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GUEST EDITORIAL

It is a pleasure to have been invited by The Canadian Journal of Urology to be the guest editor for this supplement, which deals with the Masters in Urology Meeting held in Bermuda, in July 2007. As the reader will see from the articles that follow, the topics discussed at the meeting were varied and covered a broad range of urologic practice. All speakers are recognized experts in their relevant areas and the talks delivered in all cases represent the current state of the art.

This supplement contains articles based on a number of presentations delivered at this meeting. As can be seen from the table of contents, there should be something of interest for all urologists, no matter what their areas of expertise. Hopefully, these articles will prove to be beneficial to general urologists. The articles about management of PSA recurrence and current trends in hormonal therapy for prostate cancer point out the issues concerning duration of treatment, options for multimodality therapy, and new advances in imaging technology. Another area that was extensively covered concerns renal cell carcinoma — both the management of small renal masses and current options in the treatment of advanced disease. As a urologic oncologist, these articles represent a significant area of interest for me. I hope my colleagues will find them as equally thought provoking.

For urologists interested in the management of benign prostate diseases and for specialists in female urology, multiple aspects of these topics were covered. Again, we have tried to give the reader a flavor of what was presented. Another area that was addressed is the topic of androgen replacement in men and the current controversies surrounding this issue. All in all, I hope you will find this supplement thought provoking, interesting, and easy to read.

Sincerely,

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Salvage options for biochemical recurrence after primary therapy for prostate cancer

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Despite excellent success rates with radical prostatectomy and radiotherapy for the treatment of prostate cancer, a significant number of patients will experience a rise in their serum prostate specific antigen (PSA) level. A variety of salvage options in this scenario have been investigated and the choice to pursue surveillance, single therapy or combination therapy depends on clinical assessment of risk and location of tumor recurrence. After radical prostatectomy, for example, patients with low risk local disease may not require secondary therapy or may benefit from salvage radiotherapy. Those with higher risk disease, based on PSA kinetics and tumor pathology may require systemic androgen deprivation therapy (ADT) with or without radiotherapy. Local recurrence after radiotherapy has the options of cryotherapy, brachytherapy or salvage surgery. ADT can also be applied in these patients at high risk of disease progression and cancer-specific mortality. Risk assessment in these settings is paramount as all secondary therapy options for prostate cancer have potential side effects that may significantly affect quality of life. We review the literature and discuss the current methods of risk assessment and the treatment options in prostate cancer once primary therapy fails.

Key Words: prostate cancer, radical prostatectomy, radiotherapy, salvage therapy, PSA recurrence, biochemical recurrence, locally advanced

Introduction

Continued advancements in radical prostatectomy techniques, radiotherapy technology and patient selection for primary curative treatment have improved the management of prostate cancer. Despite these advances, a significant proportion of patients will experience biochemical recurrence (BCR) in serum prostate specific antigen (PSA). As treatment options for a rising PSA after primary therapy vary, the clinician must assess for local versus metastatic extension as well as risk of prostate cancer-specific death. Those with high risk disease may benefit from aggressive secondary combined therapies while those with low risk disease may be more likely to die from unrelated causes and can therefore avoid the potential morbidity of salvage therapies. These considerations combined with patient factors such as lifestyle, age and comorbidities at the time of recurrence present a challenging scenario for the clinician. This article reviews the current treatment options available for patients with prostate cancer who experience BCR after radical prostatectomy or radiotherapy.

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PSA relapse after radical prostatectomy

Observation

In modern series, BCR after radical prostatectomy for clinically localized prostate cancer occurs in 15%-20% of patients within 5 years.[1-4] After PSA relapse, 34% will develop metastatic progression at a median of 8 years (following BCR) and of these, 43% will die of prostate cancer after an additional 5 years.[2] On average, prostate cancer is one of the more indolent adenocarcinomas in terms of progression to metastases and death as 10-year overall survival in post-prostatectomy patients with BCR is only 5% less than those without PSA relapse (88% versus 93%, respectively).[5] Patients who are older, have significant comorbidities or have low risk disease at the time of recurrence may take advantage of this aspect and elect not to pursue salvage therapy. This option may benefit the patient long-term as all secondary therapies have potential quality of life-altering side effects, which may be avoided in those who are unlikely to die from their disease.

Assessing patient risk has recently been refined by Freedland et al using updated Johns Hopkins data initially reported by Pound.[6] In this retrospective series of 379 men with BCR who had PSA doubling time data after radical prostatectomy, the authors demonstrated that pathology Gleason score (≥ 8 versus < 8), time from surgery to BCR (≤ 3 years versus > 3 years) and PSA doubling time (PSADT) were statistically significant predictors of prostate cancer-specific mortality. PSADT was the strongest predictor and patients with a PSADT less than 9 months were very likely to die from prostate cancer. Conversely, a patient with a late recurrence, low Gleason score and a PSADT of ≥ 15 months carries only a 6% risk of dying from prostate cancer within 15 years and may avoid additional therapy. Using these predictors, Dr. Freedland produced tables listing 5-, 10- and 15-year risk estimates for prostate cancer death which can be used by the clinician and patient to determine risk and the need for subsequent therapy.[6]

Salvage external beam radiotherapy

Results from clinical trials looking at applications of radiotherapy indicate that the predominant pattern of biochemical failure after prostatectomy, even in those with high risk pathologic features, is local.[7-9] Therefore, a localized secondary therapy such as salvage external beam radiotherapy (RT) may be a viable option after prostatectomy. Stephenson et al showed that when salvage RT is administered when PSA relapse is ≤ 2 ng/ml, 4-year progression-free survival ranged from 18%-81% depending on Gleason score, margin status and PSADT.[10] Those with positive margins and PSADT > 10 months had the highest response rates. In a recent update, they demonstrated that even in patients with high risk features (PSADT ≤ 10 months, Gleason 8-10) typically considered harbingers of metastatic disease, 41% were disease free at 6 years when salvage RT was given before PSA level reached 0.5 ng/ml.[11] The number of patients in this subset was small, but the data illustrates the potential role of salvage radiotherapy in high risk patients when administered early.

Salvage hormone therapy

Few studies have been performed looking specifically at salvage hormonal therapy after radical prostatectomy. In a randomized prospective trial of post-prostatectomy patients with node-positive disease, Messing et al demonstrated a survival benefit to adjuvant androgen deprivation therapy (ADT) when compared to salvage ADT given at the time of boney metastases.[12,13] Wirth et al performed a similar randomized trial comparing adjuvant flutamide 750 mg to observation in node-negative patients after prostatectomy. Although there was a significant improvement in biochemical-free survival, there was no detectable difference in overall survival at a median of 6.1 years.[14] Salvage ADT for PSA-only recurrence was studied by Moul in a retrospective analysis of 1352 patients.[15] Despite starting ADT (LHRH, LHRH + anti-androgen, or orchiectomy) at a PSA level ≤ 5 ng/ml, there was no overall improvement in development of clinical metastases when compared to delayed administration of ADT. In patients with Gleason 8-10 disease or a PSADT < 12 months, however, early ADT significantly delayed the development of metastases by approximately 2 years when compared to late or no ADT. McLeod et al, on the other hand, reported on the combined Early Prostate Cancer trial program, which although showing a significant benefit in progression-free survival, failed to show an overall or cancer-specific survival benefit with the addition of adjuvant bicalutamide 150 mg to prostatectomy patients, including those with locally advanced disease (pT3-4 or node positive).[16] The prospective trials evaluating hormone therapy after radical prostatectomy are summarized in Table 1. Further studies are required to determine the role of ADT as a salvage monotherapy, which agent is most effective and when it is best administered.

Salvage radiotherapy combined with hormone therapy

To date, there are no published randomized controlled trials assessing the addition of hormone therapy to salvage radiation in post-prostatectomy patients. RTOG

TABLE 1. **Randomized prospective trials assessing benefit of adjuvant hormone therapy when combined with radical prostatectomy**

Trial	No. Pts	Treatment arms	Duration HT	Median F/U years	Overall survival benefit	p value
Radical Prostatectomy						
ECOG 7887[12,13]	98	Immediate goserelin or ochiectomy versus same deferred	Lifelong	7.1 11.9	20% 19%	0.02 0.04
Wirth et al[14]	309	Flutamide versus no adjuvant treatment	Lifelong	6.1	None	0.92
EPC 23,24,25[16]	4454	Bicalutamide (150 mg) versus no adjuvant treatment	Max 5 years	7.4	None	0.51

HT = hormone therapy; ECOG = Eastern Cooperative Oncology Group; EPC = Early Prostate Cancer

96-01 is investigating salvage RT versus RT plus bicalutamide in 800 patients with extracapsular extension or seminal vesicle involvement and PSA relapse after prostatectomy. This trial closed in 2003 and results are expected soon. A new international trial termed RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery) is seeking to enroll over 4000 subjects to investigate adjuvant versus salvage RT in combination with nothing, 6 months or 2 years ADT.[17] Until these studies are completed, our understanding on the use of combined salvage therapy after prostatectomy is limited to retrospective data and the trends seen in adjuvant trials.

In a retrospective study by Katz involving 115 patients with post-prostatectomy PSA recurrence, ADT increased the PSA relapse-free survival 20% when combined with salvage RT compared to RT alone (59% versus 39%, respectively).[18] When these patients where stratified by predictors of PSA failure after salvage RT, those with one or more risk factors had a significant improvement in PSA control with the addition of neoadjuvant ADT (p = 0.03). The risk factors noted which may necessitate additional ADT were Gleason score 8-10, absence of extracapsular extension, seminal vesicle invasion, negative margins and a PSA > 0.6 at initiation of RT. Other retrospective reports have shown an increased survival benefit with adjuvant hormone therapy when applied to patients with high risk disease, including those with positive lymph nodes.[19-21]

Several prospective randomized trials have examined the benefit of adding hormone therapy to primary external beam radiotherapy and are listed in Table 2.[22-26] All trials showed significant improvements in either biochemical progression-free survival, local failure, metastatic development, overall survival and/or cancer-specific survival with the addition of adjuvant hormone therapy to RT. RTOG 86-01, however, failed to reach statistical significance despite a 9% survival benefit and TROG 96-01 reported no difference in overall survival in either group receiving adjuvant ADT.[24,26] Although these studies involve primary RT and overall survival benefits are meager (0%-16% at approximately 6 years), they clearly demonstrate improved disease control in high risk patients when ADT is added to radiotherapy. Hopefully, these benefits will apply to the salvage setting as well.

The duration of ADT required to achieve maximal benefit is unknown. The CUOG and TROG 96-01 studies compared different short-term regimens of neoadjuvant hormones combined with primary RT and failed to show a difference in overall survival, Table 2.[26,27] After 4 months of neoadjuvant hormones and radiotherapy, RTOG 92-02 examined an additional 2 years of goserelin versus no therapy.[28] This study reported a significant 10% improvement in overall survival at 6 years favoring longer therapy, but only in a subset of higher risk patients with Gleason score 8-10. In a pooled analysis of 311 high risk patients with advanced age (median 70) from three randomized prospective trials, the use of 3 years ADT was not associated with prolonged survival when compared to 6 months ADT.[29] Bolla, however, recently reported early results from EORTC 22961 at the 2007 ASCO Annual Meeting. In this study

TABLE 2. **Randomized prospective trials assessing benefit and duration of adjuvant hormone therapy when combined with external beam radiotherapy**

Trial	No. Pts	Treatment arms	Duration HT	Median F/U years	Overall survival benefit	p value
Radiotherapy						
RTOG 85-31[22]	977	Immediate versus deferred goserelin	Lifelong	7.6	10%	0.002
EORTC 22863[23]	385	Goserelin versus no adjuvant treatment	3 years	5.5	16%	0.0002
RTOG 86-10[24]	456	Goserelin plus flutamide versus no adjuvant treatment	4 months	6.7	9%	0.1
D'Amico et al[25]	206	LHRH plus flutamide versus no adjuvant treatment	6 months	4.5	10%	0.04
TROG 96-01[26]	802	Goserelin plus flutamide versus no adjuvant treatment	3 or 6 months	5.9	No difference (3% CSS in 6 months versus no treatment	n/a 0.4
Comparing HT duration						
CUOG[27]	361	Goserelin plus flutamide, 3 months versus 8 months neoadjuvant	3 versus 8 months	3.7	3%	0.13
TROG 96-01[26]	802	Goserelin plus flutamide, 3 months versus 6 months neoadjuvant	3 versus 6 months	5.9	No difference	n/a
RTOG 92-02[28]	1514	Neoadjuvant goserelin plus flutamide alone (4 months) versus additional goserelin (24 months)	4 versus 28 months	5.8	1.5% (10.3% in Gleason 8-10)	0.73 0.04

HT = hormone therapy; CCS = cancer-specific survival; LHRH = luteinizing hormone-releasing hormone; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; TROG = Trans-Tasman Radiation Oncology Group; CUOG = Canadian Urologic Oncology Group

comparing 6 months to 3 years ADT after primary radiotherapy, the short course of ADT was statistically inferior with respect to biochemical-free, progression-free and overall survival at a median 5.2 years.[30]

Pending results of RTOG 96-01 and similar trials, the benefit of adding hormone therapy to salvage radiotherapy for PSA relapse after prostatectomy is unclear. In the meantime, combination therapy with a minimum of 6 months ADT seems appropriate only for those with high risk pathologic features and/or PSADT less than 9 months. Additionally, as these patients are at increased risk for nodal involvement, whole-pelvic versus prostate bed-only radiotherapy should be considered.[31-33]

PSA relapse after radiotherapy

Assessing recurrence and risk

Depending on pretreatment clinical risk factors and radiation dose, approximately 10% to 60% of men treated with definitive radiotherapy for prostate cancer will experience biochemical recurrence.[34-37] Despite increased efficacy with dose escalations to 81 Gy using newer intensity-modulated radiotherapy techniques, approximately 25% of those with moderate- or high-risk disease suffer a PSA relapse.[38] A significant percentage of patients with BCR after radiotherapy are at risk for prostate cancer-specific death within 5 years.[39] Some of these recurrences will be organ confined and therefore

amenable to local salvage therapy. In patients who have received radiotherapy for prostate cancer, however, the task of assessing risk, locality and even defining PSA recurrence is more challenging than in post-prostatectomy patients.

PSA changes after radiotherapy can make diagnosis of local failure problematic, as 10% to 30% of patients exhibit PSA "bounces" within 3 years after radiotherapy and may take up to 18 months to normalize.[40,41] Distinguishing these benign PSA elevations from true recurrence has made defining BCR difficult. The definition of PSA recurrence after radiotherapy was recently updated from a Consensus Conference sponsored by the American Society for Therapeutic Radiology and Oncology (ASTRO) and the RTOG in 2005.[42] The panel recommended defining recurrence as a PSA rise of 2 ng/ml above the PSA nadir after external beam radiotherapy with or without hormonal therapy.

A large proportion of radiation failures will include local involvement as 60% to 70% of patients with BCR after radiotherapy and a negative metastatic work-up have a positive prostate biopsy.[43,44] Several imaging techniques have been applied in this setting to improve detection of metastatic disease, including PET and capromab pendetide (Prostascint) scanning. While initially favorable, especially in the case of capromab pendetide using fused CT imaging, results vary and the utility of these modalities is yet to be determined.[45-48]

As with prostatectomy patients, risk of prostate cancer mortality correlates highly with PSADT. Lee et al noted that a PSADT ≤ 8 months in patients treated with combined hormone and radiation therapy correlated with poor survival (29.7% overall at 6 years) compared to 79.1% in those with PSADT > 8 months (HR 5.6).[49] Similar results were obtained by D'Amico in patients with recurrence after radiotherapy alone, and PSADT was most predictive of cancer-specific mortality when < 3 months (HR 12.2).[50] The authors also demonstrated that a patient with a PSADT > 12 months has a 15.9%, 30.5% and 39.6% cancer-specific mortality risk at 5, 8 and 10 years, respectively. These values were double those reported for their prostatectomy cohort, indicating that observation for PSA relapse after radiotherapy may be a riskier option than when applied to post-prostatectomy patients.

Salvage radical prostatectomy

Salvage radical prostatectomy after radiotherapy is a technical challenge performed only by a subset of urologists. Normal tissue planes between the prostate and rectum are lost and most specimens exhibit significant anterior and lateral fibrosis.[51] As a result of these tissue changes, rectal injury and urethral stricture rates can be as high as 28% in experienced hands.[52]

Surgery can, however, achieve 44%-80% disease-free survival at 5 years depending on clinical risk factors.[53-55] In a series by Sanderson with 51 patients, favorable prognostic factors such as pT2N0 disease, pre-operative PSA ≤ 5 ng/ml, or Gleason score ≤ 7 yielded a 5-year progression-free survival of 100%, 80% and 67%, respectively.[56] Alternatively, those with positive lymph nodes, PSA > 10 ng/ml or Gleason score ≥ 8 fared poorly with progression-free survivals of 0%, 9% or 17%, respectively. None of the 51 patients experienced disease progression after 5 years. Bianco observed a similar relationship with pre-operative PSA citing an 86% 5-year disease-free survival if PSA was less then 4 ng/ml, compared to 28% for PSA > 10 ng/ml.[55] Studies with longer follow up cite a 65%-77% cancer-specific survival at 10 years.[53,55,57]

Salvage prostatectomy, therefore, provides excellent cancer control in properly selected patients and currently appears to offer the best chance for cure if patients have failed primary radiotherapy. It remains, however, the most technically challenging salvage option and is offered only by a fraction of urologists who perform primary radical prostatectomy. The rate of major complications has decreased in contemporary series from 33%-13%, but continues to have a significant impact on quality of life and must be factored into the decision process.[58]

Salvage brachytherapy

Reviewing retrospective data based upon small numbers of patients, disease specific survival in patients who undergo salvage brachytherapy is approximately 50% at 5 years.[59,60] As with radical prostatectomy, clinical risk factors at the time of brachytherapy are predictive of outcomes. Disease-free survival ranges from 30%-83% depending on Gleason score (≤ 6 favorable) and PSA (< 10 ng/ml favorable).[61] Major complications are observed less frequently in salvage brachytherapy compared to surgery and include urinary incontinence (6%-31%), pelvic pain (6%), urethral strictures (3%) and rectal injury (0%-15%).[59]

Salvage cryotherapy

Salvage cryotherapy for radiorecurrent prostate cancer has been explored as a less invasive, outpatient alternative to radical prostatectomy. Recent technical advances including urethral warmers, perineal mapping and smaller, gas-driven probes have reduced the complications of urethral sloughing and stricture,

rectourethral fistula and incontinence.[59,62,63] Whether these changes have an effect on established cancer control rates will need to be determined with further follow up. However, overall survival at 5 years following salvage cryotherapy ranges from 73% to 97%.[64,65] The only series to cite 8-year data had a 92% overall survival.[64] Similar to other salvage options mentioned above, patient selection and clinical variables strongly affect outcomes. In the series by Ng which included 187 patients, a pre-operative PSA < 4 ng/ml was associated with a 5-year biochemical recurrence-free survival of 56% compared to 14% in those with a PSA > 10 ng/ml.[64] Gleason score (6 or less versus 7 or greater) was the only other significant predictor of recurrence (HR 0.51).

Another study of 131 patients demonstrated that precryotherapy PSA, Gleason score, clinical stage and androgen-independent recurrence have an impact on biochemical failure.[65] Five year disease free survival rates were significantly increased in patients with a PSA less than 10 ng/ml (p = 0.0004), clinical stage T2 or better (p = 0.0041), Gleason score 8 or less (p = 0.012) or in those who had received hormone therapy with initial radiotherapy (p = 0.001).

In an older retrospective study comparing salvage cryotherapy to salvage prostatectomy in patients matched for PSA and Gleason score, 67% of the cryotherapy cohort experienced BCR compared to 29% of the prostatectomy patients (p = 0.0002).[66] This disparity is difficult to interpret as the cryotherapy cohort fared must poorer than those reported in other series.[63,64] More studies are required to determine if cancer control rates are truly dissimilar between the two salvage modalities and if this difference translates into a survival benefit favoring prostatectomy.

Hormone therapy

The benefit of hormonal therapy has been previously discussed, but the question of when to start hormone therapy in patients that have BCR after primary therapy has not been established. Messing demonstrated a survival benefit to early HT in prostatectomy patients with node-positive disease[13], but this has not been observed in node negative patients.[14,15] To address this issue in patients who have been administered radiotherapy, Shipley analyzed the subset of RTOG 86-10 patients who subsequently received salvage HT (54% of study, 247 patients).[67] For those patients with distant metastases at the start of salvage HT, overall survival was significantly reduced compared to those without metastases at the time of HT (31% versus 58% at 8 years). In the patients who received salvage HT without metastatic disease, however, overall survival was not significantly influenced by PSA at the initiation of HT (< 20 ng/ml versus > 20 ng/ml, p = 0.06). These data suggest that earlier treatment with salvage hormone therapy may improve survival, but when to start HT within biochemical failure only status is yet to be determined.

Summary

For patients with a rising PSA after radical prostatectomy or radiotherapy for prostate cancer, several salvage options exist. The choice for observation, local salvage therapy, systemic hormone therapy or a combination of the latter depends on clinical risk assessment. For both prostatectomy and radiotherapy failures, PSADT appears to be the most predictive clinical tool for prostate cancer mortality. Risk should be assessed early after PSA relapse as all salvage options appear to have improved cancer control with lower serum PSA values. In general, patients with biochemical recurrence experience relatively prolonged survival and the choice to pursue salvage therapy needs to be weighed against the potential side effects that can significantly affect quality of life.

Disclosure

Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis, and has done research for Cytogen Corporation. □

References

1. Catalona WJ, Smith DS. 5-year tumor recurrence rates after anatomical radical prostatectomy for prostate cancer. *J Urol* 1994;152:1837-1842.
2. Pound CR, Partin AW, Eisenberger MA et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-1597.
3. 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.
4. Simon MA, Kim S, Soloway MS. Prostate specific antigen recurrence rates are low after radical retropubic prostatectomy and positive margins. *J Urol* 2006;175:140-145.

5. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. *Urology* 1999;54(5):884-890.
6. Freedland, SJ, Humphreys EB, Mangold LA et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433-439.
7. 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(16):2225-2229.
8. Bolla M, van Poppel H, Collette L et al. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). *Lancet* 2005;366:572-578.
9. Thomson IM, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathologically advance prostate cancer: a randomized clinical trial. *JAMA* 2006;296(19):2329-2335.
10. Stephenson AJ, Shariat SF, Zelefsky MJ et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291(11):1325-1332.
11. Stephenson AJ, Scardino PT, Kattan MW et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25(15):2035-2041.
12. Messing EM, Manola J, Sarosdy M et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341(24):1781-1788.
13. 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;7:472-479.
14. Wirth MP, Weissbach L, Marx F-J et al. Prospective randomized trial comparing flutamide as adjuvant treatment versus observation after radical prostatectomy for locally advanced, lymph node-negative prostate cancer. *Eur Urol* 2004;45(3):267-270.
15. Moul JW, Hongyu W, Sun L et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol* 2004;171:1141-1147.
16. McLeod DG, Iversen P, See WA et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006;97:247-254.
17. Parker C, Clarke N, Logue J et al. RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery). *Clin Oncol* 2007;19(3):167-171.
18. Katz MS, Zelefsky MJ, Venkatraman ES et al. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* 2003;21(3):483-489.
19. Macdonald OK, D'Amico AV, Sadetsky N et al. Adjuvant radiotherapy in prostate cancer: predictors of prostate-specific antigen recurrence from the CaPSURE database. *Urology* 2007;70(1):106-110.
20. King CR, Presti JC, Jr., Gill H et al. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes*? Int J Radiat Oncol Biol Phys* 2004;59(2):341-347.
21. Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol* 2005;23(4):800-807.
22. Pilepich MV, Winter K, Lawton CA et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma: long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61(5):1285-1290.
23. 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;360:103-108.
24. 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(5):1243-1252.
25. D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer. *JAMA* 2004;292(7):821-827.
26. Denham JW, Steigler A, Lamb DS et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96-01 randomised controlled trial. *Lancet Oncol* 2005;6:841-850.
27. Crook J, Ludgate C, Malone S et al. Report of a multicenter Canadian phase III randomized trial of 3 months vs. 8 months neoadjuvant androgen deprivation before standard-dose radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;60(1):15-23.
28. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group protocol 92-02. *J Clin Oncol* 2003;21(21):3972-3978.
29. D'Amico AV, Denham JW, Bolla M et al. Short- vs long-term androgen suppression plus external beam radiation therapy and survival in men of advanced age with node-negative high-risk adenocarcinoma of the prostate. *Cancer* 2007;109:2004-2010.
30. Bolla M, van Tienhoven G, de Reijke TM et al. Concomitant and adjuvant androgen deprivation (ADT) with external beam irradiation (RT) for locally advanced prostate cancer: 6 months versus 3 years ADT—Results of the randomized EORTC Phase III trial 22961. *J Clin Oncol* 2007;25(18S):abstract 5014.
31. Roach M III, DeSilvio M, Lawton C et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003;21:1904-1911.
32. Roach M III, DeSilvio M, Valicenti R et al. Whole-pelvis, "mini-pelvis", or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. *Int J Radiat Oncol Biol Phys* 2006;66:647-653.
33. Spiotto MT, Hancock SL, King CR. Radiotherapy after prostatectomy: improved biochemical relapse-free survival with whole pelvic compared with prostate bed only for high risk patients. *Int J Radiat Oncol Biol Phys* 2007;69(1):54-61.
34. Kuban DA, Thames HD, Levy LB et al. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys* 2003;57:915-928.
35. Eng TY, Thomas CR, Herman TS. Primary radiation therapy for localized prostate cancer. *Urol Oncol* 2002;7:239-257.
36. Khuntia D, Reddy CA, Mahadevan A et al. Recurrence-free survival rates after external beam radiotherapy for patients with clinical T1-T3 prostate carcinoma in the prostate-specific antigen era: what should we expect? *Cancer* 2004;100:1283-1292.
37. Kupelian PA, Thakkar VV, Khuntia D et al. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes. *Int J Radiat Oncol Biol Phys* 2005;63:1463-1468.
38. Zelefsky MJ, Chan H, Hunt M et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 2006;176:1415-1419.

39. Sandler HM, Dunn RL, McLaughlin W et al. Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2000;48(3):629-633.
40. Hanlon AL, Pinover WH, Horwitz EM et al. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 2001;50:845-849.
41. Rosser CJ, Kuban DA, Levy LB et al. Prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002;168:2001-2005.
42. Roach M, Hanks G, Thames H et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65(4):965-974.
43. Zelefsky MJ, Leibel SA, Gaudin PB et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;41:491-500.
44. Zagars GK, Pollack A, von Eschenbach AC. Prostate cancer and radiation therapy: the message conveyed by serum prostate-specific antigen. *Int J Radiat Oncol Biol Phys* 1995;33:23-35.
45. Nagda SN, Mohideen N, Lo SS et al. Long-term follow-up of ^{111}In-capromab pendetide (ProstaScint) scan as pretreatment assessment in patients who undergo salvage radiotherapy for rising prostate-specific antigen after radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67(3):834-840.
46. Keane TE, Rosner IL, Wingo MS, McLeod DG. The emergence of radioimmunoscintigraphy for prostate cancer. *Rev Urol* 2006;8:S20-S28.
47. de Jong IJ, Pruim J, Elsinga PH et al. ^{11}C-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. *Eur Urol* 2003;44:32-38.
48. Vees H, Buchegger F, Albrecht S et al. ^{18}F-choline and/or ^{11}C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/ml) after radical prostatectomy. *BJU Int* 2007;99:1415-1420.
49. Lee AK, Levy LB, Cheung R, Kuban D. Prostate-specific antigen doubling time predicts clinical outcome and survival in prostate cancer patients treated with combined radiation and hormone therapy. *Int J Radiat Oncol Biol Phys* 2005;63(2):456-462.
50. D'Amico AV, Moul JW, Carroll PR et al. Surrogate end point for prostate caner-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003;95:1376-1383.
51. Link P, Freiha FS. Radical prostatectomy after definitive radiation therapy for prostate cancer. *Urology* 1991;37:189-192.
52. Rogers E, Ohori M, Kassabian VS et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol* 1995;153:104-110.
53. Cheng L, Sebo TJ, Slezak J et al. Predictors of survival for prostate carcinoma patients treated with salvage radical prostatectomy after radiation therapy. *Cancer* 1998;83:2164-2171.
54. Garzotto M, Wajsman Z. Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: results at 5-year follow up. *J Urol* 1998;159:950-954.
55. Bianco FJJ, Scardino PT, Stephensen AJ et al. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62:448-453.
56. Sanderson KM, Penson DF, Cai J et al. Salvage radical prostatectomy: quality of life outcomes and long-term oncologic control of radiorecurrent prostate cancer. *J Urol* 2006;176:2025-2032.
57. Ward JF, Sebo TJ, Blute ML, Zinke H. Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol* 2005;173:1156-1160.
58. Stephensen AJ, Eastham JA. Role of salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. *J Clin Oncol* 2005;23(32):8198-8203.
59. Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy - brachytherapy as a salvage option. *Cancer* 2007;110(7):1405-1416.
60. Beyer DC. Brachytherapy for recurrent prostate cancer after radiation therapy. *Semin Radiat Oncol* 2003;13:158-165.
61. Beyer DC. Salvage brachytherapy after external-beam irradiation for prostate cancer. *Oncology* (Williston Park) 2004;18:151-158.
62. Chin JL, Pautler SE, Mouraviev V et al. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. *J Urol* 2001;165:1937-1942.
63. Ghafar MA, Johnson CW, De la Taille A et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy. *J Urol* 2001;166:1333-1338.
64. Ng CK, Moussa M, Downey DB, Chin JL. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. *J Urol* 2007;178:1253-1257.
65. Izawa JI, Madsen LT, Scott SM et al. Salvage cryotherapy for recurrent prostate cancer after radiotherapy: variables affecting patient outcome. *J Clin Oncol* 2002;20:2664-2671.
66. Leibovich BC, Izawa J, Zinke H et al. Recurrent prostate cancer after radiation therapy: salvage prostatectomy versus salvage cryosurgery. *J Urol* 2001;165:389 (abstr 1595).
67. Shipley WU, DeSilvio M, Pilepich MV et al. Early initiation of salvage hormone therapy influences survival in patients who failed initial radiation for locally advanced prostate cancer: a secondary analysis of RTOG protocol 86-10. *Int J Radiat Oncol Biol Phys* 2006;64(4):1162-1167.

Managing prostate cancer: the role of hormone therapy

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Androgen deprivation therapy has been the mainstay of treatment for men with metastatic prostate cancer and now plays a more active role in the management of less advanced cancers as neoadjuvant and adjuvant treatment. Investigative uses include primary therapy for patients unsuitable for definitive therapy and as a complement to ablative procedures, brachytherapy, and chemotherapy. Intermittent androgen deprivation therapy is being considered as an alternative to continuous therapy and further evaluated as triple androgen blockade in conjunction with finasteride. Many accepted and potential management schemes incorporating hormonal therapy are increasingly employed despite indeterminate indications for use. Here, we review currently available data on the efficacy of hormonal therapy with regard to complete androgen ablation, primary, neoadjuvant, and adjuvant therapy. Additionally, we examine the usefulness of delayed versus immediate administration, intermittent androgen deprivation, and other prospective applications for hormonal therapy.

Key Words: hormonal therapy, neoadjuvant therapy, adjuvant therapy, intermittent androgen deprivation, prostate cancer

Introduction

Approximately 20% of men with newly diagnosed prostate cancer (CaP) will present with advanced or metastatic disease.[1] Treatment in these men aims to prolong survival and improve quality of life. Since Huggins and Hodges demonstrated malignant prostate cells respond to hormonal manipulation,[2] androgen deprivation therapy (ADT) has been the standard systemic therapy for men with advanced disease. The role of ADT has now extended beyond palliative care to include less advanced patients treated concurrently with surgery or radiation. Data from CaPSURE reveal that the use of ADT is increasing in primary and adjuvant therapy across all treatment types and risk groups, with the highest increase in prevalence detected in neoadjuvant treatment to radiotherapy,[3] Figure 1.

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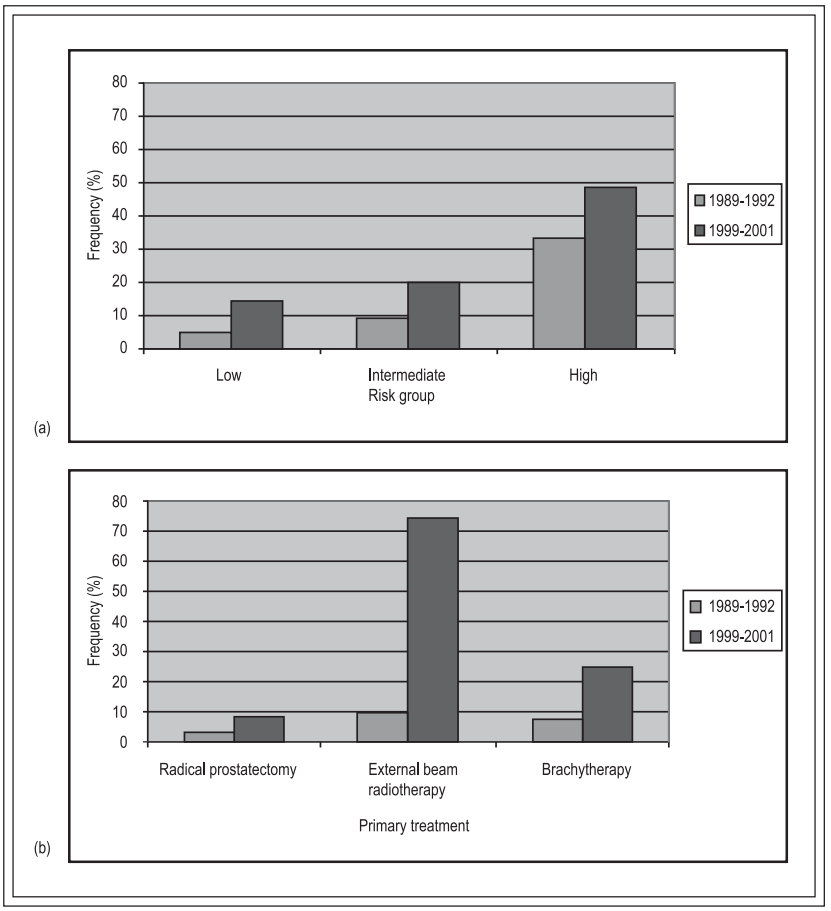

Figure 1. Analysis from 7195 patients on CaPSURE comparing trends from 1989-1992 to 1999-2001 in a) overall use of primary ADT, stratified by prostate cancer risk group and b) use of neoadjuvant ADT stratified by primary treatment type. Data from Cooperberg et al.[3]

Recognizing the absence of a definitive controlled trial, the prevailing opinion is that hormonal therapy improves disease-specific survival in metastatic CaP. However, indication for ADT as primary, adjuvant, or neoadjuvant therapy for earlier stages of CaP, as well as the timing and duration of administration in advanced CaP, are areas currently under investigation. Crucial issues for appropriate management include recognizing the most effective duration of therapy which yields the least morbidity and whether early therapy is superior to deferring treatment until clinical progression. Moreover, to minimize the side effects of androgen withdrawal and delay progression to an androgen independent state, intermittent androgen deprivation (IAD) has been evaluated as an alternative to continuous administration.

ADT for early CaP has demonstrated an improvement in clinical and pathological variables, but not a consistent gain in overall survival. Disparities in survival outcomes between various patient populations add further complexity. The appropriate role of hormonal therapy needs to be better defined to ensure treatment goals are met for individualized patients. Differences in efficacy may exist between individual therapeutic agents; however, this will not be addressed here. The objective of this overview is to present the benefits and limitations of hormone therapy as neoadjuvant, adjuvant, and primary treatment in the management of prostate cancer. Conventional, alternative, and experimental hormonal strategies will also be discussed.

ADT therapies

Complete androgen ablation

Complete androgen ablation (CAB), the combination of androgen suppression and antiandrogens, is believed to impart an advantage over androgen suppression alone. Numerous randomized trials comparing the two approaches reveal a significant survival benefit, but with minimal certainty. A Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis of 27 trials has examined mortality outcomes in over 8000 men, 88% with M+ disease.[4] Inclusion criteria included the administration of CAB for at least 1 year, androgen suppression achieved by orchiectomy or a long-term luteinizing hormone-releasing hormone (LHRH) agonist, and the addition of flutamide, nilutamide, or cyproterone acetate as antiandrogen therapy. CAB with nilutamide or flutamide offered an age-independent 2.9% increase in survival at 5 years ($p = 0.005$, 95% CI 0.4-5.4), while CAB with cyproterone acetate had a 2.7% survival disadvantage ($p = 0.04$).

This advantage was evident despite several limitations which may have undermined any potential survival benefit: many of the trials were underpowered and could never have shown the differences expected; the majority of patients had bony metastatic disease, much more advanced than normally seen today; and many patients were continued on CAB despite progression, since the effects of androgen withdrawal were unknown at the time. Moreover, no effective chemotherapy was available and the 2.9% survival advantage was an average, i.e. some patients received no benefit while others may have survived an additional

9-10 months. Currently, we have no way of identifying who will or will not gain from CAB; therefore, it may be acceptable to offer CAB routinely.

An exploratory analysis of a double-blind, placebo-controlled phase III study evaluated the efficacy of CAB in 99 Japanese patients with stage C disease.[5] Bicalutamide was administered as antiandrogen therapy and dosed at 80 mg/day, which is comparable to the 150 mg/day dosage given in the United States in terms of body mass. At a median observation period of 144 weeks, time to progression was significantly longer in patients who received CAB as opposed to those receiving LHRH monotherapy ($p < 0.01$). After stratification by age, PSA level at diagnosis, and tumor differentiation, CAB maintained superior efficacy. Patients in this trial with stage D disease also benefited from CAB, with similar survival outcomes to those reported by PCTCG. CAB has thus become a rational approach to hormonal therapy, although the costs and side effects are often reasons that some providers do not use it in individual patients.

Neo-adjuvant therapy

Laboratory research indicates that ADT suppresses tumor burden via apoptosis, reduction of distant microscopic tumor foci, and inhibition of malignant cell growth within the prostate.[6] Clinically, a decrease in tumor bulk prior to local therapy may improve locoregional control, and in the case of surgical treatment, increase the chance of cure if negative surgical margins can be achieved. Though data demonstrate a reduction in the rate of positive surgical margins with neoadjuvant ADT (NADT), it seems to have no effect on the incidence of seminal vesicle invasion and lymph node metastasis. Several studies have therefore assessed whether NADT ultimately translates into longer time to progression or increased survival.

Soloway et al conducted a multi-institutional prospective trial of 303 patients with stage cT2b prostate cancer randomized to receive radical prostatectomy with or without 3 months of leuprolide plus flutamide.[7] Although NADT resulted in a significant decrease in positive surgical margins and urethral margin involvement, there was no difference in seminal vesicle involvement, positive lymph nodes, or PSA recurrence at 5 years, regardless of Gleason score.[8] A similar prospective study of 126 patients with cT1b-T3aNXM0 validates that there is no survival advantage in using a 3-month course of NADT prior to radical prostatectomy.[9] Despite a decrease in positive surgical margins with the addition of NADT, the two groups were found to have comparable progression-free and overall survival rates at 7-year follow-up. In addition, data reveal that the duration of hormonal treatment does not seem to be a factor influencing survival. A randomized, comparative study of 547 men receiving either 3 months or 8 months of NADT preceding radical prostatectomy showed no difference in PSA recurrence at 48-month follow-up ($p = 0.4225$).[10]

In contrast, NADT has shown a survival benefit for select patients undergoing external beam radiation therapy (XRT). The Radiation Therapy Oncology Group 86-10 phase III trial randomized 471 patients with cT2-4NXM0 disease to receive 4 months of ADT initiated 2 months prior to XRT or XRT alone.[11] Analysis at 8 years revealed androgen deprivation was associated with an improvement in local control, reduction in the incidence of distant metastases, and increased clinical and biochemical disease-free survival, defined as PSA < 1.5 ng/ml, Table 1. Subset analysis demonstrated an overall survival benefit only in patients with Gleason 2-6 disease. With bulky tumors, cytoreduction before radiotherapy seems to provide valuable long-term tumor control.

TABLE 1. **RTOG 86-10 outcomes at 8 years from 471 patients randomized to RT or RT with 4 months of neoadjuvant ADT. Adapted from Pilepich et al.[11]**

	RT	RT + ADT	p-value
Local control (%)	30	42	0.016
Distant metastases (%)	45	34	0.04
Disease-free survival (%)	21	33	0.004
bNED (%)	10	24	< 0.0001
Overall survival* (%)	70	52	0.015

*Gleason 2-6 subset
RT = radiotherapy; bNED = biochemically no evidence of disease

Further studies have evaluated whether longer hormonal treatment provides any additional benefit to radiotherapy. Crook et al report the results of a multicenter phase III randomized trial of 3 months versus 8 months of NADT in patients with clinically localized CaP.[12] At 3 years follow-up, disease-free survival and types of failure (biochemical, local, and distant) were comparable in the two arms. High-risk patients (stage T3, GS 8-10 or PSA > 20ng/ml) showed improvement with longer treatment periods, but statistical significance was not reached. A large-scale randomized trial (RTOG 99-10) is currently underway to assess the optimal duration of NADT.

Common practice has been to downsize large prostates with ADT prior to brachytherapy, potentially decreasing toxicity and enhancing dosimetry. Few studies have evaluated whether the addition of ADT offers a survival advantage to the patients. In a large retrospective study, 163 patients with clinically confined CaP and prostate glands ≥ 60g underwent treatment for a median of 3.4 months before brachytherapy.[13] After matched-pair analysis to those not receiving neoadjuvant therapy, no difference was found between 5-year PSA recurrence-free survival rates (86.9% versus 87.1%, p = 0.935). Further subgroup analysis stratified by Gleason score, pretreatment PSA, and disease stage failed to demonstrate any significance. Likewise, lack of data showing a survival benefit for NADT with cryosurgery limits the role of ADT to enlarged prostates that require cytoreduction for effective local therapy.

Adjuvant therapy: immediate versus delayed

Hormone management in conjunction with definitive treatment for locally advanced CaP has been studied extensively and shown to impart a significant survival benefit following both radical prostatectomy and radiotherapy, yet controversy exists over the appropriate timing of hormone administration. Data from Messing et al support the use of immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy in patients with node-positive disease. Ninety-eight patients were randomized to receive either immediate antiandrogen therapy (goserelin or bilateral orchiectomy) or observation until clinical progression.[14] A central histological review was conducted to regrade Gleason scores for an update at a median follow-up of 11.9 years. As in the initial analysis, overall, cancer-specific, and recurrence-free survival remained significantly better among men who received immediate adjuvant therapy as opposed to those who received initial observation.[15] A recent matched-cohort analysis of over 6000 patients undergoing radical prostatectomy for node-positive CaP further substantiates the improvement in 10-year cancer-specific and systemic progression-free survival with adjuvant ADT.[16] Moreover, this survival advantage tended to decrease as ADT was administered further along in the disease process. Patients who underwent delayed ADT at PSA ≥ 2.0 ng/ml had significantly worse outcomes than those receiving immediate treatment. Multivariate analysis demonstrated ADT had no impact on survival in patients with systemic progression.

Numerous prospective, randomized trials have validated the use of ADT in high-risk patients treated with definitive radiotherapy.[17-19] RTOG 85-31 randomly assigned patients to receive XRT followed by long-term goserelin or XRT with subsequent hormonal intervention only in the event of relapse.[19] At a median follow-up of 7.6 years, the adjuvant arm benefited in regards to local and distant failure rates, PSA progression, overall survival rate, and cancer-specific mortality, Figure 2. In multivariate analysis adjusting for Gleason score, nodal

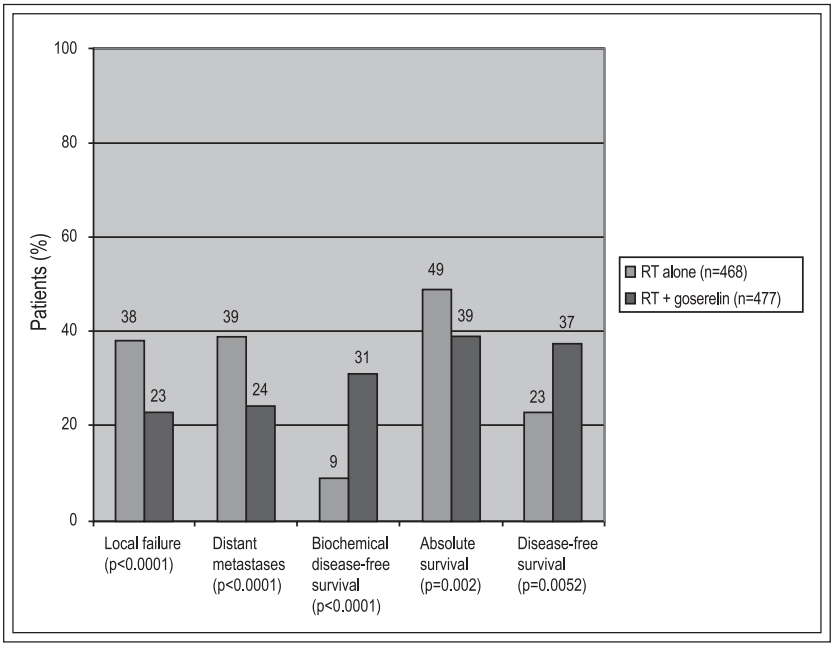

Figure 2. Results of RTOG 85-31. Data are from 945 patients randomized to receive radiotherapy or radiotherapy with adjuvant goserelin. The addition of ADT significantly improved all endpoints (10-year estimated). Data from Pilepich et al. [19]

TABLE 2. **RTOG 92-02 results: 5-year rate outcomes for 1554 patients treated with radiotherapy and either short-term or long-term hormonal therapy. Data from Hanks et al.[23]**

	XRT + ADT for a duration of 4 months	28 months	p value
Disease-free survival (%)	28.1	46.4	< 0.0001
Local progression (%)	12.3	6.4	0.0001
Distant metastases (%)	17.0	11.5	0.0035
Biochemical failure (%)	55.5	28.0	< 0.0001
Cause-specific survival (%)	91.2	94.6	0.006

*Gleason 8-10 subset only

involvement, and clinical stage, treatment remained statistically significant in favor of the adjuvant arm for all endpoints. The European Organization for Research and Treatment of Cancer (EORTC) 22863 evaluated 415 patients with T1-2 grade 3 or T3-4 N0-1M0 CaP.[20] Patients were randomized to XRT or XRT plus 3 years of goserelin. At a median follow-up of 66 months, a significant survival benefit was seen for low, intermediate, and high risk patients who received concomitant ADT.[18] While a limitation of these studies is the lack of a hormone therapy control group, the data are impressive and mandate the use of adjuvant ADT in locally advanced CaP.

Data from retrospective analyses demonstrate that the risk of cerebrovascular and cardiac events[21] and cardiac mortality[22] rises with increased duration of ADT. Shorter duration of therapy has therefore been investigated in an effort to reduce the cost and side effects of androgen deprivation, but results fail to show equivalent efficacy to more extensive therapy. RTOG 92-02 compared long-term versus short-term adjuvant therapy in combination with XRT.[23] Patients with cT2c-T4 disease received goserelin and flutamide beginning 2 months prior to radiotherapy and continuing for either 4 or 28 months. At 5.6 years, all endpoints except overall survival were significantly better in men receiving long-term androgen suppression, and subset analysis revealed an overall survival advantage in patients with a Gleason score of 8-10, Table 2. EORTC 22961 was designed to demonstrate similar survival in patients who receive 6 months of combined adjuvant ADT as in patients with 2.5 years of treatment.[24] However, at 5.2 years median follow-up, results reveal differences in progression-free, disease-free, and overall survival favoring long-term ADT, Table 3. Most patients had T2c-T3N0 disease, and data were not available when risk stratified by Gleason score. Thus, it is unknown whether patients at intermediate risk may in fact benefit equally from a shorter duration of therapy.

Primary therapy

Initially, primary ADT was reserved for those patients with metastatic disease. However, in patients unsuitable for definitive therapy, ADT is now suggested as a treatment option that may confer a survival advantage in certain patients. EORTC trial 30891 examined the effects of immediate versus deferred ADT in 985 patients with newly diagnosed T0-4N0-2M0 who either refused definitive treatment or were deemed unsuitable.[25]

TABLE 3. **EORTC 22961 5-year survival data from 970 patients treated with radiotherapy and either short-term or long-term hormonal therapy. Data from Bolla et al.[24]**

	Adjuvant ADT for a duration of 6 months (n = 483)	36 months (n = 487)	HR
PSA-PFS (%)	58.9	78.3	2.29 (98.2% CI: 1.81-2.90)
Clinical-PFS (%)	68.9	81.8	1.93 (98.2% CI: 1.49-2.51)
Ocerall survival (%)	80.6	85.3	1.43 (96.4% CI: 1.04-1.98)

PSA = prostate specific antigen; PFS = progression free survival

Median age at randomization was 73 years. At a median follow-up of 7.8 years, 55% of patients had died, mostly of CaP (35.7%) or cardiovascular disease (34.2%). Overall survival favored immediate treatment due to fewer deaths from causes other than CaP (HR 1.25, 95% CI 1.05-1.48). No difference in CaP death was found between arms, but the relatively small number of events was statistically limiting (n = 193). Moreover, results indicate significantly more pain, higher risk of pathologic fracture, and obstruction necessitating TURP in the deferred arm, while significantly more ADT side effects were present in the immediate treatment arm. Further subgroup analysis was recently conducted to determine which patients were at risk to die from CaP.[26] Patients with PSA > 50 ng/ml and/or a PSA doubling time ≤ 12 months were at increased risk of cancer-specific death and profited most from treatment. The investigators recommend immediate ADT for these high risk patients, though further exploration is needed to substantiate these results.

Expanding uses of ADT

Intermittent androgen deprivation

Based on results of animal experiments, the concept of IAD suggests that exposing surviving stem cells to androgens delays development of androgen-insensitive survival mechanisms via a conditioning effect. Recently, IAD administration has been shown to result in significantly less increase in chromogranin-A, a marker of neuroendrocrine differentiation that plays a role in progression to androgen independent prostate cancer.[27] Clinical use of ADT aims to delay progression to the hormone refractory state, induce multiple apoptotic tumor regressions, improve patient quality of life with drug holidays, and reduce the cost of therapy.

A few prospective, randomized studies have assessed the feasibility of IAD. A recent trial evaluated 335 men with D1/D2 disease randomized to either continuous (CAD) or IAD with goserelin and bicalutamide.[28] Of those on IAD, 88% were off therapy 50% of the time. A trend towards better well-being and sexual function existed in men on IAD, with a median time to progression of 16.6 months as compared to 11 months in men on CAD. However, none of these differences reached statistical significance, and no benefit was demonstrated with regards to overall quality of life or survival.

A randomized, prospective phase III trial comparing IAD to CAD in 167 patients with PSA relapse after radical prostatectomy demonstrated no significant difference with regard to androgen-independent progression.[29] However, improved quality of life and lower incidence of hyperhydrosis in the IAD arm promote its use as an alternative option. Another advantage to IAD may be reduction in bone loss. Machado et al evaluated the incidence of osteoporosis in 44 nonrandomized patients receiving IAD or CAD.[30] In both groups, half the patients developed osteoporosis. Compared to 50% of patients on CAD, 70% of patients on IAD regained bone mass, characterized by osteopenia or normal DEXA scan during the 3-year follow-up.

While IAD appears to offer certain advantages, is an approach that remains experimental until long-term survival and quality of life data are assessed. SWOG 9346, an ongoing phase III trial designed to determine whether survival with IAD is equivalent to survival with CAD, will substantiate current data. Figure 3 presents an outline of the SWOG treatment protocol, which uses established methods of stopping and restarting therapy as per predetermined PSA levels.

Alternative ADT strategies

Others have proposed IAD in combination with chemotherapy may delay the onset of androgen independence, given the volume of systemic disease and occult hormone-refractory cancer cells in advanced and/or metastatic disease. A preliminary report of 41 patients on combined IAD and weekly docetaxel administered for 4-5 monthly cycles demonstrated a 92.6% disease-specific survival at a median follow-up of 42 months.[31] A comparison study of chemotherapy-based androgen deprivation with ADT alone has yet to be elicited.

Another approach to managing CaP employs triple androgen blockade (TAB), consisting of induction with a LHRH agonist, an antiandrogen, and intracellular androgen deprivation via daily finasteride. Several studies suggest that finasteride has activity against prostate cancer and may be beneficial in prolonging the interval time between IAD cycles.[32,33] Tucker et al evaluated TAB in 77 men treated for a median of 13 months and continuing finasteride as maintenance therapy.[34] Combination therapy reportedly resulted in shorter time to undetectable PSA; however, it appears to be less useful in men with high risk features, such as Gleason 8-10 disease and those with PSA> 20 ng/ml. Other retrospective studies demonstrate that the addition of finasteride reduces PSA velocity,[35] lengthens time off intervals,[35,36] and increases quality of life.[36] Compared to standard IAD, no change has been found in progression to androgen-independent CaP.[36] A limitation of these studies is that IAD was examined as primary therapy in most patients.

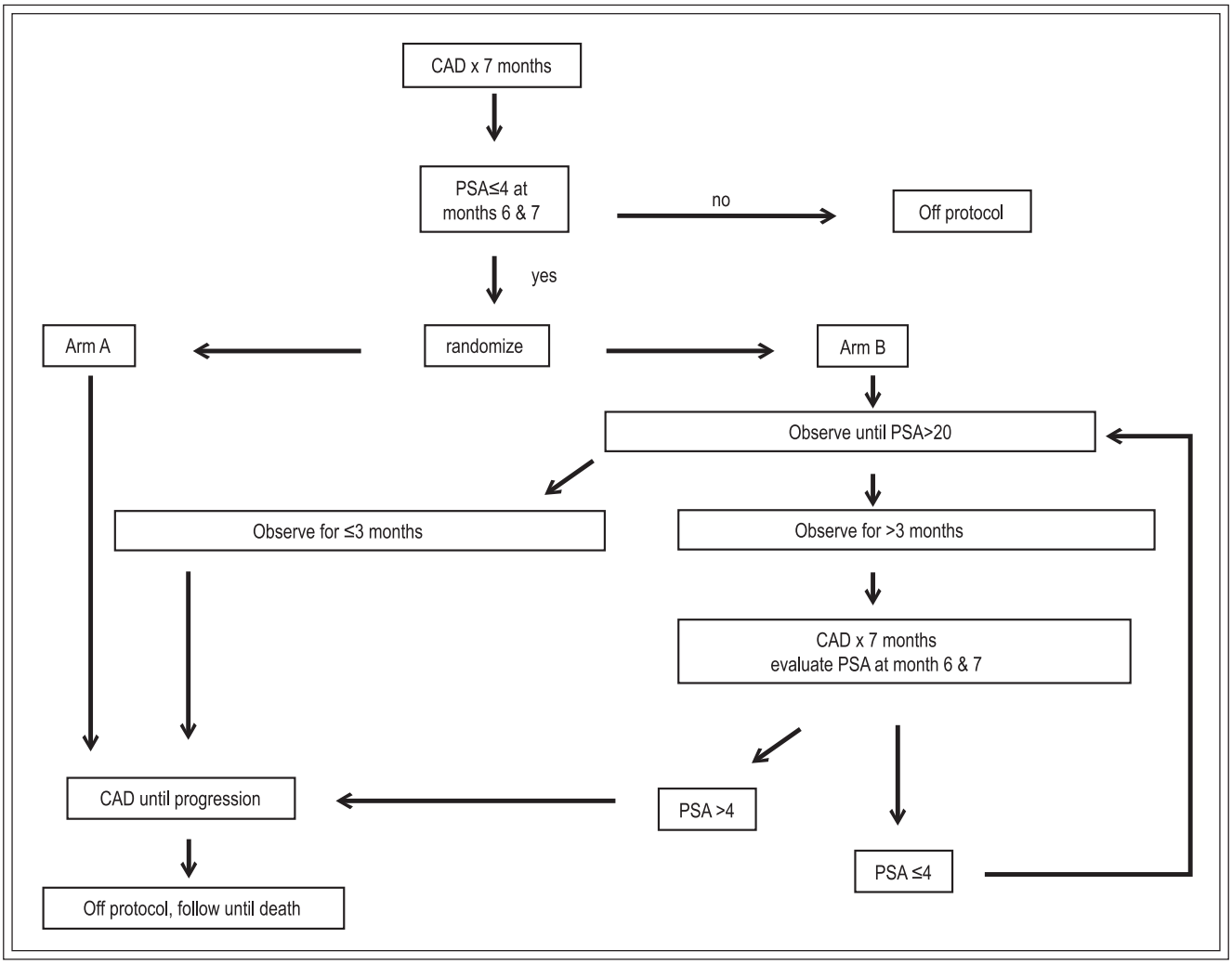

Figure 3. SWOG 93-46 randomization and treatment protocol outline. Patients in arm A receive continuous androgen deprivation, whereas patients in arm B initially receive intermittent androgen deprivation.

Conclusions

The usefulness of ADT in combination therapy is dependent on the type of primary treatment provided and the degree of disease. Though negative surgical margins may be more achievable with NADT prior to radical prostatectomy, the lack of a survival benefit does not support its clinical use for locally advanced cases. On the other hand, the addition of NADT to radiotherapy may improve disease outcome, particularly for patients with low-grade, bulky disease.

Adjuvant ADT to both radical prostatectomy and radiotherapy is an important complement to effective treatment in locally advanced cases. ADT may increase survival and decrease recurrence in patients with positive lymph nodes at surgery. As an adjunct to radiotherapy, only long-term ADT improves survival in high-risk patients, while short-term administration may be suitable for those at intermediate risk. Until prospective studies are conducted, there is no data to support a survival benefit for neoadjuvant or adjuvant ADT in patients undergoing brachytherapy or cryotherapy. However, reduction in tumor volume may be necessary for effective treatment of bulky disease. Men unsuitable for local therapy may also derive benefit from ADT in terms of enhanced quality of life and prolonged survival if they are at high risk of CaP-specific death.

Alternative strategies, such as IAD, TAB, and combination therapy with chemotherapy, remain to be established in the clinical setting. Thus far, IAD has not been proven to delay progression to androgen independence or lengthen survival time; however, improved quality of life makes it a more appealing

approach to hormonal therapy. Long-term data from prospective, randomized trials will help validate the use of IAD.

Beyond palliative care, ADT has clinical significance for many men with both local and metastatic prostate cancer, yet careful patient selection is necessary to ensure appropriate application. Future trials stratifying outcomes by risk groups will help to clarify which patients benefit most from hormonal therapy as well as determine the best strategy for administration.

Disclosure

Dr. Christopher Evans is a member of the Speakers' Bureau for Boehringer Ingelheim. He is on the advisory board for Boehringer Ingelheim and AstraZeneca and an investigator for Astra Zeneca. Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis and has done research for Cytogen Corporation. □

References

1. Studer UE, Hauri D, Hanselmann S, Chollet D, Leisinger HJ, Gasser T et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: results of the randomized trial SAKK 08/88. *J Clin Oncol* 2004;22(20):4109-4118.
2. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin* 1972;22(4):232-240.
3. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 2003;95(13):981-989.
4. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet* 2000;355(9214):1491-1498.
5. Akaza H, Arai Y, Kanetake H, Naito S, Usami M. Efficacy of CAB therapy in stage C prostate cancer: Exploratory analyses based on results of a double-blind, randomized, placebo-controlled phase III study of bicalutamide. *J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part 1* 2007;25(18S):5154.
6. Eulau SM, Tate DJ, Stamey TA, Bagshaw MA, Hancock SL. Effect of combined transient androgen deprivation and irradiation following radical prostatectomy for prostatic cancer. *Int J Radiat Oncol Biol Phys* 1998;41(4):735-740.
7. Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr, Puras-Baez A. Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. The Lupron Depot Neoadjuvant Prostate Cancer Study Group. *J Urol* 1995;154(2 Pt 1):424-428.
8. Soloway MS, Pareek K, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. *J Urol* 2002;167(1):112-116.
9. Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. *BJU Int* 2002;90(6):561-566.
10. Gleave ME, Goldenberg SL, Chin JL, Warner J, Saad F, Klotz LH et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol* 2001;166(2):500-506; discussion 506-507.
11. Pilepich MV, Winter K, John MJ, Mesic JB, Sause W, Rubin P 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(5):1243-1252.
12. Crook J, Ludgate C, Malone S, Lim J, Perry G, Eapen L et al. Report of a multicenter Canadian phase III randomized trial of 3 months vs. 8 months neoadjuvant androgen deprivation before standard-dose radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;60(1):15-23.
13. Potters L, Torre T, Ashley R, Leibel S. Examining the role of neoadjuvant androgen deprivation in patients undergoing prostate brachytherapy. *J Clin Oncol* 2000;18(6):1187-1192.
14. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341(24):1781-1788.
15. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7(6):472-479.
16. Siddiqui SA, Boorrjian SA, Inman BA, Slezak JM, Blute ML. Timing of androgen deprivation therapy and its impact on cancer-specific survival after radical prostatectomy: A matched-cohort analysis. *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):601.
17. Granfors T, Modig H, Damber JE, Tomic R. Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective randomized study. *J Urol* 1998;159(6):2030-2034.
18. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO 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(9327):103-106.
19. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61(5):1285-1290.
20. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337(5):295-300.
21. Malcolm JB, DiBlasio CJ, Womack JH, Kincade MC, Ogles M, Mancini JA et al. Association of cerebrovascular accident and myocardial infarction with androgen deprivation therapy. *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):597.
22. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for prostate cancer and the risk of cardiac mortality. *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):378.
23. Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, Venkatesan V et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in

locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;21(21):3972-3978.
24. Bolla M, van Tienhoven G, de Reijke TM, van den Bergh AC, van der Meijden AP, Poortmans PM et al. Concomitant and adjuvant androgen deprivation (ADT) with external beam irradiation (RT) for locally advanced prostate cancer: 6 months versus 3 years ADT—Results of the randomized EORTC Phase III trial 22961. *J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part 1* 2007;25, No.18S(June 20 Supplement):5014.
25. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D 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(12):1868-1876.
26. Studer UE, Collette L, Whelan P, Albrecht W, Casselman J, De Reijke T et al. Which subgroups of patients are at risk to die from prostate cancer and benefit from immediate androgen deprivation if they are not suitable for local treatment with curative intent of newly diagnosed prostate cancer T0-4 N0-2 M0 (EORTC 30891). *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):382.
27. Sciarra A, Monti S, Gentile V, Mariotti G, Cardi A, Voria G et al. Variation in chromogranin A serum levels during intermittent versus continuous androgen deprivation therapy for prostate adenocarcinoma. *Prostate* 2003;55(3):168-179.
28. Miller K, Steiner U, Lingnau A, Witzch U, Haider A, Wachter U et al. Intermittent versus continuous androgen suppression in advanced prostate cancer—A randomised prospective study. *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):LBA1723.
29. Tunn UW, Canepa G, Hillger H, Fuchs W. Intermittent androgen deprivation in patients with PSA-relapse after radical prostatectomy—Final results of a European randomized prospective Phase-III clinical trial AUO study AP 06/95, EC 507. *J Urol, AUA Annual Meeting Abstracts* 2007;177(4):600.
30. Machado M, Wroclawski E, del Giglio A. Natural history of bone loss induced by androgen deprivation in hormone sensitive prostate cancer patients: A prospective comparison between continuous and intermittent therapy. *ASCO Prostate Cancer Symposim* 2006;abstr 188.
31. Tucker S, Leibowitz R. Primary intermittent chemo-hormonal therapy (CHT) for high risk locally advanced (LAPC) or metastatic prostate cancer (MPC): Preliminary results and quality of life (QOL). *J Clin Oncol, 2005 ASCO Annual Meeting Proceedings* 2005;Vol 23, No.16S, Part I of II(June 1 Supplement):4734.
32. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349(3):215-224.
33. Tay MH, Kaufman DS, Regan MM, Leibowitz SB, George DJ, Febbo PG et al. Finasteride and bicalutamide as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate. *Ann Oncol* 2004;15(6):974-978.
34. Tucker S, Leibowitz R. Five-year follow-up of intermittent triple androgen blockade (TAB) for clinically localized prostate cancer (PC): prognostic features and preliminary patterns of failure. *Proc Am Soc Clin Oncol* 2002;21(abstr 2481).
35. Strum S, McDermed J, Madsen L, Scholz M. Intermittent Androgen Deprivation (IAD) with Finasteride (F) given during the induction and maintenance periods results in prolonged time off IAD in patients with localized prostate cancer (LPC). *Proc Am Soc Clin Oncol* 1999;abstr 1363.
36. Scholz MC, Jennrich RI, Strum SB, Johnson HJ, Guess BW, Lam RY. Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period. *J Urol* 2006;175(5):1673-1678.

Radiotherapy for localized prostate cancer

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Over 200000 cases of prostate cancer will be diagnosed in the United States in 2007. Management of this common malignancy is controversial with essentially equal long-term survival and local control with either surgery or radiation therapy stage for stage in the setting of localized disease. Factors that can affect treatment recommendations include stage and grade of disease, the pre-treatment PSA, physician bias and patient choice. This paper examines several of the radiotherapeutic options for the treatment of prostate cancer, and will also discuss evolving modalities that may offer additional treatment choices in the future.

Key Words: radiation, radiotherapy, external beam, EBRT, 3D CRT, IMRT, IGRT, brachytherapy, protons, hypofractionation

Introduction

Radiation has been an important modality for the treatment of cancer since shortly after the discovery of x-rays by Wilhelm Roentgen in November 1895. The role of therapeutic radiation in the management of cancer has evolved over the past century into a distinct medical specialty devoted to the research and treatment of a variety of neoplastic processes, including prostate cancer.

The American Cancer Society estimates that there will be over 219000 cases of prostate cancer diagnosed in the United States in 2007 with a projected 27000 deaths. African American men and Jamaican men of African descent have the highest incidence of prostate cancer in the world. As daunting as these figures might appear, however, the number of deaths from lung cancer dwarfs that of prostate cancer with nearly 90000 men expected to die in 2007.[1]

Multiple treatment options exist for the management of localized prostate cancer and depend on a variety of factors, most notably the stage and grade of the disease and the pretreatment prostate specific antigen (PSA) level. Surgical options include a standard radical retropubic prostatectomy, a transperineal prostatectomy, a laparoscopic prostatectomy or a robotic procedure. Radiotherapy options are equally varied with a choice of either some form of external beam radiation therapy (EBRT) or brachytherapy. External beam options include three-dimensional conformal radiotherapy (3D CRT) or the more technically sophisticated formats including intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). Low-dose-rate (LDR) prostate brachytherapy is an increasingly popular option for many men. Combined modality therapy using LDR or high-dose-rate (HDR) brachytherapy and some form of EBRT may also be offered for intermediate and high-risk prostate cancers. Androgen deprivation may be a useful adjunct for surgery or radiotherapy. Cryotherapy is another choice for treating prostate cancer although many centers prefer to reserve cryotherapy for salvage of radiotherapy failures. Active surveillance and watchful waiting may be offered to selected men depending on stage, grade, PSA and a variety of additional co-factors.

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Defining biochemical failure after radiation therapy

The normal range for PSA is 0 ng/ml-4 ng/ml with variation according to patient age. Settling on a definition for what constituted biochemical failure following treatment with radiation, however, proved to be a more difficult task. An American Society of Therapeutic Radiology and Oncology (ASTRO) consensus conference met in 1996 and agreed that patients with three consecutive rises in their PSA value post radiotherapy would be considered a treatment failure.[2] Multiple problems with this definition soon became evident: it was restricted to EBRT monotherapy, a sensitivity to length of follow-up, the potential for false positives due to benign PSA bounces and the lack of correlation with clinical progression of disease. In addition, there was the issue of the actual date of failure which was put at the midpoint between the end of treatment and the first PSA rise, creating a possible backdating artifact.

ASTRO recognized these problems and convened a second conference in Phoenix in 2005 leading to a new definition, PSA nadir + 2 ng/ml (or more) with failure "at call", i.e., no backdating.[3] The so called Phoenix Definition has supplanted the earlier ASTRO definition, although this earlier value still has merit when looking at the older literature.

External beam radiation therapy

Beginning in the early 1960's, the standard field arrangement for treating prostate cancer was a simple anterior-to-posterior/posterior-to-anterior (AP/PA) set-up to deliver 6000 rads to 6500 rads (radiation absorbed dose) with significant GI and GU toxicity consisting of diarrhea, urinary frequency, nocturia and dysuria. This evolved to a 4-field technique that added right and left parallel opposed fields to the AP/PA design with a modest decrease in morbidity and a slightly higher dose in the range of 6840 rads (or centiGray, cGy), delivered at 180 cGy/day in 38 fractions, Monday through Friday. The final 2340 cGy was often delivered using a smaller set of fields arranged as right and left 120 degree arcs designed to spare portions of the rectum and bladder. This technique remained popular until the mid 1990's when CT simulation, coupled with improvements in computer software, led to the development of three-dimensional reconstruction of anatomic structures. This was a major step in better understanding the true relationship between the target volume and the surrounding normal tissues, thus permitting tighter blocking schemes and subsequently leading to the safe escalation of the radiation dose. Three-dimensional CRT was initially performed with standard, bulky mounted cerrobend blocks, a fairly cumbersome arrangement given block shifts in millimeter increments that were often necessary for fine-tuning a 3D CRT set-up. This eventually gave way to the advent of multileaf collimation whereby motorized, computer-controlled leaves in the head of the linear accelerator were used to tightly shape a prospective radiotherapy treatment field with a higher degree of reproducible precision. A typical 3D CRT set up consists of six coplanar fields, usually with 10 mm-15 mm margins around the prostate.

At the same time, major academic institutions were evaluating an innovative technique for irradiating tissue with unparalleled accuracy by modifying the radiation dose as it was being delivered. The genesis of this revolutionary treatment was the aforementioned multileaf collimation that was now being used to temper the dose of radiation in real time, permitting increasingly tighter margins to be employed with similarly escalating doses. This breakthrough, known as intensity modulated radiation therapy or IMRT, is arguably the most important advance in the delivery of therapeutic radiation since the introduction of the linear accelerator in the early 1950's. Dozens of computer-controlled leaves move in and out of the radiation beam during daily treatments to attenuate the beam in such a way to provide sharp edges around the target volume, thereby sparing more normal tissue. Doses quickly escalated from 6840 cGy to 7200 cGy then to a relatively standard dose of 7560 cGy at 180 cGy x 42 fractions. Set-up typically consisted of 5-7 non-coplanar fields with an anterior margin of 7 mm-10 mm and a posterior margin of 5 mm-7 mm. Treatment usually was delivered in approximately 15 minutes. IMRT has been rightfully hailed as a significant advance in the radiotherapeutic management of prostate cancer and, with its' predecessor 3D CRT, has become the standard of care.

It was (and continues to be) universally accepted that the accuracy of radiotherapy is only as good as the daily reproducibility of the treatment field. Weekly port films have been performed for decades as a standard quality assurance measure in an attempt to document this struggle to achieve perfection. The words "image guidance", however, crept into the radiation oncologist's lexicon nearly 10 years ago when the daily use of abdominal ultrasound was employed to improve the accuracy of 3D CRT and IMRT prostate set-ups, marking the beginning of the age of image-guided radiation therapy, better known today as IGRT. On Board Imaging (OBI) is also being used with cone beam CT scans or

kV/mV films of the patient in the treatment position with images acquired daily. These images are superimposed on the original simulation film to compare the two set-ups, with positioning adjustments made in near-real time, resulting in a new paradigm in radiotherapy precision. All of the major manufacturers, including Varian (Trilogy), Siemens (Primatom) and Elekta (Synergy) have equipment capable of performing IGRT, as well as other companies such as TomoTherapy, Inc. (Tomotherapy), Novalis Brain Lab (ExacTrac) and Accuray (CyberKnife).

Prostate IGRT can be accomplished in a number of different ways but the most popular method appears to be using OBI with or without implanted fiducial markers. These markers, consisting of three gold seeds, are inserted into the prostate gland under ultrasound guidance by the urologist. CT simulation films are then obtained with daily OBI to corroborate set-up accuracy. Not everyone, however, may be an appropriate candidate for implantation of fiducial markers, nor are they absolutely necessary for employing OBI. Normal structures, i.e., bony anatomy, offer as very reasonable alternative to fiducials with little drop off in accuracy to the trained eye. The radiation treatment itself can be delivered using either an IMRT or 3D CRT technique.

The use of image-guidance with IMRT has not only permitted safer dose escalation but has also resulted in a significant improvement in treatment-related morbidity. Most patients experience some increase in urinary frequency and nocturia, often accompanied by dysuria of varying degrees. Bowel movements may also increase in frequency, rarely progressing to frank diarrhea. Potential long-term side effects include hematochezia and hematuria, both of which are uncommon.

Brachytherapy

Low-dose-rate prostate brachytherapy has grown incrementally over the past 15 years. Brachytherapy can deliver a large dose of radiation to the prostate and proximal seminal vesicles while maintaining safe doses to the bladder, rectum and urethra. So-called "open" procedures with poor dosimetry have been supplanted by ultrasound techniques with excellent coverage of the prostate gland. There are two prevailing philosophies regarding implant technique, preplanned versus real time.

Preplanned implants rely on a preoperative volume study with the number and location of the needles and seeds determined in advance. In this method, the bulk of the work is done before the actual implant with the expectation that the volume study at the time of the procedure will precisely match the plan. Real time implants, on the other hand, are designed in the operating room at the time of the procedure with needle and seed placement determined by the live volume study. There is minimal preoperative labor with this type of implant although the procedure itself usually takes longer. A well-executed preplanned implant can be done in 20-45 minutes while a real time procedure can take from 45-90 minutes. Implants are usually done under general anesthesia but spinal anesthesia and even techniques using local anesthesia may be employed. Most implants are still done in the hospital operating room although the ambulatory surgery center setting has become increasingly popular in the United States for economic reasons. Patients usually go home a couple of hours after the procedure with a 3-7 day recovery time.

The two most popular isotopes for brachytherapy are ^{125}I and ^{103}Pd. From a therapeutic standpoint, there is no significant difference between these two isotopes; they both effectively treat prostate cancer.[4] The principal difference lies in their half-lives. All isotopes require six half-lives to decay from 100% activity down to ~1% (100-50-25 etc.). The half-life of ^{125}I is 60 days, meaning that it takes nearly a full year, 360 days, for an ^{125}I implant to deliver its full dose. The half-life of ^{103}Pd, on the other hand, is only 17days with an active life of ~3 and a half months or 102 days. ^{125}I is most often used for patients with low-intermediate risk disease whereas ^{103}Pd is frequently implanted in higher risk patients. These seeds are available from a number of manufacturers and may be "loose" or "stranded". Small studies have concluded that there is no dosimetric advantage to one over the other but that the rate of seed embolization is significantly lower with stranded seeds.[5-7] Bard Urologic has developed a device called the Quicklink which uses loose seeds to custom design stranded seeds in real time for implant.

LDR brachytherapy may be used as the sole treatment for patients with low and intermediate risk disease or in combination with some form or external beam radiotherapy for patients with high risk prostate cancer, i.e., stage T2c or higher, Gleason score ≥ 8 or PSA > 20. In the high risk setting, the implant dose is reduced by one-third with the addition of an external beam dose of 4500 cGy. The rationale for combined modality treatment rests on the fact that seeds alone cannot adequately treat disease that may extend beyond the prostate capsule or into the seminal vesicles. The external beam field is designed to cover the seminal vesicles in their entirety as well as providing a margin around the prostate to accommodate the risk of extracapsular extension. The sequencing of the procedures does not appear to be

critical although patient compliance may be better with EBRT followed by implant. When a partial implant is done at the outset, EBRT usually follows after a 2-month interval.

HDR brachytherapy using a ^{192}Ir source may also be used in combination with EBRT for management of localized prostate cancer. The most common protocol is to perform two or three HDR implants following a dose of approximately 4500 cGy with EBRT. There is also growing institutional experience looking at HDR brachytherapy alone, similar to the more common LDR brachytherapy implant.

The side effects from brachytherapy are similar to what is often noted during external beam radiotherapy. Patients will usually experience an increase in urinary frequency with some urgency and dysuria. The urinary stream may also be slower. Most men, however, note little change in their bowel habits. These acute effects resolve over a period of several weeks to months. Long-term side effects include the potential for hematuria and hematochezia of varying degrees, urethral stricture and the remote chance of a urethrorectal fistula.

A look into the future

As healthcare costs continue to skyrocket, two very different treatment paradigms will take center stage for the radiotherapeutic management of prostate cancer. One, proton therapy, is technically feasible but expensive with limited availability. The other involves manipulating the radiobiology of the prostate and surrounding normal structures to devise a plan that uses conventional radiotherapy but with fewer, higher dose fractions, known as hypofractionation, with the caveat that it is demonstrably less expensive than protons and, potentially, more effective.

Protons have, literally, been around since the beginning of time. Their use in the management of cancer had been largely limited to the treatment of certain eye tumors, spine and base of skull lesions. The attraction of protons has been the deposition of energy at depth, the so-called Bragg Peak, with relative sparing of the superficial structures. Special filters are now applied to spread out the Bragg peak to conform to the tumor with a sharp dose drop off. Studies dating back into the '70's from Shipley, et al, at Massachusetts General Hospital (MGH) have demonstrated the potential for using protons as a boost for treating prostate cancer.[8] Recent data from MGH suggests that a high dose proton boost to the prostate may improve the duration of biochemical control in low and intermediate risk men but offer no discernable advantage for high risk patients with no significant difference in toxicity.[9]

Despite the lack of data to support their use in the majority of malignancies, proton centers are popping up around the US. The science of medicine suggests that there may be a role for protons in the future. The business of medicine, however, will attempt to take advantage of lucrative reimbursement for proton therapy, a situation that, in a time of diminishing resources, almost certainly will not last. Unless there are well-designed clinical trials that clearly establish the superiority of protons over photons, the future of this expensive but exciting technology may be in jeopardy.

Another school of thought is looking at the radiobiology of prostate cancer in an attempt to exploit differences in the response of the prostate and the surrounding normal structures to fewer but larger doses of radiation. This theory of hypofractionation examines the dose rate for treating prostate cancer, in particular the concept that the prostate may be more sensitive to the dose rate than the surrounding normal structures, the bladder and the rectum. It is beyond the scope of this paper to describe the nuances of the α/β ratio and the linear quadratic model but simply stated, a lower ratio suggests greater sensitivity to radiation. Several authors have postulated that the α/β ratio for the prostate is between 1 and 3 with a ratio for the rectum of 6. It is this difference that Fowler et al at the University of Wisconsin used to create their model that suggested that 10 large fractions delivered over no less than 5 weeks could yield a 15%-20% improvement in biochemical (PSA) control rates.[10]

MD Anderson treated 100 consecutive patients to 7000 cGy at 250 cGy x 28 fractions over 5 and a half weeks with a median follow-up of 66 months.[11] Using either of the definitions for evaluating biochemical failure following radiation, the results from this trial are very encouraging: overall 5-year bRFS was 97%, 88% and 70% for low, intermediate and high risk disease using the original ASTRO definition, with the Phoenix Definition giving results of 97%, 93% and 75%. Grade 3 rectal toxicity was 3% with only 1% grade 3 urinary toxicity.

Fox Chase Cancer Center in Philadelphia has also evaluated hypofractionation for prostate cancer and concluded that 270 cGy x 26 to 7020 cGy was well tolerated with acceptable acute toxicity.[12]

Building on these studies, the RTOG is currently accruing patients for a phase III randomized trial (RTOG 0415) looking at conventional doses of radiation (180 cGy x 41 fractions to 7380 cGy) versus hypofractionation (250

cGy x 28 fractions to 7000 cGy).[13] In addition, the phase III OCOG PROFIT study is accruing intermediate risk patients and will compare 78 Gy in 39 fractions versus a hypofractionation arm of 60 Gy and 20 fractions.[14] The results of these trials may provide the necessary impetus for changing the way we treat prostate cancer with EBRT using fewer, larger fractions with a potential cost savings.

Conclusion

Prostate cancer continues to be a frequently diagnosed malignancy in American men. External beam radiotherapy and brachytherapy are excellent modalities for treating this disease with acceptable morbidity. The use of protons continues to grow but hypofractionation may ultimately become the standard for EBRT with shorter treatment times and the potential for significant cost savings.

Disclosure

None □

References

1. American Cancer Society. Estimated New Cancer Cases and Deaths by Sex for All Sites, US, 2007. In: Cancer Facts and Figures 2007. Atlanta: American Cancer Society; 2007.
2. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997 15;37(5):1035-1041.
3. Roach M 3rd, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;15;65(4):965-974.
4. Cha CM et al. Isotope selection for patients undergoing prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;45(2):391-395.
5. Kaplan ID et al. A comparison of the precision of seeds deposited as loose seeds versus suture embedded seeds: a randomized trial. *Brachytherapy* 2004;3(1):7-9.
6. Spadinger I et al. Prostate brachytherapy postimplant dosimetry: a comparison of suture-embedded and loose seed implants. *Brachytherapy* 2006;5(3):165-173.
7. Reed DR et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy* 2007;6(2):129-134.
8. Shipley WU et al. Proton radiation as boost therapy for localized prostatic carcinoma. *JAMA* 1979;241(18):1912-1915.
9. Zietman AL 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(10):1233-1239.
10. Fowler JF et al. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;56(4):1093-1104.
11. Kupelian PA et al Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes. *Int J Radiat Oncol Biol Phys* 2005;63(5):1463-1468.
12. Pollack A et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2006;64(2):518-526.
13. RTOG website http://rtog.org/members/protocols/0415/0415.pdf
14. ClinicalTrials.gov website http://clinicaltrials.gov/show/NCT00304759

Salvage cryosurgical ablation of the prostate for local recurrence after radiation therapy: improved outcomes utilizing a capromab pendetide scan and biopsy algorithm

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CLARKE JR HARRY S, ESKRIDGE MR, EL-ZAWAHRY AM, KEANE TE. Salvage cryosurgical ablation of the prostate for local recurrence after radiation therapy: improved outcomes utilizing a capromab pendetide scan and biopsy algorithm. The Canadian Journal of Urology. 2007;14(Supplement 1):24-27.

Purpose: *We assessed the efficacy, complications and technical advancements in salvage cryosurgical ablation of the prostate for recurrent prostate cancer after radiation therapy.*

Methods: *A total of 58 patients were evaluated for salvage cryosurgery using an algorithm of capromab pendetide scan and prostate biopsy from January 2003–July 2007. Forty-seven patients underwent salvage cryosurgery and biochemical recurrence free survival and complications were retrospectively reviewed. Mean follow-up was 24 months.*

Results: *Seventy percent of patients achieved a nadir PSA < 0.5 ng/ml. Overall, 51% of patients achieved a durable PSA response with a pre-salvage serum PSA < 10 predictive of success. There were no major complications and minor complications were few.*

Conclusion: *Salvage cryotherapy in experienced hands utilizing third-generation technology provides for excellent biochemical control with minimal morbidity.*

Key Words: cryosurgery, prostatic neoplasms, capromab pendetide, prostate-specific antigen, salvage therapy

Introduction

Local recurrence of prostate cancer after definitive therapy with radiation has been reported in various series to be upwards of 30%.[1,2] The science and technology of delivering radiation has continued to improve, and most centers are recommending and safely delivering higher dose radiation to the prostate to improve success and decrease recurrence. The past 10 years, however, has seen a vast increase in the number of younger men diagnosed with prostate cancer electing to undergo brachytherapy in a desire to preserve potency and obviate a longer surgical convalescence.[3] A large portion of the patients with biochemical recurrence are likely to be younger men and the recommendations for treatment of this group of patients are also undergoing reevaluation. Previously, for biochemical recurrence after definitive radiotherapy and depending on the comorbidities, which in an older population were high, the treatments ranged from watchful waiting to hormone therapy, with salvage prostatectomy and salvage

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cryotherapy less than satisfactory alternatives. The reasons were the high rate of serious complications and low rate of disease free status after salvage therapy. Salvage prostatectomy is currently being revisited at several institutions with the rationale that in patients who fail brachytherapy, both the volume of disease as well as the radiation dose is limited in extent allowing for fewer complications and the possibility for greater disease free success rates.[4,5] Initial reports of salvage cryosurgical ablation of the prostate (CSAP) were also noted for significantly higher rates of complications than primary cryotherapy, and as a consequence this treatment often fell into disfavor.[6] Currently with the third generation cryotherapy equipment, small diameter cryotherapy needles and FDA approved urethral warming device, these complications have been greatly reduced and this therapy holds promise as a low morbidity minimally invasive treatment option for these patients.[7-9] This study reports our initial results for salvage CSAP using a third-generation argon-based system in patients referred for biochemical recurrence after definitive radiotherapy. Patients were evaluated for short and intermediate term biochemical disease free status as well as for the number and extent of complications.

Methods

Between January 2003 and July 2007 58 patients were evaluated at our institution for a rising PSA after definitive radiotherapy (external beam and/or brachytherapy) for prostate cancer in consideration of salvage CSAP. For staging, all patients underwent physical exam and capromab pendetide (ProstaScint, Cytogen Corporation, Princeton, NJ) scan to ensure they would be eligible for local-only therapy. Only patients with a negative or prostate-only positive (non-metastatic) scan were offered prostate biopsy and all patients who underwent salvage CSAP had biopsy-proven prostate cancer recurrence. Salvage CSAP was performed using the Galil Medical (Plymouth Meeting, Pennsylvania) argon-based ultra-thin 17-gauge cryoablation needles placed percutaneously through the perineum guided by a standard brachytherapy template and trans-rectal ultrasound. Eight needles, two per channel, were placed in a circumferential pattern, with two sub urethral needles. A urethral warmer was placed and freezing was initiated in an anterior to posterior fashion and monitored by trans-rectal ultrasound. Two freeze-thaw cycles were employed in all cases. Patients were discharged home the same day with an indwelling Foley catheter for 2 weeks. Follow-up consisted of a voiding trial in 2 weeks, and an assay of serum PSA values, which were obtained every 3 months for the first 2 years and every 6 months thereafter. Careful analysis of both early and late complications, as well as severity was recorded. Preoperative erectile function was assessed using the SHEM-7 questionnaire. Incontinence was considered significant if patients had to wear pads or underwent further incontinence-related medical or surgical intervention. Failure was considered an inability to reach and maintain a post-salvage PSA ≤ 0.5 ng/ml. Biochemical recurrence was considered a PSA ≥ 0.5 ng/ml and rising.

Results

Of the 58 patients evaluated, 7 patients (12%) had a metastatic Prostascint scan and were not considered candidates for salvage cryosurgical ablation. These patients were offered expectant management or hormonal therapy. The remaining 51 patients had a prostate-only or negative Prostascint scan indicating non-metastatic prostate cancer that would be amendable to local salvage therapy and underwent trans-rectal ultrasound prostate biopsy to confirm residual disease. Four patients out of the 51 (8%), had a negative prostate biopsy and were offered expectant management or hormonal therapy, leaving 47 patients who underwent salvage cryosurgical ablation, Table 1. The majority of patients were between the ages of 60-69, however 43% were older than age 70. On physical exam, all patients had a small, flat irradiated prostate. Seventy-seven percent of patients had a pre-

TABLE 1. **Pre-salvage clinical characteristics in 47 patients**

Age (years)	**%**
50-59	4
60-69	53
70-74	23
> 74	20
PSA (ng/ml)	
< 4	28
4-10	49
> 10	6
> 20	17
Gleason score	
6-7	83
8-10	17

TABLE 2. **Complications**

Event	Frequency (%)
Obstruction/bladder neck contracture	0
Rectal injury/fistula	0
Urethral slough	0
Incontinence	0
UTI	2
Gross hematuria/clot retention	4

salvage PSA < 10. The mean follow-up was 25 months (range 7-53 months). Eighty-three percent had a Gleason score of 6-7 and 17% had a Gleason score ≥ 8. Overall, 33 patients (70%) obtained a PSA nadir < 0.5 ng/ml. **N**ine patients (27%) had a biochemical recurrence post-salvage, thus 51% of patients obtained a durable post-salvage PSA nadir < 0.5 ng/ml. The mean pre-salvage PSA in the successful group was 5.35 ng/ml, compared to 12.81 ng/ml in the failure group (p = 0.009). Complications were few and considered minor, Table 2. Immediate complications included gross hematuria in two patients, requiring clot evacuation and readmission in one patient for an additional 24 hours. No patients experienced urethral sloughing, rectal fistula or urethral incontinence. Post-CSAP penoscrotal swelling and edema were minimal. No patients experienced prolonged pelvic discomfort or pain postoperatively. All patients had erectile dysfunction pre-salvage.

Discussion

Currently, the most studied options for locally recurrent prostate cancer after radiation therapy are salvage prostatectomy and salvage cryotherapy. Salvage prostatectomy initially fell into disfavor due to the high rate of complications, positive margin rate and lack of efficacy. Several centers are revisiting salvage surgery, as it may be more feasible after brachytherapy because of the more confined radiation dose and improved surgical technique, although morbidity is still high.[4,5]

Similarly, initial salvage CSAP series were looked upon unfavorably due to increased extent of freezing and the lack of an FDA approved urethral warming device. This resulted in poor biochemical control and an unacceptably high complication rate. In our series, we demonstrated superior outcomes and markedly decreased rate of complications by using third generation cryotherapy equipment, carefully selecting patients with the highest probability of local recurrence and several modifications to treatment techniques. Significant postoperative swelling and edema of the penis and scrotum reported in earlier series has been eliminated by avoiding freezing above the anterior aspect of the prostatic capsule thereby sparing the regional lymphatics. Urethral sloughing, stricture and urethral trauma have been obviated by the urethral warming catheter and careful peripheral placement of the cryo-needles to prevent urethral freezing. Similarly, careful monitoring of lethal ice progression to avoid the rectum inferiorly and the urinary sphincter apically has eliminated prostatorectal fistulas and urinary incontinence. Further modification of the equipment includes a variable length freeze to provide for more precise sculpting of the ice ball, which is ideal in short, postradiated glands.

In spite of a strict definition of success (nadir PSA < 0.5 ng/ml), our results are consistent with other published salvage cryosurgery series.[7,9] which used less strict criteria such as nadir + 2 ng/ml. Were we to adapt such criteria our efficacy would be undoubtedly better. Overall, 51% of patients achieved a post-salvage durable nadir PSA < 0.5 ng/ml. While arguably some of the nine patients who experienced biochemical recurrence post-salvage in our series may harbor occult metastatic disease,[10] we feel this number was significantly reduced by the selection of patients using capromab pendetide scanning and trans-rectal ultrasound biopsy.[11]

Conclusion

Salvage cryotherapy is an excellent treatment option for patients with proven local recurrence of their disease. Complication rates are low in the hands of an experienced cryosurgeon. It provides an opportunity for cure in patients who otherwise might only be offered palliative therapy. Patients with a pre-salvage PSA of less than ten have a significantly increased chance for long-term disease free survival. The future application of clinical stratification algorithms along with imaging may further aid in patient selection, thereby improving long term success rates.

Disclosure

Dr. Harry S. Clarke is a member of the Speakers' Bureau for Galil Medical and CryoSurgery Proctor. Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis and has done research for Cytogen Corporation. □

References

1. Kupelian PA, Buchsbaum JC, Patel C, Elshaikh M, Reddy CA, Zippe C, Klein EA. Impact of biochemical failure on overall survival after radiation therapy for localized prostate cancer in the PSA era. *Int J Radiat Oncol Biol Phys* 2002;52(3):704-711.
2. D'Amico, AV, Moul, JW, Carroll, PR et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003;95:1376.
3. Heysek RV. Modern brachytherapy for treatment of prostate cancer. *Cancer Control* 2007;14(3):238-243.
4. Stephenson AJ, Scardino PT, Bianco FJ Jr, Diblasio CJ, Fearn PA, Eastham JA. Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. *Urol* 2004;172(6 Pt 1):2239-2243
5. Ward JF, Sebo TJ, Blute ML, Zincke H. Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol* 2005;173(4):1156-1160.
6. Cohen JK, Miller RJ, Shuman BA. Urethral warming catheter for use during cryoablation of the prostate. *Urology* 1995;45(5):861-864.
7. Ghafar MA, Johnson CW, De La Taille A, Benson MC, Bagiella E, Fatal M, Olsson CA, Katz AE. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. *J Urol* 2001;166(4):1333-1337.
8. Han KR, Cohen JK, Miller RJ, Pantuck AJ, Freitas DG, Cuevas CA, Kim HL, Lugg J, Childs SJ, Shuman B, Jayson MA, Shore ND, Moore Y, Zisman A, Lee JY, Ugarte R, Mynderse LA, Wilson TM, Sweat SD, Zincke H, Belldegrun AS. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *J Urol* 2003;170(4 Pt 1):1131.
9. Ng CK, Moussa M, Downey DB, Chin JL. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. *J Urol* 2007;178(4 Pt 1):1253-1257
10. Sandler HM, Dunn RL, McLaughlin PW, Hayman JA, Sullivan MA, Taylor JM. Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2000;48(3):629-633.
11. Wong TZ, Turkington TG, Polascik TJ, Coleman RE. ProstaScint (capromab pendetide) imaging using hybrid gamma camera-CT technology. *AJR Am J Roentgenol* 2005;184(2):676-680.

Options and recent advances in permanent brachytherapy for prostate cancer

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Permanent interstitial brachytherapy with I-125 or Pd-103 seeds is a well-established approach as single modality for low-risk prostate cancer patients and as part of a multi-modality program for intermediate- and high-risk patients. There are multiple approaches that have been developed to deliver high-quality implants, including pre-planned and real-time intra-operative techniques. In the hands of experienced users, either approach can provide consistently excellent outcomes. We believe that the combination of real-time intra-operative dosimetry and connected seeds may provide for improved consistency due to decreased seed migration.

Key Words: prostate cancer, brachytherapy, dosimetry, loose seeds, linked seeds

Introduction

Brachytherapy using permanent interstitial placement of I-125 or Pd-103 seeds has become an established treatment modality for prostate cancer. Effective as a single modality for low-risk patients,[1-3] it has also been shown to be effective for intermediate- and high-risk patients when combined with hormonal therapy and external beam radiotherapy.[2,4,5] Long-term data with around 6 years median follow-up reveals actuarial PSA-relapse free survival rates of 91%-88% for low-risk patients at 8-12 years.[1-3] For higher risk patients, Potters et al report actuarial rates of PSA-relapse free survival of 80% for intermediate-risk patients and 66% for high-risk patients, with a mean follow-up of 82 months.[2] Kupelian and colleagues report actuarial PSA-relapse free survival of approximately 75% at 7 years with a median follow-up of 46 months.[4] Stock et al, at Mount Sinai School of Medicine (MSSM), with a median follow-up of 50 months, reports actuarial PSA-relapse free survival of 86% at 5 years for high-risk patients[5] with a combination of 9 months of hormonal therapy, brachytherapy, and external beam radiotherapy.

The importance of implant dosimetry in regards to tumor control is well recognized. One dosimetric factor that has been consistently associated with tumor control is the D90; that is, the minimum dose to 90% of the prostate. A D90 at or above 140 Gy for I-125 implants[6] or 90% of the prescription dose[2] have been shown to correlate with biochemical control. There are multiple techniques that provide for designing and implementing effective seed implants with appropriate dosimetry.[7] Two basic approaches are pre-planning and real-time intra-operative planning.

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Pre-planning approaches

The patient usually has an ultrasound study done before the date of the implant and a plan for seed placement is developed and refined based on that study. Then, once in the operating room (OR), the position that the patient was in during the planning study is reproduced as closely as possible. The seeds are then placed according to the plan developed earlier. Seeds are placed in the prostate using pre-loaded needles or strands of connected seeds prepared earlier according to the pre-plan. Some pre-planners also use gun-type applicators of loose seeds, such as the Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, New York, USA). Minor modifications can be made if there is difficulty reproducing the pre-plan.

Real-time intra-operative planning

No pre-procedure imaging study is used to develop a plan, although some form of volume study is used to determine how many seeds to order. The patient is taken to the OR and positioned to avoid pubic arch obstruction, and the plan for seed placement is developed in the OR based on the shape and position of the prostate at that moment. Real-time intra-operative dosimetry for permanent seed brachytherapy for prostate cancer has multiple advantages over pre-planning techniques, as well as some disadvantages. Real-time intra-operative planning allows for optimization during the procedure by visualizing seed deposition and the resulting isodose lines. This allows for optimization of the plan to account for changes in prostate size and shape with needle placement, needle deviation from planned position, and for seed movement after seed deposition. Disadvantages include typically longer OR times with real-time dosimetry and, commonly, use of the Mick applicator to place loose seeds, which some users find unwieldy. Advantages of the Mick applicator include the ability to place individual seeds precisely and a great deal of flexibility on seed arrangement. However, seeds can move from their original location, or migrate, a small distance or farther, even to the lungs or other remote locations.[8-10] Loose seeds seem to migrate more frequently then connected seeds, especially when seeds are placed outside the prostate.[11,12] Connected seeds have been found to improve implant dosimetry by some investigators[13] while other investigators have found no difference, at least when implanted inside the prostate.[14]

Hybrid approaches

In an attempt to combine the advantages of real-time intra-operative dosimetry and connected seeds, we have developed a method of constructing custom-made links of seeds in the OR. Computed tomography volume studies are performed 2 weeks before the date of the brachytherapy procedure. The volume of the prostate is used to determine the activity of seeds to order based on the MSSM nomograms. Patients are then taken to the OR and the general technique developed by Stock and Stone at MSSM[15] is implemented using the Variseed brachytherapy planning system (Varian Medical Systems, Palo Alto, California, USA). An initial intra-operative plan is then developed using the ProSeed™ planning module (C.R. Bard, Inc., Covington, Georgia, USA) within VariSeed. Needles are placed in the periphery of the gland approximately 1 cm apart. The plan is then re-optimized for the actual location of the placed needles. Longitudinal views of the prostate are used to measure the length of the prostate for an individual needle path. A push-button delivery system, the QuickLink device (C.R. Bard, Inc., Covington, Georgia, USA), is then used to construct links of the appropriate number of seeds for the length measured on the longitudinal view on the ultrasound, according to the real-time intra-operative plan, Figure 1. The linked seeds are then transferred to the appropriate needle already placed in the patient via a hand-held transfer device. The linked seeds are then deposited as a single unit into the prostate under ultrasound visualization on the longitudinal view, in a manner analogous to that used with a pre-loaded needle. The needle is removed as the linked seeds are placed. The process is repeated until all the peripheral needles have been used to place the peripheral seeds. Approximately 75% of the required

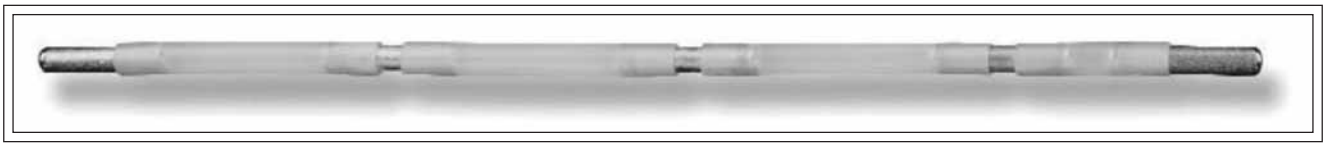

Figure 1. An example of a five-seed custom-designed link of connected seeds made with the QuickLink device (C.R. Bard, Inc., Covington, Georgia, USA) push-button delivery system. Note the non-uniform seed distribution.

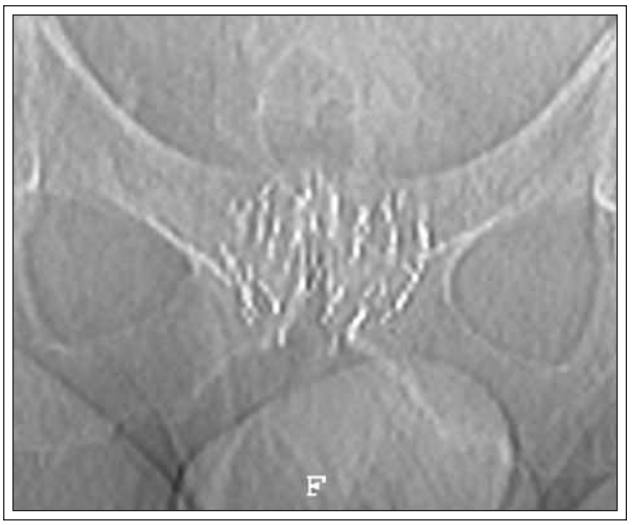

Figure 2. A computed tomography scout image of an I-125 seed implant using custom-made links of connected seeds using the QuickLink device (C.R. Bard, Inc., Covington, Georgia, USA) push-button delivery system.

activity is placed in the periphery of the gland. Next, the process is repeated for inner needles, typically 5-7, in order to place the remainder of the required activity. Most of this is implanted in the base and apex of the gland, to "cap" the prostate. The dosimetry is optimized once again to determine the optimal seed locations based on the actual location of the inner needles. Once the final plan is approved, the inner seeds are placed in the same manner as those of the peripheral needles, using custom-built links of connected seeds using the QuickLink device push-button delivery system, according to the length of the needle path in the prostate and the final intra-operative plan.

To date, 20 patients at our institution have had real-time intra-operatively planned implants with linked seeds using the QuickLink device and at least 1 month of follow-up with post-implant CT scans for dosimetry. Figure 2 displays a scout view from a post-implant CT scan of a patient treated with this approach. Fifteen patients had I-125 implants prescribed to a D90 of 160 Gy and five patients had Pd-103 implants prescribed to a D90 of 100 Gy followed by external beam radiotherapy. Post-implant CT dosimetry revealed a median D90 of 166.4 Gy (range 142.5-184.8) for the I-125 implants and 93.2 Gy (range 88.8-119.4) for the Pd-103 implants. Rectum and urethra doses were also within acceptable ranges. Only one patient required temporary urinary catheterization (crude rate of 5%). Intra-operatively planned permanent brachytherapy using real-time techniques with custom constructed linked seeds made intra-operatively with the QuickLink device is feasible and preliminary dosimetric results are encouraging. We believe this approach provides an excellent combination of the flexibility of real-time intra-operative planning with the decreased seed migration of connected seeds, and continue to refine this method at our institution.

Disclosure

Dr. Marshall is consultant for C.R. Bard, Inc.

References

1. Kollmeier MA, Stock RG, Stone NN. Biochemical outcomes after prostate brachytherapy with 5-year minimal follow-up: importance of patient selection and implant quality. *Int J Radiat Oncol Biol Phys* 2003;57(3):645-653.
2. Potters L, Morgenstern C, Calugara E, Fearn P, Jassal A, Presser J, Mullen E. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173:1562-1566.
3. Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with I-125 brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51(1):31-40.
4. Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, Carlson TP, Klein EA. Radical prostatectomy, external beam radiotherapy < 72 Gy, external beam radiotherapy > 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004:58(1):25-33.
5. Stock RG, Cahlon O, Cesaretti JA, Kollmeier MA, Stone NN. Combined modality treatment in the management of high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;59(5):1352-1359.
6. Stock RG, Stone NN, Tabert A et al. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101-108.
7. Nag S, Ciezki JP, Cormack R, Doggett S, DeWyngaert K, Edmundson GK, Stock RG, Stone NN, Yu Y, Zelefsky MJ. Intraoperative planning and evaluation of permanent prostate brachytherapy: report of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys* 2001;51(5):1422-1430.
8. Kunos CA, Resnick MI, Kinsella TJ, Ellis RJ. Migration of implanted free radioactive seeds for adenocarcinoma of the prostate using a Mick applicator. *Brachytherapy* 2004;3:71-77.
9. Nakano M, Uno H, Gotoh T, Kubota Y, Ishihara S, Deguchi T, Hayashi S, Matsuo M, Tanaka O, Hoshi H. Case Report. Migration of prostate brachytherapy seeds to the vertebral venous plexus. *Brachytherapy* 2006;5:127-130.
10. Zhui AX, Wallner KE, Frivold GP, Ferry D, Jutzy KR, Foster GP. Case Report. Prostate brachytherapy seed migration to the right coronary artery associated with an acute myocardial infarction. *Brachytherapy* 2006;5:262-265.
11. Tapen EM, Blasko JC, Grimm PD, Ragde H, Luse R, Clifford S, Sylvester J, Griffin TW. Reduction of radioactive seed embolization to the lung following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;42(5):1063-1067.

12. Fuller DB, Koziol JA, Feng AC. Prostate brachytherapy seed migration and dosimetry: analysis of stranded sources and other potential predictive factors. *Brachytherapy* 2004;3:10-19.
13. Lin K, Lee SP, Cho JS, Reiter RE, DeMarco JJ, Solberg TD. Improvements in prostate brachytherapy dosimetry due to seed stranding. *Brachytherapy* 2007;6(1):44-48.
14. Kaplan ID, Meskell PM, Lieberfarb M, Saltzman B, Berg S,Holupka EJ. A comparison of the precision of seeds deposited as loose seeds versus suture embedded seeds: A randomized trial. *Brachytherapy* 2004;3:7-9.
15. Stock RG, Stone NN, Wesson MF, DeWyngaertJK. A modified technique allowing interactive ultrasound-guided three-dimensional transperineal prostate implantation. *Int J Radiat Oncol Biol Phys* 1995;32(1):219-225.

The emergence of imaging technology in advanced prostate cancer

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Rapid advances in imaging technology have whetted our collective appetites for practical clinical applications to assist the physician and patient in therapeutic decisions. Current limitations of imaging technology are being addressed by the convergence of technology in materials science, the computer industry, and biology which have led to improvements of diagnostic imaging. Refinements in image acquisition, fusion of images, and outcomes data now suggest use for image-guided therapy. Novel imaging agents and technologies appear to provide improved capabilities to detect malignant lymph nodes. Future applications of optical coherence tomography, electron paramagnetic resonance imaging, nanotechnology, and other forms of molecular imaging promise further refinements to enhance our diagnostic armamentarium.

Key Words: prostate cancer, immunoscintigraphy, imaging, optical coherence tomography

Introduction

Despite a shift in prostate cancer demographics at time of presentation from an older population with a higher rate of advanced disease to younger men with smaller volume disease, the critical question of disease extent remains paramount. Our standard tools for initial diagnosis with digital rectal exam (DRE), serum prostate specific antigen (PSA), and transrectal ultrasound-guided (TRUS) biopsy help detect disease but do not allow accurate assessment of disease extent. Accurate prediction of local disease stage is aided by various nomograms based on biopsy information with serum PSA and DRE findings.[1,2] However, prediction of lymph node (LN) metastasis is less accurate because the nomograms only incorporate tissue samples from a limited area of possible lymphatic spread.

It has long been dogma that prostate cancer marches in an orderly fashion from the prostate through a small crossroad of the medial chain of the internal iliac lymphatic system before dispersal through the rest of the body. While this certainly is a common area for lymphatic involvement, this implies that prostate cancer differs from other cancers which follow various metastatic pathways. Yet accumulating evidence suggests that underestimation of nodal disease is higher than previously expected. Modest extension of LN dissection has resulted in a significant increase in patients with metastatic involvement. The potential for increased survival with extended pelvic LN dissection in patients with small volume metastatic nodal deposits is balanced by the 39% (4-year) and 43% (5-year) progression free rates, demonstrating the wider extent of the disease.[3,4] Stratification by risk category is useful for prognostication but nodal involvement is still underestimated even in the low risk prostate cancer population.[4] The same trend for increased positive LN detection is evident in the reports of scintigraphic sentinel LN sampling where over half of the 10% of low risk patients with LN metastases had disease outside of the sentinel nodes.[5] Very telling is a recent study of patients who underwent abdominoperineal resection for suspected LN-positive colorectal carcinoma where perirectal nodes contained prostate cancer in 4.5%.[6] The deep pelvic, presacral, and proximal common iliac LNs are not sampled in either standard or extended pelvic LN dissections.

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Various noninvasive imaging has been used to evaluate prostate cancer patients but the clinical utility of standard cross sectional imaging is limited because a relatively large volume of disease generally is required for detection. This unmet clinical need has spurred the search for new imaging modalities that incorporate molecular processes or tissue characteristics to enhance detection rates and provide further information about specific tumor biological activity.[7]

Conventional cross sectional imaging

The limitations of both computerized tomography (CT) and magnetic resonance imaging (MRI) to detect prostate cancer and nodal metastasis are recognized. Although LN size as a criterion for metastasis has low sensitivity, conventional CT and MRI use size criteria with threshold dimensions of greater than 10 mm in the short axis diameter of an elongated node or 8 mm if the lymph node is round. Sensitivity of CT for LN metastases using size criteria ranges from 25%-78%, with specificity of 77%-98%.[8-11] In one of the few studies with tissue confirmation of radiographic findings, CT sensitivity was 4% in a cohort of intermediate to high risk patients.[12] CT may fail to detect lymphadenopathy because nodes are beneath the size threshold for detection, may contain microscopic tumor deposits without enlargement, or because of technical performance of the scan and interobserver variability in interpretation.[13] When adenopathy is detected, CT does not distinguish between inflammatory and neoplastic involvement.[14] Therefore standard CT is best reserved for patients with clinical stage T3 or T4 disease and for radiotherapy pretreatment planning.[15] CT also remains useful as a conformal study for image coregistration.

Whole body MR imaging for metastatic evaluation has improved with rapid sequence techniques for image acquisition but the limitation of size criteria for metastatic LN detection applies to MRI as well.[16] MRI for LN evaluation is enhanced by an imaging agent comprised of ultra small super paramagnetic iron oxide (USPIO) particles, first reported in a murine model in 1990.[17] The 20 nm hexagonal iron oxide cores coated with dextran (Combidex, Advanced Magnetics, Inc., Boston, MA) are injected intravenously and filtered through the lymphatic system. Normal LNs are laden with macrophages while areas of tumor deposit have very few. High intensity signal is noted in all nodes initially but macrophage phagocytosis in areas of normal LN architecture creates a very dark signal due to the nanoparticle paramagnetic properties and therefore eliminates the high intensity signal on repeat MRI. Nodes with metastatic disease demonstrate continued high intensity signal in areas of tumor. Sensitivity and specificity of MRI with lymphotrophic particles (96% and 99%) were improved compared to MRI alone (29% and 87%) in LNs between 5 mm and 1 cm.[18] Several noncontiguous positive LNs were detected, corroborating previous work that reported up to 17% of patients with a solitary iliac metastasis and 7% to 14% of patients with a solitary presacral or presciatic metastasis outside of the conventional area for lymph node dissection.[19,20] Again, this is also consistent with the findings that even modestly extended lymph node dissection detects unsuspected disease.[3,4] Imaging with this contrast agent is independent of tumor metabolic activity, unlike positron emission tomography, and relies on signal intensity which denotes functional activity regardless of size. This mechanism of functional activity makes this agent useful for many other tumor types in addition to prostate cancer. Unfortunately, this agent is not available for general use at this time.

Positron emission tomography (PET)

Positron emission tomography (PET) measures metabolism of a radio-labeled analog in tissue where the higher metabolic rate of neoplasia registers an increased scintigraphic signal, especially noted in rapidly progressive tumors. Although the most commonly used radiotracer for PET is ^{18}F-fluoro-2-deoxyglucose (FDG), this analog is not particularly useful in evaluation of prostate cancer.[21] In addition to an inability to use PET to differentiate between tumor and hyperplasia, PET is also less sensitive than bone scintigraphy for detection of osseous metastases.[21]

FDG-PET has shown variable results for lymph node assessment and its use may be hampered because of relatively low glycolytic rate in prostate cancer and its metastases.[22] However, some new positron-emitting agents have promise for prostate cancer imaging not solely based on tumor metabolism. Though the mechanism of action is incompletely understood, it appears that ^{11}C-acetate is incorporated into the lipid pool of neoplastic tissues with low oxidative metabolism and high rate of lipid synthesis while choline-derived agents undergo intracellular phosphorylation and incorporation into cell membranes.[23] The ^{11}C-methionine analog is incorporated in intracellular proteins and the ^{18}F-derivative of dihydrotestosterone uses a hormonal-based pathway.[24] The ^{11}C derivatives of methionine, acetate, and choline are also attractive because they avoid renal excretion, unlike ^{18}F-FDG. Therefore, the detection of juxtavesicular disease in the pelvis is not hindered by artifactual signal in the bladder as it is with ^{18}F-FDG.[23] A recent study using PET with

^{11}C-choline yielded a sensitivity of 80%, specificity of 96%, and accuracy of 93% without tissue confirmation in 67 patients.[25] Co-registration of PET images with anatomic CT data improves anatomic localization with many tumors. While encouraging, improvements in PET detection of prostate cancer await further studies and introduction of small high resolution PET scanners for the prostate.

Immunoscintigraphy

Immunoscintigraphy acquires images through use of a radiolabeled antibody that recognizes prostate tissue. Prostate-specific membrane antigen (PSMA) is expressed in prostate cells and upregulated in higher grade cancer, androgen insensitive cancer, and metastatic deposits.[26-30] The most intensively studied monoclonal antibody conjugate to PSMA is capromab pendetide (ProstaScint, Cytogen Corporation, Princeton, NJ) which is a 100 kd type II transmembrane glycoprotein that recognizes an intracellular epitope.[31] Several other candidates have been evaluated, including those to extracellular epitopes, but none have been approved for general use.[32] Despite controversy about the utility of an antibody to an internal epitope and the question of whether this antibody recognizes live tissue, capromab pendetide has been shown to bind to live cells and there are several studies with high correlation of pathological specimens to scan results.[12,33-35]

The pivotal clinical trial demonstrated a sensitivity of 63% (compared to 4% for CT and 15% for MRI) and a negative predictive value of 92% with tissue confirmation of scan results.[12] Despite these encouraging results, capromab pendetide scan results were variable primarily because gamma camera technology was not sensitive enough and, in other cases, areas of high signal intensity could not be localized well enough to anatomic structures. In the last 5 years, however, improvements in image acquisition and processing and the introduction of image co-registration have significantly enhanced resolution and localization. The fusion (co-registration) of the functional single photon emission tomography (SPECT) provided by the 7E-11 radioimmunoconjugate with anatomic images from CT or MRI has made a dramatic difference for prostate cancer detection.[35-37] Localization accuracy has doubled and tissue confirmation of scan results now demonstrate an accuracy of 83% with fused images.[36,37]

The emergence of clinical outcomes data related to PSMA and capromab pendetide scan results strengthens the case for the use of this radioimmunoconjugate. Patients with prostate cancer that overexpress PSMA in the prostate gland have been shown to have twice the recurrence rates and a faster time to recurrence compared to those with normal expression in the gland.[38] Overexpression in the gland was shown to be the only statistically significant predictor of PSA recurrence in 450 patients (aside from actual positive LNs) in a recent study.[39] In a study with similar implications for intraprostatic PSMA expression, correlation of saturation biopsy pathological results with scans revealed an 80% overall accuracy.[40]

The question of high intensity signal on fused scans in areas distant from the prostate is now much more clearly answered as well, Figure 1. First, there is a

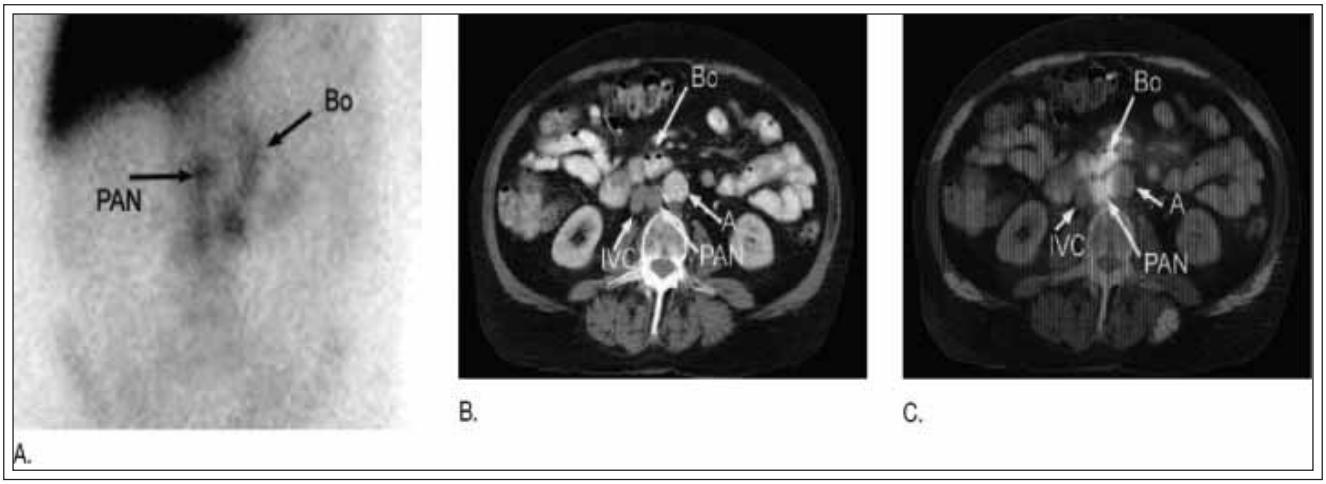

Figure 1. Capromab pendetide and CT scan fused demonstrating high intensity signal in both the intestine, which is the normal excretion of the immunoconjugate, and the para-aortic lymph nodes (PAN). (Courtesy of R. McDonald, MD Anderson Cancer Center, Orlando, FL).

growing recognition that prostate cancer may not progress orderly from the pelvis to the rest of the body which is strongly supported by autopsy data. Two distinct patterns of LN metastasis occur in prostate cancer: the commonly accepted progression from pelvic LNs on to abdominal sites and beyond, and a second pattern with little or no pelvic LN involvement but a predominant central abdominal pattern of involvement.[41] The 7-year follow up data on 239 patients undergoing brachytherapy where fused scans were used demonstrated strongly statistically significant survival for patients with no distant high signal intensity.[42] Patients with the fused capromab pendetide scans positive outside of the pelvis showed a three-fold increase in biochemical disease recurrence regardless of risk category. In another large recently published study, patients with a central abdominal pattern in a cohort of 341 were found to have ten-fold greater prostate cancer-specific death rates than those without such a pattern.[43] These findings were independent of use or timing of intervention with androgen ablation. This suggests that the scan results can be used both to predict better outcomes on the basis of the absence of distant signal intensity.

Patients with a rising PSA after prostatectomy have also been evaluated with capromab pendetide. Reports have shown mixed results with some authors demonstrating a durable complete biochemical response rate to external beam radiotherapy over a nearly 5-year period while others claim there is no advantage for the use of the scan.[44-47] However, studies with no advantage have not used fused images and generally have used older camera technology. In the modern era with fused images from higher resolution cameras, investigators report the value of immunoscintigraphy.[48] These suggest that the fused scans will be more suitable for patient selection and localization for targeted therapy.

The future of prostate cancer imaging: technologies on the horizon

Some quite fascinating imaging technologies are under development with application to prostate cancer imaging.

Electron paramagnetic resonance

Electron paramagnetic resonance (EPR) correlates tumor presence with hypoxia and localized prostate cancer is characterized by marked hypoxia and significant heterogeneity in oxygenation.[49-51] Overhauser-enhanced magnetic resonance imaging (OMRI) combines two spectroscopic techniques, nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) to provide high resolution MR images at low magnetic fields (~ 10 mT). While NMR detects species with magnetic nuclei such as water protons, EPR detects species with unpaired electrons such as paramagnetic molecules. Infusion with the paramagnetic agent before scanning with both the EPR frequency and the NMR frequency yields MR images with high spatial resolution.[50] The very small probes used require about 650-fold less energy than standard MRI. In vivo studies demonstrate that tumor accumulates significant amounts of the contrast agent yet large areas of the tumor are severely hypoxic. This unique, small, portable OMRI technique is capable of providing anatomically co-registered images of oxygen distribution, again demonstrating the value of image fusion.

Optical coherence tomography (OCT)

Optical coherence tomography (OCT) is an intriguing application of reflectance spectroscopy which employs continuous wave light (instead of sound waves) to obtain images in a manner analogous to B-mode ultrasonography. However, OCT does not require a conducting medium and can therefore image through air or water with far greater resolution than ultrasound.[52] Reflected light, generated in the near infrared spectrum by a superluminescent diode, is measured by interferometry to produce two-dimensional images. OCT images tissue *in situ* and in real time, providing resolution on the order of five to twenty microns, which is comparable to traditional confocal microscopic analysis. OCT is relatively inexpensive, portable, and can be used with existing endoscopic instrumentation.[53]

OCT imaging of human genitourinary tissue first occurred in 1997 demonstrating differentiation between the prostatic urethra and prostate, visualization of the neurovascular bundle and the prostate-adipose border, visualization of the prostatic capsule, and differentiation of the anatomic layers in the bladder and ureter.[54] A recent report has demonstrated the feasibility and high sensitivity for determination of early bladder tumor invasion.[55] OCT is currently being used to evaluate effects on prostate tissue from ionizing radiation and to locate neurovascular tissue during radical prostatectomy, Figure 2. Improvements in the ability to obtain OCT images strongly suggest that greater depth of tissue penetration will be possible with greater implications for solid tissue evaluation.

Technology convergence

The very dynamic changes in imaging technology are exciting but translation to clinical application presents obstacles to rapid integration into practice. The real value of these interesting imaging technologies will

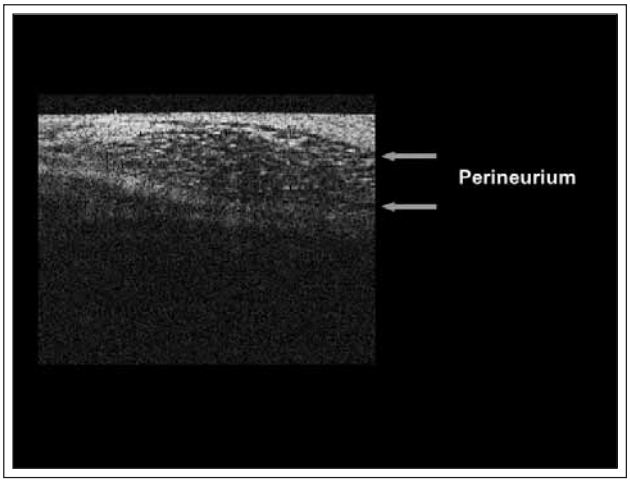

Figure 2. Optical coherence tomography of human prostate neurovascular tissue demonstrating the presence of the nerve in tangential view. (Courtesy of Imalux Corporation, Cleveland, OH).

be the fusion of information from them to provide a composite picture of a biological system and differences in signal in both normal and diseased tissues when perturbed. Fortunately, computer technology currently under development or in use will provide that opportunity due to logarithmic improvements in the ability to process signal. The ability to process the signal in real time and provide that information to the clinician is very intriguing. Capturing the data, combining it with pre-existing image information, and projecting it into the operative field is a worthy goal. We are not far from the day when we can do exactly that. Imagine the combination of archived CT, MRI, and sonographic images, combined with archived or real time immunoscintigraphy, OCT images, and anatomic data from existing databases. Technology to project that information into the surgical field exists currently with three-dimensional images with magnification in a head-mounted display, Figure 3. Image projection using a GPS chip to maintain anatomical position is now possible in a system which provides augmented reality for the surgeon.[56] One can envision a day in the not too distant future where the surgeon can respond affirmatively to the weary joke about "cutting on the dotted line" because of dramatic changes in true image-guided therapy.

Figure 3. Three-dimensional head mounted surgical display into which images can be imported or presented in real time as imaged. (Courtesy of Viking Systems, Inc., La Jolla, CA).

Disclosure

Dr. Michael J Manyak is an employee of Cytogen Corporation. He is on the Science Advisory Board for Imalux Corporation and Endocare. □

References

1. Khan MA, Partin AW, Mangold LA, Epstein JI, Walsh PC. Probability of biochemical recurrence by analysis of pathologic stage, Gleason score, and margin status for localized prostate cancer. *Urology* 2003;62:866-871.
2. Kattan MW, Eastham JA, Wheeler TM, Maru N, Scardino PT, Erbersdobler A. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. *J Urol* 2003;170:1792-1797.
3. Allaf ME, Palapattu GS, Trock BJ, Carter HB, Walsh PC. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. *J Urol* 2004;172:1840-1844.
4. Bader P, Burkhard FC, Markwalder R. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? *J Urol* 2003;169(3):849-854.
5. Weckermann D, Goppelt M, Dom R et al. Incidence of positive pelvic lymph nodes in patients with prostate cancer, a prostate-specific antigen (PSA) level of < or =10 ng/mL and biopsy Gleason score of < or =6, and their influence on PSA progression-free survival after radical prostatectomy. *BJU Int* 2006;97:1173-1178.
6. Murray SK, Breau RH, Guha AK, Gupta R. Spread of prostate carcinoma to the perirectal lymph node basin: analysis of 112 rectal resections over a 10-year span for primary rectal adenocarcinoma. *Am J Surg Pathol* 2004;28:1154-1162.
7. Manyak MJ, Javitt MC, Kang PS, Kreuger WR, Storm ES. The evolution of imaging in advanced prostate cancer. *Urol Clin North Am* 2006;33:133-146.

8. Golimbu M, Morales P, Al-Askari S, Shulman Y. CAT scanning in staging of prostate cancer. *Urology* 1981;18:305-308.
9. Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology* 1994;190:315-322.
10. Rorvik J, Halvorsen OJ, Albrektsen G, Haukaas S. Lymphangiography combined with biopsy and computer tomography to detect lymph node metastases in localized prostate cancer. *Scand J Urol Nephrol* 1998;32:116-119.
11. Weinerman PM, Arger PH, Coleman BG, Pollack HM, Banner MP, Wein AJ. Pelvic adenopathy from bladder and prostate carcinoma: detection by rapid sequence computed tomography. *AJR Am J Roentgenol* 1983;140:95-99.
12. Manyak MJ, Hinkle GH, Olsen JO, Chiacchierini RP, Partin AW, Piantadosi S et al. Immunoscintigraphy with ^{111}In-capromab pendetide: evaluation before definitive therapy in patients with prostate cancer. *Urology* 1999;54:1058-1063.
13. Ferguson JK, Oesterling JE. Patient evaluation if prostate-specific antigen becomes elevated following radical prostatectomy or radiation therapy. *Urol Clin North Am* 1994;21:677-685.
14. Platt JF, Bree RL, Schwab RE. The accuracy of CT in the staging of cancer of the prostate. *Am J Radiol* 1987;149:315-320.
15. Purohit RS, Shinohara K, Meng MV, Carroll PR. Imaging clinically localized prostate cancer. *Urol Clin North Am* 2003;30:279-293.
16. Lauenstein TC, Goehde SC, Herborn CU, Goyen M, Oberhoff C, Debatin JF et al. Whole-body MR imaging: evaluation of patients for metastases. *Radiology* 2004;233:139-148.
17. Weissleder R, Elizondo G, Wittenberg J, Lee AS, Josephson L, Brady TJ. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymph nodes with MR imaging. *Radiology* 1990;175:494-498.
18. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003;348:2491-2499.
19. McLaughlin AP, Saltzstein SL, McCullough DL, Gittes RF. Prostatic carcinoma: incidence and location of unsuspected lymphatic metastases. *J Urol* 1976;115:89-94.
20. Golimbu M, Morales P, Al-Askari S, Brown J. Extended pelvic lymphadenectomy for prostate cancer. *J Urol* 1979;121:617-620.
21. Hain SF, Maisey MN. Positron emission tomography for urological tumours. *BJU Int* 2003;92:159-164.
22. Shvarts O, Han KR, Seltzer M, Pantuck AJ, Belldegrun AS. Positron emission tomography in urologic oncology. *Cancer Control* 2002;9:335-342.
23. Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. *Sem Nucl Med* 2004;34:274-292.
24. Larson SM, Morris M, Gunther I, Beattie B, Humm JL, Akhurst TA et al. Tumor localization of 16beta-18F-fluoro-5alpha-dihydrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. *J Nucl Med* 2004;45:366-373.
25. de Jong IJ, Pruim J, Elsinga PH, Vaalburg W, Mensink HJ. Preoperative staging of pelvic lymph nodes in prostate cancer by 11C-choline PET. *J Nucl Med* 2003;44:331-335.
26. Horoszewicz JS, Kawinski F, Murphy GP. Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients. *Anticancer Res* 1987;7:927-935.
27. Israeli RS, Powell CT, Fair WR, Heston WD. Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen. *Cancer Res* 1993;53:227-230.
28. Wright GL Jr, Grob BM, Haley C, Grossman K, Newhall K, Petrylak D et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. *Urology* 1996;48:326-334.
29. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res* 1997;3:81-85.
30. Rochon YP, Horoszewicz JS, Boynton AL, Holmes EH, Barren RJ 3rd, Erickson SJ et al. Western blot assay for prostate-specific membrane antigen in serum of prostate cancer patients. *Prostate* 1994;25:219-223.
31. Troyer JK, Beckett ML, Wright GL Jr. Location of prostate-specific membrane antigen in the LNCaP prostate carcinoma cell line. *Prostate* 1997;30:232-242.
32. Smith-Jones P, Vallabhajosula S, Navarro V, Bastidas D, Goldsmith SJ, Bander NH. Radiolabeled monoclonal antibodies specific to the extracellular domain of prostate-specific membrane antigen: preclinical studies in nude mice bearing LNCaP human prostate tumor. *J Nucl Med* 2003;44:610-617.
33. Barren RJ, Holmes EH, Boynton AL, Misrock SL, Murphy GP. Monoclonal antibody 7E11.C5 staining of viable LNCaP cells. *Prostate* 1997;30:232-242.
34. Hinkle GH, Burgers JK, Neal CE, Texter JH, Kahn D, Williams RD, et al. Multicenter radioimmunoscintigraphic evaluation of patients with prostate carcinoma using indium-111 capromab pendetide. *Cancer* 1998;83:739-747.
35. Sodee DB, Nelson AD, Faulhaber PF, Maclennan GT, Resnick MI, Bakale G. Update on fused capromab pendetide imaging of prostate cancer. *Clin Prostate Cancer* 2005;3:230-238.
36. Schettino CJ, Kramer E, Noz M, Taneja S, Padmanabhan P, Lepor H. Impact of fusion of Indium-111 capromab pendetide volume data sets with those from MRI or CT in patients with recurrent prostate cancer. *AJR* 2004;183:519-524.
37. Wong TZ, Turkington TG, Polascik TJ, Coleman RE. ProstaScint (capromab pendetide) imaging using hybrid gamma camera-CT technology. *Am J Roentgenol* 2005;184: 676-680.
38. Ross JS, Sheehan CE, Fisher HA, Kaufman RP Jr, Kaur P, Gray K et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res* 2003;9:6357-6362.
39. Perner S, Hofer MD, Kim R et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. *Hum Pathol* 2007;38:696-701.
40. Ellis RJ, Kim EY, Conant R, Sodee DB, Spirnak JP, Dinchman KH et al. Radioimmunoguided imaging of prostate cancer foci with histopathological correlation. *Int J Radiat Oncol Biol Phys* 2001;1281-1286.
41. Saitoh H, Yoshida K, Uchijima Y et al. Two different lymph node metastatic patterns of a prostate cancer. *Cancer* 1990;65:1843-1846.
42. Ellis RJ, Kim EY, Zhou H et al. Biochemical disease-free survival rates following definitive low-dose-rate prostate brachytherapy with dose escalation to biologic target volumes identified with SPECT/CT capromab pendetide. *Brachytherapy* 2007;6:16-25.
43. Haseman MK, Kipper SL, Resenthal SA, Trout JR, Manyak MJ. Central abdominal uptake of IN-111 capromab pendetide (ProstaScint) predicts poor prognosis for patients with prostate cancer. *Urology* 2007;70:303-308.
44. Kahn D, Williams RD, Manyak MJ, Haseman MK, Seldin DW, Libertino JA et al. 111Indium-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy. The ProstaScint Study Group. J Urol 1998;159:2041-2046.
45. Kahn D, Williams RD, Haseman MK, Reed NL, Miller SJ, Gerstbrein J. Radioimmunoscintigraphy with In-111-labeled capromab pendetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. *J Clin Oncol* 1998;161:284-289.
46. Thomas CT, Bradshaw PT, Pollock BH, Montie JE, Taylor JM, Thames HD et al. Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. *J Clin Oncol* 2003;21:1715-1721.
47. Wilkinson S, Chodak G. The role of 111indium-capromab pendetide imaging for assessing biochemical failure after radical prostatectomy. *J Urol* 2004;172:133-136.

48. Jani AB, Blend MJ, Hamilton R, Brendler C, Pelizzari C, Krauz L et al. Radioimmunoscintigraphy for postprostatectomy radiotherapy: analysis of toxicity and biochemical control. *J Nucl Med* 2004;45:1315-1322.
49. Parker C, Milosevic M, Toi A, Sweet J, Panzarella T, Bristow R, Catton C, Catton P, Crook J, Gospodarowicz M, McLean M, Warde P, Hill RP. Polarographic electrode study of tumor oxygenation in clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:750-757.
50. Krishna MC, English S, Yamada K, Yoo J, Murugesan R, Devasahayam N, Cook JA, Golman K, Ardenkjaer-Larsen JH, Subramanian S, Mitchell JB. Overhauser enhanced magnetic resonance imaging for tumor oximetry: coregistration of tumor anatomy and tissue oxygen concentration. *Proc Natl Acad Sci USA* 2002;99:2216-2221.
51. Zhao D, Ran S, Constantinescu A, Hahn EW, Mason RP. Tumor oxygen dynamics: correlation of in vivo MRI with histological findings. *Neoplasia* 2003;5:308-318.
52. Feldchtein FI, Gelikonov GV, Gelikonov VM et al. Endoscopic applications of optical coherence tomography. *Optics Express* 1998;3:257-260.
53. Manyak MJ, Warner JW. An update on laser use in Urology. *Contemporary Urology* 2003;15:13-28.
54. Tearney GJ, Brezinski ME, Southern JF, Bouma BE, Boppart SA, Fujimoto JG. Optical biopsy in human Urologic tissue using optical coherence tomography. *J Urol* 1997;157:1915-1919.
55. Manyak MJ, Gladkova ND, Makari JH, Schwartz AS, Zagaynova EV, Zolfaghari L, Zara JM, Iksanov R, Feldchtein FI. Evaluation of superficial bladder transitional cell carcinoma by optical coherence tomography. *J Endourol* 2005;19:570-574.
56. Ritter EM, Kindelan TW, Michael C et al. Concurrent validity of augmented reality metrics applied to the fundamentals of laparoscopic surgery (FLS). *Surg Endosc* 2007;21:1441-1445.

Current management of small renal masses

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The incidence of small renal masses (< 4 cm) is increasing due to the widespread use of imaging studies. Many of these incidental lesions may remain asymptomatic or in fact be benign, and recent insight into their natural course has contributed to modifications in management. With improvements in biopsy technique and minimally invasive technologies, appropriate diagnosis and treatment of these masses are further being evaluated. Other contemporary approaches, including surveillance, laparoscopic partial nephrectomy, enucleation, ablative procedures, and high-intensity focused ultrasound, are weighed against open nephron-sparing surgery, the current gold standard for treatment. Here, we review currently available data on the efficacy of these treatment options. Additionally, we examine the natural history of small renal masses, the role of diagnostic biopsy, and follow-up strategies for proper management.

Key Words: renal cell carcinoma, nephron-sparing, nephrectomy, minimally invasive, ablation, diathermy, cryosurgery, enucleation, biopsy

Introduction

In 2007, there will be an estimated 51190 new cases of renal carcinomas in the United States amounting to 12890 deaths.[1] Since 1950, the incidence of renal cell carcinoma (RCC) has increased 126%,[2] while 5-year survival rates have risen from 51% in 1975 to 66% in 2002.[1] Extensive use of enhanced imaging modalities may attribute to the increased incidence and likely account for concomitant rises in the detection of small renal masses.

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Within a broad range of treatment options, diagnosis and management of these incidental findings can be challenging for several reasons. First, the majority of these masses are asymptomatic and the natural history has not been examined until recently. Second, since imaging is often unable to characterize these small masses and up to 40% are benign, the role of biopsy is being reconsidered. Third, the improvement of minimally invasive techniques provides options for patients potentially unsuitable for surgical intervention.

For accessible T1a tumors, nephron-sparing surgery (NSS) is now considered the standard of care. This method was initially reserved for imperative implications such as bilateral renal masses or tumor in solitary kidneys, but cancer control is now shown to be

equivalent to that of radical nephrectomy for tumors < 4 cm. Preservation of functional parenchyma, particularly with the 2%-3% risk of bilateral RCC, mandates the use of NSS when technically feasible. Yet recent data show that most small renal tumors are still being managed with removal of the entire kidney.[3,4] In settings of underutilization, especially in non-teaching and low-volume hospitals, treatment policies should be carefully reexamined. In this article we summarize the current management of small renal masses, including their natural history, a role for diagnostic biopsies, treatment options, and follow-up strategies.

The natural history

The emergence of active surveillance as an initial treatment option for select patients has helped to define the natural history of small renal masses. This characterization is important in determining biological behavior of the mass and necessity for intervention. Newer studies, although small and with short follow-up, are consistent in revealing an association of smaller renal masses with less metastatic risk and slower growth rates. Average growth rates of small renal masses are reported from 0.10 cm/year to 0.54 cm/year.[5-11]

The natural progression of incidentally detected small RCCs was examined by Kato et al.[11] Eighteen patients were initially observed for a median of 22.5 months prior to surgical removal. A mean tumor growth rate of 0.42 cm/year was noted, with grade 3 tumors growing significantly faster than grade 2 lesions (0.93 cm/year versus 0.28 cm/year). No significant difference in growth rate was observed between grades 2 and 1 (0.37 cm/year). As in other studies, growth rate was found to correlate with histological grade and apoptosis, as indicated by a positive TUNEL ratio.[12,13] A few prospective studies evaluating the natural history during active surveillance also conclude small renal masses grow relatively slowly.[14-16] Moreover, smaller tumor size is more likely to reflect benign etiology, but if malignant, associated with low grade and increased survival.[17] Therefore, assessing growth rate, as well as absolute size, may be helpful in managing small tumors.

The role of biopsy

Historically, a role for renal mass biopsy was limited, as over 90% were considered to be malignant and require removal. However, because up to 40% of small masses detected incidentally via imaging are in fact benign and many malignant tumors are indolent, a role for biopsy has rationale to potentially avoid unnecessary surgery.[18,19] However, biopsy also carries the possible risk of seeding, bleeding and infection, as well as substantial sampling error. In the past, these issues have raised concern as to whether biopsy is safe and useful prior to surgery. Today, the availability of newer treatment options and advances in diagnostic modalities such as imaging, interventional approaches, and cytologic techniques has led to a more useful role of biopsy in the management of small renal masses.

In a recent study, Neuzillet et al demonstrated that percutaneous fine needle biopsy for small renal masses can be performed with accuracy and low morbidity in an outpatient setting.[20] Eighty-eight patients with solid renal masses < 4 cm were biopsied with an 18-gauge core needle under CT guidance. Three biopsies were inadequately sampled and five were considered inconclusive due to fibrosis. Fourteen patients (15.9%) were found to have benign lesions, and biopsy results changed the management in 42 patients (47.8%). Biopsy had a reported accuracy of 92% in detecting histopathological tumor type and 69.8% in determining tumor grade, though no tumor was incorrectly graded by more than one point. Others have reported similar success rates,[18,21] degree of impact on treatment decision,[18,22] and high specificity in grading.[23-25]

Evidence supports a greater role for biopsy of small renal masses, and its use should be tailored to individual patients. For example, biopsy may be helpful in patients with metastatic disease or possible lymphoma by providing a definitive diagnosis, especially for inclusion in a clinical trial. On the other hand, lesions highly suspicious for malignancy on imaging and clinically appropriate for resection can forgo biopsy.

Treatment options

Surveillance

Based upon tumor size and grade, renal cancer may present as clinically insignificant disease and therefore never necessitate curative treatment within a patient's lifetime. This may especially apply to older patients. The greatest rise in incidence of small tumors presents in patients older than 70 years who quite often have concerning comorbidities.[26] Favorable results may be achieved with small renal tumors simply by providing active surveillance and intervention if necessary; still, strict observation is warranted since not all lesions remain indolent.[10,11] Some suggest that these tumors tend to grow slowly and the period of time from discovery to intervention may be wide enough to

warrant observation without adversely affecting the chance for cure.[27,28]

Kouba et al examined 43 patients with Bosniak IV renal masses on a watchful waiting protocol due to patient choice or comorbidity.[26] At a mean follow-up of 35.8 months, 74% of patients had an increase in tumor size (median 0.35 cm/year). Delayed intervention did not result in upstaging from initial pT1 in any of the 13 patients who underwent surgical removal, including those with rapidly growing tumors, and no patient experienced significant symptoms, disease progression, or cancer-specific mortality. Age ≤ 60 years strongly predicted for rapid growth rate and 13% of patients not undergoing definitive treatment died of unspecified causes other than RCC. These findings promote the use of surveillance in selected patients, especially the elderly and those at higher risk for mortality from other comorbidities. Indication for treatment intervention, including growth rate, absolute tumor size, and symptomatic progression, remains to be defined in clinical practice, and studies with longer follow-up would additionally confirm oncologic outcomes.

Open partial nephrectomy

Irrespective of a clinical indication to preserve renal function, open partial nephrectomy (OPN) is the established approach for localized renal tumors, setting the standard for comparison of newer minimally invasive techniques. Data from major cancer centers indicate elective NSS is analogous in providing curative treatment for single, localized tumors < 4 cm in diameter.[29-31] Not only has NSS proven to maintain equivalent efficacy, morbidity, and mortality rates in comparison with radical nephrectomy, but this approach has also been associated with a lower risk of developing renal insufficiency.[32-34] In reviewing open NSS results from nine comparative studies of 1262 patients,[30,31,35-41] Novick et al reported 88%-97.5% mean cancer-specific survival with a follow-up of 4-6 years,[42] Table 1. For tumors ≤ 4 cm, Fergany et al report cancer-specific survival rates of 98% and 92% at 5 and 10 years in their analysis of 107 patients undergoing OPN at the Cleveland Clinic.[43] Others have reported similar survival rates.[44] It should be noted that the appeal of minimally invasive procedures should not prompt the use of laparoscopic RN in lieu of NSS, since it does not replace the treatment objective.

Laparoscopic partial nephrectomy

Though OPN remains the standard of care, laparoscopic NSS is becoming more commonplace as similar outcomes have been reported. In the largest review of open versus partial nephrectomies for single, localized renal tumors, Gill et al reported on 1800 patients from three large referral centers.[45] LPN was reported to have shorter operative time, less blood loss, and shorter hospital stay, while intraoperative complications were similar to those of OPN, Table 2. Postoperative acute renal failure rates were equivalent despite increased warm ischemic time with LPN. Though patients undergoing OPN were considered to be at higher risk, 3-year cancer-specific survival rates were nearly identical in both groups with stage I disease: 99.3% and 99.2% after LPN and OPN, respectively. Similarly, Permpongkosol et al did not find any significant difference between 5-year disease-free and actuarial survival rates in 143 patients who underwent either LPN or OPN.[46] Differences between recurrence rates, metastatic occurrences, and positive surgical margins were also insignificant.

TABLE 1. **Outcome for patients undergoing nephron-sparing surgery for localized renal cell carcinoma. Adapted from Novick et al.[42]**

References	N of patients	Disease-specific survival (%)	Local recurrence (%)	Mean follow-up (months)
Moll et al[35]	142	98	1.4	34.8
Provert et al[36]	44	88	2	36
Lee et al[30]	79	96	0	40
Lemer et al[31]	185	89	5.9	44
Steinbach et al[37]	121	90	4.1	47
Hafez et al[38]	485	92	3.2	47
Barbalias et al[39]	41	97.5	7.3	39
Belldegrun et al[41]	146	93	2.7	74

TABLE 2. **Log transformed multivariate regression of select outcomes: LPN versus OPN. Adapted from Gill et al.[45]**

Covariate	Relative increase (95% CI)	p-value
Warm ischemia time	1.69 (1.62, 1.77)	< 0.0001
Operative time	0.78 (0.75, 0.81)	< 0.0001
Hospital stay	0.59 (0.56, 0.61)	< 0.0001
Intraop estimated blood loss	0.80 (0.74, 0.83)	< 0.0001

On the other hand, inexperience and technical difficulties with this approach may lead to increased morbidity. The former multicenter analysis also demonstrated significant increases in laparoscopic postoperative complications, especially urological, as well as increased incidence of postoperative hemorrhage and consequential procedures.[45] Other reports have revealed less morbidity, reduced narcotic use, and faster convalescence with laparoscopic techniques.[46-48] LPN may therefore only be appropriate under the care of an experienced surgeon, and efforts to refine techniques should persist.

Simple enucleation

Simple enucleation of small renal tumors, as elective NSS, allows for maximum preservation of renal parenchyma and a lower incidence of major bleeding and collecting system damage, thereby theoretically decreasing the incidence of complications such as urinoma and urinary fistula.[49] Despite these advantages, simple enucleation is not widely used because of the questionable adequacy of the thin 1-mm tumor margin. Traditional practice has been to excise a 1-cm margin of normal appearing parenchyma to prevent local recurrence, but current data demonstrate that narrower margins may be sufficient for low-stage RCC.[50] Additional studies indicate that margin width does not correlate with disease progression if complete excision is accomplished,[50-52] and the rate of disease recurrence with enucleation is reportedly similar to that in NSS.[49,53]

Carini et al reported the results of a retrospective analysis of 232 patients who underwent simple enucleation for T1a RCC followed for a mean of 76 months.[53] Five and 10-year cancer-specific survival rates were 96.7% and 94.7%, and progression-free survival rates were 96% and 94%, respectively. Approximately five percent of patients had blood loss requiring transfusion, 2.6% had prolonged urinary leakage requiring JJ stent insertion, and one patient developed a urinoma requiring aspiration, drainage, and a JJ stent. Overall, five patients experienced local recurrence, three of whom had tumor multifocality, and eight others were found to have metastatic progression. In all patients, the tumor was enucleated without excising an additional rim of normal tissue. These data are similar to others and comparable to those of nephrectomy with respect to postoperative complications, subsequent intervention, local recurrence rates, and survival outcomes.[44,54] Simple enucleation using a minimal margin of normal tissue may therefore be a safe and adequate approach for elective NSS.

Cryoablation

Renal tumor ablation is the least invasive treatment currently available and one form is cryoablation, which uses a liquid nitrogen-cooled cryoprobe to ablate normal and cancerous tissues at temperatures of -40ºC. Though histological proof of complete tumor eradication is not possible with this method, the ability to achieve real-time ultrasound imaging allows for precise targeting and ablation. Biopsy offers tissue sampling at lesion borders but may not provide an adequate assessment of lesion margins.

Deployment of cryoprobes can be accomplished either laparoscopically (LCA) or percutaneously (PCA). In a recent abstract, Landman et al compared the efficacy and complications of these two approaches.[55] Of the 53 patients who underwent PCA, 13.5% had minor complications; of the 35 patients treated with LCA, of which there were more anterior tumors, 11.4% experienced complications, including two major complications and one death. The LCA group also had increased EBL requiring transfusion. At a mean follow-up of 7 months, no recurrences were detected after LCA, while a 3.8% recurrence rate was demonstrated in the PCA group at 16 months. The authors concluded that both options appear to be viable, and although LCA was associated with a higher complication rate, it may prove to be more effective. Moreover, this approach may be most suitable for hilar or anterior tumors that pose considerable risk when accessed percutaneously.[56] Further intermediate data on the safety and efficacy of laparoscopic cryoablation are promising,[56,57] Table 3.

TABLE 3. **Select outcomes at 3-year follow-up in patients undergoing cryoablation**

Reference	N patients	Reduction in lesion size (%)	Undetectable lesions (%)	Local recurrence (%)	Cancer-specific survival (%)
Gill et al[57]	56	75	38	3.6	98*
Weld et al[56]	31	71	42	3.2	100

*in 51 patients who had a unilateral sporadic renal tumor

Analyses with longer follow-up will further define the role of cryosurgery in treating small renal neoplasms.

Radio frequency ablation

Radio frequency ablation (RFA) is an alternative ablative technique also under investigation, specifically in patients unsuitable for definitive nephrectomy. RFA approaches can be quite varied and allow for creativity within individualized treatment. Percutaneous means may not be suitable for certain tumors, namely those located in the left upper pole owing to splenic interference, those near the hilum due to heat sink, and those in the right upper pole adjacent the liver. A successful percutaneous transhepatic technique has been described in the literature by McGahan et al.[58] Using color ultrasonography, they were able to identify lesions and avoid hepatic and renal vessels without complications in four medically unstable or elderly patients unsuitable for prone positioning.

As tissue is not routinely acquired for analysis post-treatment, imaging every 3-6 months has been employed to measure successful tumor destruction. No evidence of growth, as well as < 10 HU contrast enhancement on CT or no qualitative evidence of enhancement with IV gadolinium on MRI, has implied cancer control. However, the adequacy of imaging surveillance is questionable. In a recent examination of 37 patients who underwent RFA, biopsy at 6 months was negative in only 64.8%, and nearly half the patients who had positive results had no enhancement on MRI.[59] In comparison, 97 cryoablated tumors revealed a 93.8% negative biopsy rate at 6 months with 100% of

TABLE 4. **Percutaneous RFA: initial outcomes. Adapted from Cambio and Evans.[66]**

Reference	N tumors	Mean tumor size (cm)	Complete tumor ablation, n/N (%)	Mean follow-up (months)	Complications
McDougal et al[60]	20	3.2	19/20 (95) with one session	55.2	One perinephric hematoma.
Merkle et al[61]	18	5.3 (cm^2)	16/18 (89)	16.1	Information not available.
Gervais et al[62]	42	3.2	36/42 (86)	13.2	One minor hemorrhage, two major hemorrhages + one ureteric stricture.
Su et al[63]	35	2.2	33/35 (94); Two patients required retreatment for residual enhancement on follow-up CT	9	Burn injury to liver. Resolved without further sequelae. Small asymptomatic perirenal hematomas identified in 8 patients by CT immediately after RFA, none required blood transfusion.
Pavlovich et al[64]	24	2.4	24/24	2	No major complications.
Ogan et al[65]	13	2.4	12/13, one tumor with persistent enhancing rim on CT	4.9	No major complications. One patient developed small perinephric hematoma that resolved without intervention.

positive biopsies demonstrating enhancement. These findings suggest that enhancement may not be an acceptable surrogate form of assessment and, although patients were not randomized to receive a specific treatment, RFA is potentially inferior to cryoablation. Only for high-risk patients in the setting of an IRB protocol do the authors recommended RFA with a follow-up protocol including biopsy.

Table 4 presents data from six studies reporting outcomes with RFA.[60-66] As with other novel therapies for the small renal mass, RFA will require larger studies to better define the indications and contraindications to ablative technologies. Furthermore, delivery of RF energy, including the method used, number of probes and duration of treatment, require further study to produce uniform results.[67]

Microwave thermal ablation

Microwave thermal ablation (MTA) is a new approach with potential advantages of technical ease and marked hemostasis. While this technique is useful in both OPN and LPN, some recommend restricting its use to small exophytic renal tumors to minimize serious damage to adjacent structures.[68,69]

Terai et al report on 19 patients who underwent laparoscopic MTA without renal pedicle clamping for tumors 1.1 cm-4.5 cm.[68] Mean operative duration was 240 minutes, with minimal blood loss in 14 patients and 100 ml-400 ml in four. One case was converted to an open procedure because of perirenal adhesions. No local or distant recurrence was observed by imaging at a median follow-up of 19 months. Complications included urine leakage, arteriovenous fistula, and renal pelvic stenosis. Others report similar, but rare, complications, most involving tumors located near the renal pelvis or hilum.[70-72]

High intensity focused ultrasound

A noninvasive, experimental approach to renal tumors is HIFU, which induces a well-defined area of coagulation necrosis by extracorporeally applying targeted ultrasound energy.[73] Theoretically, HIFU offers minimal procedure time, morbidity, and faster time to recovery. Investigational studies have demonstrated principle viability and safety of HIFU for renal lesions.[74-77] However, clinical studies are limited, and no substantial comparative results are available thus far.

A phase II clinical trial reported treating a total of 16 patients with HIFU.[76] Histological signs of tissue necrosis were identified in nine of the 14 surgically excised kidneys, and no significant side-effects were noted. One of the two tumors treated with curative intent exhibited a moderate reduction in size on MRI at 12 months. A similar phase II trial reported histological changes of thermal injury in 15 of 19 treated kidneys, though effects were variable and did not correspond to the intensity of treatment.[77]

Determining successful tumor destruction and appropriate follow-up are challenges with HIFU. Though the kidney is nicely imaged by ultrasonography, its two-dimensional nature, respiratory motion, and poor resolution present intraoperative limitations. Moreover, overlaying ribs absorb HIFU energy, making certain tumors difficult to ablate.[73] Duplex Doppler ultrasonography, CT and MRI are other methods currently under development for this application. Major technical improvements are mandatory to enable this technology as an effective treatment option for patients with small renal masses.

Follow-up

While NSS is clearly advantageous in preserving renal tissue, monitoring for recurrence is important. Local and metastatic recurrence rates after partial nephrectomy rise with increasing stage, reportedly 0%, 2%, 8.3% and 10.6%, and 4.4%, 5.3%, 11.5% and 14.9% for pathological stages T1, T2, T3a and T3bN0M0, respectively.[29] Surveillance guidelines are mandatory to adequately follow patients with different stage tumors. Table 5 presents such guidelines for localized RCC after partial nephrectomy.[78]

TABLE 5. **Guidelines for surveillance of localized RCC after partial nephrectomy. Adapted from Evans.[78]**

Pathological stage	Guidelines for surveillance
pT1-2 N0M0	Annual history, physical, systems review, chest radiograph, chem-20, complete blood count and urine analysis Abdominal CT or renal ultrasonography every 2 years
pT3N0M0	History, physical, systems review, chest radiograph, chem-20, complete blood count and urine analysis every 6 months for 2 years, then every 2 years Abdominal CT or renal ultrasonography every 6 months for 2 years, then every 2 years

Among nephron-sparing methods, only OPN, simple enucleation and LPN allow the tumor to be excised with margins that can be clearly reviewed by a pathologist. Therefore, imaging is used to follow ablative and HIFU techniques, with lack of enhancement or growth implying cancer control. Choice of imaging modality in addition to surveillance protocols after non-surgical techniques have yet to be determined.

Summary

In the absence of randomized studies, retrospective series of OPN from large-volume centers have set the standard intervention for small (< 4 cm), single, localized renal tumors. Among skilled laparoscopic surgeons, LPN is considered an equivalent option. With added insight to the natural history of small renal tumors, there now exists a role for observation, especially for non-surgical patients who have a short life expectancy and those with clinically insignificant, biopsy-proven low-grade lesions. Other minimally invasive techniques are also gaining acceptance, but have not replaced partial nephrectomy due to undetermined long-term outcomes. Possible indications need to be further examined, but may include poor surgical candidates with comorbidities, a ≥ 2-5 year life expectancy, biopsy-proven low grade disease, or those on protocol; von Hippel-Lindau lesions; and multifocal tumors ≤ 4 cm. As with all new techniques, validation requires large, uniform trials with long-term follow-up demonstrating decreased morbidity and outcomes equivalent to open partial nephrectomy. Figure 1 shows a decision tree, which proposes a model of the various treatment methods for managing small renal tumors.

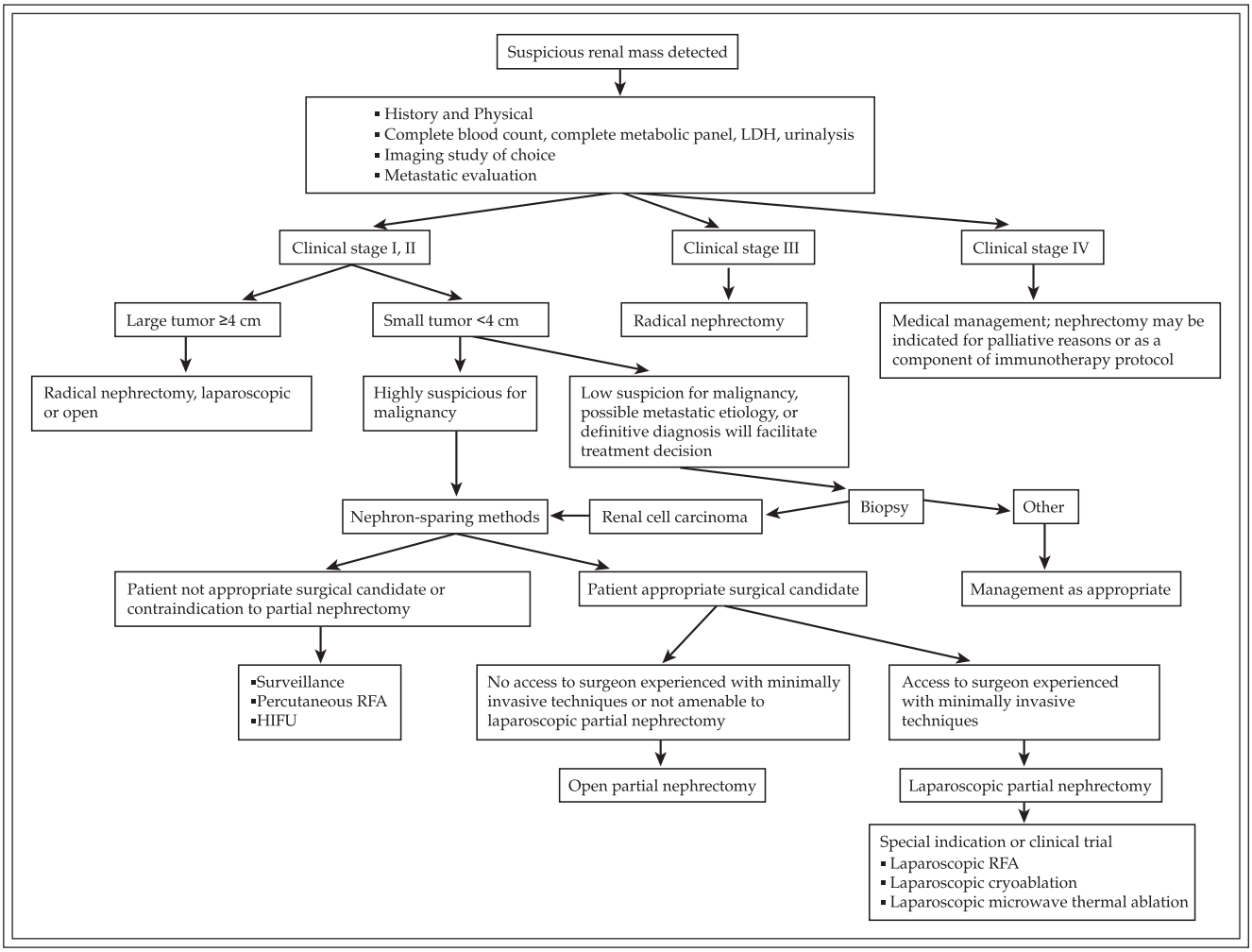

Figure 1. Decision tree for managing small renal tumors, assuming normal contralateral kidney. Adapted from Cambio and Evans, Copyright 2006 American Cancer Society.[66] This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Disclosure

Dr. Christopher Evans is a member of the Speakers' Bureau for Boehringer Ingelheim. He is on the advisory board for Boehringer Ingelheim and Astra Zeneca and an investigator for Astra Zeneca. □

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57(1):43-66.
2. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. *J Urol* 2001;166(5):1611-1623.
3. Miller DC, Hollingsworth JM, Hafez KS, Daignault S, Hollenbeck BK. Partial Nephrectomy for Small Renal Masses: An Emerging Quality of Care Concern? *J Urol* 2006;175(3):853-858.
4. Hollenbeck BK, Taub DA, Miller DC, Dunn RL, Wei JT. National utilization trends of partial nephrectomy for renal cell carcinoma: a case of underutilization? *Urology* 2006;67(2):254-259.
5. Fujimoto N, Sugita A, Terasawa Y, Kato M. Observations on the growth rate of renal cell carcinoma. *Int J Urol* 1995;2(2):71-76.
6. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: further observations on growth. *Radiology* 1995;197(3):589-597.
7. Oda T, Miyao N, Takahashi A, Yanase M, Masumori N, Itoh N et al. Growth rates of primary and metastatic lesions of renal cell carcinoma. *Int J Urol* 2001;8(9):473-477.
8. Kassouf W, Aprikian AG, Laplante M, Tanguay S. Natural history of renal masses followed expectantly. *J Urol* 2004;171(1):111-113; discussion 113.
9. Wehle MJ, Thiel DD, Petrou SP, Young PR, Frank I, Karsteadt N. Conservative management of incidental contrast-enhancing renal masses as safe alternative to invasive therapy. *Urology* 2004;64(1):49-52.
10. Rendon RA, Stanietzky N, Panzarella T, Robinette M, Klotz LH, Thurston W et al. The natural history of small renal masses. *J Urol* 2000;164(4):1143-1147.
11. Kato M, Suzuki T, Suzuki Y, Terasawa Y, Sasano H, Arai Y. Natural history of small renal cell carcinoma: evaluation of growth rate, histological grade, cell proliferation and apoptosis. *J Urol* 2004;172(3):863-866.
12. Todd D, Yang G, Brown RW, Cao J, D'Agati V, Thompson TS et al. Apoptosis in renal cell carcinoma: detection by in situ end-labeling of fragmented DNA and correlation with other prognostic factors. *Hum Pathol* 1996;27(10):1012-1017.
13. Zhang X, Takenaka I. Cell proliferation and apoptosis with BCL-2 expression in renal cell carcinoma. *Urology* 2000;56(3):510-515.
14. Volpe A, Panzarella T, Rendon RA, Haider MA, Kondylis FI, Jewett MA. The natural history of incidentally detected small renal masses. *Cancer* 2004;100(4):738-745.
15. Lamb GWA, Bromwich EJ, Vasey P, Aitchison M. Management of renal masses in patients medically unsuitable for nephrectomy—natural history, complications, and outcome. *Urology* 2004;64(5):909-913.
16. Ozono S, Miyao N, Igarashi T, Marumo K, Nakazawa H, Fukuda M et al. Tumor Doubling Time of Renal Cell Carcinoma Measured by CT: Collaboration of Japanese Society of Renal Cancer. *Jpn J Clin Oncol* 2004;34(2):82-85.
17. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising Incidence of Small Renal Masses: A Need to Reassess Treatment Effect. *J Natl Cancer Inst* 2006;98(18):1331-1334.
18. Maturen KE, Nghiem HV, Caoili EM, Higgins EG, Wolf JS, Jr., Wood DP, Jr. Renal mass core biopsy: accuracy and impact on clinical management. *AJR Am J Roentgenol* 2007;188(2):563-570.
19. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol* 2003;170(6 Pt 1):2217-2220.
20. Neuzillet Y, Lechevallier E, Andre M, Daniel L, Coulange C. Accuracy and Clinical Role of Fine Needle Percutaneous Biopsy With Computerized Tomography Guidance of Small (Less Than 4.0 Cm) Renal Masses. *J Urol* 2004;171(5):1802-1805.
21. Imaide Y, Saitoh M. Clinical implication of selective renal tumor biopsy. *Hinyokika Kiyo* 1995;41(9):745-752.
22. Wood BJ, Khan MA, McGovern F, Harisinghani M, Hahn PF, Mueller PR. Imaging guided biopsy of renal masses: indications, accuracy and impact on clinical management. *J Urol* 1999;161(5):1470-1474.
23. Herts BR, Baker ME. The current role of percutaneous biopsy in the evaluation of renal masses. *Semin Urol Oncol* 1995;13(4):254-261.
24. Cajulis RS, Katz RL, Dekmezian R, el-Naggar A, Ro JY. Fine needle aspiration biopsy of renal cell carcinoma. Cytologic parameters and their concordance with histology and flow cytometric data. *Acta Cytol* 1993;37(3):367-372.
25. Lechevallier E, Andre M, Barriol D, Daniel L, Eghazarian C, De Fromont M et al. Fine-Needle Percutaneous Biopsy of Renal Masses with Helical CT Guidance. *Radiology* 2000;216(2):506-510.
26. Kouba E, Smith A, McRackan D, Wallen EM, Pruthi RS. Watchful Waiting for Solid Renal Masses: Insight Into the Natural History and Results of Delayed Intervention. *J Urol* 2007;177(2):466-470.
27. Siu W, Hafez KS, Johnston Iii WK, Wolf JJS. Growth rates of renal cell carcinoma and oncocytoma under surveillance are similar. *Urol Oncol* 2007;25(2):115-119.
28. Wolf JS, Jr, Hollenbeck BK. A plea for judicious treatment of small renal masses. *Urol Oncol* 2007;25(4):281-283.
29. Hafez KS, Novick AC, Butler BP. Management of small solitary unilateral renal cell carcinomas: impact of central versus peripheral tumor location. *J Urol* 1998;159(4):1156-1160.
30. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. *J Urol* 2000;163(3):730-736.
31. Lerner SE, Hawkins CA, Blute ML, Grabner A, Wollan PC, Eickholt JT et al. Disease outcome in patients with low stage renal cell carcinoma treated with nephron sparing or radical surgery. 1996. *J Urol* 2002;167(2 Pt 2):884-889; discussion 889-890.
32. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000;75(12):1236-1242.
33. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002;59(6):816-820.
34. Blute ML. Nephron-sparing surgery: the 'gold standard' treatment for small renal cortical tumors. *Nat Clin Pract Urol* 2007;4(6):300-301.
35. Moll V, Becht E, Ziegler M. Kidney preserving surgery in renal cell tumors: indications, techniques and results in 152 patients. *J Urol* 1993;150(2 Pt 1):319-323.
36. Provet J, Tessler A, Brown J, Golimbu M, Bosniak M, Morales P. Partial nephrectomy for renal cell carcinoma: indications, results and implications. *J Urol* 1991;145(3):472-476.
37. Steinbach F, Stockle M, Hohenfellner R. Clinical experience with nephron-sparing surgery in the presence of a normal contralateral kidney. *Semin Urol Oncol* 1995;13(4):288-291.
38. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival, tumor recurrence and TNM staging. *J Urol* 1999;162(6):1930-1933.

39. Barbalias GA, Liatsikos EN, Tsintavis A, Nikiforidis G. Adenocarcinoma of the kidney: nephron-sparing surgical approach vs. radical nephrectomy. *J Surg Oncol* 1999;72(3):156-161.
40. D'Armiento M, Damiano R, Feleppa B, Perdona S, Oriani G, De Sio M. Elective conservative surgery for renal carcinoma versus radical nephrectomy: a prospective study. *Br J Urol* 1997;79(1):15-19.
41. Belldegrun A, Tsui KH, deKernion JB, Smith RB. Efficacy of nephron-sparing surgery for renal cell carcinoma: analysis based on the new 1997 tumor-node-metastasis staging system. *J Clin Oncol* 1999;17(9):2868-2875.
42. Novick AC. Laparoscopic and Partial Nephrectomy. *Clin Can Res* 2004;10(18):6322S-6327.
43. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. *J Urol* 2000;163(2):442-445.
44. Becker F, Siemer S, Humke U, Hack M, Ziegler M, Stockle M. Elective Nephron Sparing Surgery Should Become Standard Treatment for Small Unilateral Renal Cell Carcinoma: Long-term Survival Data of 216 Patients. *Eur Urol* 2006;49(2):308-313.
45. Gill IS, Kavoussi LR, Lane BR, Blute ML, Babineau D, Colombo Jr JR et al. Comparison of 1,800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors. *J Urol* 2007;178(1):41-46.
46. Permpongkosol S, Bagga HS, Romero FR, Sroka M, Jarrett TW, Kavoussi LR. Laparoscopic Versus Open Partial Nephrectomy for the Treatment of Pathological T1N0M0 Renal Cell Carcinoma: A 5-Year Survival Rate. *J Urol* 2006;176(5):1984-1989.
47. Schiff JD, Palese M, Vaughan ED, Sosa RE, Coll D, Del Pizzo JJ. Laparoscopic vs open partial nephrectomy in consecutive patients: the Cornell experience. *BJU Int* 2005;96(6):811-814.
48. Gill IS, Matin SF, Desai MM, Kaouk JH, Steinberg A, Mascha ED et al. Comparative Analysis of Laparoscopic Versus Open Partial Nephrectomy for Renal Tumors in 200 Patients. *J Urol* 2003;170(1):64-68.
49. Lapini A, Serni S, Minervini A, Masieri L, Carini M. Progression and long-term survival after simple enucleation for the elective treatment of renal cell carcinoma: experience in 107 patients. *J Urol* 2005;174(1):57-59.
50. Sutherland SE, Resnick MI, Maclennan GT, Goldman HB. Does the size of the surgical margin in partial nephrectomy for renal cell cancer really matter? *J Urol* 2002;167(1):61-64.
51. Puppo P, Introini C, Calvi P, Naselli A. Long term results of excision of small renal cancer surrounded by a minimal layer of grossly normal parenchyma: review of 94 cases. *Eur Urol* 2004;46(4):477-481.
52. Castilla EA, Liou LS, Abrahams NA, Fergany A, Rybicki LA, Myles J et al. Prognostic importance of resection margin width after nephron-sparing surgery for renal cell carcinoma. *Urology* 2002;60(6):993-997.
53. Carini M, Minervini A, Masieri L, Lapini A, Serni S. Simple Enucleation for the Treatment of PT1a Renal Cell Carcinoma: Our 20-Year Experience. *Euro Urol* 2006;50(6):1263-1271.
54. Stephenson AJ, Hakimi AA, Snyder ME, Russo P. Complications of radical and partial nephrectomy in a large contemporary cohort. *J Urol* 2004;171(1):130-134.
55. Landman J, Lehman DS, Hruby GW, Phillips CK, Shingleton B. Efficacy and Complications of Cryoablation for Renal Masses; Percutaneous vs. Laparoscopic Ablation. *J Urol, AUA Annual Meeting* 2007;177(No. 4, Supplement):Abstract 1299.
56. Weld KJ, Figenshau RS, Venkatesh R, Bhayani SB, Ames CD, Clayman RV et al. Laparoscopic Cryoablation for Small Renal Masses: Three-Year Follow-up. *Urology* 2007;69(3):448-451.
57. Gill IS, Remer EM, Hasan WA, Strzempkowski B, Spaliviero M, Steinberg AP et al. Renal Cryoablation: outcome at 3 years. *J Urol* 2005;173(6):1903-1907.
58. McGahan JP, Ro KM, Evans CP, Ellison LM. Efficacy of Transhepatic Radiofrequency Ablation of Renal Cell Carcinoma. *AJR Am J Roentgenol* 2006;186(Suppl 5):S311-315.
59. Weight CJ, kaouk JH, Hegarty NJ, Lane BR, Remer EM, O'Malley CM et al. MRI Is Inadequate for Monitoring Renal Tumor Destruction following Radio Frequency Ablation. *J Urol, AUA Annual Meeting* 2007;177(4):Abstract 497.
60. McDougal WS, Gervais DA, McGovern FJ, Mueller PR. Long-term followup of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. *J Urol* 2005;174(1):61-63.
61. Merkle EM, Nour SG, Lewin JS. MR imaging follow-up after percutaneous radiofrequency ablation of renal cell carcinoma: findings in 18 patients during first 6 months. *Radiology* 2005;235(3):1065-1071.
62. Gervais DA, McGovern FJ, Arellano RS, McDougal WS, Mueller PR. Renal cell carcinoma: clinical experience and technical success with radio-frequency ablation of 42 tumors. *Radiology* 2003;226(2):417-424.
63. Su LM, Jarrett TW, Chan DY, Kavoussi LR, Solomon SB. Percutaneous computed tomography-guided radiofrequency ablation of renal masses in high surgical risk patients: preliminary results. *Urology* 2003;61(4 Suppl 1):26-33.
64. Pavlovich CP, Walther MM, Choyke PL, Pautler SE, Chang R, Linehan WM et al. Percutaneous radio frequency ablation of small renal tumors: initial results. *J Urol* 2002;167(1):10-15.
65. Ogan K, Jacomides L, Dolmatch BL, Rivera FJ, Dellaria MF, Josephs SC et al. Percutaneous radiofrequency ablation of renal tumors: technique, limitations, and morbidity. *Urology* 2002;60(6):954-958.
66. Cambio AJ, Evans CP. Management approaches to small renal tumours. *BJU Int* 2006;97(3):456-460.
67. Wagner AA, Solomon SB, Su LM. Treatment of renal tumors with radiofrequency ablation. *J Endourol* 2005;19(6):643-652; discussion 652-643.
68. Terai A, Ito N, Yoshimura K, Ichioka K, Kamoto T, Arai Y et al. Laparoscopic Partial Nephrectomy Using Microwave Tissue Coagulator for Small Renal Tumors: Usefulness and Complications. *Eur Urol* 2004;45(6):744-748.
69. Hirao Y, Fujimoto K, Yoshii M, Tanaka N, Hayashi Y, Momose H et al. Non-ischemic nephron-sparing surgery for small renal cell carcinoma: complete tumor enucleation using a microwave tissue coagulator. *Jpn J Clin Oncol* 2002;32(3):95-102.
70. Akiyama T, Samma S, Fujimoto K, Fukui Y, Hirayama A. Renal arteriovenous fistula developing after tumor enucleation using a microwave tissue coagulator. *Int J Urol* 2001;8(10):568-571.
71. Murota T, Kawakita M, Oguchi N, Shimada O, Danno S, Fujita I et al. Retroperitoneoscopic partial nephrectomy using microwave coagulation for small renal tumors. *Eur Urol* 2002;41(5):540-545; discussion 545.
72. Matsui Y, Fujikawa K, Iwamura H, Oka H, Fukuzawa S, Takeuchi H. Application of the microwave tissue coagulator: is it beneficial to partial nephrectomy? *Urol Int* 2002;69(1):27-32.
73. Kohrmann KU, Michel MS, Gaa J, Marlinghaus E, Alken P. High Intensity Focused Ultrasound as Noninvasive Therapy for Multilocal Renal Cell Carcinoma: Case Study and Review of The Literature. *J Urol* 2002;167(6):2397-2403.
74. Illing RO, Kennedy JE, Wu F, ter Haar GR, Protheroe AS, Friend PJ et al. The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. *Br J Cancer* 2005;93(8):890-895.
75. Wu F, Wang ZB, Chen WZ, Bai J, Zhu H, Qiao TY. Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy. *J Urol* 2003;170(6 Pt 1):2237-2240.
76. Marberger M, Schatzl G, Cranston D, Kennedy JE. Extracorporeal ablation of renal tumours with high-intensity focused ultrasound. *BJU Int* 2005;95 Suppl 2:52-55.
77. Hacker A, Michel MS, Marlinghaus E, Kohrmann KU, Alken P. Extracorporeally induced ablation of renal tissue by high-intensity focused ultrasound. *BJU Int* 2006;97(4):779-785.
78. Evans CP. Follow-up surveillance strategies for genitourinary malignancies. *Cancer* 2002;94(11):2892-2905.

Molecular targeted therapies for renal cell carcinoma

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New advances in technology to directly target specific molecular events in the proliferation of cancer have led to promising results in renal cell carcinoma. Response rates in excess of 70% and complete responses in advanced (metastatic) renal cell carcinoma have caused a change in the paradigm of treatment from immunotherapy. Toxicities are significant, but manageable and pushing the toxicity to tolerability may increase the response rate.

Key Words: renal cell carcinoma, metastatic, therapy, molecular

Introduction

Renal cell carcinoma is the sixth leading cause of cancer deaths in the United States.[1] In the past year, there were 189000 new cases in the world and over 93000 deaths. Most cases are diagnosed after the fourth decade of life and it is twice as common in men than women.

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At the time of diagnosis, the most common sites of metastases are the lungs (50%), bones (30%-40%), lymph nodes (30%-40%), liver (30%-40%), and the brain (5%). The hallmark of renal cell carcinoma is that it is well known to metastasize to many unusual sites including the pericardium, skin, and testicle. The tumor also has a tendency to have delayed recurrences after 5 years or more.

The mortality from renal cell carcinoma has been in large part due to the lack of any effective modality other than surgery for localized disease. Most chemotherapy has had only anecdotal success at best.

From the early 1980's, immunotherapy emerged as the treatment of choice for advanced renal cell carcinoma. Initial reports with interferon and later IL-2 showed modest (5%-25%) response rates, and the median survival was still less than 3 years.[2-4] Responses are most common in the lungs with significantly lower responses in the liver, lymph nodes, primary kidney, and bone. The best results with IL-2 have only 5% complete responders. A testimony to the ineffectiveness of systemic therapy in renal cell carcinoma is that Robson in 1969 showed an 11% 5-year survival, while 30 years later Javidan showed that the 5-year survival was only 20% despite the advances in immunotherapy.[5,6]

In the past 2 years, attention has been focused on the therapy targeted to the genetic mutations of renal cell carcinoma. Linehan et al discovered the VHL mutations associated with renal cell carcinoma which were expressed not only in von Hippel-Lindau, but also in familial and wild type renal cell carcinoma.[7] When this gene is inactivated by deletion or mutation, there follows a deregulation of Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF).[8,9] VEGF causes increased angiogenesis, while PDGF is expressed on pericytes that form the structural support of the newly formed vessels.[10] Transforming Growth Factor alpha (TGF-α) is also regulated by the VHL gene. TGF-α stimulates autocrine growth in the proximal tubule by acting as a ligand for Epidermal Growth Factor Receptor (EGFR). EGFR and its relatives are glycoproteins with an extracellular ligand binding domain and an intracellular tyrosine kinase domain. All tyrosine receptors are inactive until they are stimulated by a ligand which changes them from a monomer to a dimer configuration. Ligands for EGFR, for example, include EGF and TGF-α.

Tyrosine kinase inhibitors are small molecular weight proteins that compete with ATP for binding in the catalytic tyrosine kinase domain which is a component of the receptors for growth factors such as EGF and VEGF. Since these bind to receptors that are frequently expressed in tumors, the hope would be that they would be preferentially effective on tumors with little side effects.

Multikinase inhibitors

Sorafenib

Sorafenib (NEXAVAR) is a tyrosine kinase inhibitor that actually has a dual action. In addition to inhibiting VEGFR-2 and PDGF-α, which are important in vasculogenesis, sorafenib also inhibits RAF-1 which is a key enzyme in the signaling pathway for cellular proliferation (a direct anti tumor effect). Initial work was reported in a phase II discontinuation trial in colon cancer. This involved a 12-week run in of sorafenib followed by a randomization pending the responses of the first 12 weeks. Patients who initially had a > 25% shrinkage of the tumor remained on the drug while patients who had a > 25% growth of the tumor in the first 12 weeks were discontinued. Those patients who were stable (± 25%) were randomized to either placebo or continuation of the drug for an additional 24 weeks. The primary goal of the study was to look at patients with metastatic colon cancer, but secondary goals of the study were to look at other refractory solid tumors. All patients had ECOG performance statuses of 0 or 1 and all had measurable disease. Sixty-five patients with renal cell carcinoma were included in the trial (33 randomized to placebo and 32 to sorafenib). There were no significant variances between the groups in histologic subtype, MSKCC risk category, or prior therapy. At the end of the 24-week trial, there were 16 (50%) of patients in the sorafenib arm that maintained stable disease, while only 6 (18%) of the placebo arm maintained stable disease ($p = 0.0077$). The progression free survival in the sorafenib arm was 24 weeks, while the placebo arm was 6 weeks ($p = 0.0087$). In the whole study, 48% experienced grade _ toxicity of some type, with the most common being hypertension (24%) and dermatologic (15%).

The initial phase III trial in renal cell carcinoma was the TARGETS trial which compared the overall survival of patients treated with sorafenib to placebo. Eight hundred eighty four patients with clear cell histology, ECOG performance status of 0 or 1, and having failed at least one systemic therapy in the past 8 months were entered into a 1:1 randomization trial evaluating 400 mg sorafenib versus placebo. There were no significant differences in age, gender, ECOG performance status, number or site of metatastases, type of prior therapy, MSKCC risk category, or prior nephrectomy. Seventy eight percent of the sorafenib arm and 20% of the placebo arm achieved some degree of reduction of the measurable tumor. Median performance free survival for the sorafenib patients was 24 weeks versus 12 weeks for the placebo arm (hazard ratio = 0.44, $p < 0.000001$). In every category (age, ECOG performance, etc), sorafenib showed a benefit in survival. See Figure 1. Toxicities in the sorafenib arm were predominantly fatigue (18%), diarrhea (30%), and dermatologic (23%-31%). Due to the magnitude of the progression free survival effect in the sorafenib arm, the study was eventually modified to allow crossover from placebo to the sorafenib arm, though investigators remained blinded.[11]

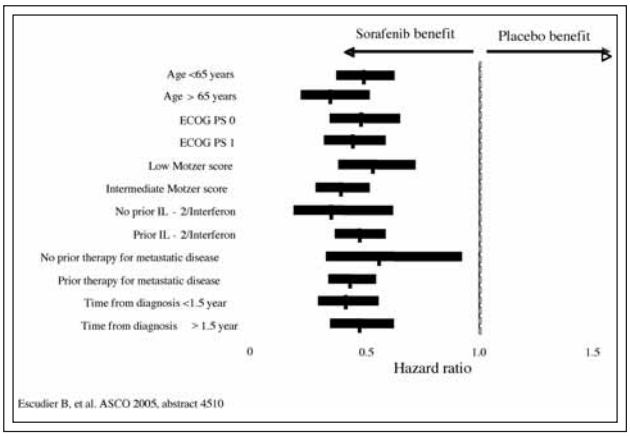

Figure 1. TARGETS trial. Progression-free survival in patient subgroups. Escudier B et al. ASCO 2005; abstract 4510.

Sorafenib was released for clinical use in December 2005 and we have used it since October 2005 initially on an investigator's trial. Our dosing schedule has been 400 mg bid 5 days on and 2 days off. Fifteen patients have been treated for metastatic renal cell carcinoma including lung, liver, nodes, bone, and pancreas. There has been no attempt to exclude patients according to histology, though the majority have been clear cell histology. Toxicities have been severe with all but one patient having at least one dose reduction for grade 3 toxicity (50% reduction). Predominant toxicities have been cutaneous including hand foot syndrome, rash, and alopecia involving all but two patients. Fatigue also had been a significant toxicity resulting in dose reduction in two patients. As patients continue to take the sorafenib, diarrhea becomes the predominant toxicity and has resulted in nearly half of the patients eventually discontinuing the medication. Currently we have two patients who had pulmonary lesions that are free of disease and off medication at 8 and 12 months from initial treatment. A third patient is currently on treatment and is NED from a metastasis to the pancreas. Four patients have had a PR and later progressed. These results exceed the reported incidence of responses, but our toxicities also exceed the reported experience suggesting that maximizing dosing to toxicity may have improve response.

Managing toxicities is clearly important in treating these patients. Hand foot syndrome is usually managed with topical agents such as Bag Balm. Generally, with time the dermatologic toxicity improves as the patient continues the treatment. Reducing or stopping sorafenib is another strategy for dermatologic toxicities, and it has been noted that when a dose reduction(s) occur, that the dose can be reescalated in time as the patient seems to develop a tolerance. Thirteen of the 14 patients who underwent dose reduction in our series were later able to reescalate their dose at least one step. GI toxicities are usually manifested as diarrhea which worsens with time. Endoscopy in these patients has shown ulceration of the colon and management includes loperamide or diphenoxylate/atropine, cholestyramine, dietary changes, or dose reduction. Grade 3 laboratory toxicities have been uncommon.

Sunitinib

Sunitinib (SUTENT) inhibits VEGFR-2 and PDGF-α, as well as other tyrosine kinases such as the type III receptor tyrosine kinase KIT encoded by the proto-oncogene c-KIT and FLT-3, a kinase expressed in the brain, placenta, primitive hematopoetic cells and found to be mutated in 30% of certain leukemias. There have been two sequentially administered single arm phase II multicenter trials reported looking at response rate, time to progression, and safety.[12,13] The first trial involved 63 patients with any renal cell histology and the second involved 106 with clear cell only. Both trials used patients who were cytokine failures and the second trial required radiographic documentation of progression and a prior nephrectomy. Patients were given 50 mg per day oral doses in repeated cycles of 4 weeks on and 2 weeks off. Dose reductions of 37.5 mg and 25 mg were allowed for grade 3/4 toxicity. Response was assessed every 1-2 cycles using the RECIST criteria. Treatments were continued until either progression of disease or inability to tolerate treatment. Overall response rates of 40% and 39% were seen in trials 1 and 2 respectively. All responses were deemed partial except 1 CR in trial 2. An additional 28% and 23% of patients achieved stable disease for ≥ 3 months. Median time to progression in trial 1 was 8.7 months. Grade 3 toxicity was observed predominantly as fatigue, GI, or dermatologic.

A phase III randomized study of 750 patients with metastatic renal cell carcinoma (clear cell histology) was carried out to compare the efficacy and safety of sunitinib versus α-interferon.[13] Patients were stratified into one of three MSKCC prognostic risk categories (favorable, intermediate, and poor). They were then randomized 1:1 to receive either sunitinib 50 mg once/day on a 4 week on/2 week off schedule (375 patients) or subcutaneous α-interferon 9 MU 3 times/week. The primary efficacy end point was progression-free survival with secondary end points as response rate (as measured by RECIST), overall survival, safety, and patient-reported outcomes (as measured by FACT-G and FACT-FKSI questionnaires). Median progression-free survival was 11 months in the sunitinib group versus 5 months in the interferon

alfa group (hazard ratio: 0.42, $p < 0.001$). Objective response rate was significantly higher in the sunitinib-treated patients than in the interferon alfa–treated patients (31%-37% versus 6%-9%, $p < 0.001$). Length of progression free survival was also longer in the sunitinib arm versus α-interferon when stratified for risk (favorable (not reached versus 8 months), intermediate (11 months versus 4) and poor risk (4 versus 1 month)groups).

Future role of multikinase inhibitors in renal cell carcinoma

Multikinase inhibitors are beginning to become the standard of care for metastatic renal cell carcinoma. There is a growing consensus that these compounds will replace cytokines as the first line treatment of patients with advanced disease. A recent case report shows that the two currently available multikinase inhibitors may be complementary with sunitinib being effective in patients who have progressed on sorafenib.[14] We currently have one patient who has progressed on sorafenib and is now responding to sunitinib. All three patients that we have switched report that their diarrhea is significantly better.

While these agents offer hope for treatment, there are caveats. One concern is that patients on multikinase inhibitors will not heal due to lack of angiogenesis, which may be problematic in patients who are having nephrectomies or other surgery after initiation of treatment with a multikinase inhibitor. There is currently no reported literature evaluating wound healing in patients on multikinase inhibitors. The second caveat is that while these drugs can be administered in a clinical setting by urologists, the toxicities can be severe and therefore these patients may be best managed by clinicians who have expertise in managing chemotherapeutic toxicities.

mTOR inhibitors

Temsirolimus

Temsirolimus (TORISEL) is a specific inhibitor of mTOR kinase, a key component of intracellular signaling involved in cell proliferation which in turn inhibits the translation of key proteins (cyclin D1, c-myc) involved in cell cycle progression (G1 growth arrest) and angiogenesis (HIF 1-alpha, HIF 2-alpha). This disruption of the signaling results in suppression of proteins that are involved in angiogenesis, making this a possible useful agent in renal cell carcinoma. Torisel was released for clinical use in May 2007 and is administered intravenously once a week (25 mg).

A three arm (1:1:1) open label clinical trial comparing temsirolimus 25 mg to α-interferon 3-18MU to temsirolimus 15 mg plus α-interferon 3-6MU was performed with a total of 626 patients with poor risk untreated metastatic renal cell carcinoma.[15] Histology was both clear cell and non clear cell renal cell carcinoma. The objectives were to compare overall survival, progression-free survival, objective response rate, and safety. All patients fulfilled at least 3/6 requirements for poor risk (LDH > 1.5 x upper limit of normal, low hemoglobin, corrected calcium > 10 mg/dl, time from diagnosis to first treatment < 1 year, performance status 60-70, or multiple sites of metastasis).

The patients in the temsirolimus arm received a median of 17 weeks of therapy while the interferon patients received a median of 8 weeks of treatment. Analysis of the data showed patients in the temsirolimus and TEMSR+IFN arms exhibited improved progression-free survival compared with the interferon arm with a median time to progression of 3.7 months versus 1.9 months ($p = 0.0001$). While temsirolimus showed an improvement in overall survival as monotherapy compared to interferon, there was no significant difference between the combination arm and interferon. Predominant grade 3 toxicities were asthenia (12%) and only 23% of patients on temsirolimus required any dose reduction.

Ligand binding agents

Bevacizumab

Bevacizumab (AVASTIN) is a monoclonal antibody directed against VEGF which binds and neutralizes the protein. It was approved by the FDA in 2004 for the treatment of carcinoma of the colon. It is generally administered on 14-day cycle intravenously. Due to its anti-VEGF activity, it has been investigated in a variety of clinical settings including renal cell carcinoma. In a phase II trial treating of 116 patients with refractory, metastatic renal cell carcinoma (histologically clear cell), patients were randomized to receive placebo, low-dose (3 mg/kg) bevacizumab, or high-dose (10 mg/kg) bevacizumab i.v. every 2 weeks.[16] Only the high dose bevacizumab arm showed any partial responses (4/39 or 10%). There was a significantly longer time to progression (TTP) in the high-dose bevacizumab arm than in the placebo arm (4.8 months versus 2.5 months; $p < .001$).

Toxicities were mild to moderate and reversible. The most common toxicity in the high dose arm was hypertension in 36% of patients (21% Grade 3).

The future for treatment of renal cell carcinoma

The treatment of metastatic renal cell carcinoma has dramatically changed in the past few years with promising agents targeting molecular pathways that are important to the growth and proliferation of renal cell carcinoma. The results show very promising response rates with acceptable toxicity. Most of these have been used as monotherapy and the opportunity to possibly use them sequentially or in combination is currently being investigated.

Disclosure

None □

References

1. Motzer RJ, Bander NM, Nanees PM. Renal-cell carcinoma. *N Engl J Med* 1996;335:865-875.
2. Krown SE. Interferon treatment of renal cell carcinoma. Current status and future prospects *Cancer* 1987;59:647-651.
3. Muss HB. The role of biological response modifiers in metastatic renal cell carcinoma *Semin Oncol* 1988;15:30-34.
4. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA* 1994;271:907-913.
5. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma *J Urol* 1969;101:297-301.
6. Javidan J, Strickler HJ, Tamboli P, Amin MB, Peabody JO, Deshpande A, Menon M. Prognostic significance of the 1997 TNM classification of renal cell carcinoma *J Urol* 1999;162:1277-1281
7. Linehan WM et al. In: *Cancer: Principles & Practice of Oncology*. 7th ed. Lippincott.
8. Zhang X, Yamashita M, Uetsuki H, Kakehi Y. Angiogenesis in renal cell carcinoma: Evaluation of microvessel density, vascular endothelial growth factor and matrix metalloproteinases. *Int J Urol* 2002;9:509-514.
9. Oka H, Chatani Y, Hoshino R, Ogawa O, Kakehi Y, Terachi T, Okada Y, Kawaichi M, Kohno M, Yoshida O Constitutive activation of mitogen-activated protein (MAP) kinases in human renal cell carcinoma. *Cancer Res* 1995;55:4182-4187.
10. Rini BI. VEGF-targeted therapy in metastatic renal cell carcinoma. *Oncologist* 2005;10:191-197.
11. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356(2):125-134.
12. Motzer RJ, Michaelson MD, Redman BG. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24(1):16-24.
13. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115-124.
14. Shaheen PE, Rini BI, Bukowski RM. Clinical activity of sorafenib and sunitinib in renal cell carcinoma refractory to previous vascular endothelial growth factor-targeted therapy: two case reports. *Clin Genitourin Cancer* 2006;5(1):78-81.
15. Hudes G, Carducci M, Tomzak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356(22):2271-2281.
16. Yang JC, Haworth L, Sherry RM et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427-434.

Medical management of benign prostatic hypertrophy

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Benign prostatic hyperplasia (BPH) is a common condition of the aging male. The bladder outlet obstruction caused by this condition occurs despite variations in prostate size. Symptoms of BPH include the irritative and obstructive voiding symptoms termed lower urinary tract symptoms (LUTS). While transurethral surgery has long been the gold standard for treatment of LUTS, medical treatment has emerged as the first line of treatment for those men who fail expectant or watchful waiting treatment. Medical options include: alpha blockers, 5α-reductase inhibitors and newly identified PDE 5 inhibitors, drugs for erectile dysfunction that have a relieving effect on the symptoms of LUTS. Newer prostate selective alpha blockers have replaced older nonselective agents as first choice in treatment of most men, especially those with smaller prostates and in whom preservation of sexual function is important. While tamsulosin has the effect of an ejaculation, alfuzosin preserves ejaculatory function. 5α-reductase inhibitors may decrease ejaculate volume, libido and sexual function. While this effect is frequently a self limited, it can be a compliance issue for many men. PDE 5 inhibitors, while effective in relieving LUTS symptoms, have not shown effectiveness in reducing post void residual volumes or increasing urinary flow rates.

Key Words: benign prostatic hyperplasia, aging male, medical management

Introduction

The management of benign prostatic hypertrophy (BPH) is one of the most common issues facing the practicing urologist today, and it will only become more important as our population continues to age. BPH has a histological prevalence of only about 8% of men in the fourth decade of life, but its prevalence increases to about 100% of men in their ninth decade.[1]

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More importantly than the presence of disease is the resultant morbidity it causes, as it is a disease process that is mostly characterized by its impact on quality of life and progression to disease related complications. BPH is the most common cause of lower urinary tract symptoms (LUTS) in the aging male.[2] Studies from North America, Europe, and Asia have shown that the prevalence of men with moderate to severe symptoms, or those necessitating treatment, increases with age.[3] These symptoms include frequency, urgency, nocturia, and hesitancy, among other things; these can be a significant detriment to the quality of life. As a result, men with moderate to

severe LUTS will report significantly decreased quality of life compared with men that have only mild symptoms.[4] Therefore as the population continues to age, the number of patients requiring treatment for BPH will continue to grow.

As this condition has become more prevalent, the trend in management has changed as well. First line medical management of this condition has become standard of care in most patients.[2]

From the years 1998-2001 the number of transurethral resection of the prostate (TURP) procedures done declined by close to 20%, while during the same period of time the number of prescriptions written for the treatment of BPH more than doubled.[5] The confounding variable to the difficulty in determining how to appropriately treat these patients medically is the cost effectiveness of these modalities. There is still no conclusive long-term data on cost effectiveness of medical therapies in the treatment of BPH versus surgical interventions using actual patients; however these trials are now ongoing. Using a computer model, the Canadian Coordinating Office of Health Technology Assessment looked at the cost effectiveness of different treatment modalities of BPH over 15 years. Their final recommendation was watchful waiting for mild symptoms regardless of life expectancy. However, for patients with moderate to severe symptoms the group noted that the more severe the symptoms, and the longer the life expectancy, the more likely that TURP would be the more cost effective strategy in the long run.[6]

Treatment

The successful treatment of BPH should be based on the attainment of certain goals. First, as a form of secondary prevention, the treatment should work to prevent the complications of BPH, (i.e., acute urinary retention, bladder stones, acute renal failure, hematuria, bladder remodeling). Second, the treatment should aim to improve the patient's quality of life by reducing their LUTS symptoms. Third, the urologist should consider the health related costs of the proposed treatment for the patient as well as society. Patients can therefore be categorized into four groups based on selected treatment: 1) watchful waiting, 2) medical management, 3) minimally invasive therapies, or 4) surgical management.[7] It is beyond the scope of this article to discuss each of these treatment arms, thus this article will focus on the medical management of BPH.

It is important to note that many patients will elect out of treatment or will be deemed appropriate for watchful waiting. The EAU guidelines from 2004 recommend watchful waiting for those patients with minimal symptoms or moderate to severe symptoms and no significant impact on the quality of their life.[7] A study of the impact of watchful waiting evaluated 556 men who were stratified to either watchful waiting or surgical intervention. The watchful waiting group had twice as many treatment failures as did the surgical group. However, when stratified by pre-operative symptom score patients with low to moderate symptoms were less likely to undergo TURP.[8] This study illustrates the natural history of disease progression with BPH. The basis of treatment for watchful waiting is continued monitoring for progression of the disease as well as lifestyle modifications to decrease the symptoms that are already present.[7]

Alpha blockers

Alpha-blocker therapy has been a part of the management of LUTS associated with BPH since the 1990's and is the first line treatment used by 80% of physicians.[9] This treatment is based on the theory that increased muscular tone in the prostatic stroma and prostatic urethra, as well as the bladder neck causes obstruction. This is mediated via α-1-adrenergic stimulation of smooth muscle cells and therefore selective α-1-blockers will cause relaxation of these smooth muscle cells.[10] This should result in relief of obstruction and improvement in symptoms.

Alfuzosin, tamsulosin, terazosin, and doxazosin are the four alpha blockers that are approved by the FDA for the treatment of LUTS associated with BPH. A meta-analysis has shown that each of these medications results in a statistically significant improvement in patient symptom scores compared to placebo. The clinical impact is usually within 48 hours of initiation of treatment. Patients typically show improvement of their symptom scores by 4-6 points, which is perceived by most patients as a meaningful difference.[11] Tamsulosin is unique compared to the others in its class in that it is an α1A-receptor blocker. The efficacy of these drugs, as proven by multiple RCTs, has been shown to be virtually equivalent.[12] In both the new AUA as well as EAU guidelines the alpha blockers are recommended equally, thus leaving the final decision to the discretion of the individual clinician.

Side effects with the alpha blockers typically include headache, dizziness, postural hypotension, rhinitis, and sexual dysfunction. This occurs in about 5%-9% of the patients taking these medications.[11]

5-α-reductase inhibitors

Whereas alpha blocking agents treat the symptoms of BPH by decreasing smooth muscle tone, 5-α-reductase inhibitors are postulated to be effective because of reduction in prostate volume. These agents are more effective in patients with prostate enlargement, glands larger than 30 ml-40 ml.[13] The largest trial to date investigated the use of finasteride for the treatment of BPH. In this multicenter, double-blinded, placebo-controlled trial of around 3000 men, there was a 55% risk reduction for the necessity of surgery for BPH as well as a 57% risk reduction of the development of acute urinary retention versus placebo. There was also a mean decrease in symptom score of 3 points in the finasteride group, an increase in urinary flow rates, as well as a significant reduction in prostate volume (20%-30%) compared with placebo.[14] Dutasteride is a second generation 5α-reductase inhibitor. It inhibits both type 1 and type 2 isoforms of the 5α-reductase enzyme. This added effect had been postulated to increase the efficacy of this drug in the treatment of BPH versus finasteride. However, studies have shown dutasteride to be similar in efficacy to finasteride.

It is important to remember that when therapy is initiated with these agents, it may take several months before activity is noted. It is also important to note that finasteride and dutasteride will decrease the PSA level in a patient by about 50%; however they do not decrease the early detection of prostate cancer.

Side effects with finasteride and dutasteride are mostly related to sexual dysfunction and include decreased libido, erectile dysfunction, and decreased ejaculation in 6%, 8%, and 4% of patients respectively.[7] However, it is important to note that these medications can be combined with the PDE-5 inhibitors safely for the treatment of these sexually related side effects.

5α-reductase inhibitors are important agents in the treatment of BPH. They have been shown to impact the complications that develop as a result of the natural history of BPH, such as acute urinary retention and the need for surgical intervention. This class of drug is a good option for patients with moderate to severe LUTS symptoms who also have benign prostatic enlargement (BPE). There is some trend now to the offering of this class of medications to those patients that simply have BPE as prevention to the progression of the disease. This has been shown to be efficacious, but the benefits of this treatment have to be weighed against the risks of sexual side effects as well as cost of long-term treatment.[7]

PDE-5 inhibitors

There has been much research recently focusing on the integrative nature of BPH, LUTS, and erectile dysfunction (ED) with evidence demonstrating a significant link between these disease processes. In a study of 5000 German men aged 30-80 years of age, approximately 70% of the men with LUTS had ED. The men in this study with LUTS had double the risk of developing ED.[15] In the Multinational Survey of the aging male looking at a group of men aged 50-90 years of age, 90% of these men were found to have LUTS. When comparing LUTS and ED a significant correlation was again present, with the severity of LUTS being the best predictor of ED.[16] In both of these studies LUTS was an independent risk factor for ED.[17]

The first major study of its kind looking at PDE-5 inhibitors and LUTS treatment was done in an andrology clinic. One hundred eleven patients were assessed with baseline IIEF and IPSS scores. They were then given oral sildenafil on demand and were reviewed with IIEF and IPSS scores at 1 and 3 months after initiation of treatment. After the initiation of treatment with oral sildenafil, the baseline IPSS scores as well as bother scores improved. Additionaly, men with lower LUTS severity had improvement in their IIEF scores as well. The proposed mechanism for this appears to be the presence of nitric oxide in the human prostate and sildenafil mediated smooth muscle relaxation through the nitric oxide pathway.[16]

The above study illustrates the possibility for PDE-5 inhibitors in the treatment of BPH. There are currently placebo controlled trials looking at sildenifil and tadalafil in the treatment of LUTS. There have also been studies demonstrating the ability to safely combine alpha blockers and PDE-5 inhibitors for the treatment of LUTS and ED. However, more studies are needed with primary end points directed towards the treatment of LUTS before determination can be made as to the efficacy and safety of these medications combined for this indication.

Combination therapy

The initial studies on combination therapy with alpha blockers and 5α-reductase inhibitors did not appear to show a benefit.[18-20] However, the results in the MTOPS trial show an added benefit for the combination therapy. Patients were followed for 4.5 years and treated with either placebo, finasteride alone, doxazosin alone, or combination therapy. The primary end point for the study was clinical progression of disease which was defined as an

increase in AUA symptom score of 4 points, acute urinary retention, renal failure secondary to BPH, urinary tract infections, and urinary incontinence. The study showed a decrease in clinical progression with finasteride of 32% and 39% in doxazosin. These results were significant compared to placebo but there was no statistical significance between the two, showing them to be equally efficacious. However, in the combination therapy group there was a 66% reduction in clinical progression compared to placebo.[21] The same research group also released a study showing that for men with smaller volume prostates (less than 25 ml) there is no added benefit of combination therapy versus monotherapy with doxazosin alone, but that in those with larger volume prostates that combination therapy is again better than either monotherapy with doxazosin or finasteride.[23] Currently the CombAT trial combining Avodart (dutasteride) and tamsulosin is underway to look at the effect of combination therapy with the second generation 5α-reductase inhibitor to evaluate if there is an added benefit compared to the first generation 5α-reductase inhibitor.

It is now becoming clear that in men with an increased risk of clinical progression that combination therapy is the best treatment to prevent progression of disease and improve patient symptom scores. Those patients with increased age, increased severity of symptoms, higher PSA values, higher total prostate volume, lower Qmax, and increased PVRs have been shown to be at increased risk of progression and should be considered candidates for combination therapy.[22]

Future directions

The BPH patient registry and patient survey is currently in development to determine the effectiveness of the above recommendations in the treatment of BPH as well as determining the actual practice patterns of clinicians in a variety of settings.[24] The information derived from this patient registry will be invaluable in the future direction of the medical management of this disease. The true efficacy of these medical interventions in a "real world" situation will then be established, as well as the ability to examine how strictly clinicians adhere to them. This will aid us in the future directions we, as urologists, need to move. This is especially important as more and more of these patients are being managed by primary care physicians. Our role may then be more useful as an educator, as opposed to the primary provider of care, for the actual patient in the appropriate medical management of BPH.

Disclosure

Dr. Cully Carson is a member of the Speakers' Bureau for Auxilium Pharmaceuticcals, Pfizer and Lilly. He is a consultant for Pfizer and Lilly. □

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132(3):474-479.
2. McConnell JD. The Pathophysiology of benign prostatic hyperplasia. *J Androl* 1991;12:356-363.
3. Homma Y, Kawabe K, Tsukamoto T et al. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. *Int J Urol* 1997;4:40-46.
4. Girman CJ, Epstein RS, Jacobson SJ et al. Natural history of prostatism. Impact of urinary symptoms on quality of life in 2115 randomly selected community men. *Urology* 1994;44:825-831.
5. Foley CL, Taylor C, Kirby RS. Counting the cost of treating benign prostatic hyperplasia. *BJU Int* 2004;93:250-254.
6. Canadian Coordinating office for Health Technology Assessment. Cost effectiveness and cost-utility analyses of finasteride therapy for the treatment of benign prostatic hyperplasia. Ottawa;CCOHTA, 1995.
7. Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004;46(5):547-554.
8. Wasson JH, Reda DJ, Bruskewitz RC et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on transurethral Resection of the Prostate. *N Engl J Med* 1995;332:75-79.
9. Denis L, McConnell J, Yoshida O et al. Recommendations of the international scientific committee: the evaluation and treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction; Proceedings of the 4th international consultation on benign prostatic hyperplasia; July 2-5, 1997;Plymouth, UK: Health Publications Ltd; 1998. Pp. 669-683.
10. Lam JS, Cooper KL, Kaplan SA. Changing aspects in the evaluation and treatment of patients with benign prostatic hyperplasia. *Med Clin North Am* 2004;88:281-308.
11. Kaplan S. Update on the American urological association guidelines for the treatment of benign prostatic hyperplasia. *Rev Urol* 2006;8(Suppl 4):S10-S17.
12. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2003;(1):CD002081.
13. Marberger M, Harkaway R, de la Rosette JJ. Optimizing the medical management of benign prostatic hyperplasia. *Eur Urol* 2004;45:411-419.
14. Roehrborn CG, Boyle P, Bergner D et al. Serum prostate-specific antigen and prostate volume predict long-term outcome in symptoms and flow rate: results of a 4 year, randomized trial comparing finasteride vs placebo. PLESS study Group. *Urology* 1999;54:662-669.
15. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Englemann U. Epidemiology of erectile dysfunction: results of the 'Cologne male survey'. *Int J Impot Res* 2000;12:305-311.

16. Rosen R, Altwein J, Boyle P et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male. (MSAM-7). *Eur Urol* 2003;44:G37-G49.
17. Carson CC. Combination of phosphodiesterase-5 inhibitors and alpha-blockers in patients with bengin prostatic hyperplasia: treatments of lower urinary tract symptoms, erectile dysfunction, or both? *BJU Int* 2006;97(2):39-43.
18. Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, Haakenson C, Machi M, Narayan P, Padely RJ. Veterans Affairs Cooperative Studies, benign prostatic hyperplasia study group. The effects of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996;335:533-539.
19. Debruyne FM, Jardin A, Colloi D, Resel L, Witjes WP, Delauche Cavallier MC et al. Sustained release alfuzosin, finasteride and the combination of both in the treatment of BPH. European ALFIN study group. *Eur Urol* 1998;34:169-175.
20. Kirby RS, Roehrborn C, Boyle P, Bartsch G, Jardin A, Cayr MN, Sweeney M, Grossman EB. Prospective European Doxazosin and Combination Therapy Study Investigators. Efficacy and toleratbility of doxazosin and finasteride, alone or in combination, in treatment of benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003;61:119-126.
21. McConnell JD, Roehrborn CJ, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM Jr, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MN, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA. Medical Therapy of Prostatic Symptoms Research Group. The long term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Eng J Med* 2003;349(25):2387-2398.
22. Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, Meehan AG, Bautista OM, Noble WR, Kusek JW, Nyberg LM, Roehrborn CG. Medical Therapy of Prostatic Symptoms Research Group. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* 2006;175(4):1422-1426.
23. Kaplan SA, McConnell JD, Roehrborn CG, Meehan AG, Lee MW, Noble WR, Kusek JW, Nyberg LM Jr. Medical Therapy of Prostatic Symptoms Research Group. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia for men with lower urinary tract symptoms and a baseline total prostate volume of 25ml or greater. *J Urol* 2006;175(1):217-220.
24. Roehrborn CG, Nuckolls JG, Wei JT, Steers W. BPH Registry and Patient Survey Steering Committee. The benign prostatic hyperplasia registry and patient survey: study design, methods, and patient baseline characteristics. *BJU Int* 2007;100(4):813-819.

Evaluation of the patient with incontinence

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The incontinent patient is evaluated in order to make a presumptive diagnosis so that treatment can be offered. The evaluation begins with a history and a physical examination. The history focuses on the description of the patient's incontinence. Assessing the patient's bother and determining their expectations of treatment may further guide how aggressive one needs to be both with the evaluation and the presentation of treatment options. The important parts of the physical exam are an examination of the abdomen and pelvis including a provocative stress test. A urinalysis and a post-void residual (PVR) should be performed in all incontinent patients.

Incontinence questionnaires, voiding diaries, and pad weight tests can provide more objective data than the history alone. Upper tract imaging is indicated in the patient with a history of hematuria and in patients with suspected hydroureteronephrosis. Other imaging may be useful to further evaluate other suspected pelvic pathology. Urodynamics are performed to determine if the incontinence is due to bladder or urethral dysfunction or both, to assess if the patient has a storage or emptying problem and lastly in an effort to identify patients whose upper tracts are at risk due to high bladder storage pressures. Cystoscopy is indicated in the work up of some incontinent patients.

The evaluation of the incontinent patient consists of a history, a physical, urinalysis and a post-void residual. Optional evaluative tests consist of a variety of urodynamic tests, imaging studies and cystoscopy.

Key Words: incontinence, evaluation

Introduction

Urinary incontinence is a significant problem accounting for more than 1.1 million office visits in 2000 in the United States at a cost estimated to be approximately $19.5 billion.[1,2] The aim of the evaluation is to establish a presumptive diagnosis so that empiric or disease specific treatment may be instituted.[3]

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History

The evaluation of the incontinent patient begins with a history and a physical examination. Although this seems rudimentary a careful history and physical examination in patients deemed to have failed treatment will often reveal additional problems contributing to their ongoing incontinence. The patient should be questioned regarding their incontinence with particular emphasis on the description of their incontinence. The patient is asked to describe the onset, frequency and severity of their incontinence. A variety of questionnaires or a diary

can be used to aid in this. The questions from the MESA questionnaire are helpful to distinguish stress from urge incontinence.[4] The symptoms of stress are: do you leak with coughing, laughing, sneezing, lifting, straining, walking, bending or getting up from sitting. The urge symptoms are:

do you leak without warning, on your way to the toilet, when you are full, when you wash your hands, in cold weather or when you drink something cold.

Incontinence may be quantified by asking the patient if he or she wears a pad or other protective garment and how often it is changed.

Patients should be questioned about their intake, as well as their voiding habits. Additional urologic symptoms are also elicited especially other lower urinary tract symptoms in males. Female patients are asked about symptoms of pelvic prolapse, such as a sensation of vaginal fullness or pressure, or the observation of a bulge in the vagina. Patients should be asked about bowel function, including being asked if they need to splint with defecation. The response to previous treatments, including drugs or prior surgical procedures is noted.

Other features of the history include previous gynecologic or urologic procedures, neurological problems, past medical problems, current medications including use of over-the-counter medication, and a social and sexual history. Assessing the patient's bother and determining their expectations of treatment can help determine in the first visit how aggressive one needs to be both with the evaluation and the presentation of treatment options.

Clinician or self-administered structured condition specific questionnaires may be used to facilitate disclosure of embarrassing symptoms, ensure the symptoms are not omitted and standardize information.[5] Although a complete history is important it is not accurate enough to define the patient's problem and it should not be the only tool used to diagnose or treat. Harvey and Versi found that the positive predictive value of the symptom of stress incontinence was 56% for the diagnosis of pure urodynamic stress incontinence and 79% for the diagnosis of urodynamic stress incontinence with other abnormalities.[6] The positive predictive value of a history of urge has been shown to be even lower, 37%.[7]

Physical

A complete physical examination is performed with emphasis on the abdominal, pelvic and rectal examination and a brief neurological assessment. In females the health of the vaginal mucosa is assessed during the pelvic exam. Healthy vaginal mucosa is pink, thick and well rugated as opposed to atrophic vaginal tissue that is thin, pale and lacking rugae. A pelvic examination with the patient supine is sufficient to determine if the urethra moves with straining or coughing. One of the most important parts of the physical exam is a provocative stress test to determine if the patient leaks with a cough or a Valsalva. This can be done supine or standing and ideally with the bladder comfortably full. If stress leakage is not demonstrated on exam in the patient who describes stress incontinence then it should be demonstrated in the urodynamic lab prior to embarking on treatment of stress incontinence.

The presence of associated pelvic organ prolapse is also noted. If the patient has symptoms of a prolapse and it is not demonstrated when the patient is supine then they are reexamined standing. Pelvic organ prolapse may contribute to the patient's voiding problems and may have an impact on diagnosis and treatment. When assessing prolapse support of the anterior and posterior vaginal wall and the apex are assessed. The presence and grade of the prolapse is determined. One of the more objective methods of grading pelvic organ prolapse is with the POP-Q exam.[8] Measurements, from a variety of points on the vagina at rest and with maximal strain, are made relative to the hymen. The genital hiatus, the perineal body and the total vaginal length are measured. The integrity of the muscular components of the pelvic floor is also assessed during a pelvic exam. A determination is made as to the patient's ability to contract her pelvic floor muscles and the strength of her contraction.

The rectal exam includes the evaluation of sphincter tone and perineal sensation. The presence or absence of a rectocele and an enterocele are also assessed with the rectal. The integrity of the external anal sphincter is assessed by examining for a defect noted either visually or on rectal exam.

In men a digital rectal exam is performed to assess the size, symmetry and consistency of the prostate gland.

Urinalysis

A urinalysis is performed in all incontinent patients to determine if there is any evidence of hematuria, pyuria, glucosuria, proteinuria, leukocyte esterase or nitrates. A positive dipstick urinalysis should prompt a urine microscopy. A urine specimen is sent for cytology if there is hematuria and/or irritative voiding symptoms. The urine is cultured if there is leukocyte esterase, nitrates, pyuria or bacteriuria. Infection should be treated prior to further investigations or interventions.

Post-void residual urine

A post-void residual (PVR) is measured either with pelvic ultrasound or directly with a catheter. PVR is variable and may need to be measured on more than one occasion. The Agency for Health Care Policy and Research (AHCPR) guidelines described a normal PVR of under 50 ml and a PVR in excess of 200 ml as abnormal.[9]

A significant PVR urine may reflect either bladder outlet obstruction or poor bladder contractility. The only way to distinguish outlet obstruction from poor contractility is with urodynamic testing.

Ancillary tests

There are a number of validated questionnaires that assess symptoms and quality of life. Use of these questionnaires during the initial evaluation can provide further insight into a patient's symptoms and the impact of their symptoms on their quality of life. Repeated use of the questionnaires with treatment assesses the results of treatment. The third International Consultation on Incontinence has highly recommended and given a Grade A to several questionnaires for use in incontinent patients.[10] The questionnaire highly recommended to evaluate symptoms and quality of life impact of urinary incontinence in men and women is the ICIQ.[11] Other questionnaires that received a Grade A are the I-QOL,[12] SEAPI QMM Quality of Life Index,[13] Bristol Female LUTS (BFLUTS)[14] and BFLUTS- short form SF,[15] ICS male[16] and ICSmaleSF, [17] Kings Health Questionnaire,[18] Urogenital Distress Inventory (UDI)[19] and UDI-6,[20] Incontinence Impact Questionnaire (IIQ)[21] and IIQ -7,[20] Incontinence Severity Index (ISI),[22] Stress and Urge Incontinence and Quality of life Questionnaire (SUIQQ),[23] Urinary Incontinence Severity Score (UISS),[24] CONTILIFE,[25] Overactive Bladder Symptom and Health-related Quality of life (OAB-q)[26] and DAN-PSS.[27] As these questionnaires have been designed to assess symptoms and or quality of life impact of incontinence alone or in the presence of lower urinary tract symptoms, including overactive bladder in men, women or both, clinicians should use the questionnaire that is most relevant and practical to their patients.

Voiding diaries, which include intake, urinary frequency, voided volume and incontinence episodes, are helpful in the initial evaluation particularly if the information is not obtained by the history. A voiding diary may also be used to detect a change in symptoms with treatment.

A pad weight test is a more objective measure than a pad count of how incontinent the patient actually is. Pad weight tests are particularly useful in male patients with stress incontinence as there is good correlation between a low pad weight test (less than 148 gm of urine loss per day) and a successful outcome with a bone anchored sling.[28]

Radiologic imaging

Upper tract imaging is indicated in the patient with a history of hematuria, the patient with suspected hydroureteronephrosis due to high bladder storage pressures or severe uterine prolapse, or in patients with a suspected ectopic ureter or ureterovaginal fistula.[29]

A transvaginal ultrasound is useful to further evaluate suspected periurethral pathology or if there is a concern about adnexal or uterine pathology. An endoanal ultrasound is useful to evaluate the patient with a defect in the external anal sphincter on exam or in the patient with fecal incontinence.

An MRI is not indicated in the routine evaluation of prolapse but may be used in certain clinical or experimental situations. MRI does have a role in the evaluation of periurethral pathology, particularly in the patient with a presumed urethral diverticula.

Defecatory proctography and rectal manometry are useful in some patients with bowel issues.

Urodynamics

Urodynamics is used in the incontinent patient to determine if the incontinence is due to bladder or urethral dysfunction or both, to assess if the patient has a storage or emptying problem and lastly in an effort to identify patients whose upper tracts are at risk due to high bladder storage pressures.

A cystometrogram assesses bladder behavior during filling. Normally, bladder pressure remains flat during filling. If bladder pressure rises incrementally during filling, a diagnosis of poor compliance is made. As the bladder pressure rises and eventually exceeds the urethral resistance, incontinence results. Poor bladder compliance in a female patient or in a patient with a neurogenic disorder makes the assessment of bladder neck and urethral function difficult, since the rise in bladder pressure may mimic stress incontinence. Poor compliance and poor urethral function may coexist.

The most common abnormality of bladder function is detrusor over activity that causes urge incontinence. Obstruction should be ruled out as the cause of urge incontinence in the female patient who has had prior incontinence procedures or in the male patient. A cystometrogram may fail to demonstrate any

detrusor overactivity in the patient with urge incontinence and detrusor overactivity may be seen in the patient without symptoms of urge.

The method to diagnosis stress incontinence remains debatable. Tests commonly performed are the measurement of the abdominal (ALPP) or the urethral pressure profile. The ALPP which is the amount of abdominal pressure required to induce urinary loss may also be called the Valsalva leak point pressure. ALPP is used to diagnose stress incontinence, since it is abdominal pressure that is the expulsive force in stress incontinence. In theory measuring the ALPP allows for quantification of the degree of urethral dysfunction. A normal urethra will not leak at any pressure, a mobile urethra will leak at high abdominal pressures and a poorly functioning intrinsic sphincter will leak at low pressures.[30] When measuring ALPP in patients with prolapse the prolapse should be reduced during the test to prevent the increase in abdominal pressure being absorbed by the prolapse. Prolapse can be reduced digitally, with a sponge forceps, a pessary, a vaginal pack, or a syringe cover from a 60 cc syringe.

Obstruction is diagnosed on urodynamics with a pressure-flow study when there is a high detrusor pressure during attempted voiding and a corresponding low flow. Simultaneous fluoroscopy may be helpful to diagnose the site of obstruction, particularly in men.

EMG may be used to assess the tone of the striated muscle of the external urethral or anal sphincter or the perineal floor muscles, with patch, plug, or needle electrodes. Normally relaxation of the external urethral sphincter occurs with a detrusor contraction. In a patient who fails to relax there is either a neurogenic problem or the patient is a dysfunctional voider. Failure of relaxation of the external sphincter with voiding may also be diagnosed with fluoroscopy.

Cystoscopy

Cystoscopy is indicated in the work up of the incontinent patient if there is concern for a diverticula, a fistula, or a foreign body such as sling material. In men with post-prostatectomy incontinence cystoscopy is indicated to evaluate the caliber of the bladder neck.

Summary

In summary, the evaluation of the incontinent patient consists of a history, a physical, urinalysis and a post-void residual. In women concomitant prolapse symptoms should be elucidated and the patient should be assessed for prolapse. In men the presence of additional lower urinary tract symptoms should be ascertained and the possibility of obstruction should be considered. The impact of incontinence on the patient's quality of life is important and can be measured objectively with questionnaires.

Optional evaluative tests consist of a variety of urodynamic tests, imaging studies and cystoscopy.

Disclosure

None. □

References

1. Litwin MS, Saigal CS, Yano EM et al. Urological Diseases in America project: Analytical methods and principal findings. *J Urol* 2005;173:933-937.
2. Hu TW, Wagner TH, Bentkover JD et al. Costs of urinary incontinence and overactive bladder in the United States: A comparative study. *Urology* 2004;63:461-465.
3. Staskin D, Hilton P, Emmanuel A et al. Initial assessment of incontinence. In: Incontinence (Edition 2005) 3rd International Consultation on Incontinence, ed. Abrams P, Cardozo L, Khoury S, Wein A, Paris, Health Publications; 2005:485-517.
4. Herzog AR, Diokno AC, Brown MB, Normolle DP, Brock BM. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. *J Gerontol* 1990;45:67-74.
5. Donovan J, Badia X, Corcos J, Gotoh M, Kelleher C, Naughton M et.al. Symptom and quality of life assessement. In: Incontinence (Edition 2002) 2nd WHO International Consultation on Incontinence, ed. Abrams, P, Cardozo L, Khoury S, Wein A, Plymouth, Health Publications. 2002:267-316.
6. Harvey MA, Versi E. Predictive value of clinical evaluation of stress urinary incontinence: A summary of the published literature. *International Urogynecology Journal* 2001;12:31-37.
7. Young SB, Pingeton DM. Office assessment of female urinary incontinence. *Clin Obstet Gynecol* 1999;42:249-266.
8. Bump RC, Mattaisson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10-17.
9. Fantl JA, Newman DK, Colling J et al. Urinary incontinence in adults: Acute and chronic management. Clinical Practice Guideline No. 2, 1996 Update (AHCPR Publication No. 96-0682), Rockville, Md, U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, March 1996.
10. Donovan J, Bosch R, Gotoh M et al. Symptom and quality of life assessment. In: Incontinence (Edition 2005) 3rd International Consultation on Incontinence, ed. Abrams P, Cardozo L, Khoury S, Wein A. Paris, Health Publications. 2005:519-584.
11. Avery K, Donovan J, Peters TJ et al. A brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol and Urodyn* 2004;23:322-330.
12. Wagner TH, Patrick DL, Bavendam TG et al. Quality of life of persons with urinary incontinence: development of a new measure. *Urology* 1996;47:67-72.
13. Stothers L. Reliability, validity and gender differences in the quality of life index of the SEAOI-QMM incontinence classification system. *Neurourol and Urodyn* 2004;23:223-228.

14. Jackson S, Donovan J, Brookes S et al. The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. *BJU* 1996;77:805-812.
15. Brookes ST, Donovan JL, Wright M et al. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: Data from a randomized controlled trial of surgery for women with stress incontinence. *Am J of Obstet and Gyn* 2004;191:73-82.
16. Donovan JL, Abrams P, Peters TJ et al. The ICS-BPH' Study the psychometric validity and reliability of the ICS male questionnaire. *BJU* 1996;77:554-562.
17. Donovan JL, Peters TJ, Abrams P et al. Scoring the ICS male SF questionnaire. *J Urol* 2000;164:1948-1955.
18. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *BJOG* 1997;104:1374-1379.
19. Shumaker SA, Wyman JF, Uebersax JS et al. Health-related quality of life measures for women with urinary incontinence: The Incontinence Impact Questionnaire and the Urogenital Distress Inventory. *Quality of Life Research* 1994;3:291-306.
20. Uebersax JS, Wyamn JF, Shumaker SA et al. Short forms to assess life quality and symptoms distress for urinary incontinence in women: The Incontinence Impact Questionnaire and Urogenital Distress Inventory. *Neurourol and Urodyn* 1995;14:131-139.
21. Wyman JF, Harkins SW, Taylor JR, Fantl AJ. Psychosocial Impact of Urinary Incontinence on Women. *Obstet and Gyn* 1987;70:378-381.
22. Sandvik H, Hunskaar S, Seim A et al. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. *Journal of Epidemiology and Community Health Medicine* 1993;47:497-499.
23. Kulseng-Hanssen S, Borstad E. The development of a questionnaire to measure the severity of symptoms and the quality of life before and after surgery for stress incontinence. *BJOG* 2003;110;983-988.
24. Stach-Lempinen B, Kirkinen P, Laippala P et al. Do objective urodynamic or clinical findings determine impact of urinary incontinence or its treatment on quality of life? *Urology* 2004;63:67-71.
25. Amarenco G, Arnould B, Carita P et al. European psychometric validation of the CONTILIFE: a Quality of Life questionnaire for urinary incontinence. *Eur Urol* 2003;43:391-404.
26. Coyne K, Revicki D, Hunt R et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. *Qual Life Res* 2003;11:563-574.
27. Hald T, Nordling J, Anderson JT et al. A patient weighted symptom score in the evaluation of uncomplicated benign prostatic hyperplasia. Scand U Urol Nephrol Suppl 1991;138:59-62.
28. Fisher MC, Huckabay C, Nitti VW. The male perineal sling: assessment and prediction of outcome. *J Urol* 2007;177(4):1414-1418.
29. Tubaro A, Artibani A, Bartram C, et al: *Imaging and other investigations*. In: *Incontinence (Edition 2005) 3rd International Consultation on Incontinence*, ed.
Abrams P, Cardozo L, Khoury S, Wein A. Paris, Health Publications; 2005:707-797.
30. McGuire EJ, Fitzpatrick CC, Wan J, et al. Clinical assessment of urethral sphincter function. *J Urol*. 1993; 150:1452-1454.

Androgen deficiency in the aging male: a guide to diagnosis and testosterone replacement therapy

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A steady decline in androgen levels occurs in males as they age. Evidence suggests that this decline may be at least partially responsible for a variety of physical and mental changes associated with the aging process. For instance, abnormally low levels of androgens can lead to profound changes in bone density, body composition, as well as sexual and cognitive function. Testosterone replacement has been shown to produce improvements in many of these areas. However, this practice is not without risks, both proven and theoretic. Also, the diagnosis of androgen deficiency and the decision to treat is not always straightforward. The purpose of this article is to familiarize the clinician with issues associated with androgen deficiency in the aging male. The clinical symptoms of androgen deficiency as well as the risks and benefits of androgen replacement will be discussed. This should help clinicians better identify those patients in whom testosterone replacement therapy should be considered.

Key Words: androgen, testosterone replacement therapy, aging male

Background

Both cross-sectional and longitudinal studies demonstrate a progressive decline in androgen levels as men age. When this biochemical decline is associated with any of a number of clinical symptoms, the entity has been described as androgen deficiency in the aging male (ADAM). Other terms used to describe this phenomenon include andropause, male menopause, male climacteric syndrome, and hypogonadism. Symptoms associated with this syndrome include those typically associated with aging such as osteoporosis, decreased cognitive function and mood, change in body composition, and declining libido and sexual function. Hormone replacement therapy can improve many of these symptoms, but therapy is not without risks. Possible side effects of testosterone replacement include hepatotoxicity, alterations in lipid profiles, sleep and mood disorders, and prostate hyperplasia or cancer. Therefore, hormone replacement therapy mandates periodic evaluation to monitor side effects of the treatment.

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Epidemiology

Estimates of the prevalence of androgen deficiency in aging males are affected by the lack of a clear definition of the phenomenon. For instance, the Massachusetts Male Ageing Study used total testosterone level < 200 ng/dl or at least three symptoms of hypogonadism with a total testosterone level between 200 ng/dl and 400 ng/dl as its definition. Based on this, the study estimated the prevalence of hypogonadism to be 6.0% of men aged 40-69 years at baseline and 12.3% at follow-up assessment 7.0-10.4 year later.[1] However, a much higher prevalence of 38.7% in men > 45 years was found in the Hypogonadism in Males (HIM) study using total testosterone < 300 ng/dl as its definition.[2] More recently, a study of 1475 men in the Boston Area Community Health (BACH) survey showed the importance of considering biochemical androgen deficiency in the context of clinical symptoms. While 24% of the subjects studied had total testosterone < 300 ng/dl, nearly 47% of the subjects at least 50 years old with low testosterone were asymptomatic. In this study, crude prevalence of symptomatic androgen deficiency was found to be 5.6% among all comers with an average age of 47.3 years. However, the prevalence increased dramatically after the age of 70 to 18.4%.[3] Despite the uncertainty regarding the current prevalence of androgen deficiency, one thing that is clear is that the population of the United States is progressively aging.[4] As such, management of age-related hormonal changes will almost certainly become a more prominent part of urologic practice in the near future. Indeed, the BACH study concluded that 6.5 million American men 30 to 79 will manifest symptomatic androgen deficiency by 2025 which represents and increase of 38% compared to 2000 population estimates.[3] Conditions such as diabetes, chronic renal failure, metabolic syndrome and chronic opioid use increase the prevalence of hypogonadism.

Hormonal alterations

It is well-known that testosterone levels decline with age. Almost 20% of men aged 60-69 and 30% of men aged 70-79 have low testosterone levels.[5] In addition to a decline in total testosterone, there is also a rise in sex hormone-binding globulin that leads to a significant decline in bioavailable and free testosterone.[1,2] Luteinizing hormone (LH) levels typically increase slightly with age, likely secondary to decreased Leydig cell testosterone production.[6] However, a majority of hypogonadal elderly men will have low or inappropriately normal LH levels, indicating hypothalamic-pituitary dysfunction as well. Extra-gonadal androgens, DHEA and DHEAS, also decline with age.[7]

Diagnosis and work-up

Precisely defining androgen deficiency is more relevant to research endeavors than to clinical practice. Determination of hypogonadism requires clinical suspicion based on symptoms and exclusion of other causes. When symptomatic hypogonadism is suspected, a morning serum total testosterone level should be obtained. If abnormal or borderline (< 300 ng/dl), the test should be repeated with free T, LH, FSH, prolactin, and possibly SHBG levels. These tests aid in determining primary gonadal failure versus pituitary dysfunction. Abnormal gonadotropin values or elevated prolactin levels should prompt further evaluation of the pituitary gland with an MRI of the sella turcica for a possible pituitary adenoma. Whether the cause of low testosterone is primary gonadal failure or pituitary dysfunction, the mainstay of treatment is testosterone replacement therapy. Prior to initiating hormonal replacement therapy, a digital rectal exam should be performed. In addition, laboratory evaluation with a complete blood count, liver function tests, and PSA should be obtained. Any abnormal DRE finding or elevated PSA should prompt further investigation to rule out prostate cancer prior to beginning testosterone supplementation.

Effects of testosterone and replacement therapy

Bone

Testosterone plays a major role in bone mineral density in men.[8] However, the majority of the effect is likely due to the action of the testosterone metabolites estradiol and estrone.[9,10] However, testosterone does appear to have a direct interaction with bone cells. Testosterone has been shown to directly inhibit osteoclast formation and bone resorption whereas estrogen exerts its effects mainly through the actions of osteoblasts.[11] A recent multi-center study of 2447 men older than 65 indicated that the prevalence of osteoporosis was 12.3% in testosterone deficient men versus 6.0% in those with normal testosterone.[12] However, the effect of hypogonadism on bone is best demonstrated by examining patients with prostate cancer treated with androgen deprivation therapy. Evidence suggests that these patients are at increased risk for osteoporotic fractures and their sequelae secondary to osteopenia and osteoporosis.[13] A recent meta-analysis examined the evidence for testosterone replacement on bone and showed that there was improvement in bone mineral density in the lumbar spine as well as decreased bone resorption markers. However, none of studies included in the analysis examined fracture risk reduction with testosterone replacement therapy.[14]

Cognitive function and mood

There is a decline in cognitive function with aging.[15] The majority of cases of dementia and cognitive decline are associated with vascular changes in the central nervous system or as a result of neurodegenerative disorders such as Alzheimer's disease. There is evidence, however, indicating more than just a temporal relationship between decreasing testosterone levels and declining cognition. A prospective longitudinal study examined over 400 elderly men with respect to multiple cognitive domains and serum measurements of testosterone. Men classified as hypogonadal showed significant declines of memory and visuospatial performance as well as faster rates of decline in visual memory.[16] Recent studies have also demonstrated a link between low testosterone levels and the development of Alzheimer's disease in aging men.[17,18] This association remains to be fully elucidated, however, animal studies have shown that androgen depletion increases levels of β-amyloid protein and decreases neuronal survival in response to toxic insults.[19,20] The results of randomized, placebo-controlled studies evaluating the effect of androgen replacement on cognition have been mixed. However, a recently published literature review of the topic indicated that, in general, testosterone substitution may have moderate positive effects on selective cognitive domains (e.g. spatial ability) in older men with and without hypogonadism. This study concluded that testosterone replacement should be considered in hypogonadal men with cognitive impairment.[21]

There has also been some suggestion that testosterone supplementation may alter mood. It is well known that the incidence of depression increases with aging. Unfortunately, there have been few trials examining the relationship between low testosterone levels and depression. Randomized trials examining the relationship between testosterone supplementation in hypogonadal men and depression symptoms have shown conflicting results.[22,23] However, these trials were relatively small and larger randomized trials are needed to fully examine the benefit of testosterone supplementation in the treatment of depression for this population subset.

Body composition

Aging is associated with a decrease in skeletal muscle mass and an increase in adipose tissue.[24] These changes can result in loss of strength and mobility, leading to an increased risk of falls, fractures, decreased independence, and depression. This effect is thought to be due to a direct effect on muscle cells by testosterone as well as through stimulation of insulin-like growth factor 1.[25] Some studies have shown improvement in both leg and arm strength with testosterone supplementation[26] while other studies have shown improvement only with the coadministration of growth hormone.[27,28] Changes in muscle mass were seen both in hypogonadal elderly men and healthy younger men.[29,30] Testosterone supplementation has also been shown to affect adiposity causing a decline in fat mass and an increase in lean muscle mass[24] as well as a redistribution of adipose to the viscera and subcutaneous tissues typical of eugonadal men.[31]

Sexual function

Sexual dysfunction, in the form of erectile dysfunction or decreased libido, is a common presenting complaint in androgen deficient males. Testosterone and its metabolites are critical to sexual development, function, and desire. Testosterone appears to have greater effect on nocturnal erectile activity and maintenance of libido in hypogonadal men.[32,33] Several studies have examined the effect of testosterone supplementation on sexual function. Response rates vary dramatically in these studies as evidenced by the results of a recent meta-analysis on the subject. However, the study populations were heterogeneous and included patients with both primary and secondary testicular failure as well as some men not classified as hypogonadal.[34,35] A more recent study examining testosterone supplementation in hypogonadal men showed an initial improvement in sexual function based on the International Index of Erectile Function at 1 month of treatment, but this benefit was not maintained. There was, however, a persistent improvement in libido.[36] One critique of these results is that patient comorbidities may have contributed to the lack of persistent effect. Also, the patients in the study were not treated simultaneously with phosphodiesterase type-5 inhibitors. Coadministration of testosterone and PDE-5 inhibitors has been shown to improve erectile function in hypogonadal men.[37] Testosterone clearly has an effect on sexual function. However, the incidence of comorbid illnesses that can lead to erectile dysfunction also increases with age making the determination of the ultimate cause difficult.[38] For this reason, larger randomized studies are needed to elucidate the true contribution of testosterone replacement to erectile function in hypogonadal men.

Risks of testosterone replacement therapy

Hepatic and hematologic

Hepatotoxicity is a known side effect of some forms of testosterone replacement therapy. However, this adverse effect has only been associated with oral preparations of testosterone (alkylated forms). Manifestations include

elevated liver function tests, cholestatic hepatitis, cystic disease of the liver, and hepatocellular carcinoma. All of the newer testosterone preparations are aromatized when metabolized which prevents liver toxicity. Other forms of replacement such as testosterone undecanoate, injectable, and transdermal preparations do not appear to be associated with hepatotoxicity.[39] Androgen supplementation is also known to increase hematocrit.[40] Patients with comorbid vascular disease may have a higher risk of adverse events as a result of the polycythemia.[41] A recent meta-analysis of randomized trials of testosterone supplementation showed that polycythemia (hematocrit > 50%) was the most common adverse effect. Patients treated with testosterone were 3.6 times more likely to develop polycythemia. The intramuscular form of testosterone appears to have a higher incidence of erythrocytosis.[42] Baseline liver function tests and a complete blood count should be obtained prior to beginning supplementation. Periodic monitoring of CBC during therapy is recommended in order to assess for polycythemia. Patients developing erythrocytosis may require withholding testosterone or, occasionally, therapeutic phlebotomy.

Cardiovascular disease and lipid profile

It has been previously and incorrectly assumed that elderly men have a higher incidence of cardiovascular events than women because of the elevated levels of testosterone. However, no clinical evidence supports this assumption. In fact, evidence points to a possible beneficial effect of testosterone on cardiovascular health. Studies have failed to show any relationship between testosterone levels and angiographic evidence of coronary artery disease.[43,44] English et al, showed that men with lower bioavailable testosterone had a higher incidence of abnormal coronary angiograms.[44] In addition, a large population study showed an inverse relationship between bioavailable testosterone levels and aortic atherosclerosis.[45] A recent meta-analysis of elderly men taking testosterone showed no statistical difference in cardiovascular events when compared with placebo.[42] Lipid profile is a well-known cardiac risk marker. A meta-analysis of 19 studies involving testosterone supplementation in men with hypogonadism showed minimal decreases in total cholesterol, LDL, and HDL that did not reach statistical significance at physiologic levels of testosterone.[42] There was, however, noted to be a dose related decrease in HDL levels with testosterone supplementation. The evidence suggests a modest change in lipid levels with testosterone supplementation in hypogonadal men.[46] The effect that these changes in lipids have on cardiovascular events has yet to be elucidated.

Prostate

The prostate relies on androgens for growth and the majority of prostate cancers are hormonally responsive. Treatment of metastatic or recurrent prostate cancer routinely relies on androgen ablation. Taken at face value, this would suggest that androgen supplementation could exacerbate voiding difficulties by encouraging prostate growth. Theoretically, androgen supplementation could even unmask an indolent prostate cancer. Several studies have examined the role of testosterone supplementation and voiding difficulties. None demonstrated significant changes in urine flow rates, post-void residual volumes, or voiding symptom scores. Prostate volumes have been shown to increase in men treated with testosterone. However, studies have shown that this increase is similar to that of age matched eugonadal men.[47-49] Studies have also examined the development of prostate cancer in men treated with testosterone supplements. A review of several randomized trials showed a low number of prostate cancers detected in patients receiving testosterone. However, the number of new cases detected was similar to the prevalence in the general population.[50] A recent meta-analysis showed that prostate events occurred significantly more in treated groups. Prostate events included diagnosis of prostate cancer, elevation of PSA, and prostate biopsies. However, none of these endpoints reached statistical significance alone.[42] Regardless, patients receiving testosterone supplementation should routinely undergo digital rectal exam and PSA screening. Further study has shown that even patients at higher risk of developing prostate cancer can safely undergo testosterone replacement therapy. Rhoden et al, compared hypogonadal men with prostatic intraepithelial neoplasia (PIN) on needle biopsy with PIN- negative controls. Only one case of prostate cancer was diagnosed in the PIN+ group after 1 year of testosterone supplementation.[50] Another concern arises in the treatment of hypogonadal patients after primary treatment for prostate cancer. Historically, this was thought to be an absolute contraindication to androgen supplementation. Recently, there has been some evidence to suggest that select patients with a history of prostate cancer may safely benefit from testosterone replacement therapy. One study retrospectively reviewed seven patients with organ-confined disease treated with radical retropubic prostatectomy that were diagnosed with hypogonadism. After initiation of testosterone supplementation, no evidence of recurrence (based on PSA) was documented.[51] Similarly, a cohort often patients were studied and also showed no evidence of disease recurrence after a median follow-up of 19

months.[52] Larger randomized trials are needed to further assess the risk of prostate cancer development during testosterone replacement therapy.

Other risks

There are several other risks associated with testosterone replacement therapy. Skin reactions may occur with transdermal testosterone delivery systems. This is more commonly seen with patches than with gel formulations. Testicular size and fertility will decrease with supplementation as the pituitary-gonadal axis is suppressed with exogenous androgen. Gynecomastia and breast tenderness are uncommon side effects. Also, there have been some associations with supplementation and the development or exacerbation of sleep apnea.[41]

Conclusions

Androgen deficiency in the aging male (ADAM) describes a common clinical condition that may affect many elderly men and is likely under diagnosed because of the vague clinical symptoms. It is apparent that testosterone supplementation may improve many of the most common symptoms including bone density, body composition, mood and cognition, and sexual function. Supplementation is not without risks which are primarily associated with prostate events. However, evidence suggests that there is no correlation with supplementation and exacerbation of BPH or development of prostate cancer over the general population. Proper monitoring is necessary however. Recommendations include digital rectal exam, PSA, blood count, and liver function tests prior to initiation of therapy. During therapy, periodic digital rectal exam, PSA, and blood counts should be closely monitored.

Disclosure

Dr. Cully Carson is a member of the Speakers' Bureau for Auxilium Pharmaceuticcals, Pfizer and Lilly. He is a consultant for Pfizer and Lilly. □

References

1. Korenman SG et al. Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab* 1990;71(4):963-969.
2. Morales A, Heaton JP, Carson CC 3rd. Andropause: a misnomer for a true clinical entity. *J Urol* 2000;163(3):705-712.
3. Araujo AB et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007 [Epub ahead of print]
4. United States Census Bureau. 2005.
5. Harman SM et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2001;86(2):724-731.
6. Morley JE et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 1997;46(4):410-413.
7. Herbert J. The age of dehydroepiandrosterone. *Lancet* 1995;345(8959):1193-1194.
8. Compston JE. Sex steroids and bone. *Physiol Rev* 2001;81(1):419-447.
9. Slemenda, CW et al. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. *J Clin Invest* 1997;100(7):1755-1759.
10. van den Beld AW et al. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 2000;85(9):3276-3282.
11. Michael H et al. *Estrogen and testosterone use different cellular pathways to inhibit osteoclastogenesis and bone resorption. J Bone Miner Res* 2005;20(12):2224-2232.
12. Fink HA et al. Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab* 2006;91(10):3908-3915.
13. Holzbeierlein JM, McLaughlin MD, Thrasher JB. Complications of androgen deprivation therapy for prostate cancer. *Curr Opin Urol* 2004;14(3):177-183.
14. Isidori AM et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(3):280-293.
15. Hijazi RA, Cunningham GR. Andropause: is androgen replacement therapy indicated for the aging male? *Annu Rev Med* 2005;56:117-137.
16. Moffat SD et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab* 2002;87(11):5001-5007.
17. Moffat SD et al. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004;62(2):188-193.
18. Rosario ER et al. Age-related testosterone depletion and the development of Alzheimer disease. *JAMA* 2004;292(12):1431-1432.
19. Ramsden M et al. Androgens modulate beta-amyloid levels in male rat brain. *J Neurochem* 2003;87(4):1052-1055.
20. Ramsden M, Shin TM, Pike CJ. Androgens modulate neuronal vulnerability to kainate lesion. *Neuroscience* 2003;122(3):573-578.
21. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. *Eur J Endocrinol* 2006;155(6):773-781.
22. Seidman SN et al. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry* 2001;62(6):406-412.
23. Pope HG Jr et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003;160(1):105-111.
24. Bhasin S. Regulation of body composition by androgens. *J Endocrinol Invest* 2003;26(9):814-822.
25. Mauras N et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab* 1998;83(6):1886-1892.
26. Snyder PJ et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(8):2647-2653.
27. Blackman MR et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 2002;288(18):2282-2292.
28. Giannoulis MG et al. The Effects of Growth Hormone and/or Testosterone in Healthy Elderly Men: A Randomized Controlled Trial. *J Clin Endocrinol Metab* 2005.

29. Bhasin S et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996;335(1):1-7.
30. Wang C. et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-2853.
31. Woodhouse LJ et al. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J Clin Endocrinol Metab* 2004;89(2):718-726.
32. Carani C et al. The effects of testosterone replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men. *Psychoneuroendocrinology* 1995;20(7):743-753.
33. Skakkebaek NE et al. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol (Oxf)* 1981;14(1):49-61.
34. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000;164(2):371-375.
35. Isidori AM et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(4):381-394.
36. Mulhall JP et al. Effect of testosterone supplementation on sexual function in hypogonadal men with erectile dysfunction. *Urology* 2004;63(2):348-352;discussion 352-353.
37. Shabsigh R et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172(2):658-663.
38. Morales A et al. Testosterone supplementation for hypogonadal impotence: assessment of biochemical measures and therapeutic outcomes. *J Urol* 1997;157(3):849-854.
39. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996;334(11):707-714.
40. Hajjar RR, Kaiser FE, Morley JE Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab* 1997;82(11):3793-3796.
41. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004;350(5):482-492.
42. Calof OM et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 2005;60(11):1451-1457.
43. Kabakci G et al. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. *Cardiology* 1999;92(4):221-225.
44. English KM et al. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J* 2000;21(11):890-894.
45. Hak AE et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab* 2002;87(8):3632-3639.
46. Whitsel EA et al. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med* 2001;111(4):261-269.
47. Morales A. Androgen replacement therapy and prostate safety. *Eur Urol* 2002;41(2):113-120.
48. Meikle AW et al. Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. *Urology* 1997;49(2):191-196.
49. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf)* 1994;40(3):341-349.
50. Rhoden EL, MorgentalerA. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003:170(6 Pt 1):2348-2351.
51. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 2004;172(3):920-922.
52. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 2005;173(2):533-536.

Peyronie's disease: update on medical management and surgical tips

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JORDAN GH. Peyronie's disease: update on medical management and surgical tips. The Canadian Journal of Urology. 2007;14(Supplement 1):69-74.

Peyronie's disease is a scarring phenomenon of the penis causing various deformities; initially pain with erection, and in most patients is associated with some element of erectile dysfunction. Studies of the natural history of the disease show that Peyronie's disease is a self-limited condition. In its stable and quiescent phase, patients have stable deformity, and in some cases that deformity then requires surgery.

For the most part, pharmacologic therapy is confined to the immature or active phase of the disease. Pharmacotherapy is aimed at trying to adjust or interfere with the scarring process, so that the resultant scar causes as little disability as possible to the patient. Most pharmacotherapy is thus useful only in the active/immature phase of disease. In the mature or quiescent phase of the disease, therapy is aimed at undoing the effects of the scarring lesion. Those therapies for the most part can be considered "scar revisions". There is no best surgical therapy, and unfortunately because the disease process generally evolves with the background of erectile dysfunction, often times with surgery there is progression of the erectile dysfunction. All patients should be counseled with regards to the option of continued watchful waiting. Patients who are operated on must be counseled with regards to realistic outcomes.

Key Words: acquired curvature, Peyronie's disease, plastic induration of penis

Introduction

Peyronie's disease is a scarring phenomenon affecting the tunica albuginea of the corpora cavernosa.[1] Scar tissue forms "plaques" that can result in pain with erection, penile curvature/deviation, penile shortening, indentations, and erectile dysfunction. It is associated with difficulty with sexual intercourse, loss of self-esteem, and depression. Peyronie's disease was probably first described in 1561 by Fallopius. However, the disease has derived its' name from Francois de la Peyronie. The disease was described by him in a manuscript in 1743. In Europe, it tends to be referred to plastic induration of the penis or induratio plastica pene. Peyronie's disease is incurable. Couples afflicted with Peyronie's disease require significant education and reassurance. Medical therapy has a place, although well performed studies proving efficacy of medical therapy for the most part have not been done. Fortunately few patients require surgery.

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Associated entities and demographics

The fibrous lesions which occur in the tunica albuginea impede expansion of the tunica albuginea causing curvature and/or indentation and/or foreshortening. These fibrous lesions are usually associated with the septal insertion usually dorsally, occasionally ventrally. Multiple lesions can occur in the same patient.

A number of entities have been implicated as being associated with Peyronie's disease. Beta blockers were felt to be causative; however, the association of beta blockers has not been proven durable. At the time beta blockers were implicated, they had just been introduced, and many of the patients treated for hypertension were on first generation beta blockers. If there is an association of beta blockers, it is probably due to the erectile dysfunction that can be caused by beta blockers. Dilantin (phenytoin) has been implicated as being associated with Peyronie's disease. During post-marketing trials of phenytoin, patients were noted to develop gingival hyperplasia, and there also were patients who developed Peyronie's disease. The two afflictions were considered possibly related; hence, phenytoin carries the warning in the Physician's Desk Reference® (PDR) that it can be associated with Peyronie's disease. The association with Paget's disease of the bone was described by Lyles[2] in a very nice study from the University of North Carolina. Subsequent studies have not been done; however, the results of that study did show an association. Diabetes mellitus has been associated with the development of Peyronie's disease. Interestingly diabetes mellitus is associated with the development of Dupuytren's disease. Whether it is the diabetes per se or again the erectile dysfunction in the case of Peyronie's disease is not clear. Dupuytren's disease is familial and is caused by an autosomal dominant gene. In patients with Peyronie's disease, coincident Dupuytren's is found in about 10%-40%. In patients with Dupuytren's, approximately 15%-30% will be found to have Peyronie's disease.[3,4] Other incidence figures vary. Jordan in 1999 reports a symptomatic incidence of 1%.[5] Lindsay in an article implicating rheumatoid arthritis and hypertension as being associated with Peyronie's disease found a prevalence of 0.4%.[6] Smith in a histologic study found asymptomatic prevalence of approximately 22%.[1] It is a disease of 45-65 with a mean age of onset of 53 years of age.[7,8] These are the years of loss of tissue elasticity, and the years of development of subtle erectile dysfunction. Whether erectile dysfunction causes Peyronie's disease, or vice versa, remains debated. I think many believe now that erectile dysfunction may be one of the causative factors leading to the development of Peyronie's disease.

Etiologic considerations and pathology

In a most commonly accepted etiology, Peyronie's disease is caused by trauma to the insertion of the septal fibers.[9-11] This trauma is then associated with inflammation, and then that inflammatory process becomes a disordered wound healing process.[12] Peyronie's disease is a self-limited condition. As the disease goes to maturity and quiescence, the patient is left with a scar that is out of proportion to any trauma that might have caused it.

The trauma to the insertion of the septal fibers causes intravasation of blood products into the traumatized area. This activates the fibrinogen cascade and mature Peyronie's plaques are found to contain fibrin deposits.[13] The midline septal insertion seems to be vulnerable with buckling. The septal fibers insert into the inner circular layer, there is no septal attachment of the inner circular layer to the outer longitudinal layer allowing for trauma to cause a delamination process.

As mentioned, Peyronie's disease is associated with Paget's disease of the bone[2] and Dupuytren's disease.[3] While certain LHRH subtypes were implicated as being related to Peyronie's disease by Leffell, however, those associations are not conclusively proven in that inadequate numbers of patients were examined.[14] Stewart proposed an association autoimmune disease,[15] however, Schiavino examined a number of autoimmune variables and found no evidence of Peyronie's disease being an autoimmune disease.[16] Diegelman has found that the plaque of Peyronie's disease is clearly associated with hyperactive wound healing.[12]

In Smith's histologic study, he found round cell infiltration in the space between the erectile tissue and the overlying tunica albuginea/developing plaque.[1] These round cells were inflammatory cells, and the notice of these cells has guided much of medical therapy sine they were noticed. Eventually this space, termed the space of Smith, becomes obliterated. Somers identified fibrin deposits in mature Peyronie's plaques and this is unusual to the scars of Peyronie's disease. The histology of the plaque is characterized by dense collagen with decreased elastin content. Plaques can undergo dystrophic calcification and in some cases cartilaginous metaplasia.[13]

If one examines the anatomy of the tunica albuginea, the tunica albuginea is bilaminar throughout most of its circumference. However, the outer longitudinal layer attenuates at roughly the 5 o'clock and 7 o'clock position, hence the ventral midline is monolaminar. The tunica albuginea is thinnest at the 3 o'clock and 9 o'clock position and thickest at the dorsal midline, and at the areas of attenuation at the 5 o'clock and 7 o'clock position.

Because the ventral tunica albuginea is monolaminar, the dorsum is felt possibly to be vulnerable to buckling trauma and this may be an explanation for the fact that most Peyronie's disease causes dorsal curvature and most Peyronie's plaques are prominently dorsal.[17]

The tunica albuginea is comprised of collagen that is brittle. The compliance of the tunica albuginea is due to the fact that collagen is arranged in helices which can straighten. Then with further distraction the collagen can slide one collagen fibril against the other. The elastin which are arranged at right angles to the collagen stretches. The elastic stretches only to a certain point, at which point the tunica becomes further noncompliant. Any further stretching occurs with displacement of the mucopolysaccharide ground substance.[18]

As mentioned, repeated mechanical stress causing microvascular trauma is felt to be associated with the development of Peyronie's disease. This causes delamination, bleeding within the tunica albuginea, and activation of the fibrinogen cascade.[13] The body floods the area with inflammatory cells which initially serve mechanical function but then secrete a number of very potent vasoactive factors.[19] In that the layers of the tunica albuginea are relatively avascular, the inflammatory reaction has been described as "trapped". Vasoactive factors such as platelet derived growth factors A&B and transfer growth factor beta 1 have been implicated. With regards the implication of transforming growth factor beta 1, this growth factor has been implicated in other soft tissue fibrosis, and is implicated in erectile dysfunction. Transforming growth factor beta 1 causes increased synthesis of fibroblasts, increased connective tissue, inhibits the activity of collagenases, and can induce its own production.[20-22]

Peyronie's disease is a disease of phases with an active or immature phase during which the patient may have painful erections, and usually notices migratory deformity. During the secondary or quiescent phase, the pain resolves, and the deformity stabilizes.[7]

Psychological aspects

The psychological aspects of Peyronie's disease are very poorly defined in the literature and much of the literature mentions the psychological aspects only in passing. Jones has described the counseling of Peyronie's patients as like unto the counseling associated with one who has suffered a death. The patient deals with many of the same mechanisms which include denial, ambivalence, anxiety, and depression. Added to this are shame, embarrassment, and self-disgust. Peyronie's patients have been described as patients with aging tissues, but a youthful libido. They are found to relate with intercourse. Peyronie's patients are not talkers, and as such they do not like to talk about their Peyronie's problem. These couples are in significant stress and many have been told that Peyronie's disease is the "end of their sex life". They admit that they are coping poorly. They do believe that "sex" is intercourse. It is imperative when initially encountering Peyronie's couples to encourage them to keep "sexual expression" alive.[23,24]

With regards to the plaques or induration, many patients are not aware of having these plaques. The fibrosis can descend along the septal fibers and the plaques can be multiple. As already mentioned, they are usually dorsal. The pain is usually only with erections, however, pain with erection and pain with intercourse should not be confused. Pain with erection inevitably resolves as the disease process enters the mature phase, however, pain with intercourse can persist. While the curvature of Peyronie's disease is usually dorsal, the curvature can be complex with significant lateral components. In most patients, some element of indentation of the corpora cavernosa can be noted.

The reported incidence of erectile dysfunction is variable. Most however would agree that a reasonable reported incidence is about 40%.[10]

Studies of Peyronie's plaques as mentioned show reduced elastin and an increase in type-3 collagen. Peyronie's disease is associated with veno-occlusive problems, Ralph feels that the cavernosal fibrosis can interfere with arterial flow. This has not been verified by other investigators. [1,13,25]

Medical/nonsurgical management

Medical management of Peyronie's disease is for the most part completely anecdotal. Agents are tried based on the intellectual aspects of their proposed mechanism of action. During the active phase, all pharmacological treatment aims to steer the process of fibrosis. Thus some agents would aim to diminish oxidative stress. Oxidative stress occurs during trauma, the free radicals are released and perpetuate further oxidative stress. Thus the number of agents is used because they purge the system of free radicals. Further healing as mentioned involves inflammation, and there appears to be some merit in addressing the entire inflammatory milieu. This should not be confused with stating that the treatment of Peyronie's disease is improved by using anti-inflammatory drugs. Most anti-inflammatory drugs address the results of the inflammatory milieu, but do nothing to diminish the inflammatory milieu. As mentioned, the phase of inflammation becomes one of

disordered wound healing governed by a number of growth factors and transforming growth factor beta 1 has been implicated. Thus drugs that purge the system of transforming growth factor beta 1 have been tried. Fibrosis involves the creation of collagen. The formation of collagen can be blocked at its inception, by either blocking the precursors to collagen or by blocking the exocytosis of collagen per se. A number of agents have been tried, vitamin E as an anti-oxidant and free radical scavenger.[26] Potaba has been proposed and is a direct blocker of fibrosis.[27] Allegra is a non-specific antihistamine and is aimed at diminishing the inflammatory milieu.[28] Colchicine[29,30] and Tamoxifen have been proposed as useful.[31,32] Carnitine which aids in blocking inflammation in blood vessels has been suggested to have efficacy.[33,34] Pentoxifylline (Trental) has been proposed.[35] This drug has the rather unique property of increasing vascularity, by diminishing the viscosity of red blood cells. Natulin was proposed and that has not been shown beneficial and has been taken off the market. There is no indication for the use of oral steroids or non-specific anti-inflammatory drugs.

The use of non-on-demand PDE5 inhibitors has been recently proposed.[36] Its use is based on the notice that in a number of situations, antifibrotic agents appear to be down-regulated. Cyclic GMP functions as an anti-fibrotic, and hence PDE5 inhibition is felt to possibly be useful in increasing the milieu of the cyclic GMP antifibrotic. Unfortunately rigorous well designed studies are lacking. As it stands now, the role of oral therapy seems to alter the progress of the disease and all oral agent use is probably limited to the acute phase of disease. Intralesional injection protocols have used steroids in the past. A WHO statement has suggested no place for the use of steroids.[37,38] Parathyroid hormone was proposed in a study by Morales.[39,40] That study did show efficacy, no further verifying studies have been done. Orgotein was proposed as an intralesional injection agent, Orgotein has been taken off of the market in all countries.[41] Verapamil, a calcium channel blocker, has been proposed as an intralesional injection agent. This agent has probably been used more than any other agents. Its use is based on the fact that fibrinectin and glycoaminoglycans are inhibited thus diminishing the production of collagen.[42,43] Interferon alpha 2 beta has also been proposed as useful, and it works by a very similar mechanism.[44] Recently clostridial Collagenase has been proposed.[45] This agent is available only in clinical trials. Collagenase being an enzyme, the method of action is different. Simply stated, the use of Collagenase suggests that it can create "chemical incisions" which can allow the plaque to expand and which can reinitiate the process of modeling. A number of topical agents have been suggested, the agent most commonly used now is topical verapamil, however, there is really no proven efficacy, single reports report anecdotal usefulness. Lithotripsy has been proposed. Its rationale for use is somewhat questionable and difficult to understand.[46,47] There are no blinded and controlled studies. There are no studies that show proven efficacy. There is a question of having ill-effects on erectile tissue, lithotripsy has been proposed as possibly useful as an adjuvant to intralesional injection therapy. A number of combined therapy protocols have been proposed.

Surgical therapy

As mentioned, future research would appear to be aimed at the topic of down regulation of "anti-fibrotics". The matrix metalloproteinase have been found to be down regulated, and appear to be selectively down regulated in Peyronie's disease.[48] Alpha 1 antitrypsin has been found to be down regulated in Peyronie's patients by Hauck.[49] However, further studies show equal down regulation in aged matched individuals. The down regulation of cyclic GMP with erectile dysfunction has already been discussed.[36]

Patients become surgical candidates when the deformity and/or the erectile dysfunction precludes intercourse. Patients must be in the stable or quiescent phase of disease and most centers would suggest at least a year from onset of symptoms. The deformity should be stable for at least 3-6 months, the patients must be pain-free (pain with erection-free). These patients benefit from detailed assessment of erectile dysfunction with stratification. It is imperative that patients be truly informed of what can be accomplished. What is accomplished is that patients can be provided a penis which is adequate for intercourse.

Generically speaking, surgical procedures can be lumped into those that shorten the long side, or those that lengthen the short side. Those that shorten the long side are either plication, tunical resection procedures, or corporoplasty procedures. There are many procedures that are described, the Peyronie's surgeon must be versed with all. Certainly plication or corporoplasty procedures have a prominent place in the surgical management of Peyronie's disease.

With regards to procedures that lengthen the short side, these are the procedures that either excise the plaque or incise the plaque and replace the corporotomy defect with graft material of some kind. By and large, excision of the plaque has been replaced by incision procedures. A number of graft materials

have been proposed. Those that have stood the test of time are dermal grafts,[50] vein grafts,[51] and some of the recently used off-the-shelf grafts. Cadaveric pericardium has been proposed as useful,[52] and the Surgisis Biodesign graft has been proposed as useful.[53]

In patients with poor erectile dysfunction and Peyronie's disease, there clearly is a place for prosthetic implantation. Wilson's[54] description of the modeling procedure has allowed patients to have their penis straightened at the time of prosthetic implantation without the need for incisions or incisions and grafting.

Summary

In summary, surgery for Peyronie's disease is palliative. It is imperative that patients have realistic expectations. It is also important that patients understand that medical therapy has not been subjected to rigorous testing, and the use of medical therapy, in large part, is anecdotal. However, the vast majority of patients with Peyronie's disease can be improved. In many, it is an improvement of their psyche by reassurance and education. However, in many surgery can restore patients to a useful sexual interaction. It must be remembered, however, that the disease is self-limited, that many of the variables that have been measured previously as indicators of pharmacologic treatment efficacy are actually part of the natural progression of the disease. The worst thing that a surgeon can do with a Peyronie's patient is rush them to the operating table in haste.

Disclosure

Dr. Gerald Jordan is an investigator and lecturer for Auxilium Pharmaceuticals, a board member of Engineers & Doctors and director, medical development of PNN. He is a speaker for American Medical Systems and a consultant for Coloplast. □

References

1. Smith BH. Peyronie's disease. *Am J Clin Pathol* 1966;45(6):;670-678.
2. Lyles KWE, Gold DT, Newton RA, Parekh S, Shipp KM, Pieper CF, Krishan R, Carson CC 3rd. Peyronie's disease is associated with Paget's disease of bone. *J Bone Miner Res* 1997;12(6):929-934.
3. Nyberg LM Jr, Bias WB, Hochbert MC, Walsh PC. Identification of an inherited form of Peyronie's disease with autosomal dominant inheritance and association with Dupuytren's contracture and histocompatibility B7-cross-reacting antigens. *J Urol* 1982;12.
4. Ralph DJ, Schwartz G, Moore W et al. The genetic and bacteriological aspects of Peyronie's disease. *J Urol* 1997;157:291-294.
5. Carson CC, Jordan GH, Gelbard MK. Peyronie's disease: New concepts etiology, diagnosis, and treatment. *Cont Urol* 1999;1(2):44-64.
6. Lindsay MB, Schain DM, Grambsch P et al. The incidence of Peyronie's disease in Rochester, Minnesota, 1960 through 1984. *J Urol* 1991;146:1007-1009.
7. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. *J Urol* 1990;144:1376-1379.
8. Williams J, Thomas G. The natural history of Peyronie's disease. *J Urol* 1970;103:75.
9. Devine CJ Jr, Somers KD, Jordan GH, Schlossberg SM. Proposal: Trauma as the cause of the Peyronie's lesion. *J Urol* 1997;157:285-290.
10. Jarow JP, Lowe FC. Penile-trauma: An etiologic factor in Peyronie's disease and erectile dysfunction. *J Urol* 1997;158:1388-1390.
11. Devine CJ JR, Horton CE. Peyronie's disease. *Clin Plast Surg* 1988;15:405-409.
12. Diegelmann RF. Cellular and biochemical aspects of normal and abnormal wound healing: An overview. *J Urol* 1997;157:298-302.
13. Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. *J Urol* 1997;157:311-315.
14. Leffell MS. Is there an immunogenetic basis for Peyronie's diease? *J Urol* 1997;157(1):295-297.
15. Stewart S, Malto M, Sandberg L, Colburn KD. Increased serum levels of anti-elastin antibodies in patients with Peyronie's disease. *J Urol* 1994;152(1):105-106.
16. Schiavano D, Sasso F, Nucera E, Alcini E, Gulino G, Milani A, Patriarca G. Immunologic findings in Peyronie's disease: a controlled study. *Urol* 1997;50(5);764-768.
17. El-Sakka AI, Hassan MU, Nunes L, Bhatnagar RS, Yes TS, Lue TF. Histological and ultrastructural alteration in an animal model of Peyronie's disease. *Br J Urol* 1998:81;444-452.
18. Brock G, Hsu GL, Nunes L et al. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. *J Urol* 1997;157:276-281.
19. Van DeWater L. Mechanisms by which fibrin and fibronectin appear in healing wounds: Implications for Peyronie's disease. *J Urol* 1997;157:306-310.
20. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. *N Engl J Med* 1994;331:1286-1292.
21. Border WA, Ruoslahti E. Transforming growth factor-beta in disease: The dark side of tissue repair. *J Clin Invest* 1992;90:1-7.
22. Moreland RB. Is there a role in hypoxemia in penile fibrosis: A viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res* 1998;10:113-120.
23. Jones WJ. Counseling men with sexual dysfunction. *AUA Update Series* 1997;XVI (Lesson 23):178-184.
24. Fisher WA, Rosen RC, Eardley I, Sand M, Goldstein I. Sexual experience of female partners of men with erectile dysfunction: the female experience of men's attitudes to life events and sexuality (FEMALES) study. *J Sex Med* 2005:2(5):675-684.
25. Ehrlich HP. Scar contracture: cellular and connective tissue aspects in Peyronie's disease. *J Urol* 1997;157(1);316-319.
26. Scardino PL, Scott WW. The 4 use of tocopherols in the treatment of Peyronie's 6 disease. *Ann N Y Acad Sci* 1949;52:390.
27. Zarafonetis CJD, Horrax TM. Treatment of Peyronie's disease with potassium para-aminobenzoate (Potaba). *J Urol* 1953;81:770-772.
28. Jordan, anecdotal use data not published.
29. Gelbard, anecdotal use data not published.
30. Mynderse L, Monga M. Oral therapy for Peyronie's disease. *Int J Impot Res* 2002:14(5);340-344.
31. Ralph DJ, Brooks MD, Bottiazzo GF, Pryor JP. The treatment of Peyronie's disease with Tamoxifen. *Br J Urol* 1992;70(6):648-651.

32. Teloken C, Rhoden EL, Grazziotin TM et al. Tamoxifen versus placebo in the treatment of Peyronie's disease. *J Urol* 1999;162:2003-2005.
33. Biogiotti G, Cavallini G. Acetyl-L Carnitine in the oral therapy of Peyronie's disease: a preliminary report. *BJU Int* 2001:88:63-67.
34. Cavallini G, Biogiotti G et al. Oral proprionyl –L-carnitine and intraplaque Verapamil in the therapy of advanced and resistant Peyronie's disease. *BJU Int* 2002;89(9):895-900.
35. Lue data not published.
36. Vernet D, Magee T, Qian A, Nolazco G, Rajfer J, Gonzales-Cadavid N. Phosphodiesterase type-5 is not upregulated by Tadalafil in cultures of human penile cells. *J Sex Med* 2006;3(1):84-94.
37. Teasley G. Peyronie's disease: The new approach. *J Urol* 1954;105:523.
38. World Health Organization Report, Sexual Medicine, Sexual Dysfunctions in Men and Women, 2nd International Consultation on Sexual Dysfunctions-Paris, 2004 (Editors: Lue T, Basson R, Rosen R, Giuliano F, Khoury S, and Montorsi F), Health Publications.
39. Morales A, Bruce AW. The treatment of Peyronie's disease with parathyroid hormone. *J Urol* 1975;114(6):901-902.
40. Walker – Biochemical and Biophysical Research, communication 1964.
41. Gustafson H, Johansson B, Edsmyr F. Peyronie's disease: experience of local treatment with Orgotein. *Eur Urol* 1981;7(6):346-348.
42. Levine L, Merrick P, Lee R. Intralesional verapamil injection for the treatment of Peyronie's disease disease. *J Urol* 1994;151:1522-1524.
43. Rehman J, Bennet A, Melman A. Use of intralesional Verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urol* 1998;51:620-626.
44. Duncan MR, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by Interferons-alpha, -beta and-gamma. *Scan J Urol Nephrol* 1991;25;89-94
45. Jordan GH. The Use of intralesional clostridial collagenase injection therapy for Peyronie's disease: A prospective, single-center, non-placebo controlled study. *J Sex Med* 2007 (In Press)
46. Bellorofonte C, Ruoppolo M, Tura M, Zaatar C, Tombolini P, Menchini Fabris GF:PossibIlity of using the piezoelectric lithotripter in the treatrment of severe cavernous fibrosis. *Arch Ital Urol Nefrol Androl* 1989;61(4):417-422.
47. Hauck EW, Hauptmann A, Schmelz HU, Bein G, Weidner W, Hackstein H. Prospective analysis of single nucleotide polymorphisms of the transforming growth factor beta-1 gene in Peyronie's disease. *J Urol* 2003;169:369-372.
48. Lin CS, Lin G, Lue TF. Cyclic nucleotide signaling in cavernous smooth muscle. *J Sex Med* 2005;2(4):478-491.
49. Hauck EW, Hauptmann A, Bohnert A et al. Prospective analysis of alpha-1-antitrypsin levels and genetic variation of the alpha-1-antitrypsin gene in patients with Peyronie's disease. *J Sex Med* 2004;(1):Supplment 1:Abstract 66:49-50.
50. Devine CJ Jr, Horton CE. The surgical treatment of Peyronie's disease with a dermal graft. *J Urol* 1974;111:44
51. Sachse H. Venous wall graft in Peyronie's disease. *Urol* A 1976;15(3) German.
52. Hellstrom WJG, Reddy S. Application of pericardial graft in the surgical management of Peyronie's disease. *J Urol* 2000;163:1445-1447.
53. Knoll LD. Use of porcine small intestinal submucosal graft in the surgical management of Peyronie's disease: Review of 97 patients. Abstract 1068. *J Urol* 2003:169(4):275.
54. Wilson SK, Delk JR II. A new treatment for Peyronie's disease: Modeling the penis over an inflatable penile prosthesis. *J Urol* 1994;152:1121-1123.

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