

Evidence Table

Clinical Area: Proton therapy for prostate cancer

Reference: Slater JD, Rossi CJ, Yonemoto LT, et al. Proton therapy for prostate cancer.: The initial Loma Linda University experience *Int J Radiat Oncol Biol Phys* 2003;59:348-352.

Study Type: Retrospective case series.

Study Aim: To review and analyze the results of conformal proton radiation therapy for localized prostate cancer.

Outcomes

- *Primary:* Freedom from biochemical evidence of disease.

Design

- *Number of subjects:* 1,255
- *Description of study population:* These were men with localized prostate cancer, treated in Loma Linda University with proton therapy alone or in combination with photon therapy between 1991 and 1997. Their ages ranged from 44-90 years (median 69 years, 51% had an initial PSA 4.1-10.0, 29% 10.1-20, 11% >20 and 9% had a PSA less than 4. Three fourths had a Gleason score 5-7, 18% 2-4 and 7% 8-10. 26% had a stage T1c, 24% T2a, 20% T2b, and 235 T2c.
- *Inclusion criteria:* Localized prostate cancer (Stages Ia-III) treated with conformal proton therapy alone or in combination with photon therapy, received no prior surgery or hormone therapy, with no evidence of distant metastases at time of treatment.
- *Consecutive patients?* The series included 1,255 patients out of 1,961 patients treated in the center.
- *Intervention:* All patients received an initial physical examination, and PSA test. Imaging studies as bone scan and endorectal MRI were performed among patients judged to be appropriate candidates according to the investigators. In the first few years of using the proton therapy the patients (N=731) received a proton boost of 30 CGE in 15 fractions delivered to the prostate and seminal vesicles, followed by 45 Gy of photon radiation therapy to a volume that included the first and second-echelon lymphatics. The photon therapy was delivered by 3-D conformal techniques. After few years of using proton therapy at this center patients were divided to 2 treatment groups. Based on the normogram used (Partin) patients with a risk $\geq 15\%$ for micrometastases in the lymph nodes received the combined proton and photon therapy, while those with lesser risk received all their treatment with protons alone to the prostate and seminal vesicles.
- *Source of outcome data:* Patients were monitored weekly during treatment. Freedom from biochemical evidence of disease was estimated using consensus definition of the American Society for Therapeutic Radiology and Oncology. Failure was defined as three consecutive rises in PSA levels.
- *Length of follow-up:* Median follow-up duration 63 months (range 1-132 months).

Validity

- *Is the study type appropriate for the question(s) being asked?* No, a randomized controlled trial would be more appropriate.
- *Were patients similar with respect to baseline characteristics?* There were variations in the patients' ages, PSA levels, stages, and grades of the disease.
- *Was the intervention and other aspects of patient care similar for all patients (or for all patients in a defined subgroup)?* No.
- *Was the process of observation likely to affect the outcome?* No.
- *Did an objective observer assess outcomes and were outcome measurements consistent?* Yes.
- *Was follow-up duration appropriate?* No.
- *Was follow-up rate sufficient?* Not discussed.

- **Conclusions regarding validity of methods:**

The study was a retrospective case series, with no control or comparison group. There were baseline differences between the patients, and there were variations in the treatments received.

Result:

Actuarial biochemical disease-free survival:

5-year survival	75%
8-year survival	73%

Effect of initial PSA on biochemical freedom from relapse at 5 years

PSA level	% biochemical freedom
≤4.0	90%
4.1-10.0	84%
10.1-20.0	68%
>20	48%
P for difference	0.0001

Effect of grade on biochemical freedom from relapse at 5 years

Gleason score	% biochemical freedom
2-4	82%
5-7	73%
8-10	50%
P for difference	p=0.8 for difference between 2-4 and 5-7 P<0.0001 for 8-10 score versus lower scores.

Treatment related morbidity

Toxicity in patients treated with protons alone 6/544 (1.1%)

Toxicity in patients treated with combined proton and photon therapy 11/731 (1.50%)

P for difference =0.52

Overall toxicity

Grade \geq 3 acute gastrointestinal (GI) or genitourinary (GU) morbidity	<1%
Grade \geq 3 late gastrointestinal or genitourinary morbidity	1%
Grade <u>4</u> gastrointestinal or genitourinary morbidity	0.2%

*Late GI toxicity**

Included Grade 3 bleeding and pain in 2 patients, and a bowel obstruction requiring colostomy in 1 patient.

*All severe GI toxicity presented within the first 2.5 years after treatment.

Actuarial 5 and 10 year rates from freedom from Grade 3 and 4 GI toxicity were both 99%

*Late GU toxicity**

Grade 3 toxicity 14 (1.1%)

*8 had urethral strictures followed by hematuria in 4 patients and dysuria in 2 patients

Actuarial 5 and 10 year rates from freedom from Grade 3 and 4 GU toxicity were both 99%

Authors' Conclusions

The authors concluded that conformal proton beam radiation therapy of prostate cancer yielded disease free survival rates comparable with other forms of local therapy and with minimal morbidity.

Reviewer's Conclusions

This was a retrospective case series with selection bias, and no comparison or control group. In the early 1990s patients with localized prostate cancer received a combination therapy with both protons and photons. Later, after the proton treatment capacity increased, the patients were selected to receive either proton therapy alone or in combination with photon therapy. This selection of treatment was based on their risk of lymph node micrometastases as calculated by Partin nomogram.