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ARTÍCULO ORIGINAL

The role of radical prostatectomy in the management of patients with high-grade prostate cancer and/or locally advanced disease†

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ABSTRACT

Objective. To analyze the outcome of patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy (RP) in whom high-grade (HGPCa) and/or locally advanced disease (LAPCa) was found at RP specimen and to evaluate the prognostic value of well-known factors in this subset of patients. **Material and methods.** Biochemical progression-free (bPFS) was determined with the Kaplan-Meier method. The effect of PSA, biopsy Gleason, clinical stage and number of adverse pathological factors was assessed with univariate and multivariate analyses. **Results.** After RP, 87 men had HGPCa (20.7%) or LAPCa (56.3%), with 20 (23%) having both criteria. Mean PSA was 15.5 ± 14.0 ng/mL and mean follow-up 50.5 ± 42.6 months. The 5-year bPFS for men with PSA < 10 ng/mL and ≥ 10 ng/mL was 54.7% and 35.7%, respectively (p = 0.03). Regarding biopsy Gleason, the 5-year bPFS was 49% and 26% for patients with a score ≤ 7 and > 7, respectively (p = 0.002). In the multivariate model, the biopsy Gleason score remained independently associated with biochemical progression. **Conclusions.** HGPCa and/or LAPCa confer poor prognosis; however, RP appears to offer acceptable control, particularly when initial PSA is < 10 ng/mL and biopsy Gleason is 7 or less.

Key words. Radical prostatectomy. Locally-advanced prostate cancer. High-grade prostate cancer.

El papel de la prostatectomía radical en el manejo de pacientes con cáncer de próstata de alto grado y/o enfermedad localmente avanzada

RESUMEN

Objetivo. *Analizar la evolución de los pacientes con cáncer de próstata (CaP) clínicamente localizado tratados con prostatectomía radical (PR), en quienes se demostró CaP de alto grado (CaPAG) y/o enfermedad localmente avanzada (CaPLA) en el análisis patológico final y evaluar el valor pronóstico de los factores ya conocidos en este grupo de pacientes.* ***Material y métodos.*** *La supervivencia libre de progresión bioquímica (SLPB) se determinó con el método de Kaplan-Meier. El efecto del APE, Gleason de la biopsia, estadio clínico y el número de factores patológicos adversos fue evaluado mediante análisis univariado y multivariado.* ***Resultados.*** *87 pacientes tuvieron CaPAG (20.7%) o CaPLA (56.3%), incluyendo a 20 (23%) con ambos criterios. El promedio de APE fue 15.5±14.0 ng/mL y de seguimiento 50.5 ± 42.6 meses. La SLPB a cinco años en pacientes con APE < 10 ng/mL y ≥ 10 ng/mL fue de 54.7% y 35.7%, respectivamente (p = 0.03). En pacientes con Gleason de la biopsia ≤ 7 y > 7 fue de 49% y 26%, respectivamente (p = 0.002). En el modelo multivariado, el Gleason de la biopsia se mantuvo como un factor de riesgo independiente de progresión bioquímica.* ***Conclusión.*** *El CaPAG y/o CaPLA confiere un mal pronóstico; sin embargo la PR brinda un control adecuado, particularmente cuando el APE inicial es < 10 ng/mL y el Gleason de la biopsia es de 7 o menos.*

Palabras clave. *Prostatectomía radical. Cáncer de próstata localmente avanzado. Cáncer de próstata de alto grado.*

† The original version of this manuscript was presented at the 23rd Annual Meeting of the European Association of Urology, held in March 2008 in Milan, Italy.

INTRODUCTION

Poorly differentiated or high-grade prostate cancer (HGPCa) is referred to as tumors with a Gleason score ranging from 8 to 10.[1] Locally advanced prostate cancer (LAPCa) comprises those tumors with extraprostatic extension (EPE), invasion to the apex, bladder neck or seminal vesicles but without lymph node involvement or metastatic disease.[1] The management of these patients remains controversial and, historically, they have not been considered candidates for surgical therapy. The arguments to spare these patients from surgery include the potential lack of benefit if the tumor is not completely excised, the fear of an increase in morbidity and the absence of survival benefit.[2] However, there is increasing evidence suggesting that radical prostatectomy (RP) is an adequate alternative in the initial approach of selected patients with HGPCa/LAPCa.[2-6] Some contemporary series have shown that surgery is safe in this scenario and that complication rates are comparable to that of localized disease treated surgically.[2,7] Furthermore, the local control of the disease appears to be similar to that obtained with the combination of external radiation therapy (ERT) and androgen deprivation therapy (ADT).[8] Indeed, according to the American Urological Association guideline for the management of Clinically Localized Prostate Cancer 2007 Update,[9] "active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and surgery remain treatment options for the patient with high-risk disease due to the lack of evidence of superiority of one therapy over another". This is an important issue, since one of the strongest predictors for the development of distant metastases in patients with LAPCa is the ability to control the tumor locally.[10] In addition, RP provides acceptable local control in terms of preventing local morbidity secondary to regional progression and invasion of adjacent structures, such as bladder outlet obstruction, ureteral obstruction and gross hematuria.[8] Moreover, when combined with adjuvant therapy, the local control and overall survival after RP are comparable to that of organ-confined disease treated with surgery alone.[8]

Our main objective was to evaluate the RP results as the first line therapeutic modality in men with clinically localized PCa in whom HGPCa and/or LAPCa was demonstrated on histopathological analysis. We also assessed the prognostic value of well-known preoperative factors of progression in these patients.

MATERIAL AND METHODS

We have previously reported our experience in the surgical management of patients with PCa and adverse pathological characteristics.[11] In the present study, we analyzed the outcome of men with clinically localized PCa in whom HGPCa and/or LAPCa was demonstrated at RP specimen from 1990 to 2008. To avoid selection bias patients with lymph node invasion were excluded from this analysis. Clinical and pathological stages were determined according to the TNM 2002 system.[12] In all cases an open RP with bilateral standard pelvic lymph node dissection was performed. Postoperative follow-up consisted of serum prostate-specific antigen (PSA) determination and digital rectal examination (DRE) every 3 months for the first two years and annually thereafter. Biochemical progression (BP) was defined as a postoperative PSA determination of 0.4 ng/ml or higher,[13-15] or the need to initiate either ERT or ADT. Additional (salvage) therapy was started when biochemical, local or systemic recurrence was demonstrated.

Table 1. Clinical and pathological characteristics of 87 patients with High-grade/Locally advanced prostate cancer treated with radical prostatectomy.

Variable	No.	%
Clinical		
PSA ng/dl (range)	15.5±14.0 (3-84)	–
Clinical Stage		
cT1a-c	47	54.0
cT2a	29	33.3
cT2b	4	4.6
cT2c-T3	7	8.1
Biopsy Gleason		
≤ 6	43	49.4
7	33	37.9
≥ 8	11	12.7
Pathological		
Pathological stage		
pT2	18	20.7
pT3a	28	32.2
pT3b	41	47.1
Surgical margins		
Negative	49	56.3
Positive	38	43.7
Final Gleason score		
≤ 6	20	23.0
7	29	33.3
≥ 8	38	43.7

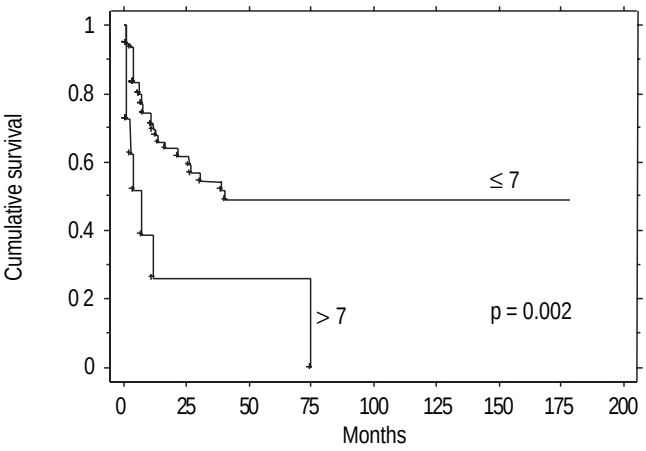

Figure 1. Biochemical progression-free survival according to Biopsy Gleason score.

Biochemical progression-free survival (bPFS) was determined with the Kaplan-Meier method and the comparison of the results was performed with the log-rank test. The prognostic role of preoperative PSA, clinical stage, biopsy Gleason and the number of adverse pathological factors discovered at RP specimen (HGPCa or LAPCa isolated or together), was evaluated univariately. The combined influence of these factors was assessed by means of a multivariate Cox proportional hazards analysis. All results were considered statistically significant with a $p < 0.05$. All tests were performed with the software StatView (SAS Institute, Cary, NC, USA).

RESULTS

A total of 94 patients had HGPCa and/or LAPCa after RP. Of these, 7 with positive lymph nodes were excluded, leaving 87 cases eligible for analysis. Patients and tumor characteristics are summarized in table 1. Mean age was 63.9 ± 7.1 years (range 45-75). Mean follow-up was 50.5 ± 42.6 months (range 3-179). Palpable disease was detected on DRE in 46% of cases and 50.6% had a biopsy Gleason 7 or higher.

At RP specimen, 18 patients (20.7%) had a final Gleason score ≥ 8 (HGPCa), 49 (56.3%) were in stage pT3a-b (LAPCa) and 20 (23.0%) had both criteria.

In all, 38 patients (43.7%) have experienced BP. The 5-year bPFS in the whole cohort was 43.8%. When stratified by initial PSA, it was 54.7% and 35.7% for those with an initial value < 10 ng/mL and ≥ 10 ng/mL, respectively ($p = 0.03$). Regarding biopsy Gleason, the 5-year bPFS was 49% and 26% for patients with a score ≤ 7 and > 7, respectively ($p = 0.002$, Figure 1).

We also analyzed survival according to the presence of adverse features. The 5-year bPFS for men having LAPCa, HGPCa and both was 51.8%, 38.6% and 32%, respectively; however this difference was not statistically significant ($p = 0.12$).

Biopsy Gleason ($p = 0.003$) and the presence of both HGPCa and LAPCa simultaneously ($p = 0.05$) were associated with the likelihood of BP in the univariate analysis. The initial PSA showed a trend towards association with BP ($p = 0.06$). Clinical stage was not related to this risk ($p = 0.54$). In the multivariate Cox proportional hazards model the Biopsy Gleason score remained as the only independent prognostic factor associated with BP (OR 2.92, 95% CI [1.23-6.90], $p = 0.01$).

DISCUSSION

The management of high-risk prostate cancer is still a matter of debate and an optimal modality of therapy has not been yet defined. In the past, patients with poorly differentiated or locally advanced disease have not been considered candidates for surgical treatment.[1] The potential absence of benefit if the tumor is not completely excised, the fear of increasing morbidity and the lack of survival advantage are some reasons to avoid surgery in this setting.[2] Nevertheless, there is increasing evidence suggesting that the combination of RP and adjuvant therapy, results in local control and overall survival comparable to that of organ-confined disease treated with surgery alone.[8] Recently, two large prospective clinical trials investigated the role of adjuvant ERT in men with LAPCa treated with RP, showing that, despite increased toxicity, this strategy decreased the risk of BP.[16,17]

In this study we evaluated the outcome of patients with clinically localized PCa in whom LAPCa, HGPCa or both (excluding those with lymph node invasion) was demonstrated at the RP specimen. Our findings suggest that surgery may offer an adequate control of the disease mainly in patients with a low biopsy Gleason score. Similar survival rates were demonstrated by Lau and colleagues in a series of 407 patients with poorly differentiated PCa.[18] These authors found a 5- and 10-year cancer-specific survival of 93% and 85%, with a bPFS of 49% and 36%, respectively. In line with our findings, they suggested that an initial PSA < 10 ng/mL is a prognostic factor for the identification of patients with high-grade disease who will potentially benefit of surgical therapy. Serni and co-workers[19] found better survival rates, with a 5-year progression-free survival of

78.1% in patients with final Gleason score ≥ 8. They suggest that the favorable outcome is due, in part, to the low incidence of positive surgical margins; however it remains unclear whether this result could be a consequence of early ADT used in a subset of their patients with positive lymph nodes (comprising 38.7% of that series).[19]

In our cohort, 54% of men with aggressive tumors had non-palpable disease, an issue previously addressed by Epstein et al.[20] These authors suggested that the presence of small-volume high-grade tumors demonstrates that PCa could be potentially aggressive since early stages, without necessarily emerging from low-grade carcinoma.

Although our study had some limitations, including its retrospective nature and the limited number of patients, our findings suggest that surgery is an adequate option in the initial management of pathologically proven high-risk disease. In contrast, we consider that the strength of our investigation lies in the fact that all patients with positive lymph nodes were excluded, allowing the evaluation of a more homogenous population. Furthermore, all patients were managed uniformly, with all of them receiving salvage therapy until recurrence was demonstrated. This policy allowed us to perform a more accurate outcome assessment and, most of all, to evaluate the actual role or surgery in this subset of patients. Nevertheless, at present, we believe that RP should be performed as part of a combined strategy based on effective local therapy and systemic modalities. The low frequency of specimen Gleason 8-10 PCa makes a prospective evaluation difficult and multimodality strategies appear to be the best alternative in this scenario.[21-23] Moreover, the detection of HGPCa/LAPCa when PSA levels are below 10ng/ml and, particularly in those with a biopsy Gleason ≤ 7, seems to be the best method to achieve acceptable outcomes after RP.

CONCLUSION

Despite the poor prognosis conferred by HGPCa and/or LAPCa, our findings suggest that RP offers an adequate control of the disease in selected patients, particularly in those who preoperatively have an initial PSA < 10 ng/mL and a biopsy Gleason ≤ 7. However, at the moment, RP should be viewed as the initial step in the setting of multidisciplinary treatment in men with clinically localized high-risk disease. Further studies are necessary to assess the role of multimodal therapy in this setting.

REFERENCES

1. Van Poppel H, Joniau S. An analysis of radical prostatectomy in advanced stage and high-grade prostate cancer. *Eur Urol* 2008; 53: 253-9.
2. Gontero P, Marchioro G, Pisani R, Zaramella S, Sogni F, Kocjancic E, et al. Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. *Eur Urol* 2007; 51: 922-9.
3. Berglund RK, Jones JS, Ulchaker JC, Fergany A, Gill I, Kaouk J, et al. Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. *Urology* 2006; 67: 1253-6.
4. Rodríguez-Covarrubias F, Larre S, De La Taille A, Abbou CC, Salomon L. The outcome of patients with pathological Gleason score ≥ 8 prostate cancer after radical prostatectomy. *BJU Int* 2008; 101: 305-7.
5. Sciarra A, Gentile V, Voria G, Mariotti G, Seccareccia F, Pastore A, et al. Role of radical retropubic prostatectomy in patients with locally advanced prostate cancer: the influence of Gleason score 8-10. *Urol Int* 2003; 70: 186-94.
6. Inman BA, DiMarco DS, Slezak JM, Sebo TJ, Kwon ED, Leibovich BC, et al. Outcomes of Gleason score 10 prostate carcinoma treated by radical prostatectomy. *Urology* 2006; 68: 604-8.
7. Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005; 95: 751-6.
8. Ward JF, Zincke H. Radical prostatectomy for the patient with locally advanced prostate cancer. *Curr Urol Rep* 2003; 4: 196-204.
9. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007; 177: 2106-31.
10. Coen JJ, Zietman AL, Thakral H, Shipley WU. Radical radiation for localized prostate cancer: local persistence of disease results in a late wave of metastases. *J Clin Oncol* 2002; 20: 3199-205.
11. Rodríguez-Covarrubias F, Castillejos R, Sotomayor M, Gabilondo F, Feria G. The outcome of patients with prostate cancer and adverse pathological characteristics treated with radical prostatectomy. *Eur Urol Suppl* 2008; 7: 251.
12. Greene FL, Page DL, Fleaming ID, et al. American Joint Committee on Cancer, Manual for staging cancer. New York, NY: Springer; 2002, p. 337.
13. Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? *J Urol* 2001; 165: 1146-51.
14. Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ Jr, Lilja H, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol* 2006; 24: 3973-8.
15. Carroll P, Albertsen PC, Greene K, Babaian RJ, Ballentine Carter H, Gann PH, et al. Prostate specific antigen best practice statement: 2009 update. Available at http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf
16. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005; 366: 572-8.
17. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically ad-

vanced prostate cancer: a randomized clinical trial. *JAMA* 2006; 296: 2329-35.
18. Lau WK, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Radical prostatectomy for pathological Gleason 8 or greater prostate cancer: influence of concomitant pathological variables. *J Urol* 2002; 167: 117-22.
19. Serni S, Masieri L, Minervini A, Lapini A, Nesi G, Carini M. Cancer progression after anterograde radical prostatectomy for pathologic Gleason score 8 to 10 and influence of concomitant variables. *Urology* 2006; 67: 373-8.
20. Epstein JI, Carmichael MJ, Partin AW, Walsh PC. Small high grade adenocarcinoma of the prostate in radical prostatectomy specimens performed for non-palpable disease: pathogenetic and clinical implications. *J Urol* 1994; 151: 1587-92.
21. Do TM, Parker RG, Smith RB, Kagan AR. High-grade carcinoma of the prostate: a comparison of current local therapies. *Urology* 2001; 57: 1121-6.
22. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Frank I, Blute ML. Impact of prostate-specific antigen testing on the clinical and pathological outcomes after radical prostatectomy for Gleason 8-10 cancers. *BJU Int* 2008; 101: 299-304.
23. Katz MH, McKiernan JM. High-risk, clinically localized prostate cancer: is monotherapy adequate? *Rev Urol* 2007; 9(Suppl. 2): S19-S27.

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Recibido el 17 de diciembre de 2008.
Aceptado el 19 de agosto de 2009.