

Carcinoma of the prostate. A historical account

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Summary

With this paper the author presents some historical notes concerning prostatic cancer. He analyses the first recorded carcinomas of the prostate, its surgical treatment,

radiotherapy, hormonotherapy and the diagnostic procedures.

Key words: hormonotherapy, prostatic carcinoma, radical prostatectomy, radiotherapy

Introduction

Giovanni Battista Morgagni (1682-1771) (Figure 1) [1] was the first to describe enlarged prostates which could refer to carcinoma of the prostate. In



Figure 1. Giovanni Battista Morgagni (1682-1771)

1793 Matthew Baillie (1761-1823) [2] stated, “the most common disease of the prostate gland is scirrhus”. But the first undoubted cases of carcinoma were described in 1832 by Sir Benjamin Collins Brodie (1783-1862) [3]. The first patient had lost weight and suffered from sciatica, and the prostate was found to be “not much enlarged but of stony hardness.” The second patient, whose prostate was much enlarged and stony-hard, developed excruciating pains in various parts of the body and became paraplegic. Richard Stafford [4], in 1839, described an “encephaloid” tumor the size of a hazelnut, containing melanotic matter, in the prostate of a 5-year-old child.

In 1844 Stanislas Tanchou [5] reviewed 1904 fatal cases of carcinoma in men and found only 5 reports of carcinoma of the prostate. In 1851, James Adams (1818-1899) [6] thought that prostate carcinoma was rare, and he was able to collect only 3 cases of cancer, 2 of which were reported as being soft, and one was described as “scirrhus”. He referred to benign hypertrophy of a “gristly hardness”, suggesting misdiagnosis in many cases. He quoted the patient of Brodie, who had a locally infiltrating tumor, an indurated gland in the groin and edema of the left leg.

In a review in 1873, Sir Henry Thompson (1820-1904) (Figure 2) [7] found only 18 reports which met his criteria for the diagnosis of a malignancy; only 2 tumors were scirrhus, a type of growth which Thompson regarded as very rare.

The typical osteoblastic metastases in bone were noted in 1891 by von Friedrich Daniel Recklinghaus-



Figure 2. Sir Henry Thompson (1820-1904).

en (1833-1910) [8], who based his report on 5 cases. The first patient presenting with symptoms due to bony metastases was recorded by Franck Sasse [9] in 1894. In 1897, Octave Pasteau (1870-1957) [10] produced evidence of the involvement of the iliac lymph nodes in 87% of cases of prostatic cancer and of the inguinal lymph nodes in 36%.

In 1900, Joachim Albarran (1860-1912) (Figure 3) [11] and Adrian Joseph Noël Hallé (1859-1927), in their study of the histology of enlarged prostates, found malignant changes in 14 of 100 glands. Their report was not well received at the time, but gradually the condition came to be recognized more frequently. Reginald Harrison in 1903 [12] was one of the earliest to assert that “carcinoma of the prostate is far more common than we have been led to think”. Between 1902 and 1905, Hugh Hampton Young (1870-1945) (Figure 4) [13] found 21% of 318 cases of bladder neck obstruction to be associated with malignant changes, and in 1913, Sir Peter Johnston Freyer (1851-1921) (Figure 5) [14] reported that 13% of his cases were cancers.

In 1935, Arnold Rice Rich (1893-1968) [15] demonstrated carcinomatous changes in the prostate in 14% of all autopsies, and in 28% of those aged over 70 years. This frequent occurrence of latent carcino-

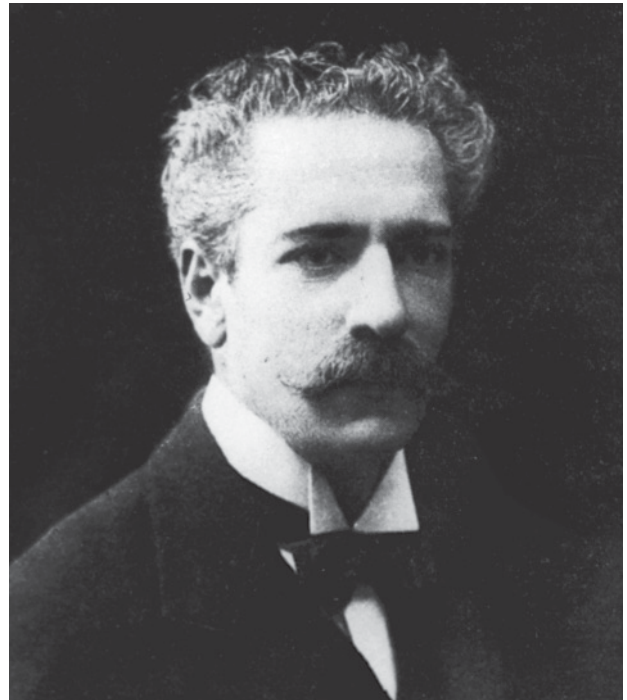


Figure 3. Joachim Albarran (1860-1912).

ma has been confirmed by many authors, including E. Baron [16] and A. Angrist (1941).

In 1936, R.A. Moore [17] observed invasion of perineural lymphatics in 77% of cancers. O.V. Batson's [18] demonstration in 1940 of the free commu-



Figure 4. Hugh Hampton Young (1870-1945).



Figure 5. Sir Peter Johnston Freyer (1851-1921).



Figure 6. Theodor Billroth (1824-1923).

nication between the prostatic venous plexus and the veins of the pelvis and vertebral veins explained the high incidence of metastases in the bones of the pelvis and the vertebrae. In 1938, A.B Gutman and Ethel Gutman [19], and B.S. Barringer [20] and H.Q. Woodard, independently reported an increase in the serum acid phosphatase of prostatic origin in many patients suffering from carcinoma of the prostate with extracapsular spread.

Surgical treatment

Removing a prostate cancer is a difficult task, due to its deep position and its anatomic relations. The beginnings and gropings about prostate cancer surgery are confounded with those of the prostatic adenoma.

The first recorded operation for carcinoma of the prostate was partial perineal prostatectomy performed in 1867 by Theodor Billroth (1824-1923) (Figure 6) [21]. A tumor the size of a duck's egg was removed from the 30-year-old patient, who died of recurrence 14 months later. In the same year, he curetted a carcinomatous intravesical middle lobe of the prostate through a perineal urethrotomy; the patient survived only a few days. The operations of partial and total prostatectomy performed by Jean Nicolas

Demarquay (1814-1875) [22] in 1871 and 1873 were for carcinoma of the rectum invading the prostate.

In 1876, Bernhard Rudolph Conrad von Langenbeck (1810-1887) excised part of a carcinomatous prostate through a perineal approach. Heinrich Wilhelm Franz Leisrink [23], who was present at the operation, remarked that von Langenbeck's example encouraged him when, in 1883, he performed a total perineal prostatectomy for carcinoma. He sutured the bladder neck to the severed urethra, and he found it necessary to remove part of the anterior rectal wall involved in the neoplasm. The patient died of "exhaustion" on the 14th day.

Perineal operations for prostatic carcinoma carried out by several other surgeons in these early days were rarely successful. In 1889, Vincenz Czerny (1842-1916) [24] performed total prostatectomy on a 47-year-old man who died 9 months later. In his second operation in the same year, local extension necessitated the removal of part of the bladder, the vesicles and the anterior rectal wall; the patient died 12 days after surgery.

In 1891, Georg Ferdinand von Kóster (1839-1930) [25] performed total cystectomy and prostatectomy with anastomosis of the ureters to the bowel. He mobilized the bladder by a suprapubic approach with resection of the pubes and completed the dissection of the prostate and bladder base through a posterolateral perineal incision; the patient died 5 days later.

The posterolateral approach was used in 1891 by Jean Verhoogen (1864-1950) [26] to excise a sarcoma of the prostate, and in 1889 by Henri Delageni re (1858-1930) [27] to remove a prostatic malignancy secondary to a carcinoma of the rectum. Other surgeons to perform radical perineal prostatectomy were Alex Stein and August Socin [24]. Radical suprapubic prostatectomy for carcinoma of the prostate, together with removal of part of the bladder wall, was carried out in 1898 by Eugene Fuller (1858-1930) [28]. Total prostatectomy with partial cystectomy for carcinoma of the base of the bladder was performed in 1902 by M.L. Harris [29], whose patient died two months later.

Furstenheim used Bottini's cautery to relieve retention of urine caused by a malignant prostate in 1904, and he commented on the advantages of this method of treatment.

In 1904, with the help of William Stewart Halsted (1852-1922), Young [13] planned and carried out a radical perineal prostatectomy for carcinoma. The gland was exposed through a curved perineal incision, the urethra was incised at the apex of the prostate for insertion of the prostatic tractor and was then divided. By blunt dissection, the entire prostate was freed, and an incision was then made through the anterior wall of the base of the bladder and carried round to the posterior aspect; the vasa were divided and the vesicles were removed with the prostate. The bladder was then anastomosed to the stump of the urethra. In 1905, he reported 4 such operations and reviewed the records of all cases of carcinoma treated at his unit. He observed that a small nodule in the prostate might well be an early carcinoma, and he advised open biopsy followed by radical surgery if this proved positive.

Radical prostatectomy gave at that time a large percentage of incontinence, regular impotence, but Young thought that it would cure the cancer because, as he put it, "the evil spirit has been put in the bottle together with the prostate". Unfortunately, local and distant recurrences appeared in a large number of cases.

This technique continued to be used with only minor modifications, including those of Edouard Belt [30], Oswald Lowsley [31] and Samuel Vest [32], and in 1937, Young [33] reported a 5-year survival of 50% in cases of carcinoma treated by this method.

Anterior perineal prostatectomy, or "ischio bulbular" prostatectomy, was carried out by Max Wilms (1867-1918) [34] in 1908 and Eug ne Soubeyran [35] in 1909. The exposure was poor and the results were discouraging.

Other techniques of prostatectomy for carcinoma never gained much favor. Freyer [36] maintained that his enucleation was a total removal of the prostate and so he practiced it for early prostatic carcinoma. In 1913, Freyer reported operations on 6 patients, none of whom had any further symptoms. In 1910, Pauchet [24] described suprapubic transvesical total prostatectomy performed through an incision in the base of the bladder. These techniques had nothing to recommend them. A combined suprapubic and perineal approach was described by Fuller [28] in 1912. The retropubic route for total prostatectomy was described in 1947 by Terence John Millin (1900-1979) (Figure 7) [37], who maintained that this procedure was technically easier than the perineal operation.

These radical operations provided the only cures of carcinoma of the prostate, and 5-year survival of 50% was reported by J.A.C. Colston [38] in 1940; however, these results were based on relatively few patients. In most patients, the malignancy had been far too advanced for curative surgery and these patients had been treated by a variety of methods, mainly directed towards relief of obstruction.

The absence of convincing and durable results, the too frequent incontinence, the impotence, and a non-negligible mortality, slowed down the development of radical prostatectomy in the United States during the first half of the 20th century, while it didn't arrive at all in Europe. The emergence of hormone therapy in 1941 was considered by many and for a long time as the ideal solution which would protect from the hazards of surgery. Coupled to the endoscopic surgery, it would allow practically to deal with



Figure 7. Terence John Millin (1900-1979).

any situation. In 1931, the invention of the resectoscope by McCarthy put the endoscopic surgery in the first place of the palliative treatment. In 1943, Barnes, in an important review, affirms that the endoscopic resection is unanimously acknowledged by urologists as the best palliative treatment of the urinary bladder's obstruction by an advanced malignant tumor. This opinion hasn't changed since.

Thus, the treatment was often limited into a palliative way of treating the urinary obstruction, since in the majority of the diagnosed cases cancer was too advanced to benefit from a radical surgery.

Before the 1930s, palliative surgery consisted, for a long time, of a pubic cystostomy for derivation when a permanent catheter could not be placed. Some preferred a transvesical enucleation in the hope to re-establish urination, knowing very well that such an action could not cure.

In 1951, J.R. Hand [39] and J.W. Sullivan found evidence of early carcinoma in 8 out of 100 patients upon whom vesicocapsular prostatectomy was performed, and they excised the posterior lamella of the prostatic capsule to ensure complete removal. They suggested that this routine removal of this part of the capsule at operations for benign hyperplasia might prevent the later development of carcinoma. S.G. Fitzpatrick [40] and A.D. Matheson reported in 1952 that, in their hands, retropubic total prostatectomy carried no greater mortality or morbidity than retropubic enucleation. In view of this, they extended the use of the radical operation to the treatment of benign hyperplasia to preclude the later development of carcinoma. A review in 1960 of 139 such operations, 90 of which were performed for hyperplasia, showed a mortality rate of 3.6%; no deaths occurred in the last 89 patients. Other surgeons supported this practice. In 1958, Riches removed the potentially carcinoma-bearing area of the prostatic capsule - posterior capsulectomy - as a routine supplement to his technique of retropubic prostatectomy.

Nowadays, radical surgery is making a comeback. Paradoxically, this renewal of interest is not due to new proof for its effectiveness in curing prostate cancer but quite simply to the technical progress which allowed to diminish in a very serious way the complications of this major surgery. Specifically, the much afraid incontinence has been limited to a 1% or 2% in certain series. Additionally, by preserving the innervation and vascularization of the erectile system, according to the technique described by Walsh and collaborators in the beginning of the '80s, half of the patients having sexual activity before the operation keep it afterwards.

Palliative methods

Young's [41] review in 1924 of 179 patients suffering from prostatic carcinoma provides a good summary of the palliative procedures used. In this group, he found only 10 cases suitable for his radical prostatectomy.

In 1931, the Stern-McCarthy [42] resectoscope supplied a welcome method of treatment of bladder neck obstruction caused by carcinoma of the prostate. In 1943 R.W Barnes [43] commented "agreement among urologists is almost unanimous in approving this operation over any other in the treatment of obstruction due to the far-advanced malignant gland".

a) Radium and x-ray therapy

In 1904, Armand Imbert (1850-1922) [44] and L. Imbert used x-ray therapy to treat an advanced prostatic carcinoma and claimed an excellent result, and in 1907 E. Loumeau [45] also reported favorable effects. In 1908, both H. Minet [46] and Ernst Desnos employed radium, carried to the prostatic urethra embedded in a catheter.

The idea of direct radium implantation into tumors is often attributed to Alexander Graham Bell [47]. In 1903, he wrote that "the Roentgen rays, and the rays emitted by radium have been found to have a marked curative effect upon external cancers, but...the effects upon deep-seated cancer have thus far proved unsatisfactory. It has occurred to me that one reason for these latter unsatisfactory experiments arises from the fact that the rays have been applied externally, thus having to pass through healthy tissue of various depths in order to reach the cancerous tissue. The Crookes tube, from which the Roentgen rays are emitted, is, of course, too bulky to be admitted into the middle of a mass of cancer, but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material. Would it not be worthwhile making experiments along this line?"

The first successful use of radium therapy for malignant neoplasms came from the Gussenbauer Clinic of Vienna (1902).

A major improvement in this technique was introduced by Robert Abbe [48], who in 1904 was the first to insert radium tubes directly into the tumors (interstitial radium implant).

By 1910, it was clear that although surface applications of radium succeeded in healing over many superficial tumors, most soon recurred. Repeated ap-

plications were followed by ulceration and local or general dissemination. Tumors beneath the skin merely regressed temporarily or showed no effect. Efforts to increase the radiation dose led to disastrous results, with much destruction of tissue, prolonged and painful ulceration, and eventual recurrence [49]. This problem led to the development of two different ways to apply radium: by means of containers or applicators inserted into the nose, mouth, rectum, or vagina and uterus or by means of small seeds or needles inserted directly into the diseased tissue (interstitial radiation).

In 1914, Desnos [50] used a source of radiation placed in the rectum and also introduced radium into the prostate through a perineal puncture. These methods, with many modifications, continued to be used, both alone and in conjunction with surgery, by Young, Barringer, Morson and many others. Deep x-ray therapy, used by C.A. Waters [51] and J.W. Pierson in 1923 for the treatment of bony metastases, produced effective relief of pain.

Reviews of the results of treatment were disappointing. H.C. Bumpus [52], in 1922, noted that life was prolonged by therapy in only 25% of the cases, and found few long-term survivors. In 1922 Clyde Deming [53] observed some response to large-dosage treatment, but the side-effects on the bladder and bowel proved discouraging,

Rubin Flocks [54], in 1952, introduced a new method - the injection of radioactive gold (Au) into the malignant prostate, regional lymph nodes and adjacent tissues via a suprapubic exposure.

Radiotherapy of prostate cancer did not really take off until the 1960s, with the incitement of Malcolm Bagshaw in the United States who, by utilizing rays of deep penetration released by multiple or rotating points of entry, hoped to irradiate with important doses the prostate without damaging the neighboring organs.

The complications of the transcutaneous radiotherapy led to the development of the techniques of modern radiotherapy. Carlton used since 1965 implants of radioactive gold which he associated with transcutaneous radiotherapy. In 1970, Whitmore began the use of radioactive ¹²⁵iodine implantation (in the form of grains implanted within the prostate), called interstitial radiotherapy or brachytherapy, for the treatment of localized cancers.

Even though those techniques have given results equivalent to those of the external radiotherapy, it was difficult to be actually established, due to the important precautions needed for any manipulation of radioactive material.

With the introduction of androgen control therapy, the use of radiation therapy was largely abandoned.

b) Hormonotherapy

John Hunter in 1786 had shown that castration in animals lead to a progressive atrophy of the prostate. Later, Civiale, Mercier and Tupper suspected the interest of castration in certain prostate tumors. At the end of the century, the operation of Ramm-White knew some success. The results were unequal and unpredictable, because at that time they couldn't distinguish adenoma from cancer. The operation fell in disuse and nobody thought anymore to castrate a prostate cancer patient or establish any hormonal treatment until 1941, date of the sensational publication of Charles Huggins (1901-1986) (Figure 8) [55]. This work begun in 1939 and its results were published in 1941. These proved carcinoma of the prostate to be hormone-dependent in the majority of cases and to respond to castration and estrogen administration. In



Figure 8. Charles Huggins (1901-1986) - Nobel Prize 1966.

the same year, A.D. Munger [56] reported good results in the treatment of advanced prostatic cancer by irradiation of the testes, and W.P. Herbst [57] also described similar success with estrogens. These methods proved remarkably effective in curing pain, relieving dysuria and in restoring health. A survey by the urologists Reed Miller Nesbit (1898-1976) [58] and W.C. Baum (1951) on the results of this therapy showed that orchidectomy plus stilboestrol was rather more effective and lasting than either method alone. The duration of the response to treatment was found to be limited; 44% of patients without metastases and 20% with metastases survived for 5 years. Further experience with androgen control therapy was reviewed in 1957 by J.D. Fergusson [59].

This eventual failure of androgen control therapy was found to be associated with increased excretion of 17-ketosteroids, and increase in size of the adrenals [57]. This and other evidence suggested that the regrowth of the malignancy was due to increased androgen production by the adrenal glands. In 1945, Huggins [60] and W.W. Scott performed the first bilateral adrenalectomy to overcome this effect. Experience of the operation showed that symptomatic relief was common and regression of the tumor occurred in some cases, but the results were too transient and too unpredictable for this to become an accepted method of treatment. More recently, attempts have been made to suppress the functions of the pituitary gland and so eliminate all androgen production. Methods used for this purpose include external irradiation [61], the implantation of radioactive preparations [62], and hypophysectomy. As with adrenalectomy, remissions have been noted but have been short-lived.

The interest of hormonal therapy, considered for 30 years as the classical and ideal treatment of prostate cancer, was questioned in the early 1970s by the publication of the "Veterans" report in the USA. That study showed that the estrogens have cardiovascular toxicity which may cancel the benefit of treatment. Those conclusions managed to reduce the administration of estrogens in lower doses and rehabilitated the castration which caused repugnance to many, especially in Europe, and which was not easily accepted by the patient.

Blocking the action of the androgens at the level of the target cells was another approach for removing the prostate and the cancer by the stimulating effect of the circulating androgens. Anti-androgens are substances which can block the androgen receptors at the level of the target cells (in particular, the prostatic cells) and prevent the circulating androgens to act on the prostate. These products are rarely uti-

lized on their own, their principal indication is that of an additional treatment to the castration (surgical or pharmacological through luteinizing hormone-releasing hormone [LH-RH] analogs) in order to block the effect of the adrenal androgens which are left intact by the castration.

The idea of obtaining a global androgenic suppression (testicular and adrenal), which was abandoned due to the equally important character of the surgical act which it entailed, was thus retaken as a result of the introduction of the anti-androgens which allowed neutralization of the adrenal secretion. This led to a "combined treatment" associating castration and anti-androgens. This treatment which was popularized by Labrie and collaborators in the beginning of the 1980s, seems to give in randomized studies (in particular, those of Brisset and collaborators) somewhat superior results by those obtained through castration alone.

Obtaining a physiological castration, without the inconveniences of the estrogens and those of castration, would become possible with the arrival of the LH-RH equivalents, described by Shalley and coworkers in the 1970s. LH-RH is a hormone secreted by the hypothalamus which causes the secretion of LH at the level of the hypophysis which, in turn, releases the secretion of testosterone by the testes.

The LH-RH equivalents are semisynthetic products, hundreds of times more powerful than the natural hormone. Their administration causes initially an increase of the LH and testosterone but their chronic administration results into exhausting the hypophysis and thus leading (after 2 or 3 weeks) into a fall of LH and testosterone to the amounts found after surgical castration. These products are today administered in a delayed-absorption formulation and have progressively replaced the surgical castration and the estrogens.

Diagnosis

The gradual introduction of radiologic and other imaging methods (intravenous pyelography, ultrasound, lymphadenography, computed tomography-CT, magnetic resonance imaging-MRI) revolutionized the diagnosis of prostatic carcinoma and influenced the treatment decision of this disease [63].

The first successful application of ultrasound to medical diagnosis was reported in 1947 by Karl Dussik [64] and his brother, Friederick. In 1949, George Ludwig [65] experimented with the detection of gallstones. His findings concerning the velocity of ultrasound in

various animal tissues served as standards for later investigators [66].

John Wild [67] discovered that echoes from tumor-invaded tissue were distinguishable from those produced by normal tissue in the same piece of an excised organ. He also noted significant echo changes as the sound beam traversed areas approaching the tumor but in which neither the eye nor palpation had detected invasion by cancer. This suggested that ultrasound might not only detect differences between normal tissues and malignant lesions but that this modality might identify tumor-invaded tissue earlier than any detection technique then available.

In 1952 Wild [68] developed a two-dimensional B-mode scanning system. He introduced the first hand-held "contact" scanner, that was applied directly over the organ. Sonic contact was achieved by the use of an aqueous jelly, in contrast to the immersion bath or enclosed water tanks employed by other pioneers of contact scanning. Using this device, Wild [69] and Reid (1956) reported a 90% accuracy in the diagnosis of benign *versus* malignant lesions. Wild also developed flexible probes for transrectal and transvaginal scanning.

Transrectal scanning offered an opportunity to insert an ultrasound probe close to deep-lying abdominal structures. The first transducer probes for entry into the body rectally were designed by Wild in the early 1950s. In the mid 1970s, Watanabe [70] and associates developed the "ultrasonic chair". The patient sat on the chair, through the seat of which protruded a thin rigid probe equipped with an ultrasonic transducer that passed through the anus and entered the rectum.

Scans of the prostate and bladder were made and were of particular value in the diagnosis of prostatic cancer. Martin Rescick [71] soon developed another transrectal probe for prostatic cancer that could be inserted with the patient in the lithotomy position. Initially providing only B-mode imaging, later versions added gray scale.

Imaging of prostatic cancer has been very limited until the development of male genitourinary ultrasonography.

Although clinical examination is still the most important part of medical diagnosis, complementary investigations are often very useful. Today the ultrasound plays an essential role in the diagnosis and staging of cancer of the prostate. In addition, the changes in the volume of cancer in relation to treatment can be monitored.

One of the major contributions of the study of the prostate cancer to oncology in general, was the

discovery of a new tumor marker, a substance whose just the presence, or its presence in an unusual quantity indicates the existence of cancer not necessarily revealed by the usual clinicolaboratory examinations.

Prostate specific antigen (PSA) has been described in 1979 by Wang and his collaborators at the Roswell Park Memorial Institute in Buffalo. Even though this substance is not specific of cancer but of the prostatic tissue, it is today the most promising marker for diagnosis, prognosis and monitoring treatment results of prostate cancer. Recently, the level of free-PSA and its relation with the total PSA may indicate the carcinomatous or benign origin of an elevated PSA.

A diagnostic procedure quite elementary, which took time to be imposed and generalized, is the prostatic biopsy. After the second World War, almost nobody did it. Urologists were convinced of the infallibility of their index. Additionally, they did endoscopic resections in obstructive and doubtful cases, because they offered the double advantage of removing the obstacle and making a correct diagnosis. The first routine prostatic biopsies were made by the perineal way, with the aid of Veenema's punch needle. They necessitated anesthesia. Silberman's needle and the disposable ones that are in use today came much later, with the last perfection being the ultrasound guidance.

Conclusion

Since the beginning of the 20th century, various methods of treatment (surgery, radiotherapy, hormone therapy) passed successively through periods of admiration and oblivion. Despite the numerous national and international conferences dedicated to prostate cancer, despite the multicentric studies realized in a considerable scale, the treatment of this disease undoubtedly remains one of the most controversial questions in urology.

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