Radical prostatectomy is one of the most effective methods of treating localized prostate cancer in men under the age of 70, yet the maturation of multiple large surgical series demonstrates that surgical failure represented by a postsurgical serum prostate-specific antigen (PSA) elevation is not uncommon. An overall actuarial failure rate of 22%, defined by serum PSA elevation, was recently reported for a very representative series of approximately 1000 men. The Mayo Clinic series reported 10-year and 15-year actuarial serum PSA progression of 48% and 60%. Another large series of 600 patients displayed a 5-year and 10-year PSA disease-free rate of 69% and 47% overall. When only patients treated after 1986 were analyzed, however, the 5-year disease-free rate measured by only serum PSA was 93%. Similarly, the review of the Johns Hopkins series of T1 and T2 patients showed a 5-year PSA-only recurrence of 13%. Clinical local recurrence at 5 years was 3% and distant recurrence in that time period was 5%. These data suggest that 10% to 40% of men who undergo a radical prostatectomy for control of localized disease will develop a detectable PSA level over 5 years. Refinements in preoperative patient selection will undoubtedly tighten this range to its lower limits, yet contemporarily a significant amount of patients will still fail surgical therapy and one of the most common signs of treatment failure will not be a change in the digital rectal examination (DRE) or an imaging test, but rather a rising serum PSA. Tumor progression rarely occurs in the absence of an elevated serum PSA. A rising serum PSA after surgical treatment for localized prostate cancer presents a diagnostic and therapeutic dilemma that does not lend itself to routine treatment decisions. Most of the clinical data pertinent to the treatment of postprostatectomy elevations must be extrapolated from earlier studies involving the treatment of gross positive surgical margins. Some of this data may not be entirely appropriate for decision making in the contemporary setting because recent refinements in preoperative evaluation of patients select a population of postsurgical patients less likely to have gross positive margins or occult spread to regional lymph nodes. Additionally, the majority of studies related to the treatment of elevated postsurgical serum PSA describe the clinical outcome of a fairly small number of patients.

Data regarding androgen ablation therapy in patients with a postprostatectomy rise in

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SERUM PROSTATE-SPECIFIC ANTIGEN ELEVATION IN THE POST–RADICAL PROSTATECTOMY PATIENT

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serum PSA are similarly extrapolated from studies of patients with advanced metastatic disease. There are no data to prove or refute the value of androgen ablation therapy in patients with a postoperative rise in serum PSA. Such treatment may be costly and the long-term sequellae of different forms of androgen ablation unknown.

The positive effect of any therapy must be balanced against the potential side effects and true potential for having a beneficial impact. This article reviews the definition of an elevated post–radical prostatectomy serum PSA, the assessment of local or distant recurrence, and treatment recommendations based on current data.

DETECTION OF RECURRENT DISEASE AFTER RADICAL PROSTATECTOMY

Postsurgical PSA Elevation

With the introduction of serum PSA, a sensitive and powerful tool for monitoring patient status after radical prostatectomy became available. Criteria for serum elevation have been meticulously developed with standard assays and have continued to be redefined with the introduction of more sophisticated methods of serum PSA determination. Because PSA has a serum half-life estimated at 2.2 to 3.5 days, sufficient time should usually be given between surgery and the first serum assay to allow levels to fall into an “undetectable range.” Another way of asking this is, what is the residual cancer detection limit (RCDL) of this assay? Using the Tandem-R assay (Hybritech, San Diego, CA), it was demonstrated that the RCDL was 0.4 ng/mL because all patients with that serum level of PSA displayed continued progression. Practically all patients who develop a pattern of rising PSA after radical prostatectomy, however, later develop clinical evidence of persistent disease. The lag time between chemical detection and clinical disease is significant and can range from 6 to 48 months. It was also significant that nearly 40% of patients who eventually displayed progression had an initially undetectable serum PSA, thus underscoring the need for serial determinations over time.

With the development of more sensitive assays, the RCDL was lowered to 0.1 ng/mL (IMx PSA assay, Abbot Laboratories, Chicago, IL). This in turn increased the clinical lag time to detection by nearly a year. Similar results were noted by investigators using the ultrasensitive Pros-Check assay (Yang Laboratories, Bellvue, WA). With the development of even more sophisticated assays, this short time from laboratory data to clinical findings shall probably be increased further. Such data may, however, be theoretically confounded by the extraprostatic production of PSA. Furthermore, its clinical use shall in part be determined by our ability accurately to localize such early recurrent disease and treat it effectively. Recently, serum PSA evaluation has been enhanced through the development of assays that measure free and complexed molecular forms. The composition of detectable postoperative serum PSA with respect to these molecular forms and the ability derive any useful clinical information in that regard is presently under investigation. Additionally, nonimmunologic methods of detecting prostate cancer have been developed through the use of PSA-specific reverse transcriptase–polymerase chain reaction technology. Its role in resolving issues of tumor recurrence and prognosis in this clinical setting is undetermined at present.

Physical Examination

The most direct route to examining the surgical bed is through the DRE, yet in the absence of an elevated PSA it is unlikely that irregularities noted on examination will reveal localized recurrent prostate cancer. The postsurgical alterations in the prostate bed are similar among men who have local recurrent disease and those who have no disease or distant disease. Biopsies performed for physical signs only are almost always negative, whereas in one study 18% of men with completely negative physical examinations and elevated PSA levels had positive biopsies. Changes on a single physical examination alone are, therefore, insufficiently sensitive or specific for the detection or localization of minimal volume recurrent disease. Serial physical examinations may, however, provide help in detecting recurrent disease especially if good documentation of examination findings is maintained.
Needle Biopsy of the Urethrovesical Anastomosis

The development of small-gauge spring-loaded needle biopsy instruments has provided the means to assess easily the urethrovesical anastomosis with a minimum of disruption. Multiple studies have suggested that the probability of obtaining a positive urethrovesical anastomosis biopsy on the basis of an elevated PSA alone is in the range of 50%. This finding does not seem to be influenced by findings on the DRE. Although transrectal ultrasound (TRUS) provides superior imaging of this area, it probably has little impact on tumor detection beyond the appropriate placement of the biopsy needle. Descriptions of the post–radical prostatectomy vesicourethral anatomy have been published and much of the resultant postoperative tissue has a hypoechoic appearance. These postoperative changes make TRUS a rather insensitive and nonspecific modality for evaluating local recurrence of prostate cancer. Again, its value during serial monitoring may be greater.

Local and Distant Imaging

Pelvic CT scan or MR imaging have little to add to an evaluation for potential locally recurrent disease. Theoretically, endorectal coil MR imaging (erMRI) may add greater sensitivity or specificity to the evaluation of local recurrence in the presence of a postoperative elevation in PSA, but this has not been studied in a systematic fashion. The imaging resolution for erMRI with present technology is 3 mm, which is appreciably better than TRUS. Any advantage with such imaging would probably be diminished by the need to correlate subtle MR imaging findings with ultrasound findings at the time of biopsy because direct erMRI imaging–guided biopsy is not feasible. In the absence of any solid data to recommend its use, erMR imaging is not an appropriate modality for the routine evaluation of elevated serum PSA findings in the post–radical prostatectomy patient.

With an elevation of the serum PSA in the patient who has undergone a radical prostatectomy, there is an inclination to obtain a bone scan, especially in those patients with high-grade disease or rapid appearance of detectable serum PSA after radical prostatectomy. Because the patient’s clinical status is changing with this new finding of an elevated serum PSA, a bone scan is warranted. A bone scan is absolutely indicated in these circumstances if the rise in serum PSA is accompanied by bone pain. The yield on bone scan in this setting, however, is quite low when the serum PSA level is below 8 ng/mL. The detection of low-volume metastatic disease is often difficult to confirm and may be aided by plain films or with body MR imaging scanning of the particular bone window. The sensitivity of finding occult disease may be improved in the future as radio-labeled tracers specific for prostate tissue are further refined.

Postsurgical PSA Elevation: Potential for Failure and Site of Recurrence

One of the more difficult issues in determining the impact of a serum PSA failure after radical prostatectomy is establishing the site of tumor recurrence. The potential for treatment failure to some extent can be determined by preoperative factors, such as the preoperative serum PSA value, physical examination, and tumor grade determined on biopsy. These parameters can provide predictive information with regard to margin positivity, seminal vesicle involvement, and to some extent lymph node involvement. There are also data that now suggest that similar information can be gathered from the tumor volume characteristics of the needle biopsies and the preoperative findings on endorectal coil MR imaging.

The surgical specimen can suggest whether the postoperative PSA value will be elevated as well as the potential for distant recurrence. In one study, 61% of patients with gross positive margins displayed an initial elevation of the postoperative PSA, whereas only 13% of organ-confined lesions had a similarly elevated PSA. In the Hopkins series only 2% of patients with organ-confined disease and 18% of positive-margin patients displayed a PSA elevation as evidence of surgical failure. In the Baylor series, 17% of patients without positive surgical margins and 36% of patients with positive margins displayed progression over 5 years. These lesions displayed true extracapsular extension and were in moderately differentiated lesions. In this series other factors, such as high tumor...
grade and seminal vesicle involvement, were of greater significance in determining overall progression.

A positive surgical margin, however, may be focal or gross. In many instances a microscopic focus or surface area of 1% or less does not have as significant a potential for PSA progression and may even be artifactual. Such patients are generally monitored with serial PSA determinations and further therapy based on chemical failure. Seminal vesicle involvement displays a much greater potential for both local and distant recurrence as does the presence of high-grade disease. While many pathologic features examined in a multifactorial analysis provide information with regard to overall PSA failure, most reports do not distinguish between local and distant failure.

Some distinction with regard to the anatomic location of tumor failure may be developed by evaluation of PSA kinetics postsurgically. In a series of 600 radical prostatectomy patients, PSA doubling times were established for 94 patients with prior adjuvant therapy. Those patients who ultimately progressed to distant disease had a median PSA doubling time of 4.3 months compared with 11.7 months in those who had clinically detected local failure or failure due to PSA elevation only.

Using a linear mixed-effects regression analysis, PSA velocity, pathologic stage, and Gleason grade best distinguished local failure from distant metastases. Those patients with low-grade disease generally had local recurrences and those with positive seminal vesicles generally failed distantly. Patients with moderate Gleason grade lesions had a mixed distribution of recurrences. A PSA velocity of 0.75 ng/mL/y or less was noted in over 90% of patients with local recurrence, whereas 50% of the patients with distant disease had a PSA velocity of greater than 0.75 ng/mL/y.

Who Benefits from Local Therapy?

The tumor location for patients with serum PSA failure after radical prostatectomy cannot be known with certainty, thus decision making with regard to the institution of regional therapy is hampered. Some logical extrapolations from the available data are sobering with regard to the potential efficacy of local treatment. Most series with long-term follow-up display a local recurrence rate of 10% to 25%. In the evaluation of an isolated serum PSA level in 79 post–radical prostatectomy patients, expectant management was instituted. In this series 42 men, 12 local and 30 distant recurrences, were detected for an approximate ratio of 1:4. In an indirect analysis, Takayama and Lange reasoned that few surgical series display an elevated serum PSA rate of greater than 50% and that many series can display a positive postoperative needle biopsy in up to 50% of postsurgical patients with an elevated PSA. This suggests a worse case scenario of 25% (0.5 × 0.5) local recurrence. Additionally, in the series of XRT therapy for isolated postoperative PSA elevations, only 23% of cases displayed an undetectable PSA level after 24 months. This suggests that local-regional therapy should be applied judiciously to attain the best outcomes. Patients with low- or moderate-grade specimen-confined lesions that are seminal vesicle negative and that demonstrate a slow PSA velocity are appropriate candidates for such therapy.

RADIATION THERAPY IN POSTPROSTATECTOMY PSA ELEVATION

The data on adjuvant radiation therapy or radiation therapy for PSA recurrence after radical prostatectomy consists of small-to-moderate size patient series generally evaluated in a retrospective fashion. Those series with a significant follow-up period represent patients diagnosed and treated prior to the widespread use of serum PSA tumor detection strategies or diagnosis by an ultrasound-guided spring-loaded needle biopsy. Classic data on recurrence patterns after radical prostatectomy demonstrated a 12% to 15% local recurrence rate. Although patient series are variable, the range of local recurrence after adjuvant radiation was 0% to 10%, with the highest level of recurrence in those patients followed up to 10 years. Androgen ablation was not included as part of these treatment regimens, yet it has been reported in other series.

In the report by Gibbons et al, a comparison of the patients treated with radiation therapy (n = 22) was made with a similar group of postsurgical patients who were followed for disease progression (n = 23). In these
patients, local recurrence in the untreated patients was 30% compared with a 4% recurrence rate in the treated group. No statistically significant survival advantage was noted in the treatment group compared with those expectantly managed, although there was a trend in that direction. Those patients receiving adjuvant therapy were less likely to develop metastasis or die a prostate cancer-related death compared with patients treated for clinically detectable local recurrence. It was also noted that long-term pelvic complications were higher in those patients treated with adjuvant radiation (14% versus 6%), yet the majority of these were related to the use of cobalt therapy.

These and other older data suggest that adjuvant radiation therapy offers superior local control to no therapy, yet it is difficult to demonstrate a raw survival or disease-free survival advantage from such small series. There is also the suggestion that immediate adjuvant therapy may be therapeutically superior to delayed therapy.

Contemporary series include data of preoperative and postoperative serum PSA levels and use PSA recurrence as a surrogate marker of treatment failure. Although modern needle biopsy technology was used in many instances and provides proof of local recurrence, often there is no tissue diagnosis of local failure, and patients have been treated on the basis of rising PSA values only. In several representative contemporary series, a low local recurrence rate of 0% to 5% is described. When comparisons with non-treated patients are made, the treated patients display significantly fewer local recurrences. These recurrence data recapitulate and even improve on classical series.

The newer data for such patients do not provide any direct or strong indirect evidence for a survival advantage secondary to radiation therapy for a rising PSA. No randomized clinical trial results are available at this time. Few series have greater than 5-year follow-up. The stage migration seen in recent years that makes surgical treatment for patients with high preoperative serum PSA levels and the potential for significant extra-capsular disease less likely also makes it more difficult to measure a true difference in real survival over a shorter time span. Among contemporary reports, a survival advantage was noted in a single institution series reported by Carter et al, in which pathologic stage pT3 patients demonstrated a 5-year mean survival of 92%. Many of these patients had high-grade and high stage C disease (C1,2,3,) decreasing the possibility that favorable results may be due to inappropriate stratification of low-stage, stage C patients in this group. Longer follow-up is necessary to validate these findings.

In several other representative series no data supporting a survival advantage has emerged. In one comparison of 77 pT3 patients who underwent radical prostatectomy for clinically local disease, the 34 who received adjuvant radiation had a mean failure rate (approximately 55%) similar to the remainder who received no radiation. No significant difference in outcome was noted when subgroup analysis was performed. In a large review of pT3 patients treated by radical prostatectomy, 131 received adjuvant radiation therapy, 103 underwent postoperative orchiectomy, and 661 received no additional therapy. At 10 years overall cause-specific survival was 81% and overall progression 44%. There were no differences noted in the survival or overall progression statistics between those treated with radiation or orchiectomy and the untreated patients. The local recurrence rate at 5 years was 16% in untreated patients and less than 5% in those treated with either radiation or orchiectomy.

The early results of radiation therapy in postprostatectomy patients with only an isolated PSA elevation have been reported by two groups. One series of 27 patients showed that 48% of patients maintained a serum PSA level of less than or equal to 0.3 ng/mL at 3 years after therapy. Those patients with a pretreatment serum PSA of less than or equal to 1.1 and no evidence of seminal vesicle involvement performed better than the remainder of patients. Also, those individuals who received therapy of 64 Gy or more displayed superior outcomes. In another report of 53 patients treated with a mean dose of 61.5 Gy, the disease-free survival (defined by undetectable serum PSA) at 2 years was only 23% and progression-free survival was 26%. Univariate analysis disclosed a prerationation therapy serum PSA level and undetectable PSA after therapy as predictors of no evidence of disease (NED) status. On multivariate analysis, however, only a prerationation therapy serum PSA value of less than or equal to 2.5 ng/mL was predictive of NED status. Postsurgical PSA doubling time was...
not a significant factor in this analysis, but the majority of patients in this study never had an undetectable postprostatectomy PSA (38/53).

The inability to demonstrate a survival advantage in patients treated with postoperative radiation therapy is not unexpected because less than one third of the patients probably have local disease only, and because the majority of analyses are retrospective descriptions involving small numbers of patients. Most adjuvant chemotherapy trials require several hundred patients to demonstrate appropriately a 10% to 20% improvement in survival. A prospective randomized intergroup trial of radiation versus observation in margin positive patients has been ongoing through the Southwest Oncology Group and continues slowly to accrue patients. Recently, those patients at high risk for recurrence after radical prostatectomy have been more precisely defined, thus identifying a cohort of patients who may be most appropriate for adjuvant trials.43

Side Effects of Radiation Therapy

The side effects of adjuvant or delayed external beam radiation therapy are potentially serious yet do not appear to occur with significant frequency, especially in contemporarily reported series. In general, 45 to 68 Gy have been delivered to the prostate bed. Most radiation oncologists feel that more than 45 Gy needs to be administered to have a therapeutic effect. Some severe classic complications, such as bowel fistula and gastrointestinal obstruction, are reported in the series using colbit therapy.23 Lower extremity edema is infrequently encountered and may have some relation to the limited lymph node dissections being performed contemporarily. Classically, 10% to 15% of patients experience short-term complications of increased bowel or bladder irritability but very few long-term complications are being reported.19, 35, 51, 59, 61, 62 Other significant complications of the radiated prostatic bed may include urethral stricture, urinary incontinence, or erectile impotence in those individuals with successful nerve-sparing surgery. Urinary incontinence has been reported from 10% to 20% in older series and 0% to 10% in recent reports of adjuvant therapy. In general, the type and degree of incontinence is often not reported, and often it is difficult to evaluate if the patient had regained maximal postoperative continence prior to receiving radiation therapy.

The side effects of adjuvant external beam radiation therapy in a large series of patients (n = 72) who had undergone a nerve-sparing radical prostatectomy were compared with a similar cohort of patients (n = 138) who declined therapy.19 Patients were treated with 45 to 54 Gy of radiation in standard fashion. Some unequal stratification was noted in the patient groups because those who underwent radiation had higher-stage and higher-grade disease. No significant difference was noted in urinary incontinence (6.1% versus 8.1%, p = 0.64), nor in erectile impotence when either bilateral or unilateral nerve-sparing procedures were used (48% versus 44%, bilateral; 33% versus 10%, unilateral; p = 0.14). In a multivariate analysis the factors that have independent impact on recovery of potency are age (less than or greater than 63 years old) and the type of nerve-sparing surgery (unilateral or bilateral). The median follow-up of these patients was 2.6 years. Although all treatment decisions need to be individualized, these types of results suggest that the contemporary use of adjuvant therapy for the treatment of margin-positive disease or a rising postoperative serum PSA should be based on the potential efficacy of therapy without significant concern for the potential of significant postradiation complications.

THE ROLE OF ANDROGEN ABLATION IN POSTSURGICAL ELEVATION OF SERUM PSA

Combined Antiandrogen and Luteinizing Hormone-Releasing Hormone Therapy

An elevated serum PSA after radical prostatectomy can be caused by the presence of persistent benign prostate tissue, persistent or recurrent local prostate cancer, regional or distant metastasis, or the combination of local and distant disease. In many instances when the tumor specimen displays very high-grade tumor or local extension to the seminal vesicles it is highly probable that the elevation in serum PSA represents the early emergence of
distant disease. At this time one must consider the role, if any, for androgen ablation.

Classically, the majority of literature in this deals with high-volume, detectable, osseous or visceral metastases and not a tumor burden detectable only through biochemical assay. It has been demonstrated in multiple studies that time to disease progression can be lengthened with androgen ablation, yet a true survival benefit from androgen ablation has not been demonstrated. It must be stated, however, that no contemporary study has been designed with sufficient statistical power to disprove that such a clinically significant survival benefit may exist. In the case of a postsurgical serum PSA elevation that is highly suspicious for local-regional and distant metastasis one must exercise clinical judgment based on extrapolations from the data on high-volume metastatic disease when considering therapy.

Combined androgen blockade, usually administered in the form of a luteinizing hormone–releasing hormone (LHRH) agonist and antiandrogen, is considered by many to be the most effective form of therapy for the treatment of metastatic prostate cancer. Much of this opinion is derived from the results of the intergroup study National Cancer Institute (NCI) No. 0036, which demonstrated an increased time to progression (7 months) and small but statistically significant survival advantage (4 months). Of greatest interest in this study was the subset analysis that suggested that those patients with low-volume metastatic disease and excellent performance status benefited the most from combined therapy. In fact, follow-up data at 60 plus months now demonstrates that in such low tumor volume patients there is an advantage in time to progression of 28 months and a survival advantage of 19 months.

Of greatest interest in this study was the subset analysis that suggested that those patients with low-volume metastatic disease and excellent performance status benefited the most from combined therapy. In fact, follow-up data at 60 plus months now demonstrates that in such low tumor volume patients there is an advantage in time to progression of 28 months and a survival advantage of 19 months.

In other studies, a confirmation of the early NCI 0036 data has been made or no apparent benefit of combined androgen blockade has been demonstrated. In a recent discussion regarding a planned overview analysis of the available combined androgen blockade data it is felt that many of the other combined androgen blockade trials are underpowered to show the benefit demonstrated in NCI 0036 and that much of the other data is immature (trial maturity heterogeneity). It is hoped that the data from intergroup (INT) 0105 (orchiectomy plus an antiandrogen versus orchiectomy plus placebo [1400 eligible patients]) will provide a more complete picture of combined androgen blockade in advanced disease. At this time the subset analysis of the NCI 0036 study appears most pertinent to the issues with which a clinician is faced when dealing with a postprostatectomy elevated serum PSA.

The use of combined androgen blockade or monotherapy with an LHRH agonist may be of maximal benefit to a patient with suspected advanced disease, yet is not without its side effects. Loss of libido and erectile dysfunction is usually of greater concern to the postprostatectomy patient and vasomotor hot flashes can be problematic for all patients, even if partial improvement can be obtained with the administration of megestrol acetate (Megace). Furthermore, prolonged androgen blockade in younger patients presents a group of problems not previously encountered and incompletely defined, such as general asthenia, loss of muscle mass, anemia, and possible changes in bone density. Additionally, the financial cost of such therapy can not be understated, especially if one considers the prolonged time frame for treatment. Even though the use of combined androgen blockade in patients with postprostatectomy PSA elevations has not been validated, it may be appropriate in some patients with suspected advanced disease.

Intermittent Androgen Blockade

One alternative to such therapy may be intermittent androgen blockade. In the androgen-sensitive Shionogi mouse mammary tumor it has been shown that intermittent androgen deprivation prolongs but does not prevent the emergence of androgen-independent tumor clones. The exact mechanism of this phenomenon is incompletely understood. It has been suggested that the adaptation of initially androgen sensitive clones to the androgen-independent state may take place. A feasibility study for the use of intermittent androgen blockade has been recently reported. Two treatment cycles of approximately 75 weeks were performed and patients were off therapy for approximately 40% to 45% of that time. During that time patients described an improved sense of well being and a return of libido and erectile activity. Approximately 20 weeks were required to
achieve a PSA nadir and serum testosterone levels returned to normal within 8 weeks (range 1 to 26). An improvement in time to progression or survival could not be deduced from this early study, and too few low-stage (T1-T2) patients (n = 4) were included for meaningful analysis. This treatment strategy is to be incorporated into future multi-institutional studies for advanced disease. There is no proof of principle for this variation of androgen ablation therapy in treating postprostatectomy PSA elevations at this time. Therefore, a treatment plan based on this concept would have to be individualized with careful counseling.

**Antiandrogen Therapy**

The use of antiandrogen therapy alone or with an agent other than orchiectomy or an LHRH agonist may be considered in the treatment of postprostatectomy serum PSA elevation. Such therapy, however, must be viewed in the context of historic data that demonstrates the inferiority of flutamide to low-dose diethylstilbesterol. Similarly, low-dose bicalutamide (Casodex) is inferior to orchiectomy in the treatment of advanced prostate cancer. Bicalutamide does display higher antiandrogen activity at higher doses. Although hot flushes may be greater with orchiectomy or LHRH therapy, patients treated with antiandrogen monotherapy generally display a greater incidence of breast tenderness or gynecomastia. For select patients with minimal volume advanced disease, such therapy may be a reasonable alternative to other forms of androgen ablation.

The combination of finasteride, 5 mg daily, and flutamide, 375 to 750 mg daily, was studied in 22 sexually active patients with stage T3 and TxN+ disease. An initial mean PSA of 42.9 nadired to 2.9 ng/mL by 6 months and was durable at 24 months. Eighty-six percent of men reported the preservation of libido and erectile function. Diarrhea of some degree was reported in 33% of patients and gynecomastia was seen in 19% of patients. Additionally, a 30% decrease in prostate volume assessed by TRUS was noted in these patients. This single-arm phase I/II study demonstrates the feasibility of this approach in future studies designed to assess time to progression and survival, but does not demonstrate proof of this approach as an appropriate course of action in the postprostatectomy patient with an elevated serum PSA. In specific situations, however, this form of therapy may be of value.

It is unknown at the present time whether antiandrogen therapy can delay or prevent the postoperative rise of serum PSA. A double-blind randomized trial of moderate course adjuvant bicalutamide versus placebo in early stage prostate cancer is underway and should be of sufficient power to provide a better understanding of the role of antiandrogens in the treatment of localized and regional disease.

**5 α-Reductase Inhibitors**

5 α-Reductase inhibitors, such as finasteride, display a minimal effect on TxNxM+ prostate cancer. This was investigated in a double-blind placebo-controlled study. At a dose of 10 mg, a 22% decrease in serum PSA could be detected at 6 weeks. This dose-level of finasteride was studied in a double-blind fashion for 12 months with a cross-over to finasteride for the next 12 months in 120 post–radical prostatectomy patients with a detectable serum PSA of 0.6 to 10 ng/mL. An average delay in the increase of the serum PSA of 14 months was noted over 2 years. Patients with a baseline serum PSA less than 1 ng/mL had no significant increase in serum PSA during the 2 years of treatment. Although fewer clinically detectable tumor recurrences were noted in the treatment group, this finding was not statistically significant. Significant sides effects in the treatment group were minimal and consisted of breast tenderness or gynecomastia in three patients. No survival data was available. Again, these data support the feasibility of this form of androgen blockade in studies evaluating the treatment of low-level postprostatectomy serum PSA elevation, but do not recommend the use of finasteride in the general treatment of this condition.

**Role of Androgen Ablation in Elevated Postsurgical PSA**

Although classic data suggest some progression but no survival benefit from androgen ablation, the subset analysis of NCI 0036 (LHRH plus antiandrogen versus LHRH
alone) displaying prolonged survival in combination blockade patients is compelling and most germaine to high-risk patients with an elevated postoperative serum PSA felt to represent early distant metastasis. Any decision to initiate androgen ablation should be made on an individual basis because the long-term side effects of such therapy are not inconsequential. Attenuated forms of androgen blockade are feasible, yet their true ability to prolong progression or improve survival will be adequately tested only in well-powered multi-institutional trials. The use of androgen blockade in patients with an elevated postoperative serum PSA can be challenged from an efficacy standpoint if one considers only survival data. In the general clinical situation, however, many patients are strongly affected by the finding of an elevated PSA and benefit from some form of therapy that can return this value to the normal level.

Although an algorithmic approach to the treatment of postoperative PSA elevation can be developed and can work well for patients with a very high probability of local disease or a very high probability of distant disease, our ability accurately to determine the location of disease recurrence in most patients is still not precise and our therapeutic options not proven. The selection of therapy, if any, in this clinical situation therefore needs to be individualized at the present time in the context of the patient-physician relationship.

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