Radical Prostatectomy for Locally Advanced Prostate Cancers—Review of Literature

N Srivatsa¹ · H Nagaraja¹ · S Shweta¹ · SK Raghunath¹

Received: 19 June 2016 / Accepted: 27 June 2016 / Published online: 5 January 2017
© Indian Association of Surgical Oncology 2017

Abstract Twenty-five to thirty percent of patients with prostate cancer present with locally advanced disease. While risk stratification remains the same with high incidence of upstaging of disease on imaging and histopathological evaluation; there have been progressive refinements in surgical therapy. With availability of reasonably robust data, radical prostatectomy in men with locally advanced prostate cancers seems to effect improvement in both cancer specific and overall survival rates in comparison to the current standard of care of radiation with androgen deprivation therapy. Studies using radical prostatectomy as a part of multimodality approach have also shown promising results. There is an imminent need for well-designed prospective studies of benefits of radical prostatectomy over radiation and androgen deprivation as well as benefits of multimodality therapy over monotherapy. Surgery for patients with locally advanced prostate cancer is technically challenging. Surgical outcomes are comparable to those of organ-confined disease when performed in high-volume centers. Neoadjuvant therapies prior to radical prostatectomy might improve surgical outcomes, but whether they will translate into a better cancer specific and overall survival are yet to be ascertained.

Keywords High risk localized prostate cancer · Locally advanced prostate cancer · Radical prostatectomy · Multimodal therapy in prostate cancer

Introduction

In the past, prostate cancer (PC) could only be detected clinically, and delayed diagnosis of locally advanced or metastatic disease at presentation was common. Prostate-specific antigen testing and magnetic resonance imaging led to PC detection in a much earlier stage. With this stage migration, further research into managing high-risk localized prostate cancers and locally advanced prostate cancers took a back seat and controversy about the best treatment for locally advanced prostate cancer (LAPC) remains. Recent refinements in surgery and radiation therapy have improved outcomes, but no comparative study has yet conclusively determined superiority of one option over the other [1].

Historically, men with high-risk PC have been managed most often with external beam radiation therapy (RT) or androgen-deprivation therapy (ADT) or both. In fact, the practice of combining these modalities for high-risk patients has become recommended following randomized clinical trials, which demonstrated a survival benefit to long-term ADT with RT for men with locally advanced PC. The current standard of care offers a modest 48 to 79% 10-year overall survival (OS) rates and much lesser prostate cancer-specific survival (PCCS) rates [1–3]. By contrast, surgical therapy (i.e., radical prostatectomy [RP]) has previously been discouraged in the setting of high-risk tumors, secondary to concerns regarding increased side effects, positive surgical margins, and inadequate disease control. With better understanding of pelvic anatomy, availability of advanced surgical tools and with better understanding of tumor biology and disease kinetics, surgical therapy is making a strong point in management of these cancers with availability of robust retrospective data. In this review, we present the definition, predictors of success, techniques, and the most recent evidence about the role of radical prostatectomy for LAPC treatment.

✉ SK Raghunath
draghunathsk@yahoo.com

¹ Department of Uro-Oncology, HCG Bangalore Institute of Oncology, Bangalore, India

Definition of Locally Advanced Prostate Cancer

One of the most critical challenges in choice of therapy and analysis of outcomes of locally advanced prostate cancer is in identifying patients with locally advanced prostate cancer. The National Comprehensive Cancer Network (NCCN), American Urological Association (AUA) as well as the European Association of Urology (EAU) follow D'Amico classification for definition of high-risk prostate cancer. However, there is no clear definition of what is locally advanced.

D'Amico defined three factors, which pose high-risk to prostate cancer. These include clinical stage $\geq$ T2c, serum PSA $\geq$ 20 ng/ml or biopsy Gleason score of $\geq$ 8 [3, 4].

Tombal et al. in 2014 summarized various guidelines for LAPC. LAPC can be defined as the one extending beyond the prostate capsule with invasion of pericapsular tissue, apex, bladder neck, or seminal vesicles but without any lymph node involvement or distant metastasis (i.e., T3-T4, N0, M0 disease). Bolla et al. also included N1 disease in the definition of LAPC as several studies reveal similar biochemical progression free, cancer specific and overall survival rates in patients with N1 disease. Nearly 20–25% of cases present as locally advanced disease in unscreened population in contrast to 6–8% in screened population. These patients are at increased risk of prostate-specific antigen (PSA) failure, metastatic progression, and cancer specific death. This definition has been often interchangeably used with the high-risk prostate cancer. While it is imperative that all locally advanced cancers are high-risk, all high-risk cancers may not be locally advanced. Lack of segregation has truncated the approach to treating such cancers [5–7].

Rationale for Surgery in LAPC

Radical prostatectomy has previously been discouraged in the setting of high-risk tumors, secondary to concerns regarding increased side effects, positive surgical margins, and inadequate disease control. With better understanding of pelvic anatomy, availability of advanced surgical tools and with better understanding of tumor biology and disease kinetics, surgical therapy is making a strong point in management of these cancers [8].

Van Poppel et al. reported that 43.8% of patients who had been previously staged as T3 actually had organ-confined tumors in the European Organization for Research and Treatment of Cancer (EORTC-30001) study. These results are in concordance with a prior study from Mayo Clinic, wherein 27% of men with LAPC were subsequently downstaged to pathologic T2 after RP. Collectively, these results indicate that a substantial amount of men classified as LAPC have actually organ-confined disease; therefore, they

would be candidates to standard surgical treatment with RP similar to men with early PC [7, 9–12].

The Scandinavian Prostate Cancer Group 4 Trial conducted by Holmberg et al. published in 2014, unequivocally concluded superiority of RP over watchful waiting in high-risk prostate cancers without significant loss of quality of life (QoL) parameters [13, 14].

In a meta-analysis of large retrospective series of RP for LAPC, Chang et al. reviewed the PCCS rates and noted it to be greater than 85% at the end of 10 years of follow-up, a result which is significantly better than the current standard of care and underscored the critical role of RP in these patients [13, 15–17].

In a large retrospective data analysis conducted from a single data registry of Sweden, Sooriyakumaran P et al. subanalyzed 34,515 men with various stages of PC and looked at the CSS of men treated with RP or the current standard of care of RT + ADT. The paper concluded that RP had a significantly favorable outcome across all stages and risk groups of prostate cancer, and the results of RP were better still in patients who were relatively younger and with less comorbidities [14, 16, 18].

Swanson GP et al. analyzed the patterns of treatment failure in men with LAPC included in the SWOG 8794 study. They observed that most disease recurrences are local in nature with only up to 16% distant metastases at presentation. This study highlights the sensitiveness of PSA following RP in identifying early failures and therefore also the ability to deliver early salvage therapy which effects better PCSS and OS rates. This is in significant difference to the current standard of care of RT + ADT where the local disease recurrence is between 10–25%, derived from meta-analyses of CaPSURE data registry published by Axel Heindenreich in 2014 [19–22].

While no prospective RCT exists to compare RP with RT + ADT, Boorjian et al. analyzed retrospective trials from the Mayo Clinic and Fox Chase Cancer Center and reported better OS in patients undergoing RP in comparison to patients receiving RT alone or RT + ADT. In this review of 1847 patients spanning over a 10-year period, the OS was 77% for men undergoing RP with nearly half of the men receiving adjuvant hormone therapy in comparison to 67% for men undergoing RT + ADT and 52% for men undergoing RT alone. This paper clearly sets aside the superiority of RP in patients with LAPC in comparison to RT alone and also to patients receiving the current standard of care of RT + ADT. Further, this paper highlights the importance of RP as a key component in multimodality treatment (MMT) of patients with LAPC [21, 23].

In the RTOG9202 study, which subsequently established RT + ADT as the standard of care for management of LAPC patients, the 10-year OS was 30%. In a subsequently conducted RTOG9601 phase III study, Shipley WU et al. concluded that combination of ADT + RT as a salvage following RP

affected a 10-year OS of 82% with a very low 2.3% cancer-specific mortality rate. This study effectively concludes the role of RP as a key therapeutic approach as a part of MMT of LAPC. RTOG9601 is a relatively newer study conducted with availability of better radiation technology in comparison to the RTOG9202 era; the OS rates are significantly different between these two studies indirectly validating the importance of RP. Similarly, a bias is also acceptable in favor of RP in RTOG9601 as better surgical infrastructure and technologies have facilitated performance of better surgeries and improving disease clearance rates as has been reported by Hsu, Ward, Serni et al. [9, 11, 14, 19, 24].

In a retrospective analysis by Zelefsky et al. comparing RP to RT with respect to CSS and OS, statistically significant survival advantage was noted in favor of RP, and the positive correlation persisted even when the disease was risk stratified in to low, intermediate, or high-risk groups. All the above studies favor utilization of RP whenever possible and also the fact that RP plays an important role in MMT [25–30].

RP as a Monotherapy

The data on surgical management of locally advanced prostate cancer has not been investigated or systematically reviewed, and no large-scale randomized controlled trial (RCT) is available to show its superiority. Comparison of RP with other treatment modalities for locally advanced prostate cancer is difficult and may not be correct because of heterogeneous group of patients and inherent selection bias of good prognosis patients in favor of surgery. A few studies have shown promising results of RP for locally advanced $\geq$ cT3 disease.

In a multicenter, non-randomized two-staged study (EORTC 30001), RP was done in clinical stage T3 patients with good prognosis factors (age < 70 years, PSA $\leq$ 20 ng/ml, biopsy Gleason score $\leq$ 7, performance status 0–1, and unilateral cT3a disease). The authors concluded that RP with extensive resection can be beneficial as a monotherapy for T3aN0M0 patients.

Van poppel et al. in their study determined the efficacy of RP monotherapy in men with clinically T3 disease. They mainly included patients with PSA values <10 ng/ml without involvement of seminal vesicles or lymph nodes and showed a 5-year biochemical recurrence free survival to be >60% [11, 12, 14, 19].

Gontero et al. in a single institution study showed that RP is technically feasible in any clinical ‘T’ extension up to M1a disease with acceptable morbidity. There were 51 patients in their study who had advanced disease compared to 152 patients with organ-confined disease. This study showed no significant difference in terms of surgical morbidity except for the blood transfusion, operative time, and lymphocele formation, which were higher in advanced stage group. The 7-year

overall and cancer-specific survival rates were 77 and 90% in advanced group vs. 88 and 99% in organ-confined groups, respectively. They also proposed that a possible advantage of surgery will be debulking the disease, and therefore prevention of complications related to local cancer progression [2, 20].

Hsu et al. in their study attempted to determine the prognostic factors for advanced prostate cancer after RP in cT3 patients in terms of biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), cancer-specific survival (CSS) and overall survival (OS) after 10 years. On multivariate analysis, they found that surgical tumor grade, margin, and lymph node status were significant factors in clinical progression-free survival and cancer-specific survival while surgical tumor grade, node status and preoperative PSA levels were significant factors in biochemical progression-free survival [9, 11, 19].

Xylinas et al. studied the role of RP for cT3 disease with the aim of disease control and showed that surgical experience is the main factor responsible to reduce perioperative complications and produce better functional results. This meta-analysis shows that the biochemical progression-free survival i.e., PSA < 0.2 ng/ml and 10 and 15 years survival ranges from 45 to 62%, 43–51 and 10–49%, respectively. In fact, these results were better than some of the series of EBRT alone or EBRT in combination of hormonal therapy (HT). The results however are not comparable because of lack of homogeneity.

Recently, a meta-analysis was published regarding the role of robot assisted radical prostatectomy for managing high-risk prostate cancer showing comparable short-term results to open prostatectomy in terms of its safety and functional outcome, however, the long-term oncological data is still awaited.

Multimodality Treatment

In a substantial number of patients, RP monotherapy will not result in a definitive cure. This fact has therefore supported the MMT approach in similar lines to cancer management of diseases of breast, colon, or rectum. Studies have been conducted in this regard and a variety of therapeutic options including ADT alone, early adjuvant or late salvage radiation with or without ADT have been considered.

A group of urologists at Mayo clinic has long been advocating RP as the first line treatment in multimodality approach for cT3 disease. Ward and colleagues in a large retrospective study with a follow-up of 15 years showed that 78% patients with pT3 disease received adjuvant and salvage treatment (HT, RT, or both) following RP. They categorized RP as an important part of multimodality approach for cT3 [31–37].

In a study by Ward et al., 78% of patients eventually needed adjuvant or salvage RT or HT compared to 56% of patients in a recent study from Hsu et al. 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. Ward et al. also reported a 15-year CSS rate of 79%. In a recent study by Gontero et al., RP appears to be a valid treatment with acceptable morbidity in patients with locally advanced prostate cancer of any T and N1. The 7-year OS and CSS rates were 77 and 90%, respectively; 89.5% of the patients received immediate adjuvant treatment after RP. This is also the opinion of Lange, who expressed the need for a randomized study testing the efficacy of RT and RP as initial therapy for locally advanced prostate cancer. In the meantime, 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 randomized studies compared postoperative RT with RP alone for locally advanced prostate cancer. Bolla et al. reported an improved biochemical progression-free survival 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. 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 USA. 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 [16, 38–41].

Technical Aspects of RP in Locally Advanced Prostate Cancer

RP in locally advanced prostate cancer requires added expertise and includes removal of whole prostate gland en-bloc with good apical dissection, wide resection of neurovascular (NV) bundle on the affected side and complete resection of both seminal vesicles. It also includes wider resection of the bladder neck and subsequent need for bladder neck reconstruction. The incidence of urinary incontinence and impotence are therefore higher in this group as compared to early prostate cancer but with increased surgical experience, the functional outcome can be improved and morbidity can be minimized. For locally advanced prostate cancer, open RP is preferred over robotic or laparoscopic approach, and it should be done in high-volume centers. Comparable short-term outcomes of robotic prostatectomy are now available. It will be difficult to

conclude non-inferiority of robotic access in such disease and robotic prostatectomy in LAPC should be at present reserved to high-volume centers.

Pelvic lymphadenectomy in cT3 disease is indispensable because of higher risk of lymph node involvement. The reported incidence of lymph node involvement is between 27 and 41% in different series. Briganti et al. recommended extended lymph node dissection (ePLND) to be carried out for patients with locally advanced prostate cancer. Heindenreich et al. compared the progression-free survival (PFS) in patients with standard vs. extended lymphadenectomy and found a 35% benefit in favor of the latter [2, 6, 13]. Traditionally, involvement of lymph nodes in prostate cancer was considered as an adverse prognostic factor associated with limited long-term survival regardless of treatment. However, new clinical data suggests the oncological benefit of local treatment even in metastatic prostate cancer. Engel et al. studied the survival rates of lymph node-positive patients with or without RP. Their study revealed twofold increased risk of death if RP was abandoned because of lymph node-positive disease, compared to patients who had completed RP. In addition, even in the case of lymph node-positive disease at diagnosis it has been shown that surgery may have a role as part of a multimodality management [42]. The outcomes are better when the number of positive lymph nodes is few or there is micro-metastatic disease. Schumacher et al. analyzed 122 consecutive lymph node-positive patients with negative preoperative staging examinations and those who did not receive any neoadjuvant therapy, and selected patients who underwent ePLND (minimum 10 lymph nodes in the surgical specimen) followed by RP. They reported median cancer-specific survival at 5 and 10 years as 84.5 and 60.1%, respectively. In patients with ≤ 2 or ≥ 3 positive nodes, median cancer-specific survival at 10 years was 78.6 and 33.4%, respectively ($p < 0.001$) suggesting that there may be a curative potential of surgical resection in the presence of a limited nodal involvement [43]. Prognostic implications of microscopic LN involvement at final specimen are still undetermined, and the role of immediate ADT is questionable. EAU guidelines recommend a follow-up by PSA and delaying the initiation of HT until biochemical recurrence is observed in patients with less than two microscopically involved lymph nodes discovered through extended nodal dissection. Further studies are required to determine if multimodality treatment may result in a better outcome [44].

Evolving Therapeutic Strategies in Surgical Management of LAPC

The aim of neoadjuvant hormonal treatment is to shrink the tumor, reduce the chance of having a positive margin and to reduce both local recurrence and distant metastasis in

intermediate and high-risk patients. However, neoadjuvant HT is not routinely recommended, and its role in clinical cT3 prostate cancer is controversial. Many studies have shown the impact of short-term (6 weeks–4 months) neoadjuvant HT (including complete androgen blockade) before RP. A decrease in postoperative positive surgical margins is consistently reported along with decrease in biochemical recurrence but no effect on global or cancer-specific survival was observed.

Similarly, combination of neoadjuvant HT along with docetaxel-based chemotherapy has been studied in the management of LAPC with early reports showing promising results regarding positive surgical margins and the time to biochemical disease recurrence. Long-term CSS and OS will need to be analyzed before advocating such therapy into routine practice for management of LAPC [45, 46].

Conclusion

RP has shown promising results in management of LAPC patients. With high probability of variations in risk stratification and clinical staging of prostate cancer, RP should always be kept in consideration as a key therapeutic strategy.

RP forms an important aspect of MMT to LAPC and can provide better outcomes (combined with adjuvant and salvage treatment if needed) than RT or ADT alone or combination of RT and ADT. Large volume prospective studies are however required to confirm these findings. With availability of better surgical infrastructure, RP can be performed with progressively improving success rates with acceptable morbidity. Neoadjuvant therapies will probably play a vital role in improving the results of MMT. Prospective, long duration studies are needed to confirm these initial opinions.

References

- Yossepowitch O, Eggener SE, Bianco FJ Jr, Carver BS, Serio A, Scardino PT et al (2007) Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. *J Urol* 178:493–499
- Joniau S, Briganti A, Gontero P, Gandaglia G, Tosco L, Fieuws S et al (2014) Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. *Eur Urol* 67: 157–164
- Gerber GS, Thisted RA, Chodak GW, Schroder FH, Frohmuller HG, Scardino PT et al (1997) Results of radical prostatectomy in men with locally advanced prostate cancer: multiinstitution pooled analysis. *Eur Urol* 32:385–390
- Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW (2004) Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. *J Urol* 172(5 Pt 1):1835–1839
- Joniau S, Hsu CY, Lerut E, Van Baelen A, Haustermans K, Roskams T et al (2007) A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. *Eur Urol* 51:388–396
- Gallina A, Chun FK, Briganti A, Shariat SF, Montorsi F, Salonia A et al (2007) Development and split-sample validation of a nomogram predicting the probability of seminal vesicle invasion at radical prostatectomy. *Eur Urol* 52:98–105
- Van Poppel H, Ameye F, Oyen R, Van de Voorde W, Baert L (1994) Accuracy of combined computerized tomography and fine needle aspiration cytology in lymph node staging of localized prostatic carcinoma. *J Urol* 151:1310–1314
- Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T et al (2014) EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013. *Eur Urol* 65:124–137
- Hsu CY, Joniau S, Van Poppel H (2005) Radical prostatectomy for locally advanced prostate cancer: technical aspects of radical prostatectomy. *EAU Upd Ser* 3:90–97
- Van Poppel H (2005) Surgery for clinical T3 prostate cancer. *Eur Urol Suppl* 4:12–14
- Hsu CY, Joniau S, Roskams T, Oyen R, Van Poppel H (2006) Comparing results after surgery in patients with clinical unilateral T3a, prostate cancer treated with or without neoadjuvant androgen-deprivation therapy. *BJU Int* 99:311–314
- Van Poppel H, Goethuys H, Callewaert P, Vanuytsel L, Van de Voorde W, Baert L (2000) Radical prostatectomy can provide a cure for well-selected clinical stage T3 prostate cancer. *Eur Urol* 38:372–379
- Briganti A, Karakiewicz PI, Chun FK, Gallina A, Salonia A, Zanni G et al (2007) 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* 51:1573–1581
- Van Poppel H, Vekemans K, Da Pozzo L, Bono A, Kliment J, Montironi R et al (2006) Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). *Eur J Cancer* 42:1062–1067
- van den Ouden D, Hop WC, Schroder FH (1998) Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. *J Urol* 160: 1392–1397
- de la Riva Isorna Martínez S, Belón López-Tomasety J, Marrero Domínguez R, Alvarez Cruz E, Santamaría Blanco P (2004) Radical prostatectomy as monotherapy for locally advanced prostate cancer (T3a): 12 years follow-up. *Arch Esp Urol* 57:679–692
- Tewari A, Divine G, Chang P, Shemtov MM, Milowsky M, Nanus D et al (2007) 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* 177:911–915
- Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, Olsson M et al (2014) Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. *BMJ* 348:g1502. doi:10.1136/bmj.g1502
- Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H (2007) Outcome of surgery for clinical unilateral T3a prostate cancer: a single institution experience. *Eur Urol* 51:121–129
- Gontero P, Marchioro G, Pisani R, Zaramella S, Sogni F, Kocjancic E et al (2007) Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. *Eur Urol* 51:922–930
- Bolla M, Van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L et al (2012) Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 380:2018–2027
- Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D et al (2006) Adjuvant radiotherapy for pathologically

- advanced prostate cancer: a randomised clinical trial. *J Am Med Assoc* 296:2329–2335
23. Lange PH (2007) Is surgery good for advanced localised prostate cancer? It's time to find out! *Eur Urol* 51:873–875
 24. Johnstone PA, Ward KC, Goodman M, Assikis V, Petros JA (2006) Radical prostatectomy for clinical T4 prostate cancer. *Cancer* 106: 2603–2609
 25. Berglund RK, Jones JS, Ulchaker JC, Fergany A, Gill I, Kaouk J et al (2006) Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. *Urology* 67:1253–1256
 26. Carver BS, Bianco FJ Jr, Scardino PT, Eastham JA (2006) Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol* 176:564–568
 27. Freedland SJ, Partin AW, Humphreys EB, Mangold LA, Walsh PC (2007) Radical prostatectomy for clinical stage T3a disease. *Cancer* 109:1273–1278
 28. Loeb S, Smith ND, Roehl KA, Catalona WJ (2007) Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. *Urology* 69:1170–1175
 29. Secin FP, Bianco FJ Jr, Vickers AJ, Reuter V, Wheeler T, Fearn PA et al (2006) Cancer-specific survival and predictors of prostate-specific antigen recurrence and survival in patients with seminal vesicle invasion after radical prostatectomy. *Cancer* 106:2369–2375
 30. Masterson TA, Pettus JA, Middleton RG, Stephenson RA (2005) 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* 66:152–155
 31. Grossfeld GD, Latini DM, Lubeck DP, Mehta SS, Carroll PR (2003) Predicting recurrence after radical prostatectomy for patients with high risk prostate cancer. *J Urol* 169:157–163
 32. Bastian PJ, Gonzalgo ML, Aronson WJ, Terris MK, Kane CJ, Amling CL et al (2006) Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. *Cancer* 107:1265–1272
 33. Lau WK, Bergstralh EJ, Blute ML, Slezak JM, Zincke H (2002) Radical prostatectomy for pathological Gleason 8 or greater prostate cancer: influence of concomitant pathological variables. *J Urol* 167:117–122
 34. Oefelein MG, Grayhack JT, McVary KT (1995) Survival after radical retropubic prostatectomy of men with clinically localized high grade carcinoma of the prostate. *Cancer* 76:2535–2542
 35. Tefilli MV, Gheiler EL, Tiguert R, Banerjee M, Sake W, Grignon D et al (1999) Role of radical prostatectomy in patients with prostate cancer of high Gleason score. *Prostate* 39:60–66
 36. Mian BM, Troncso P, Okiharan K, Bhadkamkar V, Johnston D, Reyes AO et al (2002) Outcome of patients with Gleason score 8 or higher prostate cancer following radical prostatectomy alone. *J Urol* 167:1675–1680
 37. Serni S, Masieri L, Minervini A, Lapini A, Nesi G, Carini M (2006) Cancer progression after antegrade radical prostatectomy for pathologic Gleason score 8 to 10 and influence of concomitant variables. *Urology* 67:373–378
 38. Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H (2005) Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 95:751–756
 39. Ohori M, Goad JR, Wheeler TM, Eastham JA, Thompson TC, Scardino PT (1994) Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? *J Urol* 152:1843–1849
 40. Perrotti M, Rabbani F, Russo P, Solomon MC, Fair WR (1998) Early prostate cancer detection and potential for surgical cure in men with poorly differentiated tumors. *Urology* 52:106–110
 41. Hurwitz MD, Schultz D, Richie JP, Wein AJ, Whittington R, Malkowicz SB et al (2006) Radical prostatectomy for high-grade prostate cancer. *Urology* 68:367–370
 42. Engel J, Bastian PJ, Baur H, Beer V, Chaussy C, Gschwend JE, et al (2010) Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. *Eur Urol* 57: 754–761
 43. Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE (2008) Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. *Eur Urol* 54: 344–352
 44. Briganti A, Karnes JR, Da Pozzo LF, Cozzarini C, Gallina A, Suardi N, et al (2009) Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. *Eur Urol* 55: 261–270
 45. Do TM, Parker RG, Smith RB, Kagan AR (2001) High-grade carcinoma of the prostate: a comparison of current local therapies. *Urology* 57:1121–1126
 46. Kibel AS, Nelson JB (2007) Adjuvant and salvage treatment options for patients with high-risk prostate cancer treated with radical prostatectomy. *Prostate Cancer Prostatic Dis* 10:119–126