Role of radical prostatectomy in high-risk prostate cancer

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Many methods exist to define high-risk prostate cancer. These include clinical stage, serum PSA, and pathological features such as Gleason score and the number of positive biopsies. Partin tables are widely used to stratify patients according to risk of adverse pathological features at surgery, and to identify those more likely to remain free of recurrent disease following surgery. The priority in most patients with localized prostate cancer remains the selection of a treatment that will provide them with the best chance for cure. While treatment-related morbidity is an important issue, we believe that side effects of surgery or radiation therapy are not increased in patients with high-risk cancer. Results from a small number of population studies indicate a highly significant improvement in disease-specific survival for radical prostatectomy compared to radiotherapy, and it appears that this difference may become more pronounced as the grade of the cancer increases. While acknowledging the need for adjuvant radiotherapy and/or hormonal therapy, we suggest that radical prostatectomy may offer a better primary treatment option for patients with high-grade cancer. However, urologists must be prepared for higher failure rates when performing this surgery in patients with high-risk disease compared to those with low-risk disease.

Key Words: radical prostatectomy, high-risk prostate cancer, disease-free survival

Introduction

High-risk prostate cancer can be defined in many ways, using clinical stage, serum PSA level, and pathological features, including the Gleason grade and the number of positive biopsies. Partin and colleagues have proposed nomograms to stratify patients according to risk of adverse pathological features at surgery. These nomograms have been widely used to select patients more likely to remain free of recurrent disease after surgery. This philosophy of selecting the ideal patient for treatment success is somewhat opposite to one attempting to select the optimal treatment combination for cancer control, taking into account treatment morbidity. In this latter approach, high-risk prostate cancer is defined by risk of dying from the disease.

Limited information exists on the natural history of localized prostate cancer treated by expectant management and palliative hormonal therapy. The most accurate available marker remains the Gleason grade of the biopsy. Albersten and colleagues produced a very useful table showing the risk of death from prostate cancer or other causes according to patient age at diagnosis and the Gleason grade on biopsy.[1] These tables clearly show that Gleason grade

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TABLE 1. **10-year disease-specific survival in patients with clinically localized prostate cancer according to treatment received[2]**

Treatment received	Grade 1		Grade 2		Grade 3	
	n	% survival (95% CI)	n	% survival (95% CI)	n	% survival (95% CI)
Prostatectomy*	3402	98 (97-99)	12 922	91 (89-93)	4154	76 (71-80)
Radiotherapy	4188	89 (87-92)	8456	74 (71-77)	2977	52 (46-57)
Conservative	10 133	92 (90-93)	7046	76 (73-78)	2834	43 (38-48)

*Treatment received results differed significantly ($p<0.0001$)

5 or lower is associated with a very low risk of death from cancer over 15 years, even in younger patients. Contrary to this, cancers with a Gleason score of 7 and above are associated with 100% risk of death from cancer in younger patients, and a risk of death from cancer between 40% and 60% at 10 years in men aged 70 to 75 years. The priority in most patients diagnosed with localized prostate cancer remains the selection of a treatment that will provide them with the best chance for cure. Treatment-related morbidity is an important issue, but in our opinion, side effects of surgery or radiation therapy are not increased in patients with high-risk disease. On the other hand, patients with high-risk cancer are more likely to accept morbidity due to treatment compared to patients with low-risk disease, who have many options available, including expectant management.

Treatment efficacy in high-risk prostate cancer

In the absence of randomized clinical trials, the best available information comparing different treatment strategies is based on a small number of population studies. The first and most important of these, by Lu-Yao and colleagues, reported 10-year disease-specific survival in over 55 000 patients with clinically localized prostate cancer according to treatment received and cancer grade,Table 1.[2] The authors observed a highly significant difference between radical prostatectomy and radiotherapy in all cancer grades. This difference was significantly more pronounced as the grade of the cancer increased. In grade 2 cancer, there was a 23% improvement in disease-specific survival at 10 years with radical prostatectomy compared to radiotherapy, and in grade 3 cancer, a 46% improvement in disease-specific survival. At the 2001 annual meeting of the American Urological Association, Menon and colleagues presented a similar analysis of overall survival of patients according to grade, adjusted for age, race, co-morbidity, and year of diagnosis.[3] Their study included over 3000 patients distributed equally between conservative treatment, radiotherapy, and prostatectomy. Despite a trend in favor of radical prostatectomy, there was no statistically significant difference between prostatectomy and radiotherapy in patients with low-grade disease, but both treatments offered a survival benefit over conservative treatment Figure 1a. On the other hand, in patients with high-grade cancers, radical prostatectomy was associated with a marked increase in overall survival when compared to radiation therapy, which itself was superior to conservative treatment. The median survival of patients treated conservatively was 6 years, compared to 7.5 years for radiation therapy, and 15 years for surgery Figure 1b.

The Mayo Clinic group has a long experience of radical prostatectomy in stage T3 prostate cancers. They reported 5-, 10-, and 15-year cancer-specific survival rates of 90%, 80% and 69% respectively.[4] This was in a high-risk group; 60% of patients had Gleason score of 7 or above, and 33% had positive lymph nodes. Over 60% of patients received adjuvant radiotherapy and/or hormonal therapy. Akakura and colleagues recently reported the first prospective randomized trial of radical prostatectomy and radiation therapy in high-risk prostate cancer.[5] A total of 95 patients with an average age of 68 years, stage T3 prostate cancer, and an average PSA of 20 were treated with continuous endocrine therapy initiated 2 months before randomization to radical prostatectomy or radiation therapy and continued indefinitely thereafter. The two

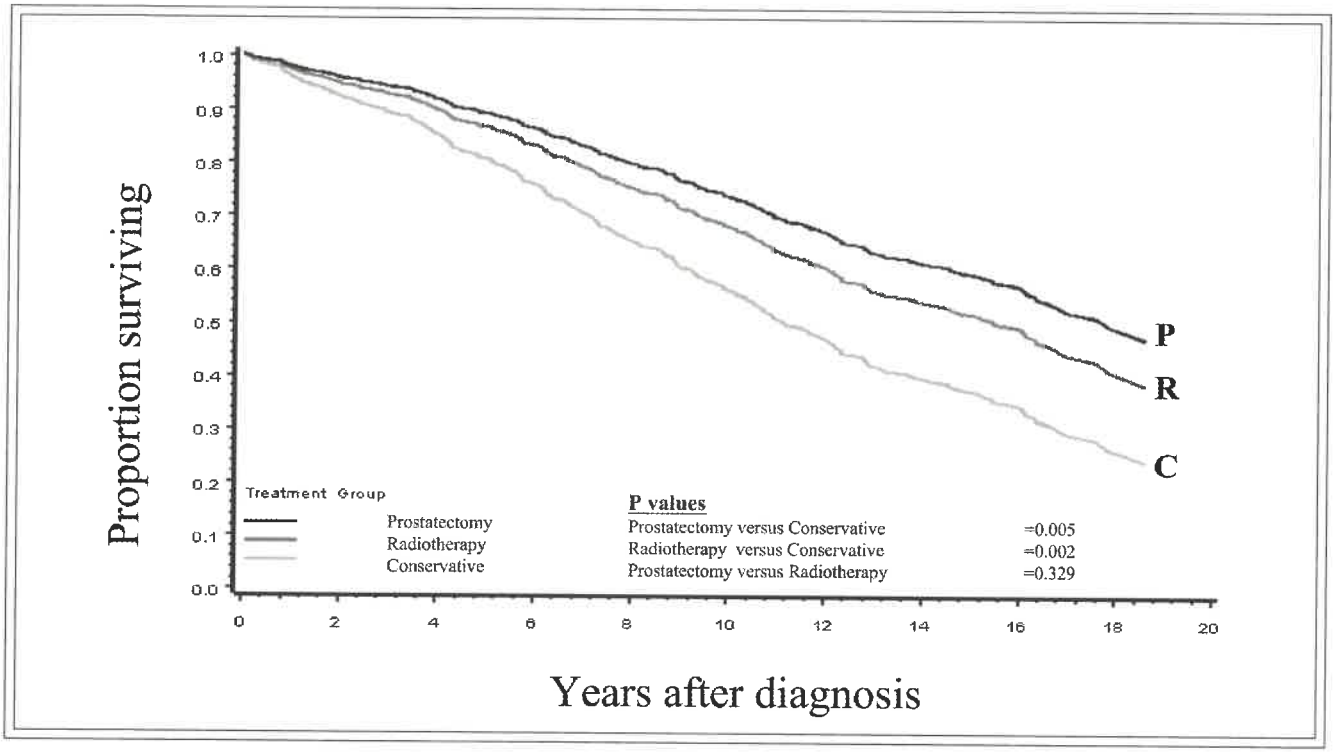

Figure 1a. Adjusted overall survival curves for grade 1 patients (adjusted for age, race comorbidity, year of diagnosis, income and grade).[3]

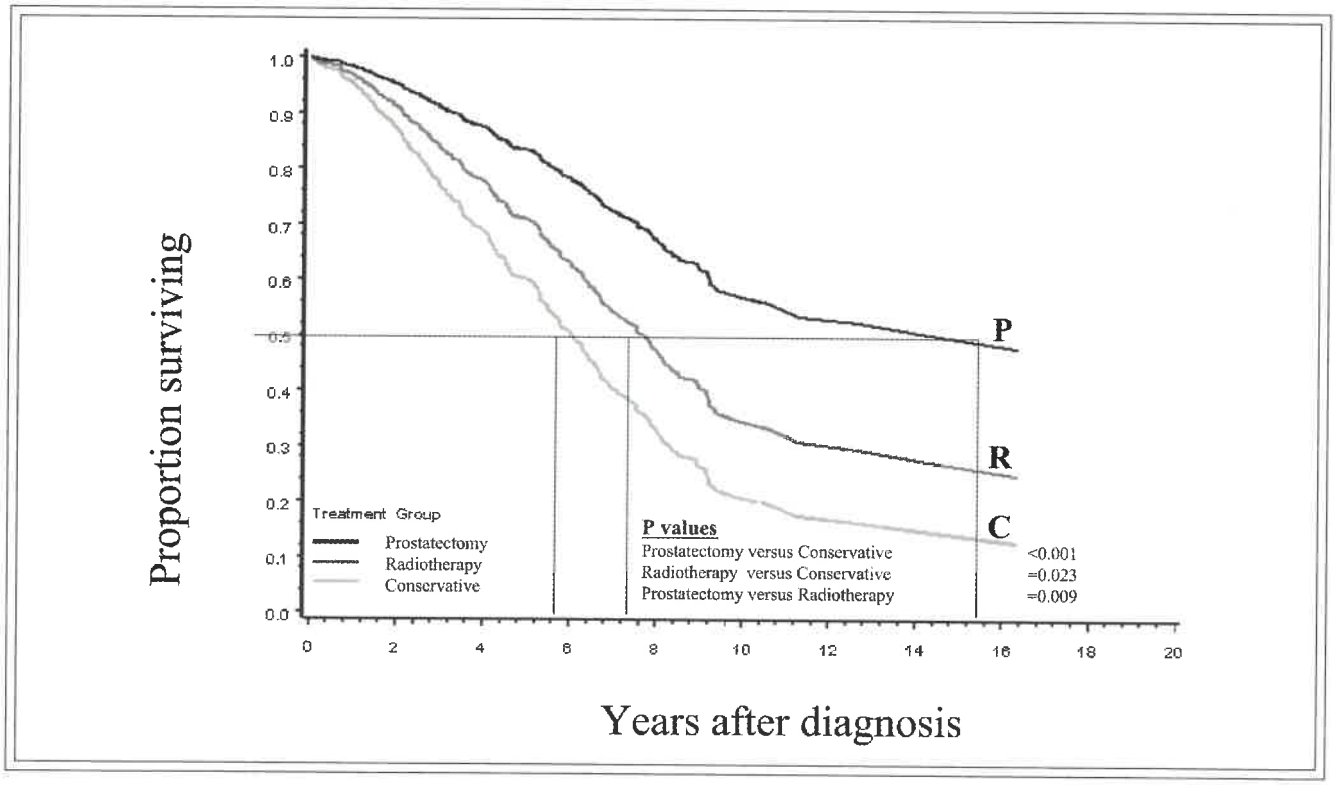

Figure 1b. Adjusted overall survival curves for grade 3 patients (adjusted for age, race comorbidity, year of diagnosis, income and grade).[3]

groups were well-balanced in terms of risk factors Table 2. The 5-year cancer-specific survival was 96.6% for patients treated with surgery, compared to 84.6% for patients treated with radiation Table 3. Despite the small sample size, this study showed that treatment of primary tumors can influence the survival of patients with high-risk prostate cancer treated with hormonal therapy.

Studies examining PSA recurrence after treatment indicate that current conformal radiotherapy is expected to provide better cancer control than the radiotherapy modalities used more than 10 years ago. However, it is clear that the amount of cancers detected by PSA failure after radical prostatectomy is significantly lower than that detected by PSA failure after radiotherapy, due to the amount of PSA produced by the prostate gland remaining in place. Moreover, in patients with local failure after radical prostatectomy, radiotherapy can still offer a 50% long-term remission. These considerations must be taken into account before making definitive conclusions on the relative efficacies of the two treatments simply based on studies comparing PSA recurrence-free survival.

TABLE 2. **Randomized trial in high-risk patients**[5]

		Surgery	Radiation
Number of patients		46	49
Age		68.1 + 7.0	68.7 + 6.6
Performance status	0	31	38
	1	15	11
Performance status	well	9	10
	moderately	25	22
	poorly	12	16
Clinical stage	B2	17	13
	C	29	36
Mean PSA		19.9	21.6

TABLE 3. **5 year survival (%)**[5]

	Progression-free	Cause-specific	Overall
Surgery	90.5	96.6	85.6
Radiation	81.2	84.6	75.9
Significance	P=0.044	P=0.024	N.S.

Radical prostatectomy in patients with metastases

Only one randomized study to date has shown a survival benefit for long-term hormonal therapy in patients with lymph node metastases treated with radical prostatectomy.[6] One important question related to the current discussion is whether radical prostatectomy in patients with metastatic disease has an impact on survival. Cadeddu and colleagues retrospectively reviewed 168 patients with positive lymph node surgery.[7] They found a significant (p=0.006) survival benefit in the 127 patients who underwent radical prostatectomy compared to the 41 who did not Figure 2. However, although the two groups were comparable with regard to age, Gleason score, and preoperative PSA, patients not treated by radical prostatectomy had a higher percentage of positive nodes (48% versus 14%, p=0.001) and larger nodes (1.2 mm versus 0.2 mm, p=0.001) compared to those who underwent surgery. The number of positive lymph nodes has recently been shown to influence cancer-specific survival in a cohort of 3463 patients.[8] Ghavamian and colleagues compared two groups matched for clinical stage, grade, and median PSA (which was 34), treated by orchiectomy alone or orchiectomy plus prostatectomy.[9] As shown in Figure 3, there was a striking and highly significant survival advantage in patients treated by radical prostatectomy plus orchiectomy compared to those treated by orchiectomy alone.

Thompson and colleagues presented a study at the 2001 annual meeting of the American Urological Association suggesting that prior radical prostatectomy could influence outcome in patients treated by hormonal therapy for stage D2 prostate cancer.[10] This analysis was stimulated by results of two randomized trials in kidney cancer which showed a significant survival advantage for radical nephrectomy in patients with metastatic disease treated by interferon. The authors reviewed a cohort of 1286 patients randomized to castration alone or to castration plus flutamide for metastatic cancer. Of this cohort, 148 patients were treated with prior prostatectomy, and 219 patients with prior radiotherapy. These treatments were performed more than 2 years before the diagnosis of metastases and randomization in the study compared to diagnosis was made less than

a year before randomization for patients without prior prostatectomy or radiotherapy. When adjusting for all variables, they found that patients with prior radical prostatectomy had a 33% reduction in risk of dying compared to patients with no radical prostatectomy. Patients with prior radiotherapy, on the other hand, had a 40% increased risk of death. These results suggest that removal of the primary tumor in high-risk cancers might have a higher impact on cancer survival than previously estimated.

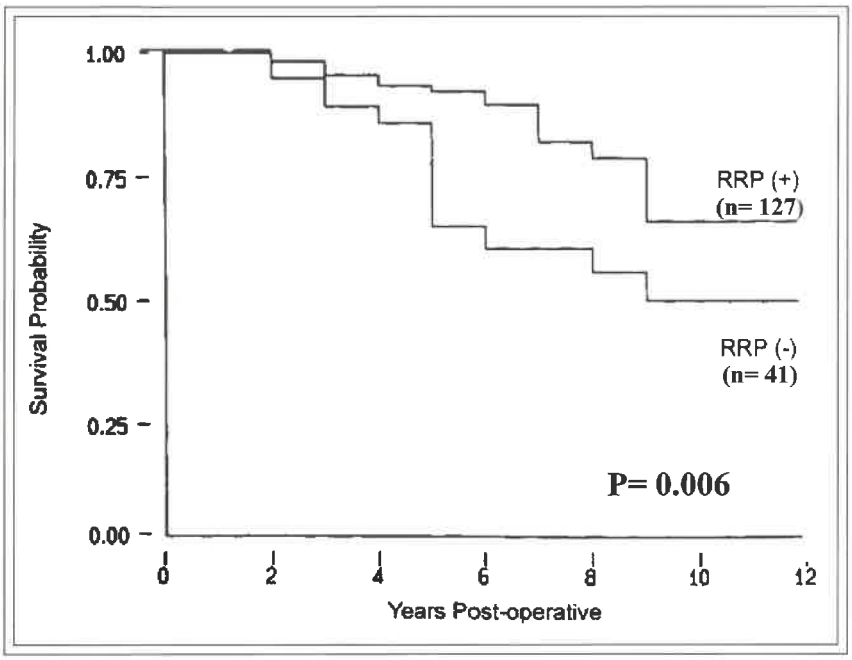

Figure 2. Cancer-specific survival of D1 patients.[7] (Reprinted with permission)

Conclusion

Based on available information, we suggest that radical prostatectomy may offer a better primary treatment option for patients with high-grade cancer, acknowledging the need for adjuvant radiotherapy and/or hormonal therapy. The morbidity of surgery is not different in high-risk than in low-risk patients, and the long-term benefit may be significantly higher. Urologists offering prostatectomy to patients with high-risk disease must, however, be prepared to deal with higher failure rates than when treating patients with low-risk disease. □

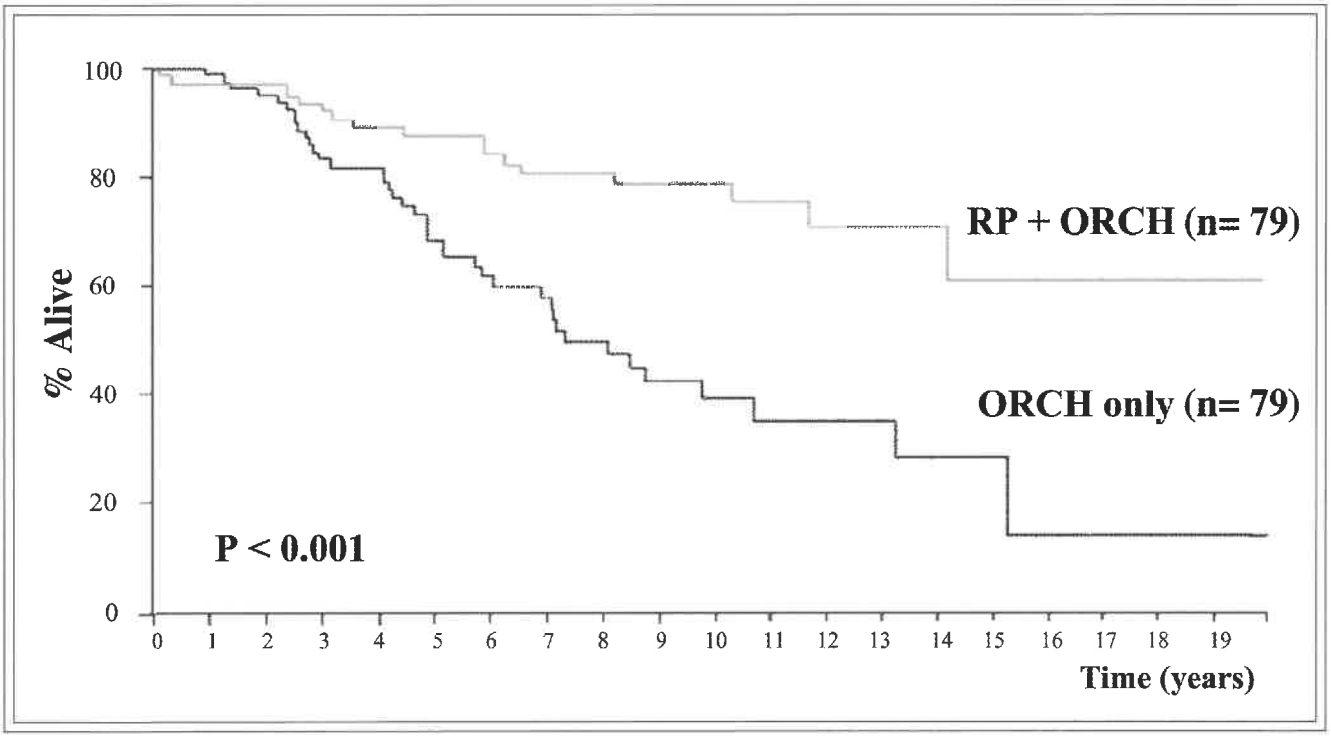

Figure 3. Cancer-specific survival of patients undergoing RP+ORCH *versus* ORCH only.[9] (Reprinted with permission)

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