While the prime goal of the needle biopsy is to diagnose prostatic adenocarcinoma (PCa), once PCa is detected further descriptive information regarding the type of cancer, amount of tumor, and grade in prostate needle cores forms the cornerstone for contemporary management of the patient and to assess the potential for local cure and the risk for distant metastasis. This review gives an update on selected pathology-related issues on routine workup of prostate biopsy with special references to adequate histologic sectioning necessary to maximize cancer yield, tumor extent measurements and methodologies, specimen orientation, and the role of immunohistochem-
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Analytical and quantitative cytopathology and histopathology in the last 2 decades. Since the advent of PSA, low-grade, low-volume, favorable-risk prostate cancer has contributed to increased detection of prostate-specific antigen (PSA) screening and extended biopsy techniques. Early detection with serum prostate-specific antigen intervention with its associated morbidity is not warranted. It is still considered atypical by a uropathology expert after negative basal cell staining, positive staining for alpha-methylacyl-CoA-racemase can help establish in 50% of these cases a definitive diagnosis of cancer. (Anal Quant Cytopathol Histopathol 2014;36:61–70)

Keywords: active surveillance, histological sectioning, immunohistochemistry, prostate biopsy, prostate cancer, specimen orientation, tumor extent.

Prostate cancer is the most common visceral malignancy in males, yet the risk of dying from prostate cancer is relatively low. In most cases prostate cancer has a long natural history, during which time intervention with its associated morbidity is not warranted. Early detection with serum prostate-specific antigen (PSA) screening and extended biopsy techniques have contributed to increased detection of low-grade, low-volume, favorable-risk prostate cancer in the last 2 decades. Since the advent of PSA, the lifetime risk of prostate cancer detection has doubled from about 8% in the pre-PSA era to 17%. Nevertheless, these techniques are invaluable in the early detection of some cases of prostate cancer that will cause significant morbidity and mortality. It is still the second-most-common cause of cancer deaths in males. A subset of patients with apparent low-risk prostate cancer will have significant disease due either to presence of higher risk cancer not apparent at the time of diagnosis or to progression to more aggressive disease. It is a challenge to identify this subset at risk early enough when they are still amenable to curative treatment.

Characterization, clinical management and follow-up of patients with prostate cancer are highly dependent on a combination of laboratory (PSA measurement), clinical (digital rectal examination) and pathologic factors. Within the diagnostic armamentarium, pathologists play an important role in identifying pathologic features in both prostatic needle biopsy and radical prostatectomy specimens that allow for appropriate risk stratification.

While the prime goal of the needle biopsy is to diagnose prostatic adenocarcinoma (PCa), once PCa is detected further descriptive information regarding the type of cancer, amount of tumor, and grade in prostate needle cores forms the cornerstone for contemporary management of the patient and to assess potential for local cure and the risk for distant metastasis. The information provided in the needle biopsy report regarding the attributes of carcinoma is used depending on the individual patient’s medical condition and preference and the treating physician’s evaluation to determine (1) whether any form of treatment is indicated and, if so, (2) the type of therapy. Further, the information in the biopsy report may be valuable in further potentially determining treatment strategies, such as the field and/or type of radiation therapy (brachytherapy, external beam, etc.), the need of adjuvant hormonal therapy, the eligibility for clinical trials, including active surveillance, the type of surgery (nerve sparing, bladder neck sparing), and sometimes the intraoperative course (using frozen sections for lymph nodes, neurovascular bundle involvement, apical and bladder neck margin or type of operation, etc.).

The aim of this review is to give an update on selected issues on routine workup of prostate biopsy with special references to adequate histologic sectioning necessary to maximize cancer yield, tumor extent measurements and methodologies, specimen orientation, and the role of immunohistochemistry in the evaluation of the prostate.

Histologic Sectioning to Maximize Cancer Yield

Multiple factors influence the diagnostic yield of prostate biopsies (Figure 1). Many of these factors are fixed and uncontrollable, including patient age, serum prostate-specific antigen, prostate volume, and imaging findings. Other factors are controlled by the urologist, including number of cores ob-
tained, method and location of biopsy, and amount of tissue obtained. Urologist training and standardization of collection and processing methods reduces variance in prostate biopsy quality, thereby optimizing cancer detection and yield. Biopsy quality was found to be a useful comparative measure in urologic practice that should be included in quality assurance programs. The yield of cancer is also controlled by the pathologist and histotechnologist.

Prostate biopsies are particularly difficult to embed and cut owing to their small size and tendency to fragment, become entangled, and curve; thus, the yield of cancer may be influenced by the histotechnologist’s technique and skill in processing and cutting. Multiple needle biopsies submitted in 1–2 containers are difficult to embed in a single plane during processing (Figure 2). The resulting loss of tissue surface area makes a definitive diagnosis difficult in many cases, resulting in equivocal pathology reports. If multiple cores are embedded in 1 cassette, it is necessary to take care that all are separated from each other. In addition, there is variation between laboratories in the number of serial tissue cuts obtained from each needle core for routine examination. To avoid the serious problem of undersampling, Bostwick and Kahane suggest obtaining up to 6 separate slices (2 adjacent sections from 3 separate levels) from the paraffin block for hematoxylin and eosin staining, additional intervening sections being placed on another slide and saved for immunohistochemical stains or special studies. They considered the recommendation of the European Randomized Study of Screening for Prostate Cancer (only 2 cuts in total) to be inadequate, probably missing up to 3% of cancers with such limited sampling. In their experience, recutting the block for additional levels with small suspicious foci is useful in about half of cases, with usually no more than 4 additional slides before the tissue specimen is exhausted. Thus, it is most prudent to obtain the deeper levels when the block is first cut. It is routine practice in the evaluation of prostate biopsies (or any biopsy) to encounter a microscopic finding that is suspicious for cancer but requires the use of standard special cell- and cancer-specific stains. The problem is that the focus of concern is very small in such instances and often lost with additional cuts of tissue deeper into the biopsy itself. To avoid this, the international standard is to apply multiple stains on a single highly selected slide (invariably an intervening slide) with tissue containing the suspicious focus of concern.

Flat embedding of the biopsy cores, for instance in a tissue cassette (Figure 3), enhances the amount of tissue that is examined by the pathologist. In our

Uncontrolled factors
- Patient risk factors
  1. Patient population (e.g., screening population vs. urologic practice)
  2. Patient symptoms
  3. Serum PSA
  4. Clinical stage
  5. Patient age
  6. Patient race
  7. Prior biopsy findings (e.g., PIN, atypical small acinar proliferation)
- Prostate-related factors
  1. Prostate volume
  2. Transrectal ultrasound and other imaging findings

Controlled factors
- Urologist-controlled factors
  1. Number of needle cores obtained
  2. Method of biopsy (e.g., random, ultrasound guided, etc.)
  3. Location of biopsy (e.g., laterally-directed biopsies vs. midline, etc.)
  4. Amount of tissue obtained (e.g., biopsy “gun” employed, operator skill)
- Pathologist-controlled factors
  1. Histotechnologist’s skill in processing and cutting prostate biopsies
  2. Number of needle cores embedded per cassette
  3. Number of tissue cuts obtained per specimen
  4. Pathologist’s skill in prostate biopsy interpretation

Figure 1 Factors that influence the detection rate of cancer in contemporary prostate needle biopsies.
experience the mean length of the cores measured on the glass slide following the application of the so-called sandwich technique is 1.4 cm. Rogatsch et al. showed that biopsy cores submitted floating free in formalin had a lower diagnostic rate for cancer (23.6%) than did those that were stretched and oriented at biopsy and before formalin fixation (30.8%). In addition, processing prostate biopsies at the same time as other tissues of differing density and consistency such as breast biopsies with abundant fatty tissue may optimize results for some tissues but may create sections that are too thick to interpret or are overstained. Excessively thick tissue specimens are 2 or 3 cells in thickness rather than the optimal 1 to 2 cells in thickness, precluding adequate assessment of nuclear and cytoplasmic details in foci of concern such as atypical small acinar proliferation (ASAP) and prostatic intraepithelial neoplasia (PIN). Similarly, overstained sections contain obscured nuclear chromatin without recognizable nucleoli. These problems are compounded in biopsies with small foci that are suspicious for malignancy and in younger patients (those in their 40s or 50s) who have abundant proliferative epithelium that may mimic malignancy.

Training and experience of pathologists also increase the yield of cancer as well as optimizing accuracy of prognostic factors such as Gleason score and cancer stage. Those with a special interest or training in urologic pathology have a higher level of accuracy in needle biopsy interpretation and Gleason grading than do general pathologists. Interobserver reproducibility of Gleason grading among urologic pathologists was in an “acceptable” range, according to Allsbrook et al., with the greatest differences of interpretation seen with low-grade cancer, cancer with small cribriform proliferation, and cancer with histology on the border between Gleason patterns. The false-negative rate (missed prostate cancer) was 0.6–1.0%, and the false-positive rate (overdiagnosis of prostate cancer) was 0.3%, indicating a small but significant error level that could be avoided by secondary pathology review. These results were invariably superior to those of general pathologists.

### Tumor Extent Measurements

Figure 4 reports the items that pathologists should evaluate in prostate biopsies with cancer. Tumor extent measurements are used in patient selection in most active surveillance protocols. Those used in the different protocols are varied (Figure 5). There is no consensus on the best tumor quantification methods, which include the following: cancer percentage in each core, greatest percentage of cancer (GPC), cancer length in each core, greatest length of cancer, total percentage of carcinoma in all cores, total length carcinoma in all cores, fraction of positive cores, total carcinoma surface area, and total percentage of carcinoma surface area in all cores.

Tumor measurements are performed as a visual estimate or using an ocular micrometer or other morphometric measurement such as computerized methods. Visual estimation of percentage without morphometric measurements is commonly performed, although many recent studies do not actually describe whether visual estimation or morphometric measurements were used. Some use a regular ruler or the side graticule available on most microscopes for estimation of length and percentage. The knowledge of the diameter of the field at each magnification for the microscope used to measure tumor extent can also help maximize accuracy of visual estimation of length. In a recent abstract Mahamud et al. found no overall difference be-

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1. Location of prostate cancer
2. Histopathologic type
3. Gleason score (or therapy-related changes)
4. Extent of involvement
5. Local invasion
6. Perineural invasion

Figure 4 Reporting of prostate biopsies with prostate cancer.
tween visual estimation and measurement when determining percent involvement of prostate biopsies assessed only by whole slide images. However, there was a significant difference between the two methods when they considered a subset of cores deemed to have 40–60% involvement by visual estimation. It is unclear whether the accuracy of visual estimation of an image can be compared with that of a tissue core on a glass slide on a microscope. Data are conflicting whether morphometric measurements are superior to visual estimation and whether differences in the two methods would affect clinical management. Computerized morphometric measurements are considered time-consuming and not practical for most pathologists. Measurements of core length given in gross descriptions should not be used as they may not always be accurate.

A few studies have assessed the value of the different methods of tumor extent measurement in prostate needle biopsy in predicting pathological stage or prognosis. Quintal et al. found that total percentage of carcinoma in all cores and number and percentage of cores with cancer were significantly stronger than other methods such as GPC or length in a single core in predicting biochemical recurrence. Total percentage of carcinoma in all cores had the strongest correlation and, when combined with preoperative PSA and Gleason score, improved prediction of pT3 in multivariate analysis. This was also independent for risk of biochemical recurrence. Bismar et al. found that although many tumor measurements such as GPC, total tumor length in millimeters, fraction of positive cores, and total percentage of carcinoma were significant in univariate analysis, only the fraction of positive cores was significant in multivariate analysis in predicting pT3 disease or positive margins. In this study all the measures were highly related to one another in a formal correlation analysis.

Park et al. examined the significance of the number of cores positive for cancer, percentage of positive biopsy cores, total linear cancer length, total percentage of carcinoma, and maximum cancer core length and found that, when considering PSA and Gleason score, none were significant in predicting pT3 disease in multivariate analysis. In a study by Brimo et al. it was found that the fraction of positive cores, total percentage of carcinoma, and both total and greatest cancer core length were closely associated with pathological stage and biochemical failure. The fraction of positive cores was found to be the factor most closely associated with pT3 disease in radical prostatectomy.

Correlating needle biopsy cancer measurements with tumor volume in radical prostatectomy, Poulos et al. found that the highest percentage of carcinoma in any biopsy site, percentage of adenocarcinoma at the biopsy site with the highest Gleason score, the number of positive biopsy sites, and tumor bilaterality were significant, with the percentage of biopsy sites positive for disease the most significant predictor of tumor volume. Sebo et al. used percent surface area in prostate needle biopsy volume assessment. They found that the joint predictors of tumor volume at radical prostatectomy were the percent cores positive for carcinoma, the percent surface area positive for carcinoma, serum PSA, and the number of S-phase nuclei. Percent surface area was not found to be significant in predicting extraprostatic extension. In a study by Lewis et al. tumor volume was best predicted by a combination of linear extent of carcinoma and number of positive cores.

In a survey sent to 93 genitourinary pathologists, the extent of cancer on needle biopsies was quantified by all the respondents, with 80% reporting the number of cores involved by cancer. Linear extent was estimated by almost all, either as a percentage (80%) or millimeters of cancer length (41%), or both (22%).

Considering the tumor quantification methods actually requested by urologists, in a 2005 study 95% of French and Belgian urologists requested the number of positive cores as compared with 53%
requesting length of cancer. In a study by Rubin et al, 67% of urologists requested the percent involvement of each core by cancer, and 33% requested the number of cores with prostate cancer and 29% the length of core involvement.

Recommendations by the College of American Pathologists, Association of Directors of Anatomic and Surgical Pathology and the World Health Organization for reporting carcinoma extent have been summarized. Given these recommendations, the extent parameters currently in use in active surveillance protocols and the evidence from the literature, it is suggested that pathologists should report the absolute number of involved cores out of total number of cores and the amount of cancer in the single core with the greatest amount of tumor expressed as the percentage involvement by carcinoma, with or without the linear extent of carcinoma in that core (Figure 6). Percentage involvement by carcinoma and/or linear extent of carcinoma in each positive core may also be provided. All other measurements are optional.

Factors Influencing the Evaluation of the Extent of Cancer on Needle Biopsy Cores

The evaluation of core involvement by prostate cancer is dependent on the final length of core in the slide. This is influenced by several technical factors involved in the tissue processing and/or slide preparation. The same technical problems can reduce the probability of making a diagnosis of cancer, due to the loss of material.

Measuring Discontinuous Foci of Cancer

This is a particular problem when there are small foci widely separated by benign intervening tissue. Some pathologists measure the entire length with cancer at each end without subtracting the benign tissue in between. This is reported as discontinuous involvement. Others just measure the length of cancer and subtract the benign tissue in between. The type of measurement used can affect the decision for active surveillance since one criterion for active surveillance eligibility is absence of >20% or 50% carcinoma involvement in any one single core. There is no clear advantage of one method over the other. Since only two studies have been published on this methodology, additional data on large numbers of patients are needed, with clinical endpoints.

Flattening Cores Between Nylon Sponges in Cassettes

Cores should be delivered and embedded after flattening between nylon sponges (Figure 7A). If flattening is not achieved, some segments of prostate tissue may not be seen on slides and will not be accessible to pathological evaluation.

Multiple Cores Submitted in a Single Cassette

Concerning the number of cores per cassette, the ideal would be one core per cassette. Two biopsies from the same location could be embedded together. It has been shown that simultaneous inclusion of 3 biopsies in the same cassette can lead to the loss of a mean length of 1.15 cm of assessable tissue, which corresponds to the average length of one prostate biopsy.

When multiple cores are submitted in a single cassette or jar by the urologist and processed in a single cassette (Figure 7B), many pathologists give the overall percentage of cancer for the entire slide as opposed to the percentage for each individual core. At the Pathology Laboratory of United Hospitals, Ancona, we attempt to give the percentage of cancer per core for each individual positive core, regardless of how many cores are on a given slide.

Measurement of Cancer on Fragmented Cores

If there are multiple fragmented small cores con-
taining cancer, an accurate assessment of percentage of cancer per core cannot be determined, and only an overall percentage of cancer per fragmented specimen can be noted. In this scenario one cannot even determine with certainty the number of positive cores.

There is evidence in the literature that there is a greater tendency to core fragmentation when >1 core is submitted in a container. It is our experience that needle biopsies collected onto gauze or paper are more likely to fragment (Figure 7C).

Minimum Acceptable Core Length

Currently there is no definition for adequate or minimum acceptable core length. The percentage of cancer in a short core (e.g., <5–10 mm) versus that in a sufficiently long core mean entirely different tumor lengths. This has implications for interpretation of percent core involvement in the setting of active surveillance. Since percent core involvement is based only on total length of prostatic parenchyma, nonprostatic elements should not be included in total core length assessment.

Specimen Orientation

Several attempts have been made to improve the preoperative topographic distribution of prostate cancer in terms of number of positive cores, laterality, area of sampling (apex, mid, base), or anterior versus posterior gland. Even 3-dimensional prostate mapping based on transperineal saturation biopsy has been proposed to guide (focal or total) treatment strategy. Since transrectal ultrasound biopsy is the technique used worldwide for prostate cancer diagnosis, marking the peripheral end of the core biopsy could easily identify the subcapsular tissue of the peripheral zone just close to the ultrasound probe, i.e., it allows for the so-called specimen orientation. The marking technique can be applied to pre-embedded specimens by a urologist, radiologist, or nurse in a few minutes just before formalin fixation. The marking technique cannot be applied to free-floating specimens in formalin vials. The proximal end of the fresh biopsy specimen is marked with ink (usually black ink) (Figure 8) on the bench soon after needle delivering. Then the specimen is placed on nylon mesh (or sponges) and then covered with another nylon mesh according to the pre-embedding methods of prostate needle biopsy specimens described by Rogatsch et al. The inked prostate biopsy end was always recognized at pathological analysis by pathologists using a microscope. Five potential clinical advantages were identified using prostate biopsy specimen orientation by marking the peripheral end: (1) tumor localization, (2) atypical lesions localization and planning rebiopsy strategy, (3) planning surgical strategy, (4) selection criteria for focal therapy and active surveillance, and (5) cost reduction. In particular, when considering tumor localization, with the inking of the proximal end of the biopsy, the following benefits can be seen, according to a recent review by Galosi et al., whose experience is based on 5,000 cases: definition of the posterior or anterior cancer location, subcapsular versus nonsubcapsular cancer, and extraprostatic cancer.
Immunohistochemistry in the Evaluation of the Prostate

Probably the most common use of immunohistochemistry in the evaluation of the prostate is for the identification of basal cells, which are absent with rare exception in adenocarcinoma of the prostate and, in general, positive in mimickers of prostate cancer. The most commonly used basal cell antibodies are high molecular weight cytokeratin (34βE12, CK5/6) and p63, which are cytoplasmic and nuclear antibodies, respectively. Several studies comparing high molecular weight cytokeratin and p63 have shown p63 to be slightly superior.36-38 One study demonstrated that CK5/6 was superior to 34βE12, although only a minority of pathologists use CK5/6. The use of a double cocktail combining high molecular weight cytokeratin (HMWCK) and p63 can increase the sensitivity of basal cell detection with a decrease in staining variability.38

Alpha-methylacyl-CoA-racemase (AMACR) is significantly upregulated in prostate cancer. Antibodies have been developed against its gene product, P504S protein. By immunohistochemistry, the majority of prostate cancers are positive for AMACR, the sensitivity varying among studies from 82–100%.39 If a case is still considered atypical by a uropathology expert after negative basal cell staining, positive staining for AMACR can help establish in 50% of these cases a definitive diagnosis of cancer.

Different cocktails have been investigated combining antibodies for AMACR and basal cell specific markers.40 One combination is with antibodies to p63 and AMACR, both labeled with a brown chromogen. Although authors have reported that this cocktail is essentially equal to each antibody used separately, a problem with this cocktail is that in some cases focal nuclear staining for p63 can be hard to detect if the cytoplasmic staining for AMACR is intensely positive. With small foci of atypical glands, the lesion may not survive sectioning to do separate stains for basal cell markers and AMACR on different slides. A triple stain cocktail using a brown chromogen for both HMWCK and p63 and a red chromogen for AMACR optimizes the preservation of tissue for immunohistochemistry and has been shown to be better than basal cell markers alone (Figure 9).

Another new molecular marker that has been proposed to help diagnose limited prostate adenocarcinoma is by assessing TMPRSS2:ERG gene rearrangement. TMPRSS2:ERG gene rearrangement is relatively specific for prostate cancer and detected in approximately 40–50% of prostate cancers. More recently, an anti-ERG antibody has been developed which highly correlates with TMPRSS2:ERG gene rearrangement status.41,42 A double immunohistochemical staining containing both ERG and basal cell marker p63 antibodies has been recently developed.

Either HMWCK (34βE12 or CK5/6 or others) or p63 or a combination of the two with AMACR in either a double or triple cocktail is recommended for the work-up of small foci of atypical glands suspicious for adenocarcinoma of the prostate. ERG is optional since it is present in only 40–50% of prostate cancers and also positive in high-grade PIN (HGPIN). The number of positive cores and/or their location could possibly affect subsequent therapy in terms of suitability for active surveillance or focal therapy, such that unless one knows with certainty that it would not affect therapy, it is justifiable to perform an immunohistochemical work-up of additional atypical foci. The advantages and disadvantages for the various antibodies for the diagnosis of limited prostate adenocarcinoma on needle biopsy are listed in Table I.

Conclusion

Multiple factors influence the diagnostic yield of prostate biopsies. Many of these factors are fixed and uncontrollable. Other factors are controlled by the urologist, including number of cores obtained, method and location of biopsy, and amount of tissue obtained. The yield of cancer is also controlled by the pathologist and histotechnologist.

It is necessary to report the number of cores sub-
mitted and the number of positive cores, thereby giving the fraction of positive cores. The percentage involvement by carcinoma with or without the linear extent of carcinoma of the single core with the greatest amount of tumor should also be provided.

Using the marking technique, we can add a new pathological parameter: pathological orientation or biopsy polarity. Cancer or atypical lesions can be accurately located within the biopsy specimen and integrated to biopsy approach. It drives several potential advantages in cancer diagnosis or isolated atypical lesions; in particular, spatial localization within the biopsy (transition versus peripheral zone, anterior versus posterior, and subcapsular versus intraparenchymal) should be easy and reliable.

Probably the most common use of immunohistochemistry in the evaluation of the prostate is for the identification of basal cells, which are absent with rare exception in adenocarcinoma of the prostate and in general positive in mimickers of prostate cancer. If a case is still considered atypical by a uropathology expert after negative basal cell staining, positive staining for AMACR can help establish in 50% of these cases a definitive diagnosis of cancer.

References


Table 1 Antibodies Used in the Diagnosis of Limited
Adenocarcinoma of the Prostate on Needle Biopsy

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<tr>
<th>Stain</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>p63</td>
<td>Less nonspecific staining</td>
<td>p63 aberrant PCa</td>
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<tr>
<td>HMWCK</td>
<td>No diffuse aberrant HMWCK PCa</td>
<td>Increased non-specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>False (–) in mimics</td>
</tr>
<tr>
<td>HMWCK/p63</td>
<td>Conserves tissue</td>
<td>May not recognize p63 aberrant PCa</td>
</tr>
<tr>
<td>AMACR</td>
<td>Positive in 80% of PCa</td>
<td>False (+) in mimics</td>
</tr>
<tr>
<td>AMACR/p63</td>
<td>See AMACR and p63 in the same cells</td>
<td>Hard to see rare p63 basal cells if both same chromogen</td>
</tr>
<tr>
<td>Triple (p63/AMACR/CK)</td>
<td>AMACR and basal cell labeling in same cells</td>
<td>Dual color technically more difficult</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May not recognize p63 aberrant PCa</td>
</tr>
<tr>
<td>ERG</td>
<td>More specific</td>
<td>Only ~40% PCa positive HGPIN (+)</td>
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<td></td>
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<td>Limited experience with mimickers</td>
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