Classical treatment options for prostate cancer consist of radical prostatectomy, anti-androgen or hormonal therapy and radiation therapy. Hormonal and radiation therapy, in particular, have well-known, often profound effects on the histological appearance of benign prostate tissue and prostatic carcinoma. Novel therapies ranging from focal ablative treatments to highly targeted molecular therapies are beginning to emerge and pathologists will play a central role in documenting the effects of these treatments on normal and malignant prostate tissue.

Take Home Message:
• Knowledge of treatment-related changes and access to basic treatment information are essential to ensure accurate interpretation and reporting of post-treatment prostate specimens by pathologists.

1. Hormonal Therapy

Therapies targeting the androgen-dependent nature of prostate cancer are widely used and can have profound effects on the histological appearance of both benign and malignant prostate tissue (see Table 1). Endocrine-based therapies historically consisted of orchiectomy and/or estrogen therapy to treat locally advanced or metastatic disease. Currently, maximal androgen blockade (MAB) using a combination of a leuteinizing hormone releasing hormone (LHRH) agonists and pure anti-androgens (steroidal, non-steroidal or non-classical) is used to produce “chemical castration”. These agents are not strictly used in combination and can be used as monotherapy. Anti-androgen therapy has been more recently used in combination with radiotherapy and in neoadjuvant settings in order to down-stage tumors prior to radical prostatectomy. In terms of chemoprevention, the use of 5α-reductase inhibitors (5ARI) appears to reduce the risk of prostate cancer development. Since hormonal treatments are commonly used, pathologists must be aware of these morphologic changes when interpreting biopsies, TURP or radical prostatectomy specimens from such patients. This is especially true when the specimen is not accompanied by accurate and complete clinical information.

Table 1: Anti-androgen therapies in prostate cancer

• Historical
  Orchiectomy
  Estrogen therapy (diethyl stilbesterol)
• Contemporary combination therapy (MAB) or monotherapy
  LHRH agonists (leuprolide, goserelin)
Anti-androgens
- steroidal (cyproterone acetate)
- non-steroidal (flutamide, bicalutamide)
- non-classical (ketoconazole, 5ARI’s such as finasteride and dutasteride).

Effects of MAB on Normal Prostate Tissue, Prostate Cancer and High-Grade Prostatic Intraepithelial Neoplasia

A spectrum of characteristic changes can be seen following MAB that varies in relation to the agent(s) and dose used as well as the duration of therapy. The commonly encountered histologic changes in normal prostate tissue include glandular atrophy, basal cell prominence, basal cell hyperplasia and vacuolization of glandular epithelium. The rupture of atrophic glands with extrusion of glandular secretions and corpora amylacea into the adjacent stroma may also be observed. Estrogen therapy is commonly associated with squamous metaplasia in normal glandular and ductal epithelium.

MAB has been associated with a marked downstaging of prostatic carcinoma in up to 50% of cases when used as neoadjuvant therapy prior to prostatectomy. This effect is largely attributed to shrinkage of the tumor(s) and is most pronounced in the setting of organ-confined (T2) disease. Tumor volume reductions in the order of 40-60% have been observed following 3 and 6 months of MAB respectively. Residual carcinoma in such prostatectomy specimens is frequently minimal in nature and may be quite challenging to identify. No residual carcinoma may be identified in up to 8% of totally embedded prostates post-MAB. An overall 22% reduction in extraprostatic extension has been observed in prostates after MAB. Margin involvement shows a roughly similar drop of approximately 20% on average, with reduced margin positivity being more pronounced in T2 as opposed to T3 disease. Significantly fewer lymph node metastases are also found following MAB.

The histological appearance of prostate cancer can be drastically altered by MAB. There is typically a decrease in the ratio of glands to stroma with the malignant glands decreasing in number and size. The malignant glands develop compressed, inconspicuous lumina and may appear as short chains or small clusters and cords of cells. It is also common to see single cells that resemble foamy histiocytes. Cytologically, the cancer cells develop clear, vacuolated cytoplasm with shrunken, pyknotic nuclei with inconspicuous nucleoli. Standard immunohistochemical staining using high molecular weight cytokeratin, p63 and AMACR is usually effective in helping to confirm a diagnosis of prostatic carcinoma in challenging cases. PSA staining is usually preserved, although it is often less intense than that seen in hormone-naïve prostate cancer. The morphologic changes typically become most pronounced after 3 months of sustained MAB, however, they are reversible should the MAB be discontinued. In particular, nucleolar size tends to return to normal within 20 days of MAB cessation.

While the architectural changes described above suggest a high Gleason score in the range of 8-10/10, the bulk of current evidence suggests that tumor cells showing the effects of MAB have lost their potential for aggressive behavior. As such, Gleason
scores in this situation have no biological relevance and should not be assigned. My approach has been to avoid assigning Gleason scores if the tumor uniformly shows pronounced treatment effect. If tumor showing treatment effect is admixed with foci showing no treatment changes, I will indicate this in a specific comment. If no treatment effect is noted despite the presence of clinical information indicating the use of MAB, I will similarly indicate this in a comment. No method for providing reliable prognostic information for prostate cancer post-MAB has been developed, although an interesting classification scheme has recently been proposed by Efstathiou et al. These investigators recognized three architectural patterns in prostatectomy specimens where pre-operative androgen blockade was used: 1) single cells, cords and small clusters, 2) small, fused glands and 3) cribriform growth with intraductal spread. Their review of 115 cases indicated that the presence of cribriform growth and intraductal spread were the strongest architectural predictors of PSA failure post-prostatectomy.

MAB generally reduces the prevalence and extent of high-grade prostatic intraepithelial neoplasia (PIN). The recognition of PIN may, however, become more difficult owing to the loss of nucleolar prominence that pathologists generally rely upon to identify it. It has been suggested that increased nuclear size, crowding and disordered nuclear arrangement can serve as adapted criteria that allow pathologists to recognize PIN post-MAB.

Effects of 5ARI Therapy on Prostate Histology

5ARI’s (finasteride and dutasteride) block the enzyme 5α-reductase that catalyzes the conversion of testosterone into the more potent androgen dihydrotestosterone. While 5ARI’s have most commonly been used to reduce prostatic volume in symptomatic benign prostatic hyperplasia, these agents are now used to treat male-pattern baldness and there has been considerable interest in examining the ability of these agents to reduce the risk of developing prostate cancer. The Prostate Cancer Prevention Trial (PCPT), published in 2003, reported a 24.8% reduction in the prevalence of prostate cancer in patients in the finasteride arm over the placebo group in the 7-year follow-up period of the trial. There was, however, a higher proportion of higher grade cancers (Gleason 7-10/10) found in the finasteride group compared to patients given placebo. This finding generated questions on the whether 5ARI’s created morphologic changes similar to MAB therapy that would render Gleason scoring post-5ARI therapy as unreliable. Studies based on blind histologic review have since indicated that 5ARI’s are not likely to cause morphologic changes that create artificially increased Gleason scores. There is currently no consensus recommendation for pathologists to avoid reporting Gleason scores in specimens obtained from patients exposed to 5ARI’s. Most of the available evidence suggests that the increased incidence of higher grade cancers found the PCPT trial were a result of reductions in biopsy sampling error associated with prostate shrinkage in the 5ARI group.

Neuroendocrine Differentiation Following MAB

Neuroendocrine (NE) differentiation in the form of small cell carcinoma or large cell NE carcinoma can occur in patients treated with MAB for usual acinar type prostatic
adenocarcinoma. The anti-androgen therapy has typically been long-term (ie: > 2 years) prior to the emergence of NE carcinoma. The morphology and immunophenotype of these tumors will be identical to such tumors found in other body sites and transitional forms showing combined acinar-type and NE morphology will occasionally be present. A common clinical scenario associated with NE differentiation is the patient on long-term MAB with stable or undetectable serum PSA and a steadily expanding tumor burden including metastases to sites not typical for acinar-type prostate cancer. It has been my experience that NE differentiation is most commonly an incidental finding in palliative TURP specimens. When NE differentiation is identified by pathologists, Gleason scoring should not be applied. The patients will most often be treated with standard chemotherapy used for NE carcinoma, however, this is usually only palliative therapy. The true frequency with which NE carcinomas develop following MAB is unknown, although evidence from a rapid autopsy study seems to indicate that this will happen in roughly 10% of cases. These tumors will most commonly show negative immunoreactivity with PSA and PSAP, a point that can create a challenge for pathologists faced with a biopsy of a metastatic NE carcinoma for which the primary site is unknown.

References


Radiation therapy (RT) for prostate cancer, whether as primary therapy, neo-adjuvant prior to prostatectomy or adjuvant, is typically provided by either interstitial brachytherapy or external beam approaches. Brachytherapy involves the implantation of radioactive seeds in the prostate and is used to treat clinically localized disease. External beam RT, including conformal and intensity modulated modalities (IMRT), is more commonly used against locally advanced prostate cancer. It is often combined with various forms of anti-androgen therapy. Radiosurgery using Gamma Knife and CyberKnife technology to deliver highly focused beams to selected targets while minimizing the damage to surrounding tissue is currently under development.

The most commonly encountered post-RT specimen will be prostate needle biopsies performed as part of research trials or in response to rising post-treatment PSA values. These biopsies will most commonly be performed 18-24 months after the final RT treatment. Prostatectomy, often referred to as a salvage procedure, is not commonly performed following RT. The morphologic changes in prostate tissue obtained following RT, with or without additional changes induced by combined anti-androgen therapy, have been well-described and can be quite pronounced. It goes without saying that proper clinical information concerning the treatment history is essential in order for the pathologist to accurately interpret post-RT biopsies. There is no evidence that the morphologic changes in normal and malignant prostate tissue differ based on how the RT was delivered.

The basic changes in normal prostate tissue associated with radiation therapy are similar to those found following MAB and include glandular atrophy, a marked increase in the amount of stroma relative glands, atrophy of the secretory epithelium and prominence of basal cells – all of which can be readily appreciated at scanning magnification. At intermediate magnification, the basal cells can display vacuolated cytoplasm and marked nuclear pleomorphism with hyperchromatic, smudged nuclei. They can also have macronucleoli mimicking those seen in invasive adenocarcinoma. Squamous metaplasia may also be seen, especially in situations where anti-androgen therapy has been combined with the radiation. Finally, there can be variable amounts of stromal fibrosis along with marked vascular changes including luminal narrowing and fibrous obliteration. These changes usually persist for years after the final radiation treatment.
As is the case with MAB, the prevalence and extent of high-grade PIN is reduced in post-RT biopsies. The basic architectural patterns of high-grade PIN (flat, tufting, micropapillary and cribriform) do not appear to be altered as a result of RT.

The appearance of adenocarcinoma following radiation therapy can be highly variable, ranging from no obvious effects to alterations so profound that the affected glands and cells may be difficult to recognize as carcinoma. The recognition of such severely distorted malignant cells and glands can be made even more challenging when the specimen is not accompanied by information that mentions the history of radiotherapy. The heterogeneous appearance can be present in needle biopsies, but is more likely to be found in larger specimens such as TURP’s or prostatectomies. Marked treatment effects typically manifest as haphazardly scattered glands or single cells with pale, vacuolated cytoplasm and enlarged nuclei with prominent nucleoli. The haphazard, infiltrative appearance appreciated at low to intermediate magnification is the key to distinguishing malignant glands with treatment effects from benign glands with radiation-induced atypia. Perineural invasion, if present, is another feature that can be helpful in identifying residual malignancy. In challenging cases, immunohistochemical staining with high molecular weight keratin and/or p63 and AMACR can be used to confirm the presence of malignancy as the radiation effects do not change the usual staining patterns with these markers.

Two-year post RT biopsy status has been shown to be strongly predictive of long-term disease free survival. The features of greatest utility in this regard include the Gleason score and the degree of treatment effect. As with MAB, marked radiotherapy effects can result in apparent increases in Gleason score. Strategies for grading the degree of treatment effects and deciding on the applicability of Gleason scores have been developed, however, these should be regarded as experimental owing to lack of large scale follow-up data. One method developed by Bocking and Aufferman in 1987 and subsequently modified by Crook et al in 1997, includes an assessment of both cytoplasmic and nuclear features according the details listed in Table 2.

Table 2: Grading scheme for treatment effects in post-radiation prostate biopsies.

- **Cytoplasmic**
  - 0 - no identifiable treatment effect
  - 1 - swelling and microvesicular change
  - 2 - more extensive vacuolization with voluminous cytoplasm, ruptured cytoplasm and lipofuscin accumulation
  - 3 - only single cells. Glands, if present, are dilated
- **Nuclear**
  - 0 - no identifiable treatment effect
  - 1 - some enlargement with smudging and still visible nucleoli
  - 2 - large bizarre nuclei with smudging and rare or absent nucleoli
  - 3 - pyknotic, small nuclei
The cytoplasmic and nuclear features are graded separately and the individual scores are added together to give a combined score ranging from 0-6. Biopsies showing total grades 0-1 are the only category for which Gleason scores should be applied. Such cases are associated with local failure rates in excess of 55%. Biopsies showing tumor with combined treatment grades of 3-4 have local failure rates in the range of 30%. Carcinoma showing severe treatment effects (total grades of 5-6) on 24 month post-radiation biopsies have 5-year disease free survival rates that are similar to negative biopsies according to a recent follow-up study by Crook et al. As such, these authors prefer the term indeterminate for tumor in the combined grade 5-6 category as opposed to referring to them as adenocarcinoma with marked treatment effects. For practical purposes, I report the tumor as showing none/minimal, intermediate or severe RT effects and provide Gleason scores only in cases showing none/minimal RT change. For biopsies showing a broad spectrum of RT effects, I report these cases descriptively and indicate the approximate proportion of tumor showing each type of treatment change.

Table 3 lists the four most common diagnoses that I use for post-RT biopsies.

**Table 3: Common diagnoses given for post-radiation therapy prostate biopsies**

- Benign prostate tissue showing effects of radiation therapy. No malignancy identified.
- Adenocarcinoma showing no treatment effect – Gleason score applicable.
- Adenocarcinoma showing marked treatment effect – no Gleason score assigned.
- Adenocarcinoma showing a range of treatment effects – see comment.

**References**


3. **Newly Emerging Focal/Ablative Therapies**

The concept that many men with low risk prostate cancer are being either over-treated by radical prostatectomy or under-treated by watchful waiting/active surveillance has provided a stimulus to develop minimally invasive, focal therapies that attempt to ablate the entire gland or only a portion of gland. Precisely targeted ablative therapies aimed at
locations from which positive cores were obtained following detailed mapping biopsies are also being developed in many centers. These emerging treatment modalities listed in Table 4. None of them have been universally accepted as first-line therapies for prostate cancer and should be regarded as being investigational at this point in time.

Table 4: Emerging focal/ablative therapies for prostate cancer

- Vascular targeted photodynamic therapy (PDT)
- Thermal or microwave ablation
- Cryoablation
- Interstitial laser thermotherapy
- High-intensity focused ultrasound (HIFU)

Information on the effects of these treatments on benign and malignant prostate tissue is only beginning to accumulate. It is likely that for the foreseeable future biopsy and prostatectomy specimens from such patients will only be encountered by pathologists working in specialized centers where these studies are conducted. Given the focal nature of these treatments, it follows that histological changes are most likely be focal and confined to the areas that were targeted for treatment. Post-treatment tissue samples generally show relatively well-circumscribed areas of coagulative necrosis, granulation tissue, inflammatory/histiocytic infiltrates and fibrosis in areas where the treatment has been effective. Ghosts of malignant glands may be appreciated in areas showing coagulative necrosis. Biopsies obtained from untreated areas or from areas where the treatment was sub-optimal or ineffective will show normal prostate tissue and/or adenocarcinoma with no apparent morphological changes.

I will briefly discuss my experience with biopsies obtained following vascular targeted PDT and HIFU therapy as these modalities are currently being evaluated at the institution where I practice. PDT involves the intravenous administration of a bacteriochlorophyll-derived photosensitizer (Tookad WST09) that absorbs light maximally in the visible portion of the spectrum ranging from 732 to 763 nm. Activating optical fibers are then inserted into the prostate triggering thrombosis and vascular coagulation around the tip of the electrode. Localized necrosis is produced in the adjacent prostate tissue. PDT is currently in use a salvage therapy after failed RT in the institution where I work. In biopsies obtained 6 months after PDT, the tissue damage typically displayed an extremely sharp demarcation with the surrounding untreated tissue, be it normal or malignant. The areas of damage are characterized most commonly by well demarcated areas of complete fibrosis with an absence of glands at 6 months post-PDT. Less commonly, organizing granulation tissue or coagulative necrosis is present. Areas of viable adenocarcinoma located immediately adjacent to the foci of damage show no obvious morphological changes that would preclude the use of Gleason scoring. It should be noted that the size of the areas of damage induced by PDT are a function of the dose of photosensitizer, the number of optical fibers placed in the prostate and the light dose per fiber. It is possible to ablate the entire gland by this method.
HIFU induces coagulative necrosis and is currently in use in several centers around the world as salvage therapy after failed RT or as primary therapy. While HIFU appears to provide acceptable short-term local control, it has not been approved as a primary therapy for prostate cancer in the United States. Several devices including Albatherm (EDAP, Lyon, France) and Sonablate-500 (Focus Surgery, Indianapolis, IN, USA) are in use for either focal or whole-gland therapy in men with low-intermediate risk prostate cancer. Biopsies obtained 3-6 months post-HIFU have been reported as being negative in up to 90% of patients, with no difference being identified between low and intermediate risk patients. Actuarial 5-year biochemical and disease free survival rates following primary HIFU for localized disease have been reported as being 75% and 66% respectively. Upwards of 12% of men have gone on to have salvage hormonal therapy, RT or radical prostatectomy in some series. The precise histological changes seen on post-HIFU biopsies, TURP’s or radical prostatectomies have not been systematically evaluated. It has been my experience that HIFU-induced treatment effects, if present, manifest as areas of coagulative necrosis, organizing granulation tissue and fibrosis. The foci of damage with HIFU do not appear to be as sharply demarcated as those induced by PDT. In areas of viable tumor, there appear to be no post-HIFU histological changes that would preclude the use of Gleason scoring. One must be aware of any history of pre-HIFU anti-androgen therapy that may have been used to shrink the gland prior to treatment, in which case Gleason scoring may not be applicable.

References


4. **Chemotherapy and Targeted Molecular Therapies**

Chemotherapy has traditionally been reserved for hormone-refractory metastatic disease and is often used as a palliative measure. The agents used include, but are not limited to, mitoxantrone, etoposide, cisplatin, vinblastine, estramustine, paclitaxel and docetaxel. There is little information on the effects of these agents on the morphology of prostatic carcinoma, as these tissues are rarely the subject of biopsies. There are many new drugs at various stages of development including those that target growth factor and signal transduction pathways, apoptosis and differentiation, angiogenesis as well as immunologic therapies and novel cytotoxic agents. Information on the effects of these therapies on prostate cancer morphology will no doubt be collected in the coming years and pathologists will play a central role in this process. It has been my experience, however, that agents such as PI3 kinase inhibitors have essentially no effect on normal or malignant prostate tissue when given neo-adjuvantly prior to radical prostatectomy. Specifically, I have not observed changes in Gleason score, tumor morphology or necrosis in radical prostatectomy specimens from men enrolled in clinical trials at my institution (unpublished personal observations).

**References**


5. **Nutritional And Herbal Supplements**

The use of vitamins D and E as well as nutritional supplements such as soy, selenium, tomato products and green tea as potential preventative agents for prostate cancer is currently under investigation. No significant morphologic changes in either normal prostate tissue or prostate cancer have been reported to date and the use of these agents will likely have no impact on the ability of pathologists to accurately diagnose and grade prostate cancer in biopsies, TURP or prostatectomy specimens. The same would appear to apply to herbal supplements used to promote prostate health, such as saw palmetto berry extract.

**Reference**