients ~ possibly 1 - 2%. Brachytherapy is also associated with initial urinary retention, which may occur in 34% of men during the first week and decrease to ~10% at 6 months, further decreasing by one year.

Incontinence: Radical Prostatectomy (RP) is associated with the most incontinence (less so for younger men); BT considerably less; andexternal beam radiotherapy (ERBT), rarely. But symptoms related to RP decline notably by the year's end. After RP an indwelling catheter is usually employed for up to several weeks.

Sexual function - a difficult area for generalization because of the multiple factors that influence "success", but often measured as the ability to have an erection sufficient for vaginal penetration. Assessment in this domain is *clearly related to pre-therapy function* and *age*; and it is recognized that, independent of any therapy, sexual function most times diminishes over time.

EBRT is reported to preserve function slightly better than BT, with a greater likelihood for potent men to more quickly return to baseline function. Both BT and ERBT are significantly superior to RP in this area. However, a successful bilateral nerve sparing RP procedure has been shown in some studies to overcome this differential (unilateral nerve sparing less so). And, due to late damage to the cavernosal nerves by radiation induced scarring, the better initial sexual function associated with radiation can deteriorate with time, with one study showing a decline in function for potent men to 53% at five years. (The average age of BT patients in the past has usually been greater than for RP patients, and this is relevant for the comparisons.) In some RP cases sexual function somewhat improves over time. "Sexual bother was more common than urinary or bowel bother after all three treatments" (Litwin).

Bowel function is the domain least affected by the three modalities of treatment, as will be shown in the graphs. However, even optimally applied BT and ERBT can lead to a minimal incidence of rectal irritation, bleeding, and incontinence, with EBRT causing less trouble than BT. Bowel dysfunction is almost never a problem with RP.

However, these comparison data are best displayed graphically as shown on page 5 of this Commentary. The graphs are reproduced from the Litwin article (page 2245) with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Now, the details - based on the Litwin report of 580 men treated at UCLA between 1999 and 2003, with information obtained from patient responses to three validated instruments. The follow-up period was 24 months and ongoing assessments were made at 1, 2, 4, 8, 12, 18 and 24 months. The clinical TMN stage was nearly 100% cT1 or cT2. Clinical T2 stage was 29.3% for RP; 43.6%, ERBT; and 18.9% for BT. Treatment mode: RP, 307 men; ERBT, 78; and BT, 90. ERBT dose (3-D Conformal or IMRT) was 68 - 77 Gy. For BT, monotherapy was used in 74.4% and was combined with ERBT in 25.6%; and in the BT cohort short term ADT was used in 23%. For RP patients 80.8% underwent bilateral nerve-sparing, 10.1% unilateral nerve-sparing, and 9.1% nonnerve-sparing. Mean age for RP, 60.1 years; ERBT, 70.8; and for BT. 68.4. Median Gleason score for all modalities was 6; and the PSA ranged between 6 and 8 ng/mL.

The Litwin graphs, Figures 1 and 2, are reproduced on page 5.

Figure 1: "Sexual function of men who were potent pre-treatment (having a UCLA Prostate Cancer Index sexual function score of at least 70, where 100 is optimal, n = 187 patients).

Figure 2: "Longitudinal changes in bother scores as measured by the UCLA Prostate Cancer Index. Bars shown represent the proportion of subjects reporting severe bother, i.e <25 on a scale where 100 = no bother, at each respective time point."

Litwin concludes: "Leveraging descriptive [QOL] data to guide interventions that improve outcomes adds value to the clinical care we provide during the long survivorship period that most patients experience."

PRIMARY TX UPDATE: Treatment Outcome Comparisons - Informative High Quality Studies Missing

The phrase "putative equivalence" was used in the previous article referring to the comparison of outcomes among primary treatment for localized prostate cancer, since, as it turns out, solid head-to-head data are very hard - if not impossible to come by. The Agency for Healthcare and Quality commissioned a review (Wilt T, Ann of Intern Med, Feb., 2008) which identified 18 candidates for high-quality, randomized, controlled trials published as of mid-September 2007. The authors found "insufficient data to compare the efficacy and safety of available treatments." The search encompassed 14,045 relevant articles. Only three direct comparisons among major treatments were found, and none of the 18 trials focused on PSA-detected cancer, despite the current preponderance of this route to diagnosis. Most studies did not report disease-specific mortality. The report concluded that "The paucity of clinically important information from high-quality randomized trials remains the main barrier to well-informed decision making."

ANDROGEN INSENSITIVE DISEASE: **Chemotherapy - Updated Survival Data from TAX 327 Study: Docetaxel Plus Prednisone Versus Mitoxanthrone Plus Prednisone for Advanced Prostate Cancer. (JCO January 10, 2008)**

The updated data collected as of March 2007 reporting median survival duration for the 1,006 men with metastatic hormone-resistant prostate cancer continued to show superiority (P=.004) for Docetaxel, 75 mg/m2 (D3P), given at three week intervals compared to Mitoxanthrone (MP), 12 mg/m2 q 3 weeks: median survival 19.2 vs 16.3 months, respectively. For Docetaxel given weekly (D1P), 30 mg/m2, the median survival was 17.8 months, which did not differ significantly from the MP arm. Prednisone 5 mg BID was given in all arms.

Docetaxel given at three week intervals "showed better palliation, with a higher probability of pain and QOL response." The study continued to show that patients on the weekly Docetaxel arm "were more likely to experience early deterioration of QOL" and that median survival in this arm was not significantly better than MP. Hence, the authors conclude that "weekly docetaxel should not be adopted."

"The percentage of patients who survived for more than 3 years in the D3P, D1P, and MP arms were 18.6%, 16.8%, and 13.5% respectively."

The authors concede that "Although the differences in median survival are relatively small, they are accompanied by improvement in pain control and QOL and are clinically meaningful ... [and] it seems reasonable to offer treatment to patients with symptoms and to those who are likely to develop symptoms in the near future."

PRIMARY TX UPDATES: Optimal Duration Of Androgen Deprivation In Patients With PSA > 20 Ng/Ml Treated With External Beam Radiotherapy - Take Home Message: Longer Is Better Than Shorter in High-Risk Disease

The conclusion: ADT duration of 12-24 or >24 months significantly improved bNED, cause-specific survival (CSS), and overall survival (OS) as compared to < 6 and 6-12 months.

This report by a British Columbia consortium in The Canadian Journal of Urology, August 2007, followed 307 men divided into four groups equally matched for age, PSA, and Gleason score. All men were treated with EBRT and an LHRH agonist: group 1, androgen deprivation for <6 months (n=71); group 2, 6-12 months (n=80); group 3, 12-24 months (n=72); and group 4, >24 months (n=84). In those groups Clinical Stage T2 and T3 was present in 84%, 69%, 68%, and 85%; and a pelvic radiation boost was delivered in 9%, 50%, 44% and 43%; and the median follow-up per group was 63, 31, 32,and 53 months, all respectively for groups 1-4. The total external beam radiation dose was 66-72 Gy, which is less than currently considered standard.

Results: "At five years the rates of bNED were 34%, 35%, 47%, and 77% for groups 1-4, respectively." At five years the CSS rates were 82%, 82%, 97% and 92%; and the OS rates were 74%, 77%, 83% and 92%, all respectively.

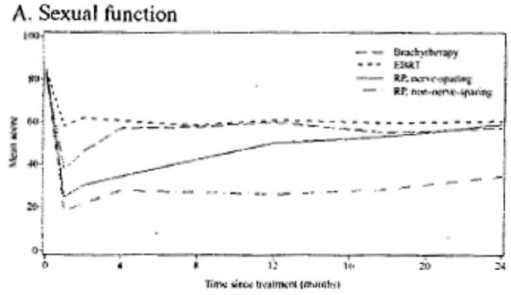
In the final analysis, "For bNED outcomes a statistically significant advantage was seen for durations of ADT of 12-24 months and >24 months as compared to shorter durations. However, significant improvement in CSS and OS was limited to patients who received >24 months of ADT."

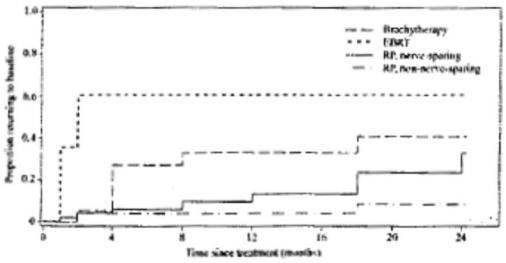
SHORT-TERM NEOADJUVANT ADT AND ERBT FOR LOCALLY ADVANCED PROSTATE CANCER

The January JCO carried the update of the well-known Roach RTOG 8610 trial of 2 months of combined androgen blockade prior to and concurrent with ERBT for high-risk cancer - i.e. bulky T2-T4 tumors. In the comparison between ADT+EBRT v EBRT alone, "There was a statistically significant improvement in 10-year disease-specific mortality, (23% v 36%; p=.01); distant metastases, (35% v 47%; p=.12); disease-free survival, (11% v 3%; p=<.0001); and biochemical failure, (65% v 80% p=<.0001) - all comparisons favoring the addition of ADT to EBRT compared to ERBT alone.

[Editors note: What's the Gestalt here? In the global picture for men with high-risk disease the benefit of longer ADT increases as the risk for recurrence increases; and, some ADT is better than none. The argument against prolonged ADT derives from the well known toxicities of protracted androgen deprivation. However, increasing usage of intermittent androgen deprivation and the utility of less toxic combinations such as dutasteride/bicalutamide have potential to improve the benefit/toxicity ratio and permit longer ADT usage.]

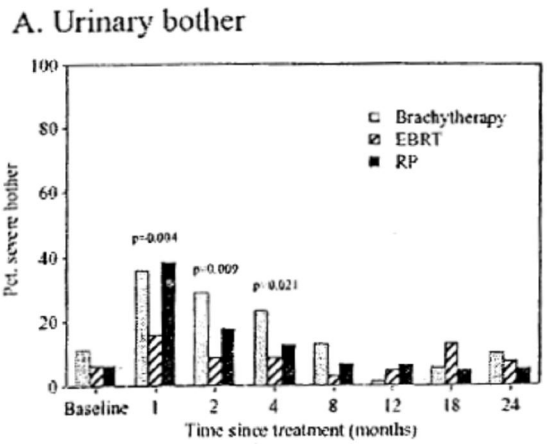
Fig. 1

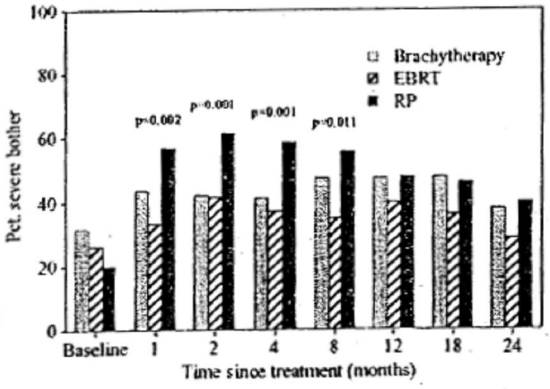


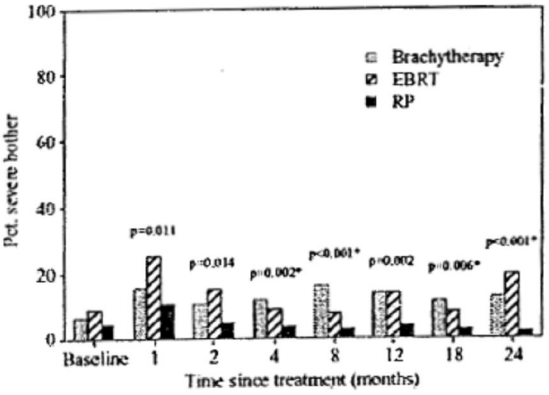


Time (mos):	0	1	2	4	8	12	18	24
Sample size (no.)	187	166	170	160	164	157	155	141

Fig. 2







Time (mos):	0	1	2	4	8	12	18	24
Sample size (no.)	475	400	420	412	402	392	385	344

This nomogram below is related to the article in the Jan/Feb PC Commentary, "Gleason Score Upgrading From Biopsy to Prostatectomy Specimen". No nomogram is perfect, but this presentation suggests the many factors that are involved and their relative importance. The nomogram was published in the article "Clinical Predictors of Gleason Score Upgrading: Implications for Patients Considering Watchful Waiting, Active Surveillance, or Brachytherapy" by Kulkami et al. in CANCER June 15, 2007 / Volume 109 / Number 12, Page 2436. Reproduced with permission of Wiley- Inc.

Figure 2. Nomograms for predicting upgrading of biopsy-derived low-risk prostate cancer. To use the nomogram, identify patient values of each variable on its representative axis. Draw a vertical line for each value to the Points axis to determine how many points are accumulated for each variable. Identify the sum of the total Points on the Total Points axis and draw a vertical line to the Probability of Upgrading axis to determine the patient's chance of harboring high-grade disease. Uro-path indicates expert genitourinary pathologist; Synt: sextant biopsy (+/-nodule/lesion); Ext. extended 10-core biopsy (+/- nodule/lesion).