

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-61.

Technical Supplement

Methods

Phone Interviews of Patients and Spouse or Partners:

CATI interviews were conducted by a phone survey facility at Michigan State University (not associated with the clinical sites) using validated, scripted interviews administered by same-gender interviewers. Mean patient interview length was 19 minutes and mean interview length for spouses or partners was 9 minutes. Subjects who missed 2 consecutive interviews were deemed lost to follow-up. Spousal distress (or bother) was determined by spouse responses to the following questions:

1. How much has your husband's or partner's urinary incontinence, such as urinary leakage or loss of urinary control been a problem for you during the last four weeks?

2. How much has your husband's or partner's urinary irritation or blockage, such as frequent urination, pain or burning with urination, urinary urgency, waking up to urinate, blood in the urine, or related difficulties in passing his urine, been a problem for you during the last four weeks?

3. How much has your husband's or partner's overall urinary function, such as urinary leakage, incontinence, frequent urination, urinary urgency, urinary burning, urinary bleeding, waking up to urinate, or other urinary difficulties been a problem for you during the last four weeks?

4. How much has your husband's or partner's bowel habits, such as rectal urgency, frequent bowel movements, leakage of stool, bloody stool, or painful bowel movements, been a problem for you during the last four weeks?

5. How much has your husband's or partner's sexual function such as his degree of sexual desire, the frequency and quality of his erections, or the level of sexual activity, been a problem for you during the last 4 weeks?

6. How much has your husband's or partner's hormone function and vitality, such as lack of energy, hot flashes, breast tenderness, weight gain, or mood changes, been a problem for you during the last 4 weeks?

(Response options included "No problem - Very small problem - Small problem - Moderate problem - Big problem")

Clinical Data Collection, Storage, and Monitoring:

Race/ethnicity data were collected by subject query at the time when informed consent was signed. Demographic and clinical data were collected at clinical sites (pre-treatment and 6, 12, and 24 months after treatment) and stored in a centralized, web-based database. Annual site audits ascertained database concordance with source documents; double data entry of a random subset ascertained database accuracy. Data and safety monitoring board review was conducted biannually.

Adverse Events

As this was an observational study, no adverse events were encountered that were attributable to the conduct of the study protocol per se. However, adverse events consequent to the treatments that were being evaluated were anticipated and thus were prospectively measured,

and the acute adverse events associated with the primary treatment (based on prospective tracking of patients' clinical course and their medical records at each clinical site) are summarized as follows:

Supplemental Table: Treatment-related Adverse Events

<u>Adverse Event Category</u>	<u>Treatment Group</u>					
	Prostatectomy		External Radiotherapy		Brachytherapy	
	N	(%)	N	(%)	N	(%)
Death	0	(0)	0	(0)	0	(0)
Serious Adverse Events						
Pulmonary embolus	2	(0.3)	0	(0)	0	(0)
Recto-urethral fistula	1	(0.2)	0	(0)	0	(0)
Other Adverse Event(s)*						
Urinary Retention	17	(2.9)	2	(0.7)	28	(9.2)
Urethral Stricture	31	(5.3)	0	(0)	1	(0.3)
Hematuria	4	(0.7)	2	(0.7)	1	(0.3)
Urinary Tract Infection	30	(5.2)	4	(1.5)	12	(4.1)
Wound or other infection	48	(8.3)	8	(2.9)	6	(2.1)
Rectal bleed or diarrhea	2	(0.3)	13	(4.7)	5	(1.7)
Transfusion	19	(3.3)	3	(1.1)	3	(1.0)
Deep Venous Thrombosis	13	(2.2)	0	(0)	1	(0.3)
Hospital or ED admit for AE	7	(1.2)	1	(0.4)	1	(0.3)

* Adverse events deemed significant were those that required intervention, eg retention or hematuria requiring urethral catheterization, diarrhea requiring immodium, etc.

Treatment Details:

For brachytherapy, pre-implant transrectal ultrasound was used for dosimetry planning. Prescribed dose was 145 Gy or 125 Gy for monotherapy performed using 125-Iodine or 103-Palladium, respectively; modified peripheral loading technique was generally employed. Patients treated with combined external radiation and brachytherapy received 45 Gy in 25 fractions to the prostate and seminal vesicles, and permanent seed implant with a dose prescription of 72 to 108 Gy for 125-Iodine or 100 Gy for 103-Palladium. External radiotherapy was accomplished using thin slice axial CT with reconstruction of the prostate, seminal vesicles and adjacent structures to create 3D targets for dose delivery. Among prostatectomy patients, the plan for nerve-sparing was collected prior to surgery to facilitate nerve-sparing analysis by intent to treat. One brachytherapy and one prostatectomy case were not completed due to unanticipated anatomic hindrance; these were included in their respective intent-to-treat groups.

Neoadjuvant hormone therapy (NHT): Among NHT recipients, NHT was administered for an average of 5 months; 89% received NHT for a duration 6 months or less and 94% received NHT

for less than 1 year. Among NHT recipients, 68% received LHRH agonist, 26% received total androgen blockade (combination LHRH agonist together with anti-androgen), and 6% received anti-androgen monotherapy. Patients underwent pretreatment interview before starting NHT in order to capture the full range of multi-modality treatment-related side effects. Based on this pattern of NHT duration, testosterone recovery would have been expected to have occurred prior to the 12 month assessment in most cases and prior to 24 month HRQOL in all but a few; however, testosterone levels were not uniformly measured during follow-up.

Analyses:

Model-building by GEE (Table 3): Separate models were fit for each treatment group and HRQOL domain using a modified backward model building procedure for variable selection. Evaluated variables included those listed in Table 1 and treatment-specific variations (nerve-sparing status for prostatectomy models, NHT for external radiation and brachytherapy models, and combination with external beam radiation for brachytherapy models). Models contained indicators for each time point and interaction terms between each factor with each time indicator. Backwards model-building was based on the Wald test, with the set of factor/time interactions that was least significant in each iteration of the model-building procedure removed until we arrived at a parsimonious model.

The relationship between patient HRQOL change and Satisfaction with Treatment Outcome (SO) one year after treatment among both patients and spouses was assessed by in two ways (Table 5). Spearman rank correlations were used to separately assess the bivariate relationship of each HRQOL domain with SO. Linear regression models were then used to determine the independent contribution of each HRQOL domain on SO while simultaneously adjusting for all other domains, with separate models fit for patient and spouse SO.^{24,25,27} Standard errors were calculated using the GEE sandwich method. Relationships of baseline covariates listed in Table 1 and the SO scale of SCA were also assessed using linear regression models with backward model-building (standard errors calculated by GEE sandwich method).

Sample size: Sample size for the analyses of Figure 1 and Tables 1, 2, and 3 is 1201. The sample size for Table 4 is 543 patients and 543 spouses (eg, 543 dyads) as this represents only those responding patients who also had participating spouses or partners at 12 months (just over one-half of patients also had participating spouses/partners). Sample size for Table 5, patients section is 1088 as this is number of all responding patients at 12 months (irrespective of whether or not they had a participating spouse/partner) and for Table 5, spouses section is 543.

Table 3 Supplemental Information: Listed in Table 3 are those factors that were significant with p values as shown, that showed association with HRQOL outcome ($p < 0.05$) in at least one timepoint of follow-up with a significant effect during the entire post-treatment follow-up overall, and (for categorical variables) that exceeded the threshold of minimally important change (MIC) as evidenced by effect size (as measured by parameter estimate) $> 0.5 * SD$ of the baseline HRQOL scores in that domain. For each continuous variable (eg age, PSA, prostate size), increasing values were associated with worse HRQOL outcome, except that larger prostate size was associated with greater post-prostatectomy improvement in Urinary Irritative-Obstructive outcome than smaller prostate size, and higher PSA was associated with better post-brachytherapy urinary irritative outcome than lower PSA. For categorical factors (eg obesity, defined as BMI > 35), the tabulated form of the variable was associated with worse outcome than that of the unlisted category (eg African American race had worse urinary incontinence than non-

African American race) with the exception of nerve-sparing (associated with better sexual outcome), lower comorbidity associated with worse vitality/hormonal change after ERT, and ERT boost, that was associated better urinary incontinence outcome than brachytherapy monotherapy.

Table 4 Supplemental Information: Only those patients who had participating spouse partners are shown; HRQOL data from all patients (including those without participating spouse/partners) are in Table 2.