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Contemporary Management of High-risk Localized Prostate Cancer

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Abstract The management of high-risk, localized prostate cancer remains a formidable challenge despite significant technical advances in surgery and radiation therapy. Treatment outcomes of radiation therapy are improved by the addition of adjuvant androgen deprivation therapy, whereas, with surgery, oncologic results are enhanced with either postoperative radiation therapy or androgen deprivation therapy in select cases. In high-risk prostate cancer, disease recurrence after primary therapy may occur at either distant or local sites. Ongoing studies are in the process of evaluating systemic therapy for the eradication of local and micrometastatic disease. Neoadjuvant therapies offer the opportunity to maximize local control as a path to improved outcomes and critically evaluate agent effectiveness in the target tissue. The treatment for high-risk localized prostate cancer is in evolution. It is likely that the development of effective strategies based on understanding prostate tumor biology will lead to significant advances in the treatment of this disease.

Keywords Prostate cancer · Neoadjuvant · Adjuvant · Gleason score · Chemotherapy · Radiation · Prostatectomy · Androgens

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Introduction

Prostate cancer is the most common visceral cancer in Western countries and the second most lethal cancer among men [1]. Presently, a man's lifetime risk of prostate cancer is about 17%. Because prostate cancer is a disease of aging, these odds are likely to rise as longevity increases due to improvements in health care and lifestyle habits. Prostate cancer is a heterogeneous disease with wide variability in clinical outcomes. Although some tumors progress rapidly despite aggressive measures, many remain indolent and localized for a number of years. Approximately 3% of all US men, or about one in six of all prostate cancer patients, will die of this disease [1]. The early identification of these lethal cases with application of effective treatment is what is needed in order to improve prostate cancer–specific mortality (PCSM). It is well known that factors such as Gleason score are highly predictive for oncologic outcomes. In a population-based study by Albertsen et al. [2], the risk of PCSM was 16-fold higher in men with high-grade cancer compared with those with low-grade cancer. This need for better characterization of prostate cancer was recently highlighted in two randomized studies of prostate cancer screening for very early cancer. With intermediate follow-up, these studies showed little or no benefit to prostate cancer screening compared with observation [3, 4]. However, in these trials less than 10% of all subjects had high-grade cancers at the time of diagnosis. Thus, they were not likely to show a survival benefit without extended follow-up.

High-risk localized prostate cancer has previously been defined as disease recurrence after primary therapy that exceeds 50% [5]. Given the biologic variability resulting in a wide variance of clinical outcomes, it is important to stratify patients into high-risk groups so that either suitable

therapy or the chance at participation in clinical trials can be offered to this select group. The availability of clinical trials that offer promising new approaches for such patients is warranted considering the high rate of disease recurrence even when treatment intensity is maximized. This review discusses the process of identification of high-risk prostate cancer along with current and investigational treatment strategies.

Identification and Staging of High-risk Prostate Cancer

A number of clinical factors are predictive of disease recurrence that aid in the selection of patients in high-risk groups. Although many of these variables have been examined individually, newer predictive models that are capable of combining several factors have resulted in refined tools that are available for clinical use. Pretreatment factors that predict outcome of either radiation or surgery failure include Gleason score, pretreatment prostate-specific antigen (PSA), and tumor stage. D'Amico and colleagues [5] developed a widely used schema based on clinical data from patients who underwent surgery or radiation with curative intent. Risk factors that predicted greater than a 50% chance of cancer recurrence included clinical stage T2c or higher, a PSA greater than 20 ng/ml, or a Gleason score≥8. More recently, pretreatment nomograms have been developed that incorporate these factors to give more individualized numbers that have served to help in counseling as well as clinical decision making [6]. These are now available in both web-based and downloadable applications for handheld devices [7]. The routine metastatic workup for high-risk patients includes a nuclear bone scan to rule out osseous metastases. Computerized tomogram scans are of limited utility in discerning the local tumor extent; however, they can be used to assess lymph node status and are indicated if the PSA is over 20 ng/ml, in the presence of T3-T4 cancer, or if the predicted chance of lymph node disease exceeds 20% [8, 9]. In the future, the use of MRI [10] and ferromagnetic nanoparticles [11] are likely to improve local and regional staging; however, further study is needed in order to bring these promising modalities into the sphere of clinical practice. We are currently evaluating a novel process for discriminating benign from malignant prostate tissues using shutter-speed modeling [12]. This has yielded promising early results in breast cancer imaging; it is our hope that it may be applied to prostate cancer detection and staging as well.

Surgery and Radiation as Monotherapy

Radiation and surgery are considered effective treatment options for low-to intermediate-risk prostate cancer; however, satisfactory therapeutic approaches have yet to be developed for patients with clinically localized, high-risk disease [13••]. The results of radical prostatectomy for patients at the Mayo Clinic who had high-grade disease have highlighted the problem [14]. In a study of 407 patients with a Gleason score of 8 or higher, only 23% of patients who were followed expectantly remained clinically free of disease at 10 years. Similarly, in a report by Pound et al. [15], the rate of remaining metastases-free at 7 years was 29% in patients with Gleason 8 or above. With radiation treatment alone in patients with high-risk disease, the 5-year rates of disease control are only 40% and 5-year survival ranges from 50% to 60% [16, 17].

Contemporary modifications to standard treatment have resulted in improved cancer-free rates in patients undergoing either surgery or radiation. An in-depth understanding of pelvic anatomy and prostate cancer spread has opened the door for technical modifications carried out at the time of prostatectomy [18]. These include wide local excision of the neurovascular bundles and a precise and thorough apical dissection [19, 20]. These have resulted in a reduced rate of positive surgical margins, which have translated into improved disease-free survival. Further improvements in the tumor staging and clinical outcome seem to result from the performance of extended pelvic lymph node dissection versus a more limited pelvic dissection [21, 22•]. These studies have shown that benefits of the extended dissection may be applicable not only to high-risk cases, but to those with intermediate-and some with low-risk cancers as well.

Improvements in the technical delivery of radiation that have been made in the past decade have also resulted in more favorable clinical outcomes. These advances were predicated on the ability to improve targeting of the prostate gland through the application of intensity-modulated radiation therapy (IMRT). IMRT allows for the reduction in treatment area with an associated reduction in toxicity. IMRT has enabled the delivery of increased doses to the prostate gland. A recent randomized trial clearly showed improved disease-free survival in men treated with 79 Gy versus 70 Gy [23]. Furthermore, with image guidance and technologies such as implantable electromagnetic transponders, it is highly likely that cancer control rates can be further improved when we account for organ motion [24].

Alternatives to standard therapy for high-risk localized prostate cancer include brachytherapy and cryotherapy. Brachytherapy was compared with radiation and surgery and found to be inferior even when hormonal therapy was coadministered [5]. The data supporting the use of cryotherapy are even less convincing. Supporters of the use of this modality often cite a study by Prepelica et al. [25], who retrospectively reviewed the results of cryotherapy for high-grade disease. However, only 15 subjects within this study had Gleason 8 or higher disease, and the

majority of these received hormone therapy. Thus, until further evidence is available, both brachytherapy and cryotherapy should be considered experimental.

Adjuvant Androgen Deprivation

Several of the most important clinical discoveries in advancing the treatment of prostate cancer have come from the use of adjuvant androgen deprivation therapy (ADT) with radiation and surgery for high-risk prostate cancer. Bolla et al. [16] reported the results of a randomized trial by the European Organisation for Research and Treatment of Cancer (EORTC) of radiation alone versus radiation plus adjuvant ADT for 3 years following treatment. There were significant improvements in both overall and biochemical-free survival in men treated with the combination of radiation and ADT. The 5-year disease-free survival was 74% in the combined treatment arm versus 40% in the radiation alone arm. Importantly, overall survival was improved by 16% in the ADT arm. These findings were strongly supported by the Radiation Therapy Oncology Group (RTOG), which found improved survival in men with high-risk cancer treated with the addition of ADT [25]. In a follow-up EORTC study, the duration of hormonal therapy was evaluated for high-risk patients. It was reported that ADT for 3 years was superior to 6 months of ADT in terms of overall survival and cancer-free survival [26], thus establishing this interval as a standard treatment duration for high-risk prostate cancer.

For patients undergoing surgery for high-risk disease, the use of adjuvant hormonal therapy has previously been studied. In a randomized trial of early versus delayed ADT after prostatectomy for node-positive disease, the use of early ADT resulted in a fourfold improvement in prostate cancer–specific survival [27••]. The use of ADT alone has also been studied for high-risk disease. In a randomized trial of early versus delayed ADT alone in nonoperable patients, there was no improvement in PCSM for those receiving early ADT [28]. Thus, it appears that treatment of the primary tumor is a critical factor in improving the response of prostate cancer to ADT. Neoadjuvant (preoperative) ADT has been evaluated by numerous investigators as well in randomized trials. These have categorically shown that although preoperative ADT may reduce the incidence of positive surgical margins and result in occasional complete responses, it does not reduce the risk of biochemical recurrence [29–33]. Neoadjuvant ADT prior to radiation was also studied by the RTOG. In this study, there was no observed benefit of neoadjuvant ADT to those with high-grade cancer compared with radiation alone [34]. Thus, it is our policy to not offer neoadjuvant ADT to any patient considering either primary surgical or radiation therapy, as it appears to offer no degree of benefit. Furthermore, attentive consideration to the use of ADT should be given to all patients, as recent data analyses suggest potential negative health consequences from even short-term use [35].

Adjuvant Radiation Therapy

Disease recurrence after radical prostatectomy or radiation therapy may occur locally in the surgical site or at distant sites. The use of current imaging modalities limits our ability to localize early disease recurrences [36, 37]; however, recent clinical trial data support the concept that residual disease in the prostatic fossa is clinically significant. In a study of 356 patients undergoing salvage radiation therapy to the prostatic fossa for biochemical recurrence, 67% achieved a complete biochemical response [38]. These benefits extended to those with high-risk features as well and were of particular benefit to those with positive surgical margins—a fact that emphasized the importance of adequate local control of the cancer at the time of surgery. These findings have been supported by results from a phase 3 trial (EORTC 22911) of adjuvant pelvic radiation therapy postprostatectomy versus observation for high-risk prostate cancer [39]. In this study, men treated with adjuvant radiotherapy after prostatectomy had 52% reduction in either biochemical or clinical progression. Similarly, a Southwest Oncology Group (SWOG) trial showed that adjuvant radiation after prostatectomy resulted in a 25% reduction in metastases or death [40•]. Localized radiation reduced the risk of PSA recurrence by 57% and increased the time to PSA failure from 2.2 to 9.2 years [41•]. In a secondary analysis using updated trial data, Thompson et al. [42••] showed that adjuvant radiation resulted in a statistically significant increase in metastasis-free survival (12.9 years versus 14.7 years) and overall survival (13.3 versus 15.2 years) in the group receiving early postoperative radiation therapy. Thus, adjuvant radiation should be considered a standard treatment option for prostate cancer with high-risk features after prostatectomy.

New Directions

Adjuvant Chemotherapy

Adjuvant chemotherapy has the theoretical advantage of killing residual cancer cells after either radiation or surgery, thus eradicating micrometastatic disease, regardless of location. Adjuvant chemotherapy is a treatment standard for a number of tumor types, but has not been critically evaluated in prostate cancer to date. Docetaxel chemotherapy has been

Table 1 Summary of prior neoadjuvant chemotherapy trials in high-risk prostate cancer

Institution	Patients, *n*	Regimen	Outcomes
MSKCC	36	TEC	Median PSA nadir 0.17 ng/ml
University of Michigan	21	EMP plus docetaxel	50% or greater PSA decline in 100%
UBC	72	Docetaxel plus ADT	Complete pathologic responses in 2 subjects (3%)
Dana Farber	15	Docetaxel	67%>50% PSA decline
OHSU	54	Docetaxel plus mitoxantrone	Negative surgical margins in 67%

ADT androgen deprivation therapy, *EMP* estramustine phosphate, *MSKCC* Memorial Sloan-Kettering Cancer Center, *OHSU* Oregon Health & Science University, *PSA* prostate-specific antigen, *TEC* paclitaxel, estramustine phosphate, carboplatin, *UBC* University of British Columbia.

shown to improve PCSM and overall survival in patients with androgen-independent disease in two separate clinical trials [43••, 44]. This demonstration of significant activity against advanced cancer encouraged investigators to examine its effects in other scenarios. Currently this drug is under study in both the postradiation and postprostatectomy settings. RTOG 0521 is a study comparing radiation plus ADT with or without adjuvant docetaxel chemotherapy [45], whereas the Veterans Administration CSP 553 trial is comparing prostatectomy with pelvic lymph node dissection with or without docetaxel chemotherapy [46]. These two studies hold the promise of defining a role for adjuvant docetaxel chemotherapy after primary therapy, just as prior studies defined a role for ADT as effective adjuvant treatment.

Neoadjuvant Chemotherapy

The use of taxanes prior to surgery has been studied by several investigative groups [13••]. These studies have shown that taxanes can be administered with an acceptable safety profile in the preoperative setting (Table 1). Docetaxel therapy resulted in significant PSA reductions and was associated with modest histologic changes in many of the trials. Taxanes have also been studied in combination with ADT as neoadjuvant therapy [47, 48]. In these studies, pronounced changes in PSA values and the tumor histology were observed, with a 3% incidence of complete tumor eradication [49]. Although these antineoplastic effects could be the result of ADT alone, they are encouraging, nonetheless. These results have led to the design and execution of a Canadian-led phase 3 trial to study the benefit of neoadjuvant docetaxel plus ADT compared with surgery alone [50]. In a multicenter trial conducted at our institution, we studied the role of multiagent chemotherapy prior to prostatectomy [51]. Patients received combination docetaxel plus mitoxantrone for four cycles prior to prostatectomy. Pathological examination showed that negative surgical margins were achieved in 67% of cases, which were improved over historical controls and were comparable to the results achieved with docetaxel plus ADT. Biochemical disease-free survival was 66% at 2 years. Importantly, we identified several significant predictors of cancer recurrence after chemotherapy and prostatectomy, which included prechemotherapy PSA, histologically positive lymph node metastases, and postchemotherapy tissue vascular endothelial growth factor expression. Furthermore, characterization of tumor tissues from this study has identified important molecular factors in treatment resistance of prostate cancer [52, 53]. Although the relative effectiveness of neoadjuvant therapy may appear promising in select trials, ultimately these must be critically evaluated in randomized trials comparing them with the standard of care.

Novel Therapies for High-Risk Prostate Cancer

Recent advances in the understanding of the cellular factors that drive the progression of prostate cancer have led to the design and evaluation of agents with a high degree of biologic specificity. Many of these agents are being studied as neoadjuvant therapy prior to prostatectomy (Table 2).

Table 2 Current neoadjuvant trials for high-risk localized prostate cancer

Institution	Agent	Pathway	Primary end point
UCSF	Sipuleucel-T	Active cellular immunotherapy	Immune response in tumor tissue
MSKCC	Vorinostat plus ADT	Histone deacetylase inhibitor	Pathologic complete response
Hoosier Oncology Group	Dasatinib plus ADT	SRC family tyrosine kinase inhibitor	Pathologic complete response
University of Washington	IMC-A12 plus ADT	IGF-IR inhibitor	Pathologic complete response
Duke University	Preoperative radiation	DNA damage	Safety
OHSU	Docetaxel plus radiation	DNA damage via cell cycle	Pathologic complete response

ADT androgen deprivation therapy, *IGF-IR* insulin-like growth factor-I receptor, *MSKCC* Memorial Sloan-Kettering Cancer Center, *OHSU* Oregon Health & Science University, *UCSF* University of California, San Francisco. (Data from www.clinicaltrials.gov.)

These novel agents are designed to selectively affect critical pathways or processes such as the cell cycle, androgen receptor signaling, survival pathways, and growth factor receptors. Findings from these trials will enable translational scientists to validate target tissue effectiveness for these agents. Once validated, these agents can be further studied in either high-risk prostate cancer or in advanced metastatic cancer. One such agent that has been evaluated through this rigorous process is OGX-011, an antisense molecule to the cytoprotective chaperone protein clusterin [54]. Based on these findings, the combination of OGX-011 plus docetaxel is being compared with docetaxel alone in a randomized, phase 3 trial for patients with androgen-independent prostate cancer. The early identification of efficacy through either clinical effects or through biomarker analysis will promote the rapid advancement of agent development and, in turn, an improvement in clinical outcomes.

Conclusions

Numerous developments in the fields of surgery and radiation have improved treatment outcomes in high-risk prostate cancer. However, continued advancements in these monotherapies are limited by the tolerability of extended surgery as well as the dose limitations of radiation. Improvements to these modalities have been made in survival through the selective application of both adjuvant androgen deprivation and radiation therapy. Further advances in the treatment of high-risk prostate cancer are dependent upon the discovery of effective novel therapies that can be applied in conjunction with surgery and radiation as mainstays.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Jemal A, Siegel R, Ward E, et al.: Cancer statistics, 2009. CA Cancer J Clin 2009, 59:225–249.
2. Albertsen PC, Hanley JA, Fine J: 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005, 293:2095–2101.
3. Andriole GL, Crawford ED, Grubb RL 3rd, et al.: Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009, 360:1310–1319.
4. Schroder FH, Hugosson J, Roobol MJ, et al.: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009, 360:1320–1328.
5. D'Amico AV, Whittington R, Malkowicz SB, et al.: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998, 280:969–974.
6. Stephenson AJ, Scardino PT, Eastham JA, et al.: Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005, 23:7005–7012.
7. Memorial Sloan-Kettering Cancer Center: Prediction tools: a tool for doctors and patients. Available at http://www.mskcc.org/mskcc/html/5794.cfm. Accessed February 2010.
8. Greene KL, Albertsen PC, Babaian RJ, et al.: Prostate specific antigen best practice statement: 2009 update. J Urol 2009, 182:2232–2241.
9. Mohler JL: The 2010 NCCN Clinical Practice Guidelines in Oncology on Prostate Cancer. J Natl Compr Canc Netw 2010, 8:145.
10. Fuchsjager M, Akin O, Shukla-Dave A, et al.: The role of MRI and MRSI in diagnosis, treatment selection, and post-treatment follow-up for prostate cancer. Clin Adv Hematol Oncol 2009, 7:193–202.
11. Harisinghani MG, Barentsz J, Hahn PF, et al.: Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003, 348:2491–2499.
12. Huang W, Li X, Morris EA, et al.: The magnetic resonance shutter speed discriminates vascular properties of malignant and benign breast tumors in vivo. Proc Natl Acad Sci U S A 2008, 105:17943–17948.
13. •• Sonpavde G, Chi KN, Powles T, et al.: Neoadjuvant therapy followed by prostatectomy for clinically localized prostate cancer. Cancer 2007, 110:2628–2639. *This paper concisely outlines the rationale and outcomes of recent studies using the neoadjuvant approach for high-risk prostate cancer. Future implications of ongoing studies are discussed.*
14. Lau WK, Bergstralh EJ, Blute ML, et al.: Radical prostatectomy for pathological Gleason 8 or greater prostate cancer: influence of concomitant pathological variables. J Urol 2002, 167:117–122.
15. Pound CR, Partin AW, Eisenberger MA, et al.: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999, 281:1591–1597.
16. Bolla M, Collette L, Blank L, et al.: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002, 360:103–106.
17. Roach M, Lu J, Pilepich MV, et al.: Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. Int J Radiat Oncol Biol Phys 2000, 47:609–615. (Erratum appears in Int J Radiat Oncol Biol Phys 2000, 48:313 Note: Mohuidden M [corrected to Mohiuddin M].)
18. Walsh PC: 2008 Whitmore Lecture: radical prostatectomy–where we were and where we are going. Urol Oncol 2009, 27:246–250.
19. Hull GW, Rabbani F, Abbas F, et al.: Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002, 167(2 Pt 1):528–534.
20. Ward JF, Zincke H, Bergstralh EJ, et al.: The impact of surgical approach (nerve bundle preservation versus wide local excision) on surgical margins and biochemical recurrence following radical prostatectomy. J Urol 2004, 172(4 Pt 1):1328–1332.
21. Wagner M, Sokoloff M, Daneshmand S: The role of pelvic lymphadenectomy for prostate cancer–therapeutic? J Urol 2008, 179:408–413.

22. • Briganti A, Blute ML, Eastham JH, et al.: Pelvic lymph node dissection in prostate cancer. Eur Urol 2009, 55:1251–1265. *The importance of an adequate lymph node dissection for both staging and therapeutic reasons are discussed. A thorough understanding of pelvic anatomy with attention to the spread of metastases is essential to properly performing this component of the prostatectomy.*
23. Zietman AL, DeSilvio ML, Slater JD, et al.: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005, 294:1233–1239.
24. de Crevoisier R, Kuban D, Lefkopoulos D: Image-guided radiotherapy by in-room CT-linear accelerator combination [in French]. Cancer Radiother 2006, 10:245–251.
25. Lawton CA, Winter K, Murray K, et al.: Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001, 49:937–946.
26. Bolla M, de Reijke TM, Van Tienhoven G, et al.: Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009, 360:2516–2527.
27. •• Messing EM, Manola J, Yao J, et al.: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006, 6:472–479. *In this study, 3 years of androgen deprivation was compared with 6 months of treatment after radiation. This showed definitive improvements in overall and PCSM without an increase in cardiovascular morbidity, favoring the 3-year arm.*
28. Studer UE, Whelan P, Albrecht W, et al.: Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006, 24:1868–1876.
29. Aus G, Abrahamsson PA, Ahlgren G, et al.: Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int 2002, 90:561–566.
30. Gleave ME, Goldenberg SL, Chin JL, et al.: Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. J Urol 2001, 166:500–506; discussion 506–507.
31. Hurtado-coll A, Goldenberg SL, Klotz L, Gleave ME: Preoperative neoadjuvant androgen withdrawal therapy in prostate cancer: the Canadian experience. Urology 2002, 60(3 Suppl 1):45–51; discussion 51.
32. Rabbani F, Perrotti M, Bastar A, Fair WR: Prostate specific antigen doubling time after radical prostatectomy: effect of neoadjuvant androgen deprivation therapy. J Urol 1999, 161:847–852.
33. Soloway MS, Pareek K, Sharifi R, et al.: Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. J Urol 2002, 167:112–116.
34. Pilepich MV, Winter K, John MJ, et al.: Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001, 50:1243–1252.
35. Nanda A, Chen MH, Braccioforte MH, et al.: Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009, 302:866–873.
36. Hricak H, Schoder H, Pucar D, et al.: Advances in imaging in the postoperative patient with a rising prostate-specific antigen level. Semin Oncol 2003, 30:616–634.
37. Scattoni V, Montorsi F, Picchio M, et al.: Diagnosis of local recurrence after radical prostatectomy. BJU Int 2004, 93:680–688.
38. Stephenson AJ, Shariat SF, Zelefsky MJ, et al.: Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004, 291:1325–1332.
39. Bolla M, van Poppel H, Collette L, et al.: Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005, 366:572–578.
40. • Thompson IM Jr, Tangen CM, Paradelo J, et al.: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006, 296:2329–2335.
41. • Swanson GP, Hussey MA, Tangen CM, et al.: Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007, 25:2225–2229.
42. •• Thompson IM, Tangen CM, Paradelo J, et al.: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009, 181:956–962.
43. •• Petrylak DP, Tangen CM, Hussain MH, et al.: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004, 351:1513–1520. *The above four papers highlight the need to improve upon local therapies for prostate cancer, as the risk of local recurrence is over 50% in high-risk cases.*
44. Tannock IF, de Wit R, Berry WR, et al.: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004, 351:1502–1512.
45. Patel AR, Sandler HM, Pienta KJ: Radiation Therapy Oncology Group 0521: a phase III randomized trial of androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with docetaxel/prednisone for localized, high-risk prostate cancer. Clin Genitourin Cancer 2005, 4:212–214.
46. Montgomery B, Lavori P, Garzotto M, et al.: Veterans Affairs Cooperative Studies Program study 553: chemotherapy after prostatectomy, a phase III randomized study of prostatectomy versus prostatectomy with adjuvant docetaxel for patients with high-risk, localized prostate cancer. Urology 2008, 72:474–480.
47. Hussain M, Smith DC, El-Rayes BF, et al.: Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locally advanced prostate cancer. Urology 2003, 61:774–780.
48. Konety BR, Eastham JA, Reuter VE, et al.: Feasibility of radical prostatectomy after neoadjuvant chemohormonal therapy for patients with high risk or locally advanced prostate cancer: results of a phase I/II study. J Urol 2004, 171(2 Pt 1):709–713.
49. Chi KN, Chin JL, Winquist E, et al.: Multicenter phase II study of combined neoadjuvant docetaxel and hormone therapy before radical prostatectomy for patients with high risk localized prostate cancer. J Urol 2008, 180:565–570; discussion 570
50. Eastham JA, Kelly WK, Grossfeld GD, Small EJ: Cancer and Leukemia Group B (CALGB) 90203: a randomized phase 3 study of radical prostatectomy alone versus estramustine and docetaxel before radical prostatectomy for patients with high-risk localized disease. Urology 2003, 62(Suppl 1):55–62.
51. Garzotto M, Higano CS, O'Brien C, et al.: Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer. Cancer 2010 Feb 8 (Epub ahead of print).
52. Qian DZ, Huang CY, O'Brien CA, et al.: Prostate cancer-associated gene expression alterations determined from needle biopsies. Clin Cancer Res 2009, 15:3135–3142.
53. Qian DZ, Rademacher BL, Pittsenbarger J, et al.: CCL2 is induced by chemotherapy and protects prostate cancer cells from docetaxel-induced cytotoxicity. Prostate 2010, 70:433–442.
54. Zoubeidi A, Chi K, Gleave M: Targeting the cytoprotective chaperone, clusterin, for treatment of advanced cancer. Clin Cancer Res Feb 9 (Epub ahead of print).