Asian Journal of Urology (2014) 1, 40–45

HOSTED BY

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

REVIEW

Locally advanced and high risk prostate cancer: The best indication for initial radical prostatectomy?

Hendrik van Poppel

Department of Urology, University Hospitals Leuven, Leuven, Belgium

Received 1 August 2014; received in revised form 19 August 2014; accepted 5 September 2014
Available online 13 September 2014

KEYWORDS
Prostate cancer;
High risk;
Radical prostatectomy;
Extracapsular extension;
High-grade prostate cancer

Abstract High risk prostate cancer is a deadly disease that needs aggressive treatment. High risk prostate cancer is often treated with androgen deprivation therapy or combined radiohormonotherapy while there is a place for surgery in cases of operable and resectable locally advanced or high risk disease. This review summarises the results of the different treatment strategies for locally advanced and high risk prostate cancer. Radical prostatectomy monotherapy or in combination with radiotherapy and/or hormonal treatment are analysed. They show that radical prostatectomy is an effective treatment modality for these tumours. After surgery, the results of the pathology and the follow-up of serum PSA may indicate the need of additional adjuvant or salvage treatment strategies.

1. Introduction

For many years urologists have proposed radical prostatectomy (RP) as the gold standard for localised prostate cancer in often low risk and intermediate risk prostate cancer patients. Today, surgery for these patients is often considered overtreatment. Since the issue of high risk prostate cancer, that was often undertreated (with androgen deprivation therapy or combined radiotherapy and androgen deprivation therapy), oncologic urologists have more and more focused on high risk prostate cancer.

Locally advanced prostate cancer has extended clinically beyond the prostatic capsule, with invasion of the pericapsular tissue, bladder neck, or seminal vesicles, but without lymph node involvement or distant metastases. It is referred to as T3–T4 N0 M0 prostatic cancer. High-grade prostate cancer, also called poorly differentiated prostate cancer, has Gleason scores from 8 to 10.

Based on preoperative parameters (clinical stage, initial PSA and Gleason Score), Yossepowitch et al. [1] defined eight different categories amongst high risk prostate cancer (HRPC) patients and concluded that these HRPC patients do

E-mail address: hendrik.vanpoppel@uzleuven.be.
Peer review under responsibility of Chinese Urological Association and SMMU.

http://dx.doi.org/10.1016/j.ajur.2014.09.009

not have a uniformly poor prognosis after RP. Joniau et al. [2] analysing a multi-institutional database have shown that there are three distinct categories with different cancer specific survival rates considering three prognostic parameters: initial PSA, clinical stage, and Gleason score. Many patients classified as being at high risk have pathologically organ-confined cancer and may be cured by RP alone [1]. Historically, patients with locally advanced disease and high-grade prostate cancer have not been viewed as good candidates for RP, due to the high incidence of positive pelvic lymph nodes and poor long-term survival rates [3,4]. The advent of prostate-specific antigen (PSA) screening and modern imaging modalities allow early detection of high-grade tumours. The use of these screening techniques has led to stage migration and decreased morbidity after RP, sparking renewed interest in the use of surgery in men with advanced prostate cancer. Nevertheless, the optimal therapy for patients with locally advanced and high-grade tumours remains unclear.

2. Surgery for locally advanced and high-grade prostate cancer

Until recently, surgical treatment has not been used in clinical T3—T4 disease and high-grade prostate cancer. Over-staging (pT2), over-grading, and under-staging (pT4 or pN+) are common clinical errors. Nomograms have been developed to predict the pathologic stage of the disease and seminal vesicle invasion at RP [5, 6]. In addition, nodal imaging with computed tomography (CT) scans, seminal vesicle invasion (SVI) imaging with magnetic resonance imaging (MRI), or directed needle core biopsies of the nodes or seminal vesicles can be helpful in recognising patients who for some time were deemed not to benefit from a surgical approach [7].

The European Association of Urology (EAU) guidelines on prostate cancer state that RP can best be proposed to patients with locally advanced prostate cancer when the PSA is $<$20 ng/mL, with a clinical stage $\leq$cT3a, and a biopsy Gleason score $\leq$8). However, patients with more advanced or poorly differentiated tumours are also considered to potentially benefit from surgery [8]. Surgical treatment in locally advanced T3 prostate cancer involves a radical prostate extirpation, including an extended lymph node dissection, clean apical dissection, neurovascular bundle resection at the tumour-bearing side, complete resection of the seminal vesicles, and most often resection of the bladder neck [9,10]. Increased overall surgical experience results in improved positive surgical margin rates over time (75% in 1987—1994, 42% in 1995—1999, and 10.4% in 2000—2004) [11].

Extended lymph node dissection (LND) is mainly advised in locally advanced disease and high-grade prostate cancer, due to a higher risk of node-positive disease. In older surgical series of cT3 disease, the node-positive rate is between 27% and 41% [12]. Other series had a much lower rate of pN+ cases (11%), respectively, probably due to more accurate and dedicated CT scanning of the pelvis and methods of patient selection [13]. The percentage of positive biopsy cores can help to predict lymph node invasion in patients undergoing RP and extended pelvic LND [14]. The most common postoperative complications are urinary incontinence and sexual dysfunction, which occur immediately after RP and tend to improve over time. In early stages of the disease, the incidence of these complications can be reduced by nerve-sparing surgery. In men with T3 disease, however, non-nerve-sparing RP must be carried out at least at the tumour bearing side. Increased overall surgical experience leads to decreased operative morbidity and better functional results [15].

3. Locally advanced prostate cancer

3.1. Studies with RP monotherapy

RP monotherapy may be an acceptable treatment option for cT3 disease. This is true not only in over-staged patients (pT2), but also in true unilateral pT3a, especially if the tumour is specimen-confined (R0). In cT3 disease, the cancer-specific survival (CSS) rate after RP at 5- and 10-year follow-up is 85%—100% and 57%—72%, respectively. The overall survival (OS) rate at 5- and 10-year follow-up is $>$75% and 60%, respectively [4, 16, 17].

RP monotherapy is an effective treatment in men with T3 disease, particularly in patients with a serum PSA value $<$10 ng/mL and uninvolved lymph nodes and seminal vesicles. Clinical T3a patients with PSA values $<$10 ng/mL had a 5-year biochemical recurrence-free survival rate exceeding 60% [13]. Other authors evaluated 83 surgically treated cT3a patients at a mean follow-up of 68.7 months and reported OS and CSS rates of 97.6% and 100%, respectively. The authors used very strict selection criteria: limited cT3a on digital rectal examination combined with $<$T3a on transrectal ultrasonography [17].

These results support the use of RP monotherapy as a possible treatment for selected locally advanced prostate cancer. The possible occurrence of complications is not seen as a valid reason for not performing RP in cT3 disease because only few serious events were reported.

3.2. Multimodality treatment

In a substantial number of patients, RP monotherapy will not result in a definitive cure; therefore, early adjuvant or late salvage radiation (RT) or hormone treatment (HT) should be considered.

In a study by Ward et al. [12], 78% of patients eventually needed adjuvant or salvage RT or HT compared to 56% of patients in a recent study from Hsu et al. [18]. These studies reveal excellent 5-, 10-, and 15-year OS and CSS rates, comparable to those obtained in cT2 patients. In addition, the Ward and Hsu studies had similar survival rates, with 5-year CSS rates of 95% and 98.7%, respectively, and 10-year CSS rates of 90% and 91.6%, respectively [12,18]. Ward et al. [12] also reported a 15-year CSS rate of 79%.

In a recent study by Gontero et al. [19], RP appears to be a valid treatment with acceptable morbidity in patients with locally advanced prostate cancer of any $T \geq 3$, N0-1. The 7-year OS and CSS rates were 77% and 90%, respectively; 89.5% of the patients received immediate adjuvant treatment after RP [19]. This is also the opinion of Lange [20], who expressed the need for a randomised study testing the efficacy of RT and RP as initial therapy for locally advanced prostate cancer. In the meantime, RP

series revealed survival rates that surpass those for RT alone and comparable to those of 3 years of androgen-deprivation therapy combined with external RT.

Two randomised studies compared postoperative RT with RP alone for locally advanced prostate cancer. Bolla et al. [21] reported an improved biochemical progression-free survival (BPFS) in patients treated with adjuvant postoperative RT (74% *vs.* 52.6%, $p < 0.0001$) with an extended follow-up, but no improved cancer specific survival. Thompson et al. [22] showed that adjuvant postoperative RT significantly reduced the risk of PSA relapse (median PSA relapse-free survival, 10.3 years for RT *vs.* 3.1 years for observation, $p < 0.001$) and disease recurrence (median recurrence-free survival, 13.8 years for RT *vs.* 9.9 years for observation, $p = 0.001$).

Our belief that RP has a place in the treatment of locally advanced prostate cancer is supported by a few studies conducted in the United States [23—28]. Another study showed that patients who underwent RP ($n = 72$) for cT4 disease had a better survival than those who received HT alone or RT alone and comparable survival to that of men who received RT plus HT [29].

4. High-grade prostate cancer

4.1. Studies with radical prostatectomy monotherapy

A Gleason score $\leq$7 in an RP specimen, when the biopsy specimen was scored from 8 to 10, is defined as pathologic downgrading. A recent study reported that the incidence of downgrading was 45% and that downgraded patients had an increased BPFS probability (56% *vs.* 27%). Moreover, patients with a biopsy Gleason score of 8 and a clinical stage of T1c were more likely to be downgraded and, thus, had a better BPFS probability. Of these patients, 64% were free of biochemical or clinical recurrence [30]. In a study from Manoharan et al. [31], the incidence of downgrading was reported as 31%, with patients having a lower biochemical recurrence rate (32% *vs.* 41%). Grossfeld et al. [32] assessed the surgical outcome of 114 men with high-grade prostate cancer and noted downgrading in 38% of the patients. In a study from Bastian et al. [33], 34% of men in the patient cohort were downgraded and had a 5- and 10-year estimated BPFS of 62% and 38%, respectively. In the Shared Equal Access Research Cancer Hospital (SEARCH) database, 55% of men were downgraded and had a 5- and 10-year estimated BPFS of 34% and 34%, respectively.

These results suggest that one third of patients with a biopsy Gleason score $\geq$8 may in fact have a specimen Gleason score $\leq$7 with better prognostic characteristics. Therefore, refusing RP, which is an excellent treatment for those patients, would be incorrect. A number of reports have addressed the success rates of RP monotherapy in high-grade cancer. Donohue et al. [30] examined the outcome of RP monotherapy in 238 patients with high-grade prostate cancer and found a 5- and 10-year BPFS of 51% and 39%, respectively, in agreement with rates reported in other series [34—36]. Mian et al. [37] assessed the outcome of patients with a specimen Gleason score $\geq$8 treated with RP alone. The reported 5- and 7-year BPFS of 71% and 55%, respectively, are better than the rates reported by Donohue et al. [30] and other studies [34—36]. In addition, the rate of lymph node metastasis was only 6% compared to 20% in the Donohue study. In a study analysing 79 high-grade patients treated with RP at a mean follow-up of 55 months, the overall biochemical failure rate was 38% (41% if Gleason score was $\geq$8, and 32% if it was $\leq$7). Manoharan et al. [31] concluded that RP is a reasonable treatment option for patients with a biopsy Gleason score $\geq$8 and clinical stage T1—2, especially if their PSA level is $\leq$20 ng/mL.

Serni et al. [38] evaluated the outcome of 116 patients with Gleason scores $\geq$8 who underwent RP. The 3- and 5-year progression-free survival rates for all patients were 84.6% and 78.1%, respectively. The 5-year BPFS for those with Gleason scores of 8 and 9 were 72.1% and 38.2%, respectively ($p \leq 0.05$).

Bastian et al. [33] reviewed the data of men with Gleason scores of 8—10 treated with RP at the Johns Hopkins Hospital ($n = 220$; 3.8% of the total cohort) and those within the SEARCH database ($n = 149$; 7.7% of the total cohort). The authors reported 5- and 10-year estimated BPFS rates of 40% and 27%, respectively, for the Johns Hopkins cohort, and 32% and 28%, respectively, for those within the SEARCH database. In conclusion, patients undergoing RP with biopsy Gleason scores of 8—10 do not necessarily have a poor prognosis. Although most high-grade tumours extend outside the prostate, those that are confined to the prostate at histopathologic examination have a good prognosis after RP [39].

PSA screening enables detection of high-grade tumours with smaller volume at an earlier stage, thus improving the organ- and specimen-confined disease rates [37]. Two separate studies reported the incidence of organ-confined disease at 26% [34] and 31% [37]. Mian et al. [37] showed that patients with organ- and specimen-confined disease had a higher 5-year disease-free survival rate than those with non-specimen-confined disease (82%, 84%, and 50%, respectively). A favourable disease-free survival could be expected in patients treated with RP alone, especially if the cancer is confined to the prostate or surgical specimen. Bastian et al. [33] found higher 5- and 10-year estimated BPFS among men with organ-confined disease and negative surgical margins (79% and 50% *vs.* 40% and 27% for the entire cohort, respectively).

Serni et al. [38] reported that the incidence of organ-confined node-negative disease is 11.2%. At a mean follow-up of 46 months, all patients with organ-confined disease were free of biochemical recurrence. These results emphasise the importance of early diagnosis and indicate that intracapsular tumours are less likely to metastasise, even with a high Gleason score. The incidence of pT3, specimen-confined, node-negative disease (29.3%) was greater than those has been reported in other series [35,36,40]. Serni et al. [38] reported that the 5-year BPFS rates for pT3a specimen-confined, pT3a non-specimen-confined, and pT3b disease were 68.2%, 53.3%, and 10.5%, respectively. These results show that high-grade tumours that have invaded the capsule can also be cured by surgery. The finding of negative margins improves the BPFS, although the presence of histologically confirmed SVI indicates a poor prognosis. Using the anterograde technique

minimises the incidence of positive surgical margins in high risk patients and increases the pT3a specimen-confined rate [38].

Grossfeld et al. [32] noted a 5-year disease-free survival rate of 47% in high-grade patients with PSA ≤10 ng/mL *vs.* 19% in those with PSA >10 ng/mL. Patients with high-grade disease might therefore be appropriate candidates for RP if the PSA value is ≤10 ng/mL and the % PBCs <66%.

A study by Hurwitz et al. [41] assessed the surgical outcome of 168 men with high-grade prostate cancer. Patients with PSA <10 ng/mL and % PBCs <50% had a 5-year BPFS probability of 67% *vs.* 23% for all other patients. Both studies suggest that the PSA value and the % PBCs can be helpful in selecting men with high-grade prostate cancer most likely to benefit from RP. Interobserver variations in pathologic staging are well documented and need consideration.

4.2. Comparison among conservative treatment, RP, and RT

Tewari et al. [42] compared the use of conservative treatment ($n = 197$), RP ($n = 119$), and RT ($n = 137$) in high-grade prostate cancer. The study was conducted as a single institutional, retrospective cohort study including 453 patients with biopsy Gleason scores ≥8. Using propensity-scoring analysis, the median OS rate for conservative treatment was 5.2 year, for RT it was 6.7 year, and for RP it was 9.7 year. Median CSS was 7.8 year for conservative treatment and >14 year for both RT and RP. The risk of cancer-specific death after RP was 68% lower than after conservative treatment and 49% lower than after RT ($p < 0.001$ and $p < 0.053$, respectively).

From a recently published large observational study analysing data of the Swedish prostate cancer registry, it was shown that after 15 years surgery in men with non-metastatic prostate cancer leads to better survival than does radiotherapy. The authors concluded that younger men and those with less comorbidity who have intermediate or high risk localised prostate cancer may have a greater benefit from surgery [43].

4.3. Multimodality treatment

To achieve complete elimination of local disease and to improve outcomes, multimodality treatment is often recommended for high-grade prostate cancer. Lau et al. [34] reported that treatment with adjuvant HT in patients with high-grade cancer appears to improve the 10-year progression-free survival rate after RP but does not significantly reduce death from prostate cancer within 10 year. Postoperative RT in the treatment of high-grade prostate cancer may improve outcomes, but its role remains controversial. In men with high-grade prostate cancer, Do et al. [44] reported a 5-year BPFS of 65% in patients treated with RP and postoperative RT compared with 30% after RP alone, and 25% after RT alone. The clinical progression-free survival was also improved with the addition of postoperative RT compared with RP and RT alone (80%, 60%, and 35%). Other reports have indicated that adjuvant RT is associated with a lower risk of biochemical recurrence, although there is no significant improvement in CSS rates at 10-year follow-up [34, 35]. Loeb et al. [26] reviewed the data of 288 men who underwent RP, 254 of whom were high-risk patients (cT2b, a Gleason score of 8—10, PSA >15 ng/mL). For the high-risk patients, the 10-year progression-free survival, CSS rate, and OS rate were 37%, 88%, and 75%, respectively. Patients received adjuvant or salvage treatment when needed.

Bastian et al. [33] recommend multimodality therapy for high-grade tumours. This often consists of RT plus HT; however, newer possibilities exist, such as a combination of RP plus neoadjuvant or adjuvant (chemo)-HT or RP with adjuvant RT [33]. A recent paper reviews the use of a combination of external-beam RT and systemic agent with RP for HRPC patients [45].

5. Conclusion

It is very likely that RP is an effective form of treatment for locally advanced and high-grade tumours. The best candidates for RP are patients who were clinically over-staged or over-graded by the puncture biopsy and whose tumours were subsequently found to be locally confined, to have limited extracapsular extension, or to be moderately differentiated. However, this does not mean that more advanced stages or grades are necessarily a contraindication for surgery. In younger patients, even advanced tumours and Gleason scores ≥8 are best managed initially by surgery. The increased use of nomograms and modern imaging techniques is helpful in recognising patients with locally advanced disease or high-grade disease most likely to benefit from surgical treatment.

Urologists must use the pathologic results, which indicate the need for additional postoperative treatment, to improve the final outcome. Further studies will be required to clarify whether neoadjuvant (chemo)-HT, adjuvant/salvage (chemo)-HT, and adjuvant/salvage RT can improve the results of RP.

5.1. Locally advanced prostate cancer

RP monotherapy provides tumour control in selected patients with cT3 disease, with 5- and 10-year CSS rates of >85% and 57%, respectively. The OS rates at 5- and 10-year are >75% and 60%, respectively.

In well-selected patients, RP, combined with adjuvant or salvage treatment when needed, may result in better outcomes than RT alone, similar to the combination of RT plus HT therapy. These findings should be confirmed in randomised, prospective studies.

5.2. High-grade prostate cancer

In a recent study, patients with high-grade prostate cancer who underwent RP monotherapy had 5- and 10-year BPFS rates of 51% and 39%, respectively. This is in agreement with rates reported in other series. Studies show that up to one third of patients with high-grade prostate cancer are subsequently downgraded and have a better BPFS probability after RP. Disease-free survival after RP can also be expected if the cancer is confined to the prostate or

surgical specimen. PSA value and the % PBCs can be useful in selecting men with high-grade prostate cancer most likely to benefit from RP. Patients with high-grade prostate cancer are likely to be good candidates for multimodality treatment, often consisting of RP with adjuvant or salvage RT and HT, although newer treatment combinations are being tested.

Conflicts of interest

The author declares no conflict of interest.

References

[1] Yossepowitch O, Eggener SE, Bianco Jr FJ, Carver BS, Serio A, Scardino PT, et al. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol 2007;178:493—9.

[2] Joniau S, Briganti A, Gontero P, Gandaglia G, Tosco L, Fieuws S, et al. Stratification of high risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol 2014; 67:157—64.

[3] Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW. Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. J Urol 2004;172(5 Pt 1):1835—9.

[4] Gerber GS, Thisted RA, Chodak GW, Schroder FH, Frohmuller HG, Scardino PT, et al. Results of radical prostatectomy in men with locally advanced prostate cancer: multiinstitution pooled analysis. Eur Urol 1997;32:385—90.

[5] Joniau S, Hsu CY, Lerut E, Van Baelen A, Haustermans K, Roskams T, et al. A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. Eur Urol 2007;51:388—96.

[6] Gallina A, Chun FK, Briganti A, Shariat SF, Montorsi F, Salonia A, et al. Development and split-sample validation of a nomogram predicting the probability of seminal vesicle invasion at radical prostatectomy. Eur Urol 2007;52:98—105.

[7] Van Poppel H, Ameye F, Oyen R, Van de Voorde W, Baert L. Accuracy of combined computerized tomography and fine needle aspiration cytology in lymph node staging of localized prostatic carcinoma. J Urol 1994;151:1310—4.

[8] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent — update 2013. Eur Urol 2014;65:124—37.

[9] Hsu CY, Joniau S, Van Poppel H. Radical prostatectomy for locally advanced prostate cancer: technical aspects of radical prostatectomy. EAU Upd Ser 2005;3:90—7.

[10] Van Poppel H. Surgery for clinical T3 prostate cancer. Eur Urol Suppl 2005;4:12—4.

[11] Hsu CY, Joniau S, Roskams T, Oyen R, Van Poppel H. Comparing results after surgery in patients with clinical unilateral T3a, prostate cancer treated with or without neoadjuvant androgen-deprivation therapy. BJU Int 2006;99: 311—4.

[12] 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.

[13] Van Poppel H, Goethuys H, Callewaert P, Vanuytsel L, Van de Voorde W, Baert L. Radical prostatectomy can provide a cure for well-selected clinical stage T3 prostate cancer. Eur Urol 2000;38:372—9.

[14] Briganti A, Karakiewicz PI, Chun FK, Gallina A, Salonia A, Zanni G, et al. Percentage of positive biopsy cores can improve the ability to predict lymph node invasion in patients undergoing radical prostatectomy and extended pelvic lymph node dissection. Eur Urol 2007;51:1573—81.

[15] Van Poppel H, Vekemans K, Da Pozzo L, Bono A, Kliment J, Montironi R, et al. Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). Eur J Cancer 2006;42:1062—7.

[16] van den Ouden D, Hop WC, Schroder FH. Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. J Urol 1998;160:1392—7.

[17] Isorna Martínez de la Riva S, Belón López-Tomasety J, Marrero Domínguez R, Alvarez Cruz E, Santamaría Blanco P. Radical prostatectomy as monotherapy for locally advanced prostate cancer (T3a): 12 years follow-up. Arch Esp Urol 2004;57: 679—92.

[18] Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121—9.

[19] 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—30.

[20] Lange PH. Is surgery good for advanced localised prostate cancer? It's time to find out! Eur Urol 2007;51:873—5.

[21] 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 2012;380:2018—27.

[22] Thompson Jr IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomised clinical trial. J Am Med Assoc 2006;296:2329—35.

[23] 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.

[24] Carver BS, Bianco Jr FJ, Scardino PT, Eastham JA. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. J Urol 2006;176:564—8.

[25] Freedland SJ, Partin AW, Humphreys EB, Mangold LA, Walsh PC. Radical prostatectomy for clinical stage T3a disease. Cancer 2007;109:1273—8.

[26] Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007;69:1170—5.

[27] Secin FP, Bianco Jr FJ, Vickers AJ, Reuter V, Wheeler T, Fearn PA, et al. Cancer-specific survival and predictors of prostate-specific antigen recurrence and survival in patients with seminal vesicle invasion after radical prostatectomy. Cancer 2006;106:2369—75.

[28] Masterson TA, Pettus JA, Middleton RG, Stephenson RA. Isolated seminal vesicle invasion imparts better outcomes after radical retropubic prostatectomy for clinically localized prostate cancer: prognostic stratification of pt3b disease by nodal and margin status. Urology 2005;66:152—5.

[29] Johnstone PA, Ward KC, Goodman M, Assikis V, Petros JA. Radical prostatectomy for clinical T4 prostate cancer. Cancer 2006;106:2603—9.

[30] Donohue JF, Bianco Jr FJ, Kuroiwa K, Vickers AJ, Wheeler TM, Scardino PT, et al. Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. J Urol 2006;176: 991—5.

[31] Manoharan M, Bird VG, Kim SS, Civantos F, Soloway MS. Outcome after radical prostatectomy with a pretreatment prostate biopsy Gleason score of $\geq$ 8. BJU Int 2003;92:539—44.
[32] Grossfeld GD, Latini DM, Lubeck DP, Mehta SS, Carroll PR. Predicting recurrence after radical prostatectomy for patients with high risk prostate cancer. J Urol 2003;169:157—63.
[33] Bastian PJ, Gonzalgo ML, Aronson WJ, Terris MK, Kane CJ, Amling CL, et al. Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. Cancer 2006;107:1265—72.
[34] 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.
[35] Oefelein MG, Grayhack JT, McVary KT. Survival after radical retropubic prostatectomy of men with clinically localized high grade carcinoma of the prostate. Cancer 1995;76:2535—42.
[36] Tefilli MV, Gheiler EL, Tiguert R, Banerjee M, Sake W, Grignon D, et al. Role of radical prostatectomy in patients with prostate cancer of high Gleason score. Prostate 1999;39:60—6.
[37] Mian BM, Troncoso P, Okiharan K, Bhadkamkar V, Johnston D, Reyes AO, et al. Outcome of patients with Gleason score 8 or higher prostate cancer following radical prostatectomy alone. J Urol 2002;167:1675—80.
[38] 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.
[39] Ohori M, Goad JR, Wheeler TM, Eastham JA, Thompson TC, Scardino PT. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? J Urol 1994;152:1843—9.
[40] Perrotti M, Rabbani F, Russo P, Solomon MC, Fair WR. Early prostate cancer detection and potential for surgical cure in men with poorly differentiated tumors. Urology 1998;52:106—10.
[41] Hurwitz MD, Schultz D, Richie JP, Wein AJ, Whittington R, Malkowicz SB, et al. Radical prostatectomy for high-grade prostate cancer. Urology 2006;68:367—70.
[42] Tewari A, Divine G, Chang P, Shemtov MM, Milowsky M, Nanus D, et al. Long-term survival in men with high grade prostate cancer: a comparison between conservative treatment, radiation therapy and radical prostatectomy—a propensity scoring approach. J Urol 2007;177:911—5.
[43] Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, Olsson M, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ 2014;348:g1502. http://dx.doi.org/10.1136/bmj.g1502.
[44] 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.
[45] Kibel AS, Nelson JB. Adjuvant and salvage treatment options for patients with high-risk prostate cancer treated with radical prostatectomy. Prostate Cancer Prostatic Dis 2007;10:119—26.