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Sakr WA, Grignon DJ.

Department of Pathology, Harper Hospital, Karmanos Cancer Institute, Detroit, MI 48201, USA.

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Prostate Cancer: Indicators of Aggressiveness

Wael A. Sakr
David J. Grignon

Department of Pathology, Harper Hospital, Karmanos Cancer Institute and Wayne State University, Detroit, Mich., USA

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Abstract
In spite of the slow progression rates common to most prostate cancers, it is well recognized that a subset of patients will experience a more aggressive course with many losing their lives to this malignancy. As the number of patients diagnosed with prostate cancer continues to increase, there is a growing pressure to refine and supplement the three most important prognostic parameters for this disease (tumor pathologic stage, its histologic differentiation (Gleason score) and the level of prostate specific antigen). While this review emphasizes the value of these factors in stratifying patients into risk groups, it also explores the prognostic significance of additional commonly used and evolving non-traditional markers (DNA ploidy, proliferation, tumor angiogenesis, and the status of tumor suppressor genes).

Introduction

The following is an attempt to summarize our current understanding of the value of traditional parameters and 'biomarkers' in assessing the biological potential (aggressiveness) of prostatic carcinoma. Clinical and pathologic stage, histologic grade (Gleason score) and serum prostate-specific antigen (PSA) with its 'molecular variants' remain the most powerful prognosticators of prostate cancer. While these factors individually or in different combinations have a good ability to predict organ-confined and therefore potentially curable prostate cancer, it is becoming increasingly clear that there is a growing need for additional prognostic markers that can supplement and refine the prognostic value of the traditional parameters. This is true not only in terms of predicting organ confinement, but also for assessing the biologic potential of this disease and in providing better insight into the management of the individual patient with newly diagnosed prostate cancer. It is important to point out that most of the molecular biomarkers have been investigated in tissue samples from radical prostatectomy specimens with attempts to correlate the results with biochemical recurrence reflected usually by rising PSA following surgery. In recent years, however, there has been growing literature attempting to 'move' these marker studies to the diagnostic biopsy samples in order to help predict pathologic stage and treatment approaches. We will start with the traditional pa-

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Wael A. Sakr, MD
Department of Pathology, Harper Hospital
3990 John Road
Detroit, MI 48201 (USA)
Tel. (313) 745-2525, Fax (313) 745-9299

rameters, stage and grade, and since PSA is dealt with elsewhere in this issue, we will not include it in this summary.

Pathologic Stage

Pathologic stage remains the most powerful predictor of tumor behavior and patient outcome [1–3]. Prostate cancer patients' chances of cure and survival sharply decrease as the pathologic stage changes from organ-confined disease to extension at the surgical margins, penetration into extraprostatic tissue, definitive invasion of the seminal vesicles and finally to cancers with local and worse, distant metastases.

Several issues with regard to the recently widely accepted TNM staging system are worth mentioning. Clinical stages T1a, T1b, T1c and T2a have no pathologic correlate in the radical prostatectomy specimen [4]. For T2 cancers, the value of classifying this category into a ı, T2b and T2c is not apparent. There are no data to indicate that for pathologically organ-confined prostate cancer these subcategories influence biochemical recurrence as evaluated by PSA failure. The T3 category is perhaps the one that needs the most clarification. While T3a and T3b characterize a unilateral and a bilateral extraprostatic extension, respectively, we and others have shown that more important than documenting bilaterality of extraprostatic extension is the quantitation of the amount of tumor outside the gland [4]. It is also important to clarify the 'positive surgical margin' phenomenon in the radical prostatectomy specimen (a concept that is not incorporated into the TNM staging system). At least three different categories of positive margins can be recognized:

(a) Tumor extending to the inked margin of resection of a seemingly intact and well-preserved anatomical boundary of the prostate. The tumor follows the 'curve' of ɔ organ with a smooth rounded contour that reaches the ink. Previous reports have indicated that patients in this category show similar recurrence rates to those with organ-confined tumors [3].

(b) Tumor that extends to an irregular, shattered or to a sharp, straight inked margin indicating a surgical technique-induced positive margin. This category is often encountered in the areas of the prostatic apex and/or in procedures aiming at preserving the neurovascular bundle.

(c) A tumor that shows definitive extraprostatic extension to the inked margin of the fat/soft tissue pad surrounding the gland. This category is clearly a stage T3 cancer.

These considerations should be borne in mind when older series dealing with the impact of pathological staging of prostatic carcinoma on progression and survival are evaluated. In addition, these concerns are essential when tissue sampling techniques and reporting standards including certain prognostic parameters for prostate cancer samples – particularly radical prostatectomy specimens – are recommended.

This refined pathologic staging correlates directly with biochemical failure. Patients with tumor involving the surgical margins but without documented extraprostatic extension experience PSA failure rates situated between those of patients with confined tumors and those with extraprostatic disease. Moreover, we have also found that 'quantitation' of positive surgical margins and extraprostatic extension correlates with the PSA failure rates following radical prostatectomy: patients with limited involvement of the surgical margins (we defined a cutoff point of 8 mm) suffered PSA failure rates that were significantly lower than those with a longer collective length of surgical margin positivity. Similarly, patients with only 2 or less high power microscopic fields of extraprostatic tumor, which we defined as focal, experienced PSA failure rates similar to those with pathologically organ-confined disease, while those with more extensive tumor outside the gland, defined as nonfocal according to the above criteria, experienced significantly higher failure rates [5–7].

Segregating the T3c category is important since the prognosis of patients with prostate cancer that invaded the muscularis of the seminal vesicle is significantly worse than that of T3a or T3b patients [8].

Differentiation 'Histologic Grade'

Adenocarcinoma of the prostate is a tumor which is characterized by a remarkable heterogeneity in terms of its histologic differentiation, microscopic growth patterns and biological aggressiveness. Most prostatic cancers are multifocal with significant variations in tumor grade between anatomically separate tumor foci and perhaps more interestingly, within the same tumor nodule. It is indeed not unusual to identify neoplastic components with a spectrum of histologic differentiation in close microscopic proximity [9]. These properties can result in significant sampling errors when the histologic grade of prostate cancer is established from limited tissue specimens (usually

needle core biopsies). Since the Gleason grading system has enjoyed uniform acceptance by physicians diagnosing and treating prostate cancer in recent years [10–13], the question has been raised as to how well the Gleason score of the biopsy correlates with that of the radical prostatectomy specimen. Several studies have investigated this issue in recent years. In one study, Bostwick [14] evaluated over 300 biopsies with the matching radical prostatectomy specimens, and found that the grades of the two samples were highly correlated but with a tendency for the radical specimen to harbor a higher Gleason score particularly when the biopsies were in the well to moderately differentiated range (score 4–6). Catalona et al. [15] correlated the histologic tumor grade in the needle biopsy and the subsequent radical prostatectomy specimen in 66 consecutive patients and found that the biopsies showed a lower, a correct and a higher grade in 33, 59 and 8%, respectively. Gleason [16] attributed these discrepancies to sampling errors and to the fact that, when evaluating needle biopsies harboring small amounts of tumor, some pathologists tend not to acknowledge the minor component of the higher grade cancer, particularly grade-4 carcinoma. Perhaps the key concept integral to the Gleason system is the 'quantitation' of the neoplastic components of prostatic carcinoma. Therefore, the 'lumping' of grades into three categories of well, moderately, and poorly differentiated carcinomas corresponding to histologic scores 2–4, 5–7 and 8–10 can be very misleading. The middle group encompasses tumors with remarkably heterogeneous biological aggressiveness ranging from the low malignant potential of score 5 to the moderate course of score 6 and the higher level of malignant behavior expected for score 7. Furthermore, we have demonstrated that even in the single Gleason score of 7, the proportion of Gleason grade-4 component in patients correlates significantly with advanced pathologic stage, DNA aneuploidy, cellular proliferation and with a trend towards higher biochemical recurrence rates [17].

In conclusion, while the Gleason grading system can be somewhat handicapped by limitations of reproducibility, sampling errors and the inherent histologic heterogeneity of prostatic adenocarcinoma, it remains a powerful parameter in the assessment of patients with this disease. Moreover, when the Gleason score of the biopsy is combined with other pre-operative parameters such as serum PSA levels and clinical stage, the ability to predict the pathological stage and therefore to help determine treatment options for the individual patient can be greatly enhanced [18].

Tumor Volume

There are conflicting reports with respect to the independent value of determining tumor volume for prostate cancer. At this point it is not clear whether this parameter adds significant prognostic information to that furnished by pathologic stage and tumor grade [19–21].

Nontraditional Parameters

Although an array of biologic markers have become widely available and some have been extensively used lately, the practical utility of most 'nontraditional' prognostic markers in the management of prostate cancer patients still needs to be proven. Despite the widespread availability and application of many biologic markers, little information is available to allow for the logical application of these in the daily practice. This status has not substantially changed since the 1994 conference sponsored by the College of American Pathologists, which resulted in guidelines for the critical evaluation of these markers [22]. Furthermore, the recommendations of that conference were largely adopted at a consensus conference supported by the American Cancer Society, the American Urological Association and the National Cancer Institute among others [23]. The criteria proposed by the College of American Pathologists for the evaluation of prognostic markers stressed the following three parameters: clinical importance; independence of known prognostic markers, and significance. Additionally the recommendations classified prognostic markers into three categories: (I) parameters that are well supported by the literature, tested in phase-III trials, generally used in patient management; (II) parameters that have been extensively studied biologically or clinically (a) tested in clinical trials and (b) biologic correlative studies done, few outcome studies, and (III) parameters that currently do not meet criteria for categories I or II.

When all the available traditional and nontraditional markers were reviewed, pathologic stage and histologic grade were the only two parameters that fulfilled the criteria.

Finally, it may be relevant to emphasize a few points from an important review by Simon and Altman [24]. This paper addressed the statistical analysis of prognostic marker studies which the authors classified along similar lines as clinical trials (phases I, II and III). According to this system, the vast majority of prognostic marker studies in prostate cancer have been of the phase I and II

types. Most are retrospective introducing significant problems with missing data points. The assumption that missing data are random is almost always incorrect. The frequent incompleteness of data on other parameters of potential significance is another major limiting factor. Prospective studies have major advantages in addressing these concerns. Another problem relates to the stratification of patients according to continuous variables such as a proliferation index. This is typically done by dividing cases into below and above the median. However, this assumes that exactly one half of the patients are at high risk and one half at low risk for failure – an assumption of limited biologic validity. Additonally, the order by which prognostic factors are 'entered' using logistic regression statistics (e.g. Cox analysis) can influence the results generated. Finally, the number of cases required is dependent on several factors including the number of known significant variables, the number of categories for each variable, the number of events (failures), the prevalence of the marker in the population and the power of the marker (relative risk). After this rather cautionary introduction we will discuss selected, more commonly used biomarkers.

Tumor DNA Content (DNA Ploidy)

Perhaps more than any other technique, tumor DNA ploidy status in prostate cancer has been the subject of numerous studies and reports. Many studies have indicated that DNA aneuploidy correlates with progression, metastasis and poor survival. Some studies suggested that this correlation was independent of tumor grade and stage [25]. The value of DNA ploidy in stage T2 prostate cancer was studied primarily in tumor samples from radical prostatectomy specimens. Since more than 90% of pathologic stage T2 patients enjoy a 10-year disease-specific survival following radical prostatectomy with relatively few patients dying of disease, it may be difficult for any marker to prove to be significant. Our experience with this group indicates that Gleason score and possibly preoperative PSA levels remain the more important prognostic factors for patients with organ-confined tumors [25–27]. In patients with pathologic stage T3 disease DNA ploidy appears to provide significant prognostic information. It is, however, not clear at this point whether this parameter will be independent of accurate pathologic staging and/or preoperative PSA levels. Of particular interest regarding ploidy in this stage, on the other hand, are the reports indicating that DNA ploidy can predict the response to hormonal therapy and that diploid T3 cancers respond better to this treatment modality [28]. Finally, the few available studies dealing with the value of ploidy in metastatic prostate cancer have not been consistent with at least two reports showing contradictory results [29, 30].

In the most recent few years, there has been a tremendous push to perform DNA ploidy analysis on needle biopsies with the implication that the results could be utilized to influence treatment decisions [31, 32]. Not unlike the issue with grading, biopsies are handicapped by limited, potentially underrepresentative sampling in association with the intratumoral heterogeneity of the DNA content in prostate cancer. Some studies have demonstrated a relatively good correlation between DNA ploidy status on needle biopsy specimens and the results obtained from the subsequent radical prostatectomy specimen. Konchuba et al. [33] agitated fresh needle biopsy specimens in saline and demonstrated that cases with >22% hyperdiploid cells correlated with high pre-operative PSA levels but not with clinical stage or grade. Ross et al. [34] evaluated needle biopsies by image analysis in patients undergoing radical prostatectomy and found that DNA aneuploidy correlated with higher pathologic stage, PSA failure and metastases (in this study grade did not correlate with any of these!). Centano et al. [35] studied needle biopsies from patients with clinically localized prostate cancer treated with radiation therapy and found no correlation between ploidy and survival. In contrast, Pollack et al. [36] studied a similar patient group treated by radiation therapy and found DNA ploidy to be an independent predictor for survival. Van den Ouden et al. [37] evaluated needle biopsy specimens in patients with lymph node metastases and found that aneuploid tumors progressed more rapidly than diploid or tetraploid cases. Finally, Jorgensen et al. [38] studied DNA ploidy on needle biopsies of patients with bone metastases and found no correlation between ploidy and time to progression and death.

Considering these data collectively, there has been little progress in this regard since the international DNA Cytometry Consensus Conference which reviewed the literature in 1993, and concluded that the clinical significance and biologic basis of DNA ploidy needed further investigation [39]. On a technical note, while determination of DNA ploidy by flow cytometry has been standardized, the methodology for the more widely used DNA determination technique by image analysis on needle biopsies is still in need of standardized methodologies, quality assurance and quality control procedures.

Our data based on flow cytometric analysis of close to 500 fresh prostate cancers from radical prostatectomy specimens performed at Harper Hospital showed that while overall aneuploidy predicted higher PSA failure rates following radical prostatectomy, there was no correlation between aneuploidy and PSA failure when controlled for stage in any of the individual stage categories [40].

In conclusion, DNA ploidy analysis has good potential as a prognostic marker, but technical issues need to be resolved and proof of an independent value added to stage and grade is required. Currently, the most applicable use of this technology appears to be in radical prostatectomy specimens from patients with pathological stage T3 prostate cancer.

Nuclear Morphometry

Measurement of nuclear roundness and other nuclear morphometric features have been reported to provide prognostic data in prostate cancer. Difficulties with methodology relevant to tissue handling, user dependency, standardization of automated and computerized equipment, quality assurance controls and reproducibility of results all remain major concerns in this area [41–45].

Tumor Proliferative Activity

The different techniques used to assess nuclear proliferation (flow cytometry, immunostaining for proliferating cell nuclear antigen and Ki-67 or bromodeoxyuridine labeling) have repeatedly shown a low level of proliferation in most prostate cancers. With notable exceptions, most studies that have addressed the prognostic importance of proliferation in prostate cancer have failed to demonstrate a significant correlation between this parameter and outcome. Our group and others have shown that higher proliferative indices correlate with higher grade and more advanced stage but did not influence outcome when stage and grade were controlled for [40]. Overall, there have been relatively few studies done to assess the prognostic value of proliferation markers in this tumor system. Within specific components of tumor grading, Schroeder et al. [46] demonstrated the presence of mitoses to be significant. Few flow cytometric studies have provided data on the significance of S-phase fraction analyses as a prognostic marker and, in only one was a prognostic significance indicated. Studies using immunostaining for proliferating cell nuclear antigen and Ki-67 or bromodeoxyuridine labeling involved small numbers of patients and have generally shown a correlation between higher proliferative activity and more advanced stage and higher tumor grade. The outcome component of these results remains inconsistent [47–50].

Apoptosis

The apoptotic index (assessed usually by immunohistochemical staining for the bcl-2 oncogene, an inhibitor of apoptosis) has been reported to be an important factor for both prognosis and response to therapy of prostate cancer. The bcl-2 gene is located on chromosome 18 and functions to prevent apoptosis [51]. While normal human prostatic secretory cells do not express this protein, hormone refractory prostate cancer tissue derived from hormone-treated patients show strong bcl-2 expression. This suggests that the increased expression of this protein provides prostate cancer cells with the ability to survive without the hormonal milieu [52, 53]. In vitro experiments indicate that the elevated expression of bcl-2 oncoprotein enables the normally androgen-sensitive LNCaP prostate cancer cell line to survive in an androgen-depleted environment. Therefore there are in vitro and in vivo preliminary data to suggest that overexpression of bcl-2 correlates with resistance to hormone therapy [54, 55]. These results are promising and they may have future implications for the selection of therapy for prostate cancer patients.

Tumor-Suppressor Genes

Tumor-suppressor genes are important markers of neoplastic transformation. Considering that these genes are responsible for the negative regulation of cellular proliferation by maintaining apoptosis, their inactivation should result, at least in theory, in uncontrolled proliferation, which is a crucial step in the complex process of carcinogenesis. Although several known tumor-suppressor genes have been studied in prostate cancer, to date only p53 and to a lesser extent the retinoblastoma (Rb) gene have been studied in sufficient clinical material to warrant further discussion.

p53

This gene is located at 17p13 and encodes for a 53-kD cellular protein. It is the most frequently studied suppres-

sor gene in human neoplasia. It is thought to induce cell arrest in the G1 phase of the cycle and to be responsible for the initiation of apoptosis.

Mutations of the naturally present wild-type p53 permit cells with altered genomic composition to maintain proliferation which in turn can result in the acquisition of additional genetic abnormalities. Since the mutated p53 protein persists in the cytoplasm of affected cells, it is relatively easily detected using immunohistochemistry [56–58]. Several studies have shown p53 mutations to be relatively infrequent in prostate cancer in general but to be much more frequent in advanced and high-grade tumors [59, 60]. This has suggested that p53 abnormalities indicate an aggressive subset of prostate cancers. Results reported to date have not been uniform [61, 62]. A recent report has indicated that p53 expression may be used to predict response to neoadjuvant total androgen blockade prior to radiation therapy [63]. The clinical utility of these determinations remains to be proven. In addition considerable technical work remains to be performed as to the best methodology to evaluate these abnormalities and as to how results should be interpreted.

Retinoblastoma Gene

This gene is situated on the short arm of chromosome 13. It is associated with the development of Rb in the immature retina (mutated gene is present in all clinical cases of this malignancy). Since this is an autosomal recessive gene, it requires either somatic or germ line mutation of both alleles. Rb mutations have been reported in osteosarcoma, soft-tissue sarcomas, lung, breast and bladder cancers. Meikle and Stanish [64] demonstrated Rb allelic loss in 27% of prostate tumors studied. However, Sarkar et al. [65] could neither detect a single short mRNA transcript in 7 cases examined nor demonstrate Rb promoter alterations in any of the 24 cases evaluated for this abnormality. These conflicting results clearly indicate the need for further studies in this area.

Detection of Circulating Tumor Cells in Serum

The first study describing the detection of circulating PSA-producing cells in the serum using a polymerase chain reaction (PCR) technique in prostate cancer patients [66] provoked tremendous interest. It was subsequently followed by several studies with similar design but, unfortunately, with conflicting results [67, 68]. Israeli et al. [67] used reverse transcriptase (RT)-PCR to detect both prostate-specific membrane antigen and PSA. These authors reported a detection rate of 72% in patients with pathologically organ-confined disease (pT2). Considering that this group of patients has a favorable outcome and an estimated cancer recurrence rate of less than 10%, the interpretation and significance of these results become very difficult. The methodology and technical issues are essential components of this approach. Finally, since it has recently been reported that production of PSA mRNA as detected by RT-PCR can be encountered in cells that are not of prostatic origin, there are even greater difficulties with applying this technique to routine use at this time [69].

HER-2/neu (c-erbB-2) Oncogene and Growth Factors

A limited number of studies have investigated the role and significance of the HER-2/neu oncogene and various growth factors in prostate cancer. Some have yielded contradictory results. This is likely related to significant differences in the sensitivity and specificity of the many available antibodies. Although biologically these are of considerable interest, clinical data are scant and contradictory [70–74].

Tumor Angiogenesis

In the last few years, tumor angiogenesis has become a topic of great interest in several solid tumors including prostate cancer. Recent data have clearly suggested that the assessment of angiogenesis in prostate cancer may have significant prognostic relevance [75–79].

Neuroendocrine Differentiation

Prostate cancers have been shown to contain variable proportions of neuroendocrine cells. With only rare exceptions, most studies have reported that this component does not have an impact on prognosis [80–83].

Allelic Loss and Cytogenetic Analysis

Allelic loss is found with high frequency in prostatic adenocarcinoma. Collective reports from multiple authors indicate a more than 50% loss of heterozygosity for chromosomal loci on 8p, 10q, and 16q and even the Y

chromosome [84–90]. The high frequency by which abnormalities in the 8p region are reported indicates the potential presence of a tumor-suppressor gene(s). Allelic loss appears to be more common in less differentiated, more advanced tumors [91]. While an increasing number of cytogenetic studies in prostate cancer continue to be published, their contribution at this stage is to gain further understanding of the biology of this disease. Currently there is no practical clincial use for the results of these studies.

References

1 Schroeder FH, Hermanek P, Fair WR, et al: The TNM classification of prostate cancer. Prostate 1992;4:129–138.
2 Epstein JI, Pizov G, Walsh PC: Correlation of pathologic findings with progression after radical retropubic prostatectomy. Cancer 1993;71: 3582–3593.
3 Humphrey PA, Frazier HA, Vollmer RT, Paulson DF: Stratification of pathologic features in radical prostatectomy specimens that are predictive of elevated initial postoperative serum prostate-specific antigen levels. Cancer 1993; 71:1821–1827.
4 Sakr WA, Henson D, Mostofi FK, Blute ML, Wojno KD, Zincke H, Budo M: Staging and reporting of prostate cancer: Sampling the radical prostatectomy specimen. Cancer 1996;78: 366–368.
5 Sakr WA, Grignon DJ, Lovisolo J, Banerjee M, Wood D, Cher M, Powell IJ, Pontes JE, Crissman JD: Refined pathologic staging is a powerful predictor of outcome for patients with clinically localized prostate cancer (PCa) (abstract). Mod Pathol 1997;10:88.
6 Sakr WA, Grignon DJ, Visscher DW, Wolman SR, Crissman JD: Evaluating the radical prostatectomy specimen. I. A protocol for establishing prognostic parameters and harvesting fresh tissue samples. J Urol Pathol 1995;3–4: 377–384.
7 Vernick J, Sakr WA, Grignon DJ, Swiriduk M, Wood D, Powell IJ, Pontes JE, Banerjee M, Crissman JD: Does the extent of tumor involvement of surgical margins or the amount of extraprostatic tumor in the radical prostatectomy specimen correlate with biochemical recurrence? (abstract). Mod Pathol 1997;10:94.
8 Ohori M, Wheeler TM, Kattan MW, Goto Y, Scardino PT: Prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 1995;154:1818–1824.
9 Aihara M, Wheeler TM, Ohori M, Scardino PT: Heterogeneity of prostate cancer in radical prostatectomy specimens. Urology 1994;43: 60–67.
10 Bostwick DG: Grading prostate cancer. Am J Clin Pathol 1994;102(suppl):538–556.
11 Veenema RJ, Gursel EO, Lattimer JK: Radical retropubic prostatectomy for cancer: A 20-year experience. J Urol 1977;117:330.
12 Murphy GP, Whitmore WF Jr: A report of the workshops on the current status of the histologic grading of prostate cancer. Cancer 1979; 44:1490.
13 Bain GO, Koch M, Hanson J: Feasibility of grading prostatic carcinomas. Arch Pathol Lab Med 1982;106:265.
14 Bostwick DG: Gleason grading of prostatic needle biopsies: Correlation with grade in 316 matched prostatectomies. Am J Surg Pathol 1994;18:796–803.
15 Catalona WJ, Stein AJ, Fair WR: Grading errors in prostatic needle biopsies: Relation to the accuracy of tumor grade in predicting pelvic lymph node metastases. J Urol 1982;127: 919–922.
16 Gleason DF: Histologic grading of prostate cancer: A perspective. Hum Pathol 1992;23: 273–279.
17 Sakr WA, Grignon DJ, Swiriduk M, Littrup P, Wood D, Cher M, Powell IJ, Pontes JE, Crissman JD: Gleason score VII prostate cancer, a heterogeneous entity? Correlation with clinicopathologic parameters and biochemical recurrence (abstract). Mod Pathol 1997;10:88.
18 Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, Walsh PC: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol 1993;150:110–114.
19 McNeal JE: Cancer volume and site of origin of adenocarcinoma in the prostate: Relationship to local and distant spread. Hum Pathol 1992; 23:258–266.
20 McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA: Histologic differentiation, cancer volume, and pelvic lymph node metastasis in adenocarcinoma of the prostate. Cancer 1990;66:1225–1233.
22 Epstein JL, Carmichael M, Partin AW, Walsh PC: Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of follow up. J Urol 1993;149:1478–1481.
22 Grignon DJ, Hammond EH: Clinical relevance of prognostic markers in solid tumors: Report of Prostate Cancer Subcommittee. 26th CAP Conference 1994. Arch Pathol Lab Med 1995; 119:1122–1126.
23 Hutter RW, Montie JE, Busch C, Grignon DJ, et al: Current prognostic factors and their relevance to staging. Cancer 1996;78:369–371.
24 Simon R, Altman DGT: Statistical aspects of prognostic factor studies in oncology. Br J Cancer 1994;69:979–985.
25 Adolfssen J: Prognostic value of deoxyribonucleic acid content in prostate cancer: A review of current results. Int J Cancer 1994;58:211–216.
26 Fordham MVP, Burdge AH, Matthews J, Cooke T: Prostatic carcinoma cell DNA content measured by flow cytometry and its relation to clinical outcome. Br J Surg 1986;73: 400–403.
27 Montgomery BT, Nativ O, Blute ML, Farrow GM, Myers RP, Zincke H, Therneau TM, Lieber MM: Stage B prostatic adenocarcinoma: Flow cytometric nuclear DNA ploidy analysis. Arch Surg 1990;125:327–331.
28 Nativ O, Wirder HZ, Raz Y, Therneau TM, Farrow GM, Myers RP, Zincke H, Lieber MM: Stage C prostatic carcinoma: Flow cytometric nuclear DNA ploidy analysis. Mayo Clin Proc 1989;64:911–919.
29 Zincke H, Bergstralh EJ, Larson-Keller JJ, Farrow GM, Myers RP, Lieber MMJ, Barret DM, Rife CC, Gonehoff NJ: Stage DI prostate cancer treated by radical prostatectomy and adjuvant hormonal treatment. Cancer 1992;70: 311–323.
30 Miller J, Horsfall DJ, Marshall VR, Rao DM, Leong ASY: The prognostic value of deoxyribonucleic acid flow cytometric analysis in stage D2 prostatic carcinoma. J Urol 1991;145: 1192–1196.
31 Leung C-S, Zbieranowski I, Demers J, Murray D: DNA image cytometry of prostatic carcinoma: A comparison of needle core biopsy specimens and subsequent prostatectomy specimens. Mod Pathol 1994;7:195.
32 Takai K, Goellner JR, Katzmann JA, Myers RP, Lieber MMJ: Static image and flow DNA cytometry of prostatic adenocarcinoma: Studies of needle biopsy and radical prostatectomy specimens. J Urol Pathol 1994;2:39–47.
33 Konchuba AM, Schellhammer PF, Kolm P, Clements MA, Wright GL Jr: Deoxyribonucleic acid cytometric analysis of prostate core biopsie specimens: Relationship to serum prostate specific antigen and prostatic acid phosphatase, clinical stage and histopathology. J Urol 1993;150:115–119.
34 Ross JS, Figge H, Bui HX, et al: Prediction of pathologic stage and postprostatectomy disease recurrence by DNA ploidy analysis of initial needle biopsy specimens of prostate cancer. Cancer 1994;74:2811–2818.