

## Review

# Histopathological changes induced by therapies in the benign prostate and prostate adenocarcinoma

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**Summary.** The effect of androgen deprivation and other hormonal therapies, radiation therapy, thermal ablation therapies, chemotherapy, and other systemic treatments is evident in the histology of non-neoplastic and neoplastic human prostate gland. Androgen deprivation may be achieved with: a. orchidectomy, b. exogenous oestrogen administration, c. drugs with the capacity to deplete the hypothalamus of luteinizing hormone-releasing hormone, d. antiandrogens administration: drugs, which block the conversion of testosterone to its active form of 5- $\alpha$  dihydrotestosterone (i.e. finasteride, dutasteride), and drugs which block the androgen receptor on individual cells (i.e. flutamide). Androgen deprivation therapies cause atrophy of non-neoplastic and neoplastic prostatic epithelium, as the result of apoptosis, and are mainly used as a palliative measure in metastatic prostate cancer or as neoadjuvant or adjuvant treatment, in clinically localized prostate cancer. Morphological tumour regression may complicate the recognition and grading of treated carcinomas in radical prostatectomy specimens. Radiation therapy may be applied in the form of external beam, interstitial implantation (brachytherapy), or a combination, as a mainstay or adjuvant (external beam) treatment in localized prostate cancer. The primary effect is the damage of endothelial cells, which cause ischemia that leads to atrophy. The difficulty of post-radiation prostate needle biopsy interpretation includes the distinction of treatment effect in normal prostatic tissue from recurrent or residual tumour. Histological changes after thermal ablation mainly include lesions observed in prostatic infarcts due to periurethral coagulative type necrosis of variable volume. The correlation between the histopathological effects of the above therapies and their clinical significance is not absolutely clear.

**Key words:** Prostate gland, Prostate cancer, Therapy, Total androgen blockade, Radiation

### Introduction

Prostate cancer is the leading malignancy in men today and an increase in detected localized prostate cancers is observed. Radical prostatectomy and radiation therapy are the mainstay treatments and have been proved to be effective for long-term survival and probable cure in the management of localized prostate cancer. Furthermore, efforts are made to provide other minimally invasive alternative treatment options, such as thermal ablation. However, after these treatments, some patients will undergo either prostate-specific antigen (PSA) or clinical progression. The multimodality approach to treating patients at high risk for progression is gaining popularity. The strategies used can include the use of preoperative neoadjuvant hormonal therapy (NHT) and a variety of adjuvant approaches such as hormonal and external beam radiation therapy (Bostwick, 1997; Montironi and Schulman, 1998; Gomella et al., 2003; Kitagawa et al., 2003; Magi-Galluzzi et al., 2003).

The hypothesis surrounding the use of NHT before either radical prostatectomy or definitive radiation treatment suggests that NHT may be able to downstage the disease and decrease the positive margin rate. The pathological examination of radical prostatectomy specimens after NHT shows a recognizable impact on morphology and immunohistochemistry of adenocarcinoma of the prostate. Morphological signs of tumour regression are consistent findings, complicating the recognition and grading of treated carcinomas. However, whether NHT before surgery has a real long term influence on tumour behaviour and prognosis still has to be established (Van de Voorde et al., 1994; Bostwick, 1997; Montironi and Schulman, 1998; Gomella et al., 2003; Kitagawa et al., 2003).

The interpretation of prostate needle biopsy after

radiation therapy is still a great diagnostic challenge with significant pitfalls. The difficulty of post-radiation prostate needle biopsy interpretation includes the distinction of treatment effect in normal prostatic tissue from recurrent or residual tumour (Magi-Galluzzi et al., 2003).

Using grading systems, the histopathological follow-up of local tumour regression of prostate cancer under hormonal or radiation treatment is an objective standard to determine a therapeutical success. The conformity of histopathological grading of regression and clinical therapy effect, such as PSA value and locally palpable finding, is under evaluation (Dhom and Degro, 1982; Van de Voorde et al., 1994).

In this review we describe the morphological changes in benign and cancerous prostate tissue after androgen deprivation therapy, radiation therapy, thermal ablation and other treatments. We discuss the difficulties in diagnosing cancer in tissue specimens after these therapies and the correlation between treatment morphological changes and disease progression.

### **Androgen deprivation therapy**

Androgen deprivation may be achieved with: a. castration (orchidectomy), b. exogenous oestrogen administration, c. drugs with the capacity to deplete the hypothalamus of luteinizing hormone-releasing hormone (LHRH), d. antiandrogens administration: drugs, which block the conversion of testosterone to its active form of 5-alpha dihydrotestosterone (DHT), and drugs which block the androgen receptor on individual cells (i.e. flutamide) (Epstein and Murphy, 1997). Generally all these therapies cause atrophy of non-neoplastic and neoplastic prostatic epithelium, as the result of apoptosis (Armas et al., 1994; Polito et al., 1996). It is well established that androgen removal leads to reduction of cell proliferation (decrease of Ki-67 [MIB-1]/PCNA indices), diploid DNA content and increase of p53-dependent/independent apoptosis, characterized by fragmentation of tumour DNA and appearance of apoptotic bodies (Magi-Galluzzi et al., 1993; Armas et al., 1994; Ferguson et al., 1994; Van de Voorde et al., 1994; Grignon and Sakr, 1995; Polito et al., 1996; Montironi et al., 1998; Wilkstrom, et al., 1999). The underlying mechanisms are not fully explained, and several oncogenes, oncosuppressor genes and growth factors, such as p53, bcl2, c-myc, glutathione S-transferase, heat shock protein, c-fos, testosterone-repressed prostate message may contribute to this combined pattern of regulation (Schenken et al., 1942; English et al., 1989; Kyprianou et al., 1990; Vailancourt et al., 1996; Wilkstrom et al., 1999). In Szende et al. (2001) study, histological evaluation of mitotic and apoptotic index, Ki-67, and p53 expression in repeated biopsies seemed to contribute to predicting the value of androgen ablation. A decrease in mitotic index, increase in apoptotic index, lower Ki-67 and mutant p53 expression pointed to favourable effect of antiandrogen treatment. Mazzucchelli et al. (2000) found that VEGF

expression is downregulated in prostate cancer by hormonal manipulation, except in the population of neuroendocrine cells. Furthermore, it has not been proved if the effectiveness of the androgen ablation depends on the number of androgen receptors of the cancer cells, but most studies infer that heterogeneity in their expression is associated with poor response (Armas et al., 1994).

### **5-alpha-reductase inhibitors**

DHT is converted from testosterone by the enzyme 5-alpha-reductase. There are two isoenzymes of this nuclear bound enzyme. The type 1 is predominantly expressed in the skin and liver, locations in which type 2 is also present. Expression of 5-alpha-reductase type 2 isoenzyme in the prostate is detected in basal epithelial cells and stromal cells. Thus, most intraprostatic DHT synthesis is accomplished by the type 2 isoenzyme. DHT acts in a paracrine fashion on the androgen dependent secretory epithelium. Furthermore, DHT produced in the skin and liver can act in a true endocrine fashion on prostate cells (Montironi and Schulman, 1998; Iczkowski et al., 2005).

Androgen deprivation with 5-alpha-reductase inhibitors (i.e. finasteride – proscar, dutasteride) has been used for preoperative tumour shrinkage and treatment of prostatic hyperplasia. Reduction in the size of the prostate with an increase in the stroma, lack of the characteristic undulations at the epithelial border, and mild focal acinar atrophy may be observed. After prolonged treatment the lobular atrophy may be extent and squamous and transitional metaplasia have been also observed. Karyometric analyses have shown a reduction of the nuclear and nucleolar size of the secretory cells (Montironi et al., 1996; Bostwick, 1997; Pomante et al., 1999; Sun et al., 1999; Yang et al., 1999). In a recent study of Yang et al. (1999), it has been shown that finasteride treatment for benign prostate hyperplasia (BPH) does not cause difficulty in the diagnosis of cancer in prostate needle biopsies, because it does not influence dramatically histology of benign and malignant prostatic tissue, probably due to its weak antiandrogen effect. Finasteride blocks only the type 2 isoenzyme of 5-alpha reductase, inhibiting partly the conversion of testosterone to DHT. Dutasteride is a dual 5-alpha-reductase inhibitor, blocking both type 1 and type 2 isoenzymes. In a recent study, Iczkowski et al. (2005) showed that dutasteride induces significant phenotypic alterations in both the benign and the neoplastic prostate, supportive of a chemopreventive or chemoactive role.

### **Oestrogens**

Schenken et al. (1942) first described the histological changes in prostate adenocarcinoma after oestrogen treatment. They noticed nuclear size reduction in up to 56% of cases, loss of recognizable nucleoli, chromatin condensation, nuclear pycnosis, and

cytoplasmic vacuolation. Similar results, as well as reduction of the mitotic activity, squamous metaplasia, basal cell hyperplasia and absence of acid phosphatase secretion, have been drawn from following studies (Foster and Ke, 1998; Young et al., 2000).

#### LHRH agonists ± antiandrogen (flutamide)

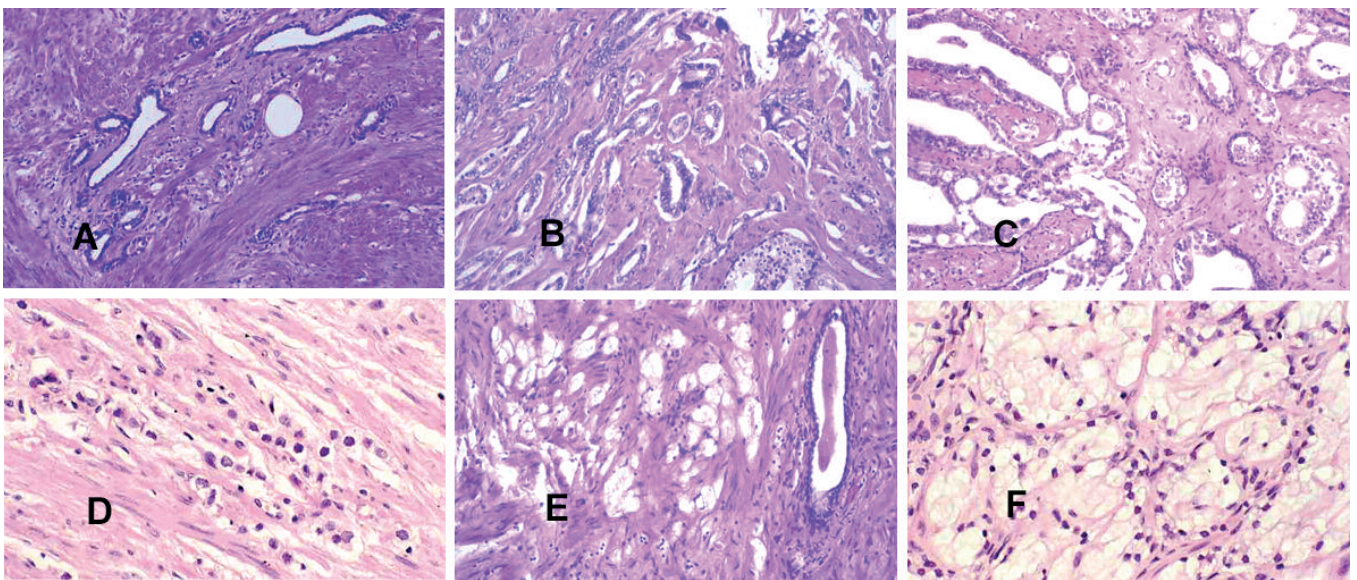
Androgen ablation (usually total androgen blockade-TAB) is mainly used as a palliative measure in locally advanced and metastatic prostate cancer. It is also applied as NHT, for usually three or six months before radical prostatectomy or definitive radiation treatment, in clinically localized prostate cancer, in order to downstage the disease, and decrease the positive margins rate and therefore the risk of recurrence. There is conflicting evidence among the different studies regarding pathological downstaging, with some studies suggesting benefit and others no benefit of NHT, probably related to incomplete sampling of the prostates and difficulties associated with the pathological evaluation. Most series have shown that NHT in clinical T2 but not in T3 tumours, is associated with a decrease in positive margins in radical prostatectomy specimens. However, randomized clinical trials have not shown that NHT improves long-term survival rate after surgery. Long-term follow up data based on biological (PSA) and clinical failures, time to progression and survival will be needed for definitive conclusions from this approach (Soloway et al., 1995; Montironi and Schulman, 1998; Schulman et al., 2000; Scolieri et al., 2000; Bullock et al., 2002; Hachiya et al., 2005). Moreover, any

correlation between histopathological changes after NHT and the risk of clinical progression is not well established. Kitagawa et al. (2003) suggest that despite preoperative high-risk factors, patients showing good pathological effects after NHT tend to have a favourable prognosis after radical prostatectomy.

The histological changes of LHRH agonists administration (i.e. leuprolide), in combination with or without flutamide (TAB or incomplete androgen blockade), are very characteristic and induced within a very short time after beginning treatment (Civantos et al., 1995; Irisawa et al., 1996; Drew et al., 1997). Tetu et al. (1991) and Murphy et al. (1991) first described them in detail.

#### Effects on benign prostate

The most prominent feature described in the non-neoplastic prostatic tissue has been marked lobular and acinar atrophy with small, shrunken, round, or comma-shaped acini (Fig. 1A). The basal cells appear more prominent and basal cell hyperplasia has been frequently observed. Depletion and vacuolation of the secretory cells is a common feature. Nuclei are small and hyperchromatic. The proliferative compartment (basal cell layer) of the prostate epithelium contains a small stem cell population, which gives rise to all epithelial cell lineages via intermediate phenotypes. These differentiation processes within the prostatic cell system are most probably regulated in a balanced vectorial manner by a combination of circulating steroid hormones together with a local non-steroidal paracrine



**Fig. 1.** **A.** Non-neoplastic prostatic tissue after total androgen blockade (TAB) with lobular and acinar atrophy (H-E, x 100). **B.** Prostate cancer (PC) after TAB with decreased glandular density and increased periglandular dense collagenous stroma (H-E, x 100). **C.** PC after TAB with apoptosis and degeneration, leading to branching pattern (H-E, x 100). **D.** Infiltrative pattern of PC after TAB (H-E, x 200). **E.** Nucleolus-poor clear cell pattern of PC after TAB (H-E, x 100). **F.** PC after TAB with extravasation of secretions, resembling mucinous carcinoma (H-E, x 200).

effect. Oestrogens and androgen ablation cause basal cell hyperplasia *in vivo*, indicating that the differentiation process from basal to secretory luminal cells is arrested. Squamous and transitional metaplasias may be observed but are not constant and usually not extensive. The usual undulating appearance of the epithelium in hyperplastic glands is lost (Murphy et al., 1991; Tetu et al., 1991; Grignon and Sakr, 1995; Civantos et al., 1996; Epstein and Murphy, 1997; Guinan et al., 1997; Foster and Ke, 1998; Rosai, 2004). Decreased glandular elements are usually accompanied by increased, sometimes hypercellular with prominent nuclei, stromal tissue, and scattered foci with lymphocytic infiltrates (Armas et al., 1994; Ferguson et al., 1994).

#### *Effects on prostate cancer*

Histologic changes of neoplastic prostatic epithelium related to leuprolide ( $\pm$ flutamide) are distinctive and include reduction in gland size with decreased glandular density and increased periglandular dense, often hyalinized collagenous stroma (known as classic LHRH effect) (Fig. 1B) (Tetu et al., 1991; Smith and Murphy, 1994; Civantos et al., 1995). The significant decrease in the number (density) of cancer glands has been confirmed by quantitative image analysis (Tetu et al., 1991; Hellstrom et al., 1997). Atypical microacini characterized either by compressed or absent lumens, or by single cell lining with cleared or vacuolated cytoplasm and small hyperchromatic nuclei compose the most common pattern. These cells then may desquamate into the lumen of the malignant glands where they resemble histiocytes and lymphocytes (Murphy et al., 1991; Tetu et al., 1991; Armas et al., 1994; Ferguson et al., 1994; Smith and Murphy, 1994; Civantos et al., 1995; Grignon and Sakr, 1995; Civantos et al., 1996; Guinan et al., 1997; Epstein and Yang, 2002; Epstein et al., 2004). A pattern of branching clefts lined by a few scattered tumour cells with pycnotic nuclei and degenerated tumour cells with foamy vacuolated cytoplasm is also caused by androgen deprivation induced programmed cell death. This degeneration and individual cell necrosis, resulting in branching spaces, was described by Tetu et al. (1991) as hemangiopericytoma-like arrangement (Fig. 1C). An infiltrative pattern with ribbons and nests of cells, as well as individual cells resembling inflammatory cells, is not uncommon (Fig. 1D) (Civantos et al., 1996; Bostwick, 1997; Epstein and Yang, 2002). Nuclei are small, round, hyperchromatic, and centrally located. Nucleoli may be large, but are usually inconspicuous leading to Ellison et al. (1993) to apply the term "nucleolus-poor" clear cell adenocarcinoma (Fig. 1E). Large clear tumour cells with a dense inflammatory response, composed of lymphocytes and histiocytes, have been also referred to, mainly in cases with tumour necrosis and with scant residual tumour (Civantos et al., 1995). The cells of cancerous glands may be almost completely degenerated, leaving irregular acid mucinous pools with a cleftlike configuration, and rare cancerous

cells at the secretion/stroma interface. Some glands may exhibit partial loss of neoplastic epithelium with extravasation of secretions and accompanying granulomatous reaction. Extravasated secretions may be the only evidence of ablated tumour in a prostatectomy specimen after treatment. This posttreatment pseudomyxoma ovariilike change in prostatic adenocarcinoma is a distinctive alteration that may be the only evidence of regressed tumour and can be potentially confused with mucinous carcinoma [Figure 1F]. No correlation between this change and dose/duration of therapy and prognosis have been reported (Epstein and Murphy, 1997; Tran et al., 1998). Squamous metaplasia can arise, mainly in treated adenocarcinoma with necrotic features (Civantos et al., 1995). The immunoreactivity for PSA and prostate-specific acid phosphatase (PSAP) is variable but often reduced in intensity (Vernon and Williams, 1983; Grignon and Troster, 1985; Helpap, 1985; Murphy et al., 1991; Tetu et al., 1991; Van de Voorde et al., 1994; Guinan et al., 1997). No differences have been noticed in the expression of neuroendocrine markers. However, during the androgen ablation therapy, the cancer cell population is enriched by neuroendocrine cells that contribute to the development of androgen-independence (Van de Voorde et al., 1994). It is inferred that the degree of effect after androgen ablation is not the same for all patients and that about 50% of cases have areas of residual tumour showing little androgen deprivation effect (Murphy et al., 1991; Tetu et al., 1991; Civantos et al., 1995; Epstein et al., 2004). A good correlation between the degree of tumour regression after androgen ablation, and clinical response or progression has been suggested (Dhom and Degro, 1982; Leistenschneider and Nagel, 1983; Schmeller et al., 1986; Bocking and Auffermann, 1987). The effectiveness of TAB for cancer prophylaxis has not been well proved and literature data are limited, although a significant reduction in the presence and the extent, as well as architectural changes of high grade prostatic intraepithelial neoplasia (PIN) has been suggested. It has also been described that the basal cell layer of glands with PIN is more prominent than in untreated glands. The presence of MIB-1 immunoreactive nuclei in PIN lesions in treated prostates suggests that they have the potential to expand after cessation of therapy (Tetu et al., 1991; Ferguson et al., 1994; Civantos et al., 1995, 1996; Polito et al., 1996; Tostain et al., 1997; Balaji et al., 1999; Van der Kwast et al., 1999; Epstein and Yang, 2002).

#### *Effects on tumour grade*

The grading of a prostate cancer obviously affected by androgen deprivation is controversial. Most studies suggest that treated tumours are of a significantly higher Gleason score, although the morphological characteristics of atypia are reduced. This elevation is much higher than expected in radical prostatectomy specimens due to the well-known phenomenon of undergrading in needle biopsies. Two of Gleason's

criteria are significantly affected: decrease in gland size and increased stroma between glands. The upgrading is considered an artifact of treatment and is the result of an increase in the frequency of Gleason pattern 5. The collapse of malignant glands leads to a pattern of infiltrating single cells, small clusters of cells, or cells in single file, which convert Gleason patterns 3 and 4 to pattern 5. Thus, biopsy-graded Gleason score 6 or 7 carcinomas may be converted to a 'pseudo-Gleason' 8 or 9 in the radical prostatectomy specimens (Montironi and Schulman, 1998; Bullock et al., 2002). Studies utilizing DNA content and proliferating cell nuclear antigen (PCNA) have shown less proliferative activity in areas of apparently poor differentiation than in nontreated carcinomas with similar patterns, suggesting that the "upgrading" is artifactual. It is believed that the histological grading using the Gleason system for treated cancers may be an inaccurate assessment of biologic behaviour, because it usually provides a false impression of dedifferentiation, and adenocarcinoma following therapy is probably not more clinically aggressive than when untreated (Schmeller and al., 1986; Bocking and Auffermann, 1987; Murphy et al., 1991; Tetu et al., 1991; Armas et al., 1994; Ferguson et al., 1994; Smith and Murphy, 1994; Civantos et al., 1995; Grignon and Sakr, 1995; Bostwick, 1997; Bullock et al., 2002; Epstein et al., 2004). However, outcome data are not available and it cannot be totally excluded if this pattern reflects aggressive androgen-independent clones or collapsed carcinoma of low viability (Bostwick, 1997). From a practical point of view, cases showing marked treatment effect should not be graded. In situations where the neoadjuvant treatment has relatively little effect on tumour pattern, a grade can be rendered (Montironi and Schulman, 1998; Bullock et al., 2002). The reports about the tumour effect versus grade and stage of the prostate cancer before treatment are not absolutely in agreement. However, low grade/stage tumours seem to be more susceptible to therapy (Nielsen et al., 1992; Drew et al., 1997; Young et al., 2000).

#### *Effects on tumour stage and surgical margins*

It is confirmed that in about 50% of patients with clinically organ-confined disease, the pathological examination reveals extraprostatic extension, and in about 30% of them positive surgical margins. The degree of downstaging varies among the several studies and the ultimate role for NHT remains to be determined by long term outcome data from clinical trials (Armas et al., 1994; Grignon and Sakr, 1995; Civantos et al., 1996; Polito et al., 1996; Tostain et al., 1997; Bullock et al., 2002). Complete tumour regression of small organ-confined prostate cancers (vanishing cancer phenomenon) has also been observed (Fair et al., 1993; Armas et al., 1994; Lopez Lopez et al., 1996; Young et al., 2000). In a study of Montironi et al. (1999), TAB before radical prostatectomy caused significant pathological downstaging and decrease in the number of positive margins in clinical stage B, but not in clinical C

tumours. The effects have been more pronounced after six than after three months of therapy. Bono et al. (2001) found also that TAB before surgery is beneficial mainly in men with clinical stage B disease. The effects were more pronounced after 6 months of treatment than after 3 months. The changes of neoadjuvant androgen ablation may contribute to underdetection of prostate cancer capsular involvement and positive surgical margins. Cytokeratin immunohistochemistry may help at the determination of pathologic stage of prostate cancer following androgen ablation (Bazinet et al., 1997; Bullock et al., 2002).

#### *Differential diagnostic problems after androgen blockade*

In the differential diagnosis of cancer following androgen deprivation are included benign and malignant lesions, mainly with clear cell appearance (Bostwick, 1997). Clear cell cribriform hyperplasia, sclerosing adenosis, acinar atrophy, atypical adenomatous hyperplasia, mucinous metaplasia, atypical basal cell hyperplasia, paraganglioma with clear cell pattern, epithelioid leiomyoma, cowper's glands, granulomatous prostatitis, xanthoma and mesonephric remnants are included in the differential diagnostic panel of benign conditions. Poorly differentiated clear cell prostate cancer, transition zone cancer with clear cell pattern, mucinous and signet-ring cell carcinoma, epithelioid leiomyosarcoma, clear cell carcinoma of the bladder, metastatic clear cell renal carcinoma and other secondary malignancies, and signet ring cell lymphoma are included in the differential diagnostic group of malignant conditions. The differential diagnosis of isolated or groups of tumour cells that have a benign appearance after therapy, from lymphocytes, histiocytes, myocytes and stromal fibroblasts may be extremely difficult. PSA, PSAP and pankeratin immunoreactivity, as well as the lack of basal cell-specific keratin 34 $\beta$ E12 immunoreactivity by prostate carcinoma after androgen deprivation therapy, may help in distinguishing it from its mimics (Armas et al., 1994; Bostwick, 1997; Epstein et al., 2004). Although the histological effects of androgen deprivation are not absolutely diagnostic, they may be recognized by an experienced pathologist with a high sensitivity and specificity, even in the absence of clinical history (Smith and Murphy, 1994; Bostwick, 1997; Drew et al., 1997). The knowledge and the ability to recognize these changes are very important in order, firstly to identify residual tumour, particularly in small specimens and lymph node metastases, and secondly to distinguish this favourable indicator from dedifferentiation of prostate cancer during therapy, which is an unfavourable factor (Smith and Murphy, 1994; Bostwick, 1997; Epstein and Murphy, 1997). Features favouring androgen deprivation include discrete small round glands separated by fibrous tissue, difficult to discern at low magnification, lack of nuclear atypia and large nucleoli, and scanty, pale or vacuolated cytoplasm. Features favoring poorly differentiated carcinoma include infiltrating and easily discerned

pattern, irregular glands, nuclear anaplasia and prominent nucleoli, and acidophilic or slightly basophilic cytoplasm (Smith and Murphy, 1994).

The histologic changes after 2nd line hormonal treatment have not been well studied. They probably cause increase of the connective tissue and the effect on the cancer tissue must be poor (Zalatnai et al., 1988).

### **Radiation therapy**

The management of clinically localized prostate cancer includes radical prostatectomy, radiation therapy, and “deferred” (“expectant”) treatment (Young et al., 2000, Rosai, 2004). Radiation therapy has been applied in the form of external beam, interstitial implantation (brachytherapy), or a combination, and has also been used as an adjuvant therapy after radical prostatectomy (Rosai, 2004).

After radiation therapy, the prostate gland is usually small and hard. In contrast to hormonal therapy, the histological changes associated with radiation therapy have not been rigorously studied (Dhom and Degro, 1982; Grignon and Sakr, 1995). There are no comparative studies of pre- and post- treatment prostate tissues that include a large number of patients, so that descriptions of the variation in the histology of the primary tumour, as well as that of the tissue responses to various x-rays doses, are limited. Nevertheless, the radiation effects of an external beam or implantation administration seem to be completely dose related (Bocking and Auffermann, 1987).

#### *Effects on benign prostate*

The primary effect of radiation is the damage of endothelial cells, which cause ischemia that leads to acinar distortion and atrophy. The histological changes induced in the normal prostate tissues have been well described (Bostwick et al., 1982; Dhom and Degro, 1982; Siders and Lee, 1992; Grignon and Sakr, 1995; Cheng et al., 1999; Magi-Galluzzi et al., 2003). The secretory epithelial cells of the atrophic small acini may have reduced or vacuolated cytoplasm. Multilayering of epithelium and streaming of cells parallel to basement membranes, atypical basal cell hyperplasia and immature squamous metaplasia may be observed. Nuclei are usually small and pycnotic; however, some are enlarged with occasional nucleoli. It is noticeable that the induced cytologic atypia (of degenerative nature) is greater in benign than in neoplastic glands. The degree of atypia of the atrophic benign glands may be so severe as to cause differential diagnostic problems from carcinoma. Basal cells can be small and shrunken, making their identification even more difficult than on normal tissues (Grignon and Sakr, 1995; Epstein and Murphy, 1997). Immunohistochemical studies using antibodies against antigens of basal and secretory cells may be helpful (Helpap and Koch, 1991; Grignon and Sakr, 1995; Cheng et al., 1999). Vascular changes, including endothelial cell degeneration with

hyalinization of vascular walls, myointimal proliferation, luminal narrowing, and accumulation of foamy, lipid-laden macrophages, are always prominent (Bostwick et al., 1982). Stromal fibrosis with granulation tissue formation and occasional atypical, polynuclear, and bizarre fibroblasts are also found. Heterologous changes, such as osseous metaplasia have rarely been observed (Helpap, 1985; Locke et al, 1986; Cheng et al, 1999) (Fig. 2A).

Magi-Galluzzi et al. (2003) found less atypia of benign prostate epithelium in men biopsied >48 months after external beam radiation, compared with those with a shorter interval between biopsy and treatment. However, they did not find any change over time in epithelial atypia in men treated with brachytherapy or combined external beam radiation and brachytherapy. Furthermore, there was more atypia in cases treated with combined therapy than external beam radiation. That means that the type of radiation therapy is a major factor in the degree and duration of postradiation epithelial atypia.

#### *Effects on prostate cancer*

The degree of radiation induced changes on prostate cancer tissue is variable among patients and even among different areas of the same tumour with some glands showing marked radiation effect and others showing no evidence of radiation damage. The neoplastic glands become fewer and smaller, and are haphazardly arranged, but usually there are not dramatical changes in the morphology (Fig. 2B). Sometimes the carcinoma loses its glandular pattern, resulting in clustered cells or individual cells. The nuclei become irregular in shape and size, pycnotic or large with clumped chromatin. Nucleoli are often lost. At radiation's maximum effect, the cytoplasm may be greatly increased in amount with a clear to finely granular appearance and PAS positivity. The cells may appear to have only cytoplasm without visible nuclei. Paneth-like cells may also be prominent. The stroma is often sclerosed, particularly following radioactive seed implantation. In the latter the stromal hyalinization is often sharply delineated. The incidence of PIN seems reduced in salvage radical prostatectomy specimens following radiation therapy when compared with prostatectomies without prior radiation (Dhom and Degro, 1982; Helpap, 1985; Siders and Lee, 1992; Grignon and Sakr, 1995, Sun et al., 1999; Epstein et al., 2004; Rosai, 2004). It is suggested that regressive changes are much more distinctly expressed in the low grade carcinomas (Helpap and Koch, 1991).

#### *Effects on tumour grade*

Although the identification of residual tumour after radiation, is the main work of the pathologist, grading of unaffected carcinoma is essential too. Cancer showing treatment effect should not be histologically graded (Epstein and Murphy, 1997; Crook et al., 2000). The effect of radiation on histological grade is variable.

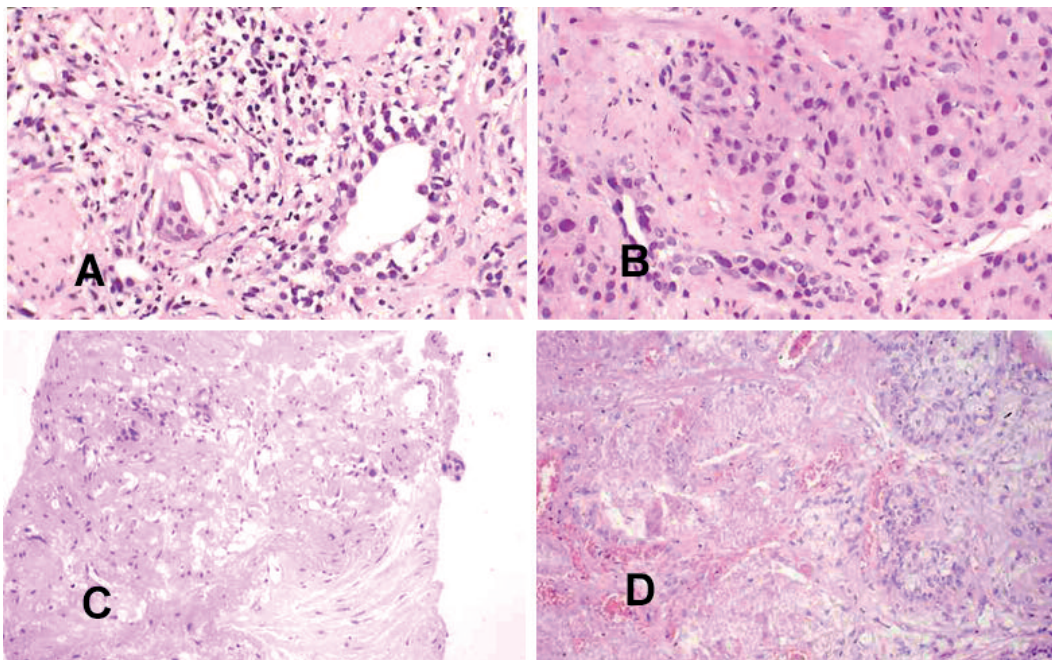
## Prostate histology and therapies

Usually a significant increase in Gleason score is noticed, which probably does not reflect a dedifferentiation phenomenon, as it is apparent that a tumour with the most marked effects will have only scattered single cells and Gleason score 10 pattern (Bostwick et al., 1982; Wheeler et al., 1993). In contrast, tumours occurring locally after radiation therapy, usually exhibit increased tumour aggressiveness by both histologic (Gleason score) and biologic (DNA ploidy) parameters (Siders and Lee, 1992; Wheeler et al., 1993; Grignon and Sakr, 1995).

### Differential diagnostic problems after radiation therapy

Following radiation therapy, prostatic biopsy should be diagnosed as no evidence of cancer, cancer showing no or minimal radiation effect, or cancer showing significant radiation effect, or a combination of the above. Although schemes for grading radiation effect have been devised, these are not recommended for routine clinical practice (Bocking and Aufermann, 1987; Crook et al., 2000; Epstein et al., 2004). Foci of residual carcinoma can be found in follow-up biopsy specimens or in transurethral resection performed to treat obstruction symptoms. The rate of positivity in such biopsies has varied from 20% to 93%, with the majority of series reporting numbers in the 50-60% range (Mollenkamp et al., 1975; Kiesling et al., 1979). Several factors, including selection of patients for biopsy, method of biopsy, timing of the biopsy, and type of the radiation therapy used, may cause these differences. No definitive method, including histological and immunohistochemical studies, can identify the viability of the residual tumour. In needle biopsies,

distinguishing small acini with radiation induced atypia from microacinar carcinoma can be a difficult diagnostic problem. The most reliable diagnostic criterion of residual malignancy after radiation therapy is the recognition of an infiltrative pattern. In contrast, within the radiated normal prostate, glands maintain their lobular architecture. Irradiated benign glands are often atrophic, in contrast to gland-forming prostatic adenocarcinomas that typically have abundant cytoplasm. On higher magnification, whereas glands of prostatic carcinoma are lined by a single layer, there is a piling up of the nuclei within irradiated normal prostate as well as an occasional recognizable basal cell layer. Scattered markedly atypical nuclei in glands as well as nuclei with a degenerative, hyperchromatic smudgy appearance are typical of radiated benign glands. Prostatic carcinomas that are sufficiently differentiated to form glands rarely manifest the degree of atypia seen with radiation, and if present would be more uniformly present in all cells. When cribriform structures, fused glands, solid sheets and cords are identified, the diagnosis can usually be made with confidence (Bostwick, 1997; Epstein and Murphy, 1997; Young et al., 2000; Epstein and Yang, 2002). In Scardino et al. (1986) study, residual carcinoma has been detected in 35% of the biopsies of patients without obstructive symptoms, between 6 months and 3 years after treatment. Almost all biopsies from symptomatic patients, performed more than 18 months after completion of radiation, have included residual cancer. Most specialists believe that needle biopsies are the best method for assessing local tumour control, but mustn't be performed before one year after treatment, due to the delayed manifestation of tumour cell death. It has been



**Fig. 2.** **A.** Irradiated benign prostatic tissue with acinar distortion and granulation tissue formation (H-E x 200). Cytoplasmic vacuolation and some pycnotic enlarged nuclei in an atrophic acinus. **B.** Prostate cancer after external beam radiation. Infiltrative growth and haphazard arrangement of neoplastic glands, with irregular pycnotic nuclei. An adjacent benign acinus with some enlarged nuclei (H-E x 200). **C.** Negative prostate biopsy after brachytherapy with stromal fibrosis and occasional atypical fibroblasts (H-E x100). **D.** Prostatic infarct after cryotherapy (H-E x 200).

found that tumour continues to regress 6-12 months after treatment (Crook et al., 1993). Many authors also believe that a histologically apparent tumour twelve months after radiation is probably biologically active. Taking serial specimens can minimize a sampling error (Kiesling et al., 1979; Mahan et al., 1980; Dugan et al., 1991; Helpap and Koch, 1991; Kabalin, 1992; Siders and Lee, 1992; Wheeler et al., 1993; Bostwick, 1997). Histological changes in conjunction with serum PSA can offer more reliable clues to the viability of the residual tumour, but only if trends can be established and the variability is in a single direction (up or down) (Crook et al., 1993; Rosai, 2004). Musselman et al. (1987) observed monolayer growth from explants of prostatic carcinoma two years or more after radiation. Conversely, Mollenkamp et al. (1975) could not culture any irradiated tumour, but it is noticeable that their success rate in the cultivation of untreated tumours was also pure. The fact that most irradiated tumours show immunoreactivity for PSA and PSAP, can lead to the suggestion that tumour cells capable of protein production may also retain the potential for cell division and metastatic spread. Furthermore, these antibodies along with pankeratins are very helpful to detect isolated residual tumour cells, which can be overlooked in H&E stained sections (Mahan et al., 1980; Ljung et al., 1997; Young et al., 2000; Epstein et al., 2004). Keisling et al. (1979) have found no ultrastructural changes in prostatic adenocarcinoma after radiation, suggesting that residual tumour is viable.

Several pretreatment characteristics have been found to correlate with a positive postirradiation therapy biopsy, including clinical stage, pelvic lymph node status, histologic grade, serum PSA, and cell proliferation and apoptotic index (Dugan et al., 1991; Crook et al., 1993; Grignon and Sakr, 1995). It has been well established that the presence of tumour after completion of therapy correlates with an increased risk of local recurrence, distant metastases, and death from prostate cancer (Kiesling et al., 1979; Scardino et al., 1986). However, there is a subset of patients with positive biopsy findings who do not show progression. In a large series of Crook et al. (2000), biopsy pathology predicted prognosis with positive biopsies having a worse outcome than negative biopsies and cancers with treatment effect having an intermediate prognosis. It has been observed that the expression of immunohistochemical cell proliferation markers (Ki-67/PCNA) is usually associated with high progression rate (Crook et al., 1994; Epstein and Yang, 2002).

The role of brachytherapy is becoming more defined in the treatment of large, bulky prostatic neoplasms as a way of improving the dose distribution achieved between normal and tumour tissue (Porter and Forman, 1993). Helpap et al. (2002) observed that in cases with low Gleason score, low PSA levels and clinically organ defined tumours, long-term results after brachytherapy appear to be equal to those after radical prostatectomy and conventional radiotherapy. Furthermore, based on morphological analyses they noticed that the immediate

success of brachytherapy may be impressive, but a very high density of the seeds is needed for definite damage of the whole tumour (Fig. 2C). It is noteworthy that Kucway et al. (2002) concluded in their study that androgen deprivation therapy before brachytherapy is a method of downsizing the prostate to overcome anatomical limitations, including larger gland volume and pubic arch interference.

### **Thermal ablation**

The prostate is located in the pelvis and is easily accessible through the rectum and the urethra and percutaneously through the perineum. Because of easy accessibility of prostate, new treatments using thermal ablation have been applied, including not only heating but also freezing of the pathological tissue. Heat applied to prostate tissue (hyperthermia) results in cytoplasmic and nuclear protein denaturation, DNA and RNA changes and cellular membrane function change. Cell death is achieved and extensive coagulative necrosis is obtained. Cell death after freezing (cryoablation) may occur due to chemical damage or intra-cellular ice formation. Compared with hyperthermia that requires a temperature change of less than 10°C from body temperature in order create cell death, cryoablation requires more than 70°C of temperature change, creating a rather unclear boundary of necrosis with a tissue mixed with vital and non-vital cells at the edge (Shinohara, 2004; Pareck and Nakada, 2005).

### *Thermal energy application for BPH*

The current concept of thermal therapy of BPH is to destroy the hypertrophic tissue in the peri-urethral area by increased tissue temperature, using a transurethral approach, without damaging the urethra. These ablation techniques are called minimally invasive treatments of BPH and include interstitial laser coagulation (ILC), transurethral microwave therapy (TUMT), transurethral needle ablation (TUNA) and heated water induced thermotherapy (WIT). ILC is a laser treatment by a placement of a needle shaped laser fibre in the prostate adenoma through the urethra. TUMT uses a catheter with microwave antennae in order to heat the adenoma tissue. TUNA uses radiofrequency energy and WIT uses heated water. All the above treatments result in haemorrhagic infarcts due to periurethral of coagulative type necrosis of variable volume (Fig. 2D). The necrotic tissue is gradually absorbed. The central necrosis is accompanied by extensive peripheral haemorrhage, containing vessels with a partially obliterated lumen, and by partially necrotic tissue with squamous and transitional metaplasia, and residual glands and glandular acini lined with flattened epithelium cells having scant cytoplasm and lacking the characteristic features of normal prostatic epithelium (Orihuela et al., 1995; Boni et al., 1997; Mauroy et al., 1997; Sulser et al., 1997; Shinohara, 2004). Basal cell hyperplasia, cell swelling, stromal hyalinization, fibrosis, granulomatous



inflammation, haemosiderin deposits, foci of calcification and bacterial colonization have been also described. The changes strongly correlate to intervals from the treatment's onset (Borkowski et al., 1996).

#### *Thermal energy application for prostate cancer*

Carcinoma of the prostate is usually located in the peripheral zone of the prostate and may be multi-focal. Therefore, it generally requires ablation of the entire gland, frequently using percutaneous transperineal insertions of energy sources. The following treatments are used: cryoablation (cryosurgery), TUMT, radiofrequency interstitial tumour ablation (RITA), high intensity focused ultrasound (HIFU) and ferromagnetic thermal ablation (Shinohara, 2004). Cryosurgery has been approved for clinical usage (Littrup et al., 1994; Borkowski et al., 1996; Falconieri et al., 1996; Koppie et al., 1999). Several cryosurgical devices are available using needle-shaped probes and several cryogens. Furthermore, HIFU is an ideal energy delivery technique for prostate cancer, as it does not require invasive insertion of a needle in the tumour, avoiding cancer spillage. However, all these newer treatments are still under investigation. Even cryoablation, which has been recognized as an established treatment for prostate cancer, requires more advancement in order to achieve comparable efficacy and morbidity of radical prostatectomy or radiation therapy as a primary treatment. Furthermore, studies have shown that local recurrence after radiation therapy can be safely treated with these techniques (Suzuki et al., 1995; Khair et al., 1999; Shinohara, 2004; Pareek and Nakada, 2005). According to the available data, after these therapies pathologists have to refer if there is residual tumour and if this is viable. No change in the morphology and grade of residual carcinoma has been mentioned; however, the reported studies are few. Pathological analysis of salvage prostatectomies performed after failed cryotherapy have revealed viable carcinoma in areas thought to be destroyed by intraoperative transrectal ultrasound (Borkowski et al., 1996; Falconieri et al., 1996; Epstein and Murphy, 1997; Young et al., 2000).

#### **Chemotherapy**

Chemotherapy has been used in metastatic prostate cancer as 2nd line treatment, after failure of all hormonal manipulations, and usually in combination with corticosteroids or hormonal agents. Its usefulness has been proved of limited benefit (Wozniak et al., 1993). The studies on the influence on chemotherapy on prostate non-neoplastic and neoplastic tissue are extremely limited and mainly concern animal models. Necroses, reduction of mitotic activity, and fibrosis have been described (Kunzle et al., 1997).

#### *Systemic treatments and treatments of adjacent organs*

The influence of systemic treatment or therapy of

adjacent organs on the pathology of the prostate gland haven't been well studied, except from the effect of intravesical instillation of BCG for the management for superficial bladder cancer (Mukamel et al., 1990). BCG traverses the prostatic ducts, enters the acini and, in virtually 100% of patients followed with biopsy, has produced a granulomatous prostatitis (Gardner and Bennett, 1992). Nodular collections of histiocytes, and both caseating and noncaseating sarcoid-like granulomas have been observed and if the history is known, it is not necessary to test the patient for tuberculosis infection (Mukamel et al., 1990). Epithelioid granulomas usually appear in the first three months after BCG installation and may be found in the prostate more than a year after BCG therapy. Acid fast bacilli can be demonstrated by specific stains (Gardner and Bennett, 1992). Nevertheless this type of granulomatous prostatitis may coexist with prostatic carcinoma and, in the presence of indicative clinicolaboratory findings, must lead to biopsy (Epstein and Murphy, 1997).

#### **Conclusions**

The histopathological changes in adenocarcinoma of the prostate following therapy, such as androgen deprivation or radiation therapy, often present a significant diagnostic and clinical challenge. Pathologists must be able to recognize the characteristic histological findings after each therapy in order to avoid diagnostic pitfalls, mainly when no reliable clinical history is provided. In prostatectomy specimens after NHT, tumour regression may cause difficulties in tumour recognition, grading and staging. The ability to recognize these changes is very important, in order to identify residual tumour and distinguish this favourable indicator from dedifferentiation of prostate cancer during therapy that is an unfavourable factor. In post-radiation biopsies the radiation induced atypia in benign glands may cause differential diagnostic problems from residual or recurrent carcinoma. The clinical challenge is to predict which tumours will respond to these therapeutical approaches and which will benefit and not progress.

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