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Metastatic progression, cancer-specific mortality and need for secondary treatments in patients with clinically high-risk prostate cancer treated initially with radical prostatectomy

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A B S T R A C T

Purpose: To determine our results in high risk (HR) prostate cancer (PCa) patients treated with radical prostatectomy (RP) and to establish preoperative prognosis factors.
Material and methods: Retrospective study of 925 RP. Mean follow-up for the HR group was 89.8+/–53.6 months. Following NCCN criteria, we operated 210 (22.7%) HR and 715 (77.3%) low/intermediate risk patients. The endpoint was metastatic progression. Kaplan-Meier method for survival comparison among groups and Cox regression model for multivariate analysis of preoperative prognostic factors were used.
Results: Revised period; 1986-2007. Fifty-four patients (25.7%) were free of disease and 8 patients (3.8%) died for other causes free of disease. Disease progressed in 148 patients (70.5%); death due to tumour progression occurred in 42 cases (20%) and due to other causes in 25 patients (11.9%). Seventy-nine patients in HR group (38%) vs 549 low/intermediate risk group (78.5%) did not deserve further treatments (p<0.001). The uni and multivariate analysis for metastatic progression showed both Gleason score at biopsy (RR=1.922; 95% CI 1.106-3.341, p=0.020) and clinical stage (RR=2.290; 95% CI 1.269-4.133, p=0.006) showed independent prognostic value for metastatic progression, but not PSA.
Conclusions: An HR patient can be cured in a third of the cases and will need multimodal treatments in more than half of the times. We prompt surgery in a young healthy patient with a resectable tumour, mainly if just one bad prognostic factor is present and defiantly if this is just PSA elevation.

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Progresión metastática, mortalidad cáncer específica y necesidad de tratamientos de segunda línea en pacientes con cáncer de próstata de alto riesgo tratados inicialmente mediante prostatectomía radical

Palabras clave:
Muerte
Gleason score
Metástasis
Predicción
Cáncer de próstata
PSA
Prostatectomía radical
Grupos de riesgo
Fallo de tratamiento

RESUMEN

Objetivos: Determinar nuestros resultados en pacientes con cáncer de próstata (CaP) de alto riesgo (AR) tratados mediante prostatectomía radical (PR) y establecer criterios pronósticos preoperatorios.

Material y métodos: Estudio retrospectivo de 925 PR. El seguimiento medio fue 89,8+/–53,6 meses para el grupo de CaP de AR. Siguiendo los criterios NCCN, operamos 210 (22,7%) PR de AR y 715 (77,3%) de riesgo bajo/intermedio. Se utilizó el método Kaplan-Meier para análisis de supervivencia y el modelo de Cox para el análisis multivariado de factores pronósticos para progresión metastática.

Resultados: Periodo revisado; 1986-2007. Cincuenta y cuatro pacientes de AR (25,7%) estaban libres de progresión y 8 pacientes (3,8%) murieron por otras causas libres de enfermedad. El CaP progresó en 148 pacientes (70,5%). Murieron por progresión tumoral 42 pacientes (20%) y por otras causas 25 pacientes (11,9%). Setenta y nueve pacientes de AR (38%) frente a 549 de riesgo bajo/intermedio (78,5%) no necesitaron más líneas de tratamiento ($p < 0,001$). Los análisis uni y multivariados demostraron que tanto el score Gleason en biopsia (RR = 1,922; IC 95% 1,106-3,341, p = 0,020) como el estadio clínico (RR = 2,290; IC 95% 1,269-4,133, p = 0,006) mostraron valor pronóstico independiente para progresión metastásica, pero no el PSA.

Conclusiones: Un paciente con CaP de AR que se opere tiene un 25% de posibilidades de curarse y podrá necesitar un tratamiento multimodal en más de la mitad de los casos. Recomendamos PR en un paciente joven si el tumor se considera resecable, sobre todo si el único factor pronóstico que lo encasilla como AR es la elevación del PSA.

Introduction

Consensus is still far from being established in relation to the treatment of high-risk (HR) prostate cancer (PCa). The clinical guides of the European Association of Urology recommend radical prostatectomy (RP) with a life expectancy of over 10 years, with grade C recommendation.[1] Relevant series[2,3] report disease-free survival (DFS) and cancer-specific survival (CSS) rates comparable to those afforded by combinations of radiotherapy (RT) and hormone therapy (HT).[4,5]

The possible advantages of RP are the resolution of the micturition symptoms, improved local control, easier follow-up and rescue treatments, removal of the radioresistant clones, and improved HT response without primary tumor in metastatic progression.[6] The disadvantages focus on the peroperative morbidity and the frequent need for second line treatments.[7]

Due to their adaptability to our database, we have chosen the criteria of the National Comprehensive Cancer Network (NCCN) for defining HR PCa as a tumor of stage cT3a and/or a Gleason score at biopsy of 8-10, and/or PSA >20 ng/ml.[8]

Our first objective is to know our own results in HR patients, in an attempt to compare them with those of the literature, with a view to improving our therapeutic strategy in the future. Secondly, we aim to establish preoperative prognostic factors or combinations of such factors that can help in counseling our patients on the best treatment options for HR PCa.

Material and methods

Patients: Following approval by the Ethics Committee of the Valencian Oncology Institute (Valencia, Spain), we retrospectively reviewed 925 open or laparoscopic RPs performed between 1986 and October 2007 by 10 urologists, after the signing of informed consent in each case. We included 104 patients subjected to neoadjuvant HT in the complete series (11.3%), since the evidence obtained from randomized trials indicates no differences in biochemical progression with respect to the group without such treatment.[9]

In most cases lymphadenectomy (LA) was limited to the obturator fossa up until 2007. From that time onwards, extensive LA was established as a general rule (obturator, external and internal iliac bundles) in HR patients. With the exception of adjuvant HT for the patients with positive lymph nodes, adjuvant treatments with RT or HT were not used in patients with a poor prognosis after RP. Rescue RT and/or HT were used considering the PSA kinetics in disease progression, and based on the clinical and pathological prognostic criteria.

Our endpoints were metastatic progression, CSS and overall survival (OS). We also quantified the need for second line therapies. Biochemical recurrence was considered when PSA = 0.4 ng/ml.

Statistical analysis: Comparisons between groups were made based on the t-test for continuous variables and the chi-square test for categorical variables (Fisher test, table 2). Survival comparisons between groups were made using the Kaplan-Meier method and the log-rank test. In the analysis of progression-free survival (PFS), we established a univariate model based on the Cox regression model for each possible pretreatment factor, and on multivariate analysis for prognostic factors identified in the univariate analysis with a level of significance of 10. In all analyses, use was made of a two-sided test and $p < 0.05$ (two-tailed) for considering statistical significance.

Results

Follow-up: The mean duration of follow-up in the global series was 69.9 months (standard deviation, SD ± 48.4), with a range of 1-233 months. The HR patients had a longer mean follow-up 89.8±53.6 months; range 1-222). A total of 131 (62.3%) and 64 (30.4%) HR patients were followed-up on for more than 5 and 10 years, respectively.

Descriptive analysis of the series: We respectively performed 774 and 151 open and laparoscopic RPs during the study period. Most of the HR patients (203, 96.7%) were subjected to open surgery. The descriptive data of the series are reported in table 1. Based on the clinical stage, PSA concentration and Gleason score at biopsy, two groups were established following the criteria of the NCCN: HR group (210 patients, 22.7%) and low risk or intermediate risk group (LR & IR)(715 patients, 77.3%).

Neoadjuvant HT was associated to the HR group in the series (p=0.001). Since the year 2000, the RPs carried out in the HR group represented 14.6% of all those performed. Figure 1 shows the distribution of RPs performed according to the groups studied. The HR patients were significantly older (p=0.004), and were more often classified as presenting ASA score III/IV (p=0.023). There were differences in MI between the groups (p=0.652). Surgery time was longer (p=0.018) and the transfusion requirements were greater (p>0.001) in the HR group. The clinical or surgical complications rate in the postoperative period (up to 30 days) was similar in both groups (25.1% and 30.8%), with no statistically significant differences (p=0.113). Three patients, including one HR individual, died peroperatively.

Pathology findings: Excluding 52 patients with neoadjuvant HT, 53 (33.5%) and 105 (66.5%) HR patients had organ-confined (= pT2b) and locally advanced disease (= pT3a), respectively. In the case of the LR & IR group, these data were: 421 (63.5%) and 242 (36.5%)(p<0.0001). Among 16 tumors in stage cT3a, 4 (25%) corresponded to stage pT2b. If the patients with neoadjuvant HT are not excluded, we operated upon 32 stage

Table 1 – Descriptive statistics of the study series

Total n(%)	HR n(%)	LR & IR n(%)	
Total	925 (100)	210 (100)	715 (100)
Age (years)			
Mean (SD)	63.1 (6.3)	64.2 (6.2)	62.8 (6.3)
Median (range)	64 (40-80)	64 (45-76)	64 (40-80)
Preoperative PSA			
<10	528 (57.1)	30 (14.4)	498 (69.7)
10-20	241 (26.1)	24 (11.5)	217 (30.3)
>20	155 (16.8)	155 (74.2)	
Gleason score at biopsy			
≤6	707 (76.5)	118 (56.5)	589 (82.4)
7	155 (16.8)	29 (13.9)	126 (17.6)
≥8	62 (6.7)	62 (29.7)	
CT			
≤cT2b	893 (96.5)	178 (84.8)	715 (100)
≥cT3a	32 (3.5)	32 (15.2)	
Gleason score of surgical piece			
≤6	495 (55.2)	85 (42.5)	410 (58.9)
7	309 (34.5)	74 (37.0)	235 (33.8)
≥8	92 (10.3)	41 (20.5)	51 (7.3)
PT			
≤pT2b	529 (57.2)	74 (35.2)	455 (63.6)
≥pT3a	396 (42.8)	136 (64.8)	260 (36.4)

HR=high risk; LR & IR=low and intermediate risk.

Table 2 – Results of the univariate analysis for metastatic progression with the preoperative factors

	Hazard ratio	95% CI	p-value
PSA			0.246
<20	Baseline		
≥20	0.694	(0.374-1.287)	
Gleason (biopsy)			0.018
≤7			
≥8	1.959	(1.123-3.416)	
Clinical stage			0.005
≤2b	Baseline		
≥3a	2.305	(1.295-4.102)	
Age (years)			0.590
≤60	Baseline		
61-70	0.813	(0.430-1.536)	
>70	0.640	(0.273-1.504)	
BMI			0.666
≤25	Baseline		
25-30	1.363	(0.695-2.673)	
>30	1.231	(0.543-2.793)	
ASA score			0.878
ASA I-II	Baseline		
ASA III-IV	1.044	(0.601-1.814)	

cT3a cases, and 25% were moreover over-staged. Positive resection margins were recorded in 50.7% of the HR patients and in 31.1% of the patients in the other group (p<0.001). The same data in relation to perineural infiltration were 66.3% and 40.8% (p<0.001).

In 200 of the HR cases we were able to establish correspondence between the Gleason score at biopsy and in the surgical piece; in 99 cases (49.5%) the scores coincided, in 48 cases (23%) the score was overgraded in the biopsy, and in 55 patients (27.5%) the score was undergraded in the cores.

Obturator fossa LA was performed in 190 cases and extensive LA in 6 cases in the HR group, and in 415 and two cases in the LR & IR group, respectively. The mean number of lymph nodes removed was 6 (range 1-24), with a significantly larger number of pN+ findings (25 cases, 13%) in the HR group than in the other group (14 cases, 3.4%) (p<0.001).

Oncological follow-up: With a median follow-up of 86 months in the HR group, 54 patients (25.7%) were free of disease and 8 patients (3.8%) had died of intercurrent causes while free of disease. The disease progressed in 148 patients (70.5%); deaths attributable to tumor progression totaled 42 (20%), while deaths due to intercurrent causes in the presence of disease progression totaled 25 (11.9%). Up until the last review date in October 2009, a total of 42, 26 and 13 patients presented biochemical, local or metastatic progression, respectively.

Figure 2 shows clear differences in biochemical progression-free survival (2a) and in metastatic progression-free survival (2b) between the two study groups (p<0.001). Figure 3 shows differences in overall survival (p<0.001), and figure 4 shows differences in cancer-specific survival (p<0.001).

Seventy-nine HR patients (38%) and 549 patients in the LR & IR group (78.5%) required no second line therapy after RP (p<0.001). Ninety-four HR patients (45.2%) never required HT. Rescue RT was targeted to the prostate fossa in 63 HR patients (30.3%) and in 96 LR & IR patients (23.7%)(p<0.001).

Prognostic study: An analysis was made of the possible pre-RP prognostic factors with metastatic progression as the endpoint, including variables such as PSA (<20 vs >20 ng/ml), the Gleason score at biopsy (≤7 vs ≥8), cT (≤T2b vs ≥cT3a), age (<60, 61-70, >70), body mass index (BMI)(<25, 26-30, >30), and ASA surgical risk score. Table 2 shows the results of the univariate analysis. On fitting the model for variables with a level of significance of over 10%, we found that both the Gleason score at biopsy and the clinical stage were statistically significant, though not so PSA (table 3 and fig. 5).

Discussion

A recent study comparing 8 definitions of high risk (HR) in prostate cancer (PCa) revealed great variability in incidence depending on the criteria selected (4-40%). Between 41-72% of the cases remained free of progression, and the majority remained without metastatic progression after more than 10 years of follow-up.[2]

High-risk patients have decreased in number. The most common practice is to classify them as being at high risk based more on the Gleason score at biopsy than on clinical staging or elevations in PSA levels.[10,11] One-third of all subjects with a Gleason score of 8-10 at biopsy in fact may have Gleason ≤7 in the radical prostatectomy (RP) piece.[12] In our series this occurred in 23% of the cases. Tumors in stage cT3a were recorded in 10.3% of a series of 2273 RPs,[13] the cancer-specific survival (CSS) being similar to that of cT2 patients of the RP arm of a study contrasting patient monitoring versus RP.[14] Our multivariate analysis found that PSA > 20 ng/ml is not indicative of a poor prognosis, in

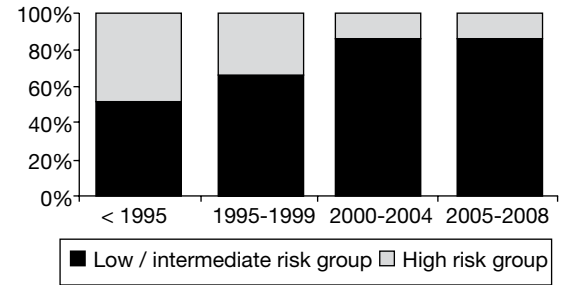

Figure 1 – Frequency of radical prostatectomies performed during the study period.

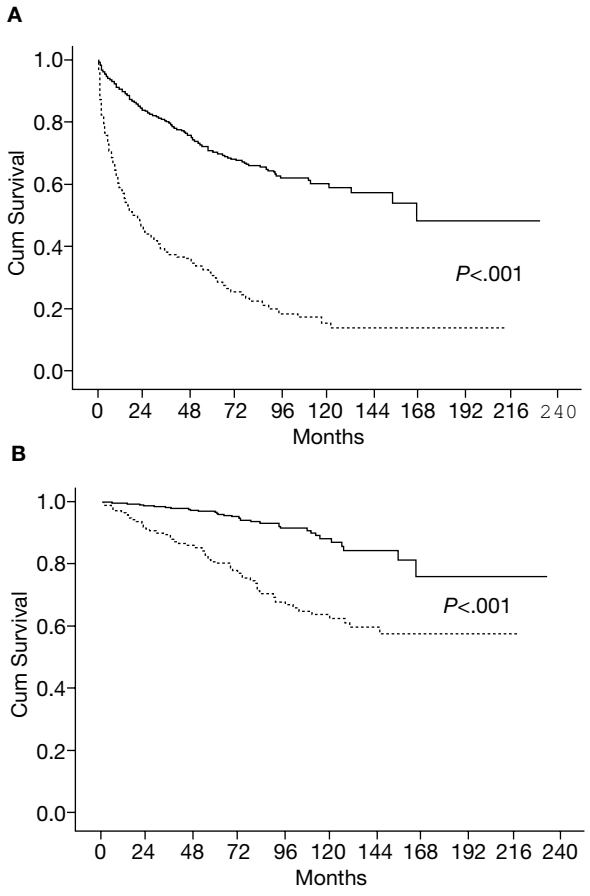

Figure 2 – A) Differences in biochemical progression-free survival between the high risk (dotted line) and low / intermediate risk groups (solid line). B) Differences in metastatic progression-free survival between the high risk (dotted line) and low / intermediate risk groups (solid line).

coincidence with the observations of other authors,[15] even with PSA > 50 ng/ml.[16]

Classically, HR patients have more often received RT, or have even been regarded as incurable and have been administered hormone therapy (HT) on a palliative basis.[17,18] We consider that our proportion of operated HR patients (14.6%) is in line with that of other current research groups.

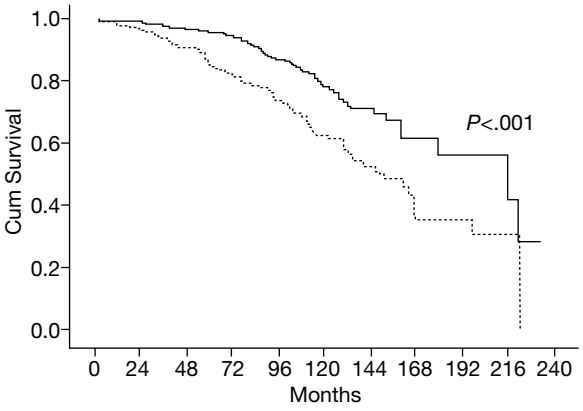

Figure 3 – Differences in overall survival between the high risk (dotted line) and low / intermediate risk groups (solid line).

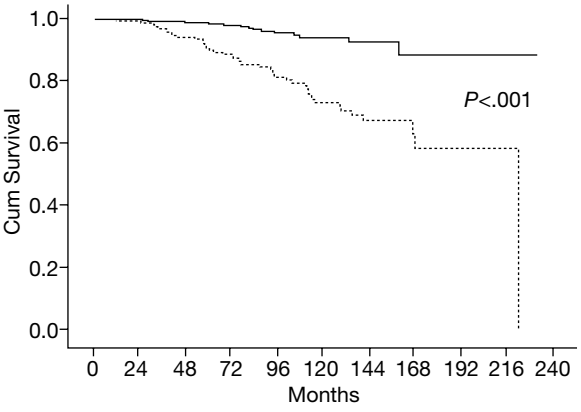

Figure 4 – Differences in cancer-specific mortality between the high risk (dotted line) and low / intermediate risk groups (solid line).

As regards the different treatment options, difficulties are posed by the comparison of data in most cases obtained on a retrospective basis. In addition, the patients treated with RT in many cases have poorer pre-treatment characteristics and have been treated in the Radiation Therapy Oncology Group (RTOG) trials with doses lower than those used at the present time.[19] However, when only considering tumor grade for comparing HR patients subjected to monitorization, surgery or irradiation, the lowest mortality risk due to tumor progression corresponded to the operated patients in a single-center study.[20] When using the criteria of the NCCN for selecting patients subjected to RT, the oncological findings are fully comparable, being better for RP on contrasting RP and RT.[4,5]

The progression-free survival (PFS) rates of the Memorial Center after 5 and 10 years were 58% and 50% (hazard ratio 4.4, 95%CI 3.7-5.1), the metastatic progression-free survival rates were 88% and 78% (hazard ratio 6.5, 95%CI 5.0-8.5), and the CSS rate after 12 years was 91%.[2,21] In our series, the PFS rate was 29.5%, with a metastatic progression-free survival rate of 73.8% and a CSS rate of 80% (table 4).

Table 3 – Results of the multivariate analysis for metastatic progression with the preoperative factors

	Hazard ratio	95%CI	p-value
Gleason (biopsy)			0.020
≤7	Baseline		
≥8	1.922	(1.106-3.341)	
Clinical stage			0.006
≤2b	Baseline		
≥3a	2.290	(1.269-4.133)	

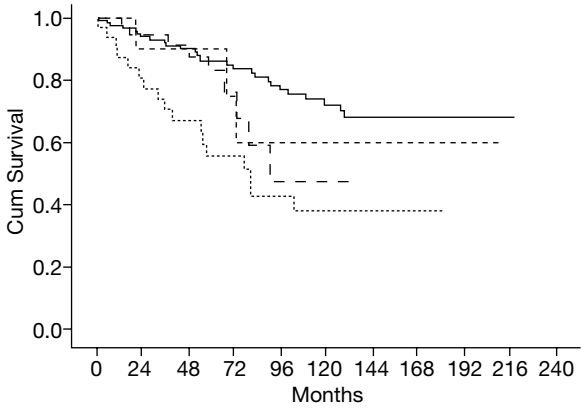

Figure 5 – Metastatic progression-free survival according to the presence of only one or more than one factor defining high risk. The combination of two criteria is seen to yield the poorest survival (dotted line). The definition of high risk by cT only (short segments line) or by the Gleason score at biopsy (long segments line) shows intermediate behavior, and the inclusion of high risk based only on PSA elevation (solid line) is predictive of improved survival.

Radical prostatectomy in HR patients has not been shown to involve a greater incidence of complications in our experience, and has not been seen to produce poorer incontinence rates (data not shown) compared with RP in the LR & IR patients. In our protocol, preservation of the neurovascular bundles in the HR group practically has never been attempted, since we understand that the aim of preserving erectile function in this group implies risks which the patient must be made aware of.[21-23]

In our HR group, 38% of the patients never received any second line treatment, 69.7% never received RT, and – most importantly – 45.2% never received HT. These data coincide with those of other authors.[2] However, series involving 15 years of follow-up have shown that 78% of 841 patients with cT3 tumors required RT or HT in the course of follow-up.[22]

The EORTC 22.911 trial randomized patients with pT3 tumors or positive resection margins to either adjuvant RT (50 Gy) or monitorization (observation). The PFS rate was seen to improve from 78% to 85% (p=0.0009), though the 5-year metastasis-free survival, CSS and overall survival (OS) rates did not differ.[24] These same findings have been confirmed by other smaller and non-randomized studies.[16,23] In the SWOG 8794 study, 425 HR patients were randomized either to receive 60-64 Gy over the prostatic fossa or to monitorization - showing for the first time that adjuvant RT significantly reduces the risk of metastasis, despite an almost two-fold greater use of hormone therapy in the observation (monitorization) arm of the study.[25]

As regards rescue RT in the follow-up of operated HR patients, it has been shown that even in a patient with a rapid PSA doubling time (PSADT) and/or a Gleason score of 8-10 there is a non-negligible probability of lasting response if there moreover are positive resection margins and RT is administered with PSA <2 ng/ml.[26] In another study, rescue RT was associated with an increase of up to three times in CSS rate when compared with the group not administered RT (hazard ratio 0.32; 95%CI 0.17-0.69, p=0.003). This benefit was limited to those patients with a PSADT of under 6 months, and proved independent of the Gleason score, pathological stage, and the timing of HT association to rescue RT.[27]

We follow the guidelines of the European Association of Urology and only administer adjuvant HT in cases with positive adenopathies.[28] Data from the CaPSURE show that HR patients initially subjected to RT have an up to 3.5-fold greater probability of receiving adjuvant HT than those subjected to RP.[11] Another factor to be taken into account is the problem of local failure after RT, which has been regarded as the most important predictor of the development of metastasis in a multivariate analysis.[29] In addition, all urologists known the difficulties posed by the local control of obstructive micturition symptoms and pain in the case of post-RT relapse.

We are aware of the limitations of our study. In this context, its retrospective nature reproduces our true life clinical practice. Radiotherapists in our same center reviewed the results of rescue RT and found the median time to administration of the latter from RP to be 22 months, with a median PSA concentration prior to rescue RT of > 2 ng/ml in 55% of the cases - the latter finding being identified as the poorest prognostic factor in their multivariate analysis in relation to the development of biochemical disease progression.[30] Our protocol has always comprised rescue RT with a dose of 66 Gy (range 60-70), though its application has gradually been decided earlier in response to biochemical progression over the last four years. Previously, it was more common to wait until macroscopic local disease relapse could be confirmed. This is one of the reasons why we can deduce that the global results of our series of RP in HR PCa patients are slightly inferior to those found in the literature. We therefore consider that our results in this group of patients can be improved in the future by applying rescue RT earlier,

Table 4 – Literature findings in relation to organ-confined pathological stages and cancer-specific survival (CSS) in patients with high risk prostate cancer according to criteria similar to those used in our series subjected to radical prostatectomy

Author/year	Definition HR	n	% pT≤2b n (%)	CSS at 10 years n (%)
Berglund/2006	PSA≥15 or cT≥2b or Gleason 8-10	281	132 (47)	NR
Loeb/2007	PSA≥15 or cT≥2b or Gleason 8-10	288	123 (43)	201 (70) -267 (93)*
Yossepowitch/2008	PSA≥20 or cT≥3a or Gleason 8-10	938	318 (34)	862 (92)
Serie IVO/2009	PSA≥20 or cT≥3a or Gleason 8-10	210	74 (35)	168 (80)**

HR: high risk; N: number; CSS: cancer-specific survival.
*% CSS varies according to the pathology results.
**CSS at 7.2 years.

improving our extensive lymphadenectomies, and selecting patients for RP with only one poor prognosis criterion of the three criteria established by the NCCN - fundamentally when the mentioned criterion is PSA elevation.

In conclusion, in treating HR PCa patients, we inform them that RP as monotherapy is able to heal 25% of the cases, but that multimodal treatment may be needed in over half of all cases. We recommend open or laparoscopic surgery in the case of a young patient with a tumor considered to be resectable – particularly in the presence of only one poor prognosis factor, and particularly when the latter is PSA elevation (fig. 5). Probably the best strategy for this group of individuals is a multimodal approach, though such an approach remains to be protocolized.

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Conflicts of interest

The authors declare no conflicts of interest.

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