Clinical Pharmacology & Biopharmaceutics
ISSN: 2167-065X
Morgia et al., Clinic Pharmacol Biopharmaceut 2013, 2:2
DOI: 10.4172/2167-065X.1000113
Review Article
Open Access

Application of New Biotechnologies for Prostate Cancer Treatment (Comparative Analysis of Brachytherapy, Cryosurgery, Laparoscopy, Robotic Arm and Cyberknife Methods)

Giuseppe Morgia*, Chaled Alnakib and Giorgio Ivan Russo
Department of Urology, University of Catania, Italy

Abstract

Prostate cancer is the second most commonly diagnosed non-dermatologic malignancy among American men and the 6th most fatal cancer worldwide.

Open field radical prostatectomy is the gold standard procedure for treatment of prostate cancer. Yet, several novel methodologies have been emerging lately, promising to be mini-invasive, to reduce complications related to surgery and to offer the patient a better quality of life thereafter. Among the latter, preservation of urinary and sexual function appear to be the most important. Some of such alternative treatments may be found applicable to patients with a life expectancy less than 10 years, or those unfit for surgery for other reasons.

The present manuscript has been aimed to overview the most prominent novel methods for prostate cancer treatment, in attempt to point out the options and the rationale for choosing a method, or a combination of methods, for the best and the most effective treatment of prostate cancer.

Keywords: Prostate cancer; Radical prostatectomy; Brachytherapy; Cryotherapy; Cyberknife

Introduction

Among the most commonly diagnosed malignancies in males, prostate cancer is justly holding the second palce. Worldwide, prostate cancer is considered the cause number 6 of overall cancer deaths [1].

Progression of prostate cancer embraces a wide variety of phases, ranging from an inactive, low-risk stage up to the extremely aggressive, high-risk stage of the disease [2]. During the past decade, a significant advance in identifying prostatic cancer at its early stages is noticeable. According to recent data provided by American Cancer Society, a majority of the diagnosed tumours (80% or more) used to be recognised in the past only when already advanced and/or metastatic, whereas only 10% could be detected at early phases of development [3-7]. At present, however, this trend is quickly and radically changing. Thus, comparing with 141,520 early diagnosed tumours in USA in 1995, only a decade later the number of early detected prostate cancers increased two-fold, reaching 306,600 diagnosed cases [8]. In other words, a majority of prostatic cancers can be identified nowadays at their initial stage, when the tumour is yet organ-localised and highly susceptible to curative therapy. Such progress became possible firstly due to the development of novel prostate cancer biomarkers, such as tumor immunohistochemistry, proteomic analysis, tissue DNA and protein/RNA microarrays, microRNA recognition, analysis of CTC (circulating tumor cells) [9,10].

Secondly, we owe this progress to the implementation of various new screening programs for early diagnosis of prostate cancer. Indeed, improved survival of patients diagnosed with early, organ-localised, forms of prostate cancer is so prominent that within the first 5 post-treatment years it reaches the rate of 100%.

Swift progressive increase in the number of early diagnosed prostate cancers is overwhelming. According to the latest statistic prognoses for 2030, one can expect as much as 1.7 million of *de novo* diagnosed prostate cancer patients, along with about 500,000 cases of the disease-related deaths [11,12]. The situation is therefore prompting us, along with improving the diagnostics methods, to search for new technologies providing the prompt and effective treatment of early diagnosed prostate cancer [13,14].

The aim of the present manuscript was to survey in a nutshell the latest advancements in the methods of treatment of early diagnosed prostate cancer.

Different Approaches to Treatment of Patients with Prostate Cancer

Surgical intervention and external or interstitial radiotherapy deservingly remain the most common therapeutic treatments for prostate cancer patients. In a majority of European countries, such as Italy, France, Spain or Germany, surgical intervention is applied in as many as 42%-60% of the patients. The exception would be UK, where radiotherapy is considered preferable to surgical intervention. Both surgery and radiotherapy are commonly combined with, or followed by, pharmacologic intervention. The latter comprises chemotherapy, biologic therapy (engagement of patient's immune system for fighting cancer), and/or hormone-based therapy. In addition, targeted therapy (use of drugs, antibodies or other substances for finding and attacking specific cancer cells without harming normal tissues), is widely applied. Combined therapy is frequently used, for example, in Italy, where about 29% of patients receive combination of two or more therapeutic procedures.

In elderly non-symptomatic patients, mainly those in whom

***Corresponding author:** Giuseppe Morgia, Professor, Department of Urology, University of Catania, Italy, E-mail: gmorgia@policlinico.unict.it

Received June 26, 2013; **Accepted** September 26, 2013; **Published** September 28, 2013

Citation: Morgia G, Alnakib C, Russo GI (2013) Application of New Biotechnologies for Prostate Cancer Treatment (Comparative Analysis of Brachytherapy, Cryosurgery, Laparoscopy, Robotic Arm and Cyberknife Methods). Clinic Pharmacol Biopharmaceut 2: 113. doi:10.4172/2167-065X.1000113

prostate cancer has been discovered during a screening test; watchful waiting combined with active surveillance is recommended [15]. The patient's condition is closely monitored without therapy application, unless there are changes in symptoms and/or lab test results. Such treatment, although of a limited therapeutic value, is important for timely discovering and relieving the painful symptoms, thus substantially improving the patient's quality of life.

The last but not least mentioned should be a variety of novel methodologies for treatment of patients with prostate cancer, appearing as a result of constantly ongoing research in biotechnology and clinical trials. Among the latter, cryosurgery, high-intensity focused ultrasound and proton beam radiation therapy deserve the utmost attention.

Treatment of early detected prostate tumours by surgical intervention

Open radical prostatectomy, which includes the removal of seminal vesicles and the surrounding tissue, is undoubtedly the oldest and the most widespread option for treatment of early detected prostate cancer, provided the patient is in good health and his tumor yet remained local. In addition, since early 1990s, radical prostatectomy by laparoscopy methods became available [1]. There are two main techniques of radical prostatectomy, and both may be carried out either by open surgery or by laparoscopy:

a) Retropubic prostatectomy, either anterograde or retrograde, when the prostate is removed via an incision made in abdominal wall, with concomitant elimination of nearby lymph nodes;

b) Perineal prostatectomy, when the prostate is cut out through an incision made in perineum area. In this case, a separate abdominal incision has to be performed for the lymph nodes removal.

Radical prostatectomy by open surgery

Retrograde retropubic prostatectomy performed by open surgery remains the most preferable method. Pelvic lymphadenectomy, the oldest technique applied when the lymph nodes are involved, is considered the gold standard in radical prostatectomy [10]. Opinions vary, however, with respect to the extent of the procedure, its therapeutic value, and the least necessary number of lymph nodes to be removed for effective, secure lymphadenectomy. Regulated, limited lymphadenectomy, restricted to the external obturator iliac lymph nodes and regarded previously as adequate for radical prostatic surgery, lately proved insufficient for reaching the therapeutic goals in oncologic patients. Thus, a recent study by Burkhard et al. [16] demonstrated that about 58% of patients with prostate cancer subjected to lymphadenectomy, further presented lymph node involvement along the hypogastric vessels. In 19% of the cases, the lymph node partaking was restricted only to this site. The authors concluded that limited lymphadenectomy ran the risk of interfering with adequate neoplastic staging and allowed the left out lymph node sites to participate in further tumour progression [16]. In addition, Burkhard et al. [16] demonstrated that survival of patients subjected to extensive lymphadenectomy technique was 25% higher compared to those who underwent limited lymphadenectomy. In a different report, Heidenreich also insisted that for high risk prostate cancer patients only the extensive lymphadenectomy is effective [10]. Restricted lymphadenectomy may be applied only to patients with favourable prognosis (PSA<10, Gleason<6, stage T1c-T2a).

For retropubic prostatectomy with concomitant elimination of nearby lymph nodes, either median or transversal annenstiel suprapubic incision, usually not exceeding 8 cm length, are recommended. A Balfour or a Book-Walker retractor is usually used, allowing the surgery procedure to be performed by no more than two operating personnel. Various magnifying loops and xenon light lamps placed on the surgeon's forehead are available, to provide spacious and clear surgical field.

The first step in open radical prostatectomy consists of opening the endopelvic fascia bilaterally and preparing the prostatic apex with resection of the puboprostatic ligaments. Then Santorini's venous plexus is ligated, sectioned, and the urethra is exposed. After the anterior urethral plate has been sectioned and the catheter inserted, the posterior urethral plate is detached, in order to isolate the vesicle-prostatic block. At this point, the surgeon may proceed to bilateral sparing of the neurovascular bundle [17]. The bladder neck is separated from the prostate, and the complex of prostate, vasa deferentia and the seminal vesicle is removed "en bloc". If the bladder neck is not intended for sparing, it is packaged via racket remodelling and destruction of the mucosa of the neocervix. The bladder neck is then sutured by 4 to10 stitches on the urethral wall and thereafter on the bladder, with packaging of the urethral vesicle anastomosis.

Postoperative complications after radical prostatectomy by open surgery

Postoperative incontinence and/or erectile deficiency are the most common complications after radical surgery for prostate cancer [2]. In general, these complications tend to affect the elderly more heavily than the younger men. Both bladder control and/or erectile capacity may gradually return to normal within several weeks or months. However, the individual patient's responses can never be predicted for sure. In order to allow faster postoperative recovery from incontinence, certain modifications of the standard techniques have been proposed. Walsh et al. [2] proposed to support the neocervix by bringing the vesical lateral laminae closer. This procedure reinforces the posterior vesical walls and the neobladder, especially the parts which often have to be reconstructed in order to make the calibre of the urethra adequate. According to Walsh et al. [2], application of this technique resulted in 93% recovery of continence levels within 12-18 months after surgery.

In early 1990's, a nerve sparing technique was developed, intended to protect the patients' erigen nerves responsible for erection and thus preserving their erectile potency after radical surgery. Erigen nerves run along posterior-lateral surface of the prostate and are branches of the pelvic plexus, which in turn originate in the S2, S3 and S4 sacral roots. The fibres of these nerves spread towards the urethra in numerous nerve endings which reach the corpora cavernosum urethrae. For obvious reasons, nerve sparing techniques can be applied only in patients at age less than 60 years, with localised tumours, Gleason count less than 6, pre-operative PSA<10 ng/ml, and life expectancy more than 10 years. The patients must have good pre-operative erectile function, be highly motivated to resume a satisfactory sex life, and comply with all rehabilitation techniques and postoperative prophylactics [18]. To carry out this technique, one needs a special device, called "water jet dissection", which transmits a jet of water at high velocity, allowing accurate and easy performance, excellent operative view and keeping the operation field clean. In brief, the operation is performed strictly adjacent to the lateral surface of the prostate. All the vesical-prostatic junctions are carried into the space between the prostatic fascia and the prostatic capsule. Recently, Mani Menon proposed a variation of the original technique, the so called "Veil of Aphrodite". The latter constitutes preservation of the integrity of all lateral lamina of the prostatic gland, from the most anterior to the most posterior part. This technique is based on the fact that the entire vascular and nerve

structures responsible for erection are found in lamina [19,20].

Thus far, in accordance with our own experience, this technique has provided excellent results. When applied correctly, it allows preservation of postoperative erectile capacity in 85% -90% of patients less than 60 years old. For patients of age above 60 years, the success rate may be less prominent, ranging in various reports from 25-30% to 75-80% [20]. Such differences in the results may be the outcome of incorrect or completely absent preoperative evaluation of the erectile functions of the patient, the experience level of the operating staff, the patient's expectations and/or the time point chosen for postoperative evaluation.

Radical prostatectomy by laparoscopic techniques

Laparoscopic radical prostatectomy (LRP) was introduced in USA in1999. Compared to standard radical prostatectomy, LRP is characterized by less aggressive surgical procedures: the prostate is removed via small incisions performed by laparoscopic surgical tools. The latter comprise special long instruments suitable for insertion into the small incisions and performance of prostatectomy. A small video camera is present at the end of one of the instruments, letting the surgeon see the inside of the abdomen. Although no official long-term observations on the USA experience in LRP are yet available, this technique appears to produce results at least as good as the open radical prostatectomy but be beneficial for the patient by causing less blood loss and less pain, as well as shortening the patient's hospital stay and recovery time. The rates of side effects after LRP are similar to those following open prostatectomy [21]. The recovery of bladder control may take a little more time, however the nerve-sparing procedure for preservation of normal erectile functions after the operation, is apparently as successful with LRP as it is in case of the open surgery.

In addition, there is also an option to perform a robotic-assisted laparoscopic radical prostatectomy (RALRP), by means of a robotic device named the "da Vinci system". In RALRP, prostatectomy is executed using a remote control panel for precise direction of the robotic arms. The da Vinci system is capable of performing the entire surgery via a number of small incisions in the patient's abdomen under such remote supervision. RALRP, similarly to LRP, is advantageous for the patient's wellbeing, in terms of decreasing blood loss, attenuating pain and shortening the recovery time [22]. Some physicians might favor RALRP for the reasons of convenience, flexibility, dexterity and movement precision. Yet, as far as the patient's health is concerned, there are no sound reasons for preferring RALRP over the direct LRP, or vice versa. Therefore, the choice between the methods should be made based on the individual skills and experience of the surgeon.

Radiation therapy

Two types of radiation therapy are available for treatment of prostate cancer: External Beam Radiation Therapy (EBRT) and internal radiation therapy, or brachytherapy.

External beam radiation therapy, or *EBRT*, was first used for treatment of cutaneous neoplasia at St. Louis Hospital, Paris, in 1901, a short time after the discovery of radioactivity by Marie and Pierre Curie at the end of the 19th century. At present, ERBT is performed mainly using a 3-dimensional (3-D) picture of the tumor created by a computer [18]. The shape, direction and location of the irradiation beam are calculated by a computer software program, so as to precisely fit the tumor.

Internal radiation therapy, or *brachytherapy*, constitutes a rather revolutionary approach to application of irradiation in medicine: unlike EBRT, the radiation source is inserted, through the skin between the scrotum and rectum, directly at the site of the area requiring treatment, guided by transrectal ultrasound or computed tomography (CT) images [18]. The first radio-implantations were carried out for treatment of prostate cancer by Withmore et al. at early 1970's, about two decades before introduction of the transperineal ultrasonographic method.

The implanted radioisotope is enclosed in a protective radioactive substance sealed in a special needle, seed or catheter wire, allowing the ionizing radiation to escape and destroy the tumor and the surrounding tissue, albeit preventing it from moving further and dissolving in body fluids. Only the tumor and the specific surrounding area are affected, whereas any damage to healthy tissues is prevented or, at least, highly reduced. Even when the patient changes his location, or the tumor starts moving within the body during treatment, the radiation source retains its correct position in relation to the tumor. This way, brachytherapy allows to treat the tumor with relatively high doses of radiation applied locally, reducing the unnecessary damage of the surrounding healthy tissues.

Depending on radioisotope, the implanted capsule may be either removed later or remain indefinitely. The most widely used radiation sources are Iodine-125, Strontium-89 and Palladium-103. The half-lives of the isotopes are different: 50 days for iodine-125 and 17 days for Palladium-103. The ideal candidates for brachytherapy are patients with PSA<10 ng/ml, Gleason<6, cT1-2, IPSS<10, Qmax>15 ml/sec., and prostatic volume<50cc [23].

Brachytherapy consists of three separate phases: preplanning of the treatment, implanting of the irradiation source and post-treatment planning. During the pre-planning, the dose which is to be administered to the prostatic gland and the positioning of the radioactive implant within the prostate are determined. The preplanning phase requires application of echography under anaesthetic procedure before the implanting. Anterior-posterior scanning of the gland is performed from apex to the base of the gland, at 0.5 cm intervals. The images are transferred to the software. Dose and distribution route of the radioactive source throughout the whole prostate are calculated, to ensure that the entire gland receives the optimal and sufficient dose of radiation. The optimal dose, measured in Gray units (Gy), varies depending on the type and stage of cancer. In case of the prostate cancer treatment, the standard dose is generally about 140-145 Gy.

The implantation phase starts with preparation of needles containing the radioactive seeds. The distal ends of the needles are closed with a layer of bone wax and loaded with seeds prepared according to the treatment preplanning. The patient is placed in a lithotomic position and subjected to either peripheral or central anaesthesia. The needles are inserted by brachy stepper device, according to the pre-established coordinates, under echographic and fluoroscopic guidance. Fluoroscopic check-up for possible dislocation of some of the seeds is conducted at the end of the implanting procedure.

The post-planning phase starts 30 days after the implantation, with a pelvic CT, or CT in combination with NMR, using an image fusion technique.

Brachytherapy is certainly a valid therapeutic option, yielding excellent results that are comparable with those of radical surgery and are considered by many authors to be better than those of external-beam radiation therapy. Following 12 years post-therapy, the disease-free survival rates reach 70%-75% [24].

Post-radiation complications

Males subjected to radiation therapy for prostate cancer are at increased risk for developing bladder and/or rectal cancer. Radiation therapy can also bring about impotence and urinary problems. Part of the patients may develop temporary complications, e.g. cystitis (70-90% of the patients), proctitis (2-9%), AUR (10-22%), haematuria, perineal pain. In some cases, delayed complications are evident: protracted dysuric syndrome (5%), urethral stenosis (1-9%), rectal fistulas (<1%), etc [25].

Cryosurgery

Cryosurgery is a method applied for treating prostate cancer at early stage of disease, preferably in males with large prostate glands. This method consists of passing cold gases through hollow needles inserted into prostatic gland through the skin between the anus and scrotum. Tiny ice balls are thus created, which damage and destroy tumor tissue. The whole procedure is performed under spinal or epidural anesthesia and is guided by transrectal ultrasound (TRUS). Ultrasound images are necessary for ensuring the tumor destruction without too much damage to nearby tissues. Concomitantly, warm saltwater is circulated through a catheter in the urethra, to prevent the latter from freezing. Following cryosurgery procedure, the catheter is left for additional 3 weeks of the recovery process.

Cryosurgery, otherwise named *cryoablation* or *cryotherapy*, was first used for tumour treatment in 1850, when James Arnott applied ice-containing saline solutions to operations on breast and uterine cervix tumours. Prostate cryosurgery started in the mid-1960s, when Gonder developed and modified a suitable apparatus and probes (needles) for transurethral freezing of prostatic tissue during the surgery [26].

Further progress in first-generation cryosurgery was made in early 1970s. Unfortunately, since TRUS guidance and urethral warming were unavailable in those years, the percentage of complications, such as incontinence, impotence and rectal fistulas, was immense. As a result, the method was abandoned until the 1980's.

Second generation cryotherapy was based on development and improvement of echographic methods and urethral warming.

Finally, the third, presently used, generation of cryotherapy methods was proposed by Wong in 1997 and supported later by Chin and his collaborators. Liquid nitrogen was proposed to be replaced with inert gases, such as argon: this way, the freezing process could start and stop almost simultaneously. As an inert gas, argon is easily stored, does not evaporate and is always ready for immediate use. Cryotherapy tubing system for argon is much smaller. The proposed cryoneedles allow direct transperineal probe placement, without tract dilatation and insertion kits. Finally, the third generation cryotherapy methods can be easily combined with brachytherapy techniques, in terms of using the same or similar instruments and employing expertise of the same specialists in radiation techniques. It should, however, be mentioned that cryosurgery, advantageous as it is for early detected cancers, is less effective for more advanced prostate tumors (T2c to T3b stage) [27].

According to the indications, three different categories of cryotherapy can be identified: primary therapy, saving therapy and palliative therapy [28]. Primary cryotherapy is a curative method considered an alternative to surgery, or to external radiotherapy, or to brachiotherapy. Patients considered for this form of therapy are those for whom surgery is not the best choice: those with early diagnosed, localised forms of the disease, Jehovah's witnesses, patients persistently treated with anticoagulants, etc. Saving therapy and, as the final step, palliative therapy, are probably the most widely accepted therapeutic options suitable for patients receiving local cancer anti-recurrence treatments following external beam radiation therapy or brachytherapy, since these patients have an increased incidence of complications, in particular incontinence and rectal fistulas [29].

There are few contraindications for cryotherapy procedure. Among them, previous prostatic operation of a benign tumor (BPH) with a resultant extensive urethral defect, an enlarged prostate (>50-60 g) and previous history of major rectal pathologies, should be mentioned [29].

Post-cryosurgery complications

Despite the fact that cryosurgery is less invasive than radical prostatectomy, thus ensuring less blood loss, less pain and shorter hospitalization and recovery periods, this method is hardly the first choice for treatment of prostate cancer: the current cryosurgery techniques, such as ultrasound guidance and precise temperature monitoring, have become available only recently, so little is known about either the long-term effectiveness or the long-term complications of cryosurgery. It is known, though, that cryosurgery complications tend to be worse in males with previous history of radiation therapy. Most men present macrohematuria for a day or two after cryosurgery, soreness in the areas of needle insertion, swelling of the penis or scrotum. The freezing procedure may also bring about painful and burning sensations in bladder and intestines, and frequent urge to empty the bladder and bowels. Most functions recover back to normal over a short time period. Freezing during cryosurgery procedure may also cause impotence in up to 4 out of 5 patients. Erectile dysfunction after cryosurgery is more common than after radical prostatectomy. About 1% of patients may develop a fistula between the rectum and bladder. This would allow urine to leak into the rectum, often requiring an additional surgery to repair this problem [29].

With respect to the cryosurgery-induced negative effects on prostatic tissue, two major mechanisms have been thus far described: vascular injury and cellular injury [30]. Vascular injury is mainly represented by vascular thrombosis and hypoxia of the adjacent tissue. At the cellular level, according to the experience of cell cryopreservation in tissue culture research, the extent of the damage depends on the choice of appropriate techniques. Thus, sudden drastic reduction of tissue temperature and crystallisation of extracellular fluid during cryosurgery brings about augmentation of extracellular osmotic pressure, particularly in the unfrozen components, and efflux of the intracellular fluid to the extracellular space. Consequent changes in intracellular PH and denaturation of cellular proteins, may lead to massive cell death when the temperature falls below -20°C [31]. However, if the temperature falls gradually and slowly from 0°C to -20°C, the damage may be restricted only to a "solution effect injury" which is not lethal. In turn, thawing of the tissue after the surgery must be as prompt as possible.

Cryosurgery methods of prostatic cancer treatment applied in our medical center

We employ cryosurgery techniques using the inert gases and the17-gauge CryoNeedles™ (Oncura, Inc., Plymouth Meeting PA). The patients are placed in an exaggerated lithotomic position, the perineum being slightly above the operating table edge, oriented about 90° to the floor. Cystoscopy is carried out concomitantly with a guide wire installation. The latter is helpful for positioning of the urethral heating catheter thereafter. During cystoscopy, a supra pubic Foley catheter is also positioned via cystotomy. During the operation the latter is kept closed. A brachytherapy template is stabilized with a stepper in front of

the perineum. Transrectal echography (TRUS) allows us to constantly measure the prostate and transfer online the data to the computer. The cryoprobes are percutaneously inserted and echoguided, starting at the superior thread. They are positioned at a distance of 1 cm from each other and at a distance of 0.5 cm from the prostatic capsule and the bladder neck. The number of cryoprobes varies between 5 and 20, depending on the form and dimensions of the prostate. They are positioned as groups of three (prostate height 3.5 cm or less) or four (prostate height greater than 3.5 cm), each group containing 2 to 5 cryoprobes. Thermo sensor needles are then inserted, one being positioned at the periphery of the prostatic gland, and the other two in the Denonvilliers' fascia, between the prostate and the rectal wall.

Following the insertion of the necessary needles and thermo sensors, the warming urethral catheter is positioned using the guidewire previously inserted during the cystoscopy. Freezing begins from the superior threads towards the inferior ones. Care must be taken to ensure that the rectal temperature does not fall below 0°C and, if necessary, this place must be heated. When a temperature of -30°C or, even better, -40°C is reached, it is maintained for about 10 minutes until freezing stops. Following a few minutes, warming with helium begins, both actively and passively, for short periods of about 1 min. Normally, two cycles are performed. The patients are discharged the next day, with antibiotic therapy and a suprapubic Foley catheter, which is removed after about 7 days. After removal of the catheter, alpha lithic therapy is advisable for about one month.

Efficacy (defined as the biochemical tumour marker free survival) of the primary stage of cryotherapy, reported by different authors employing the third generation of cryosurgical devices, are presented in Table 1. It is noteworthy that the rate of biochemical disease-free survival (BDFS) is between 75% and 86% depending on the authors, although it must be pointed out that only a limited number of patients were enrolled in most of the studies and that, with the exception of the study by Prepelica et al. the follow-up was only about 12 months. Nonetheless, the rate of complications reported in these studies was very low, by contrast with those using the equipment of the second and first generations. The reported rate of incontinence was about 3 to 5% with a median value of 4.7%, while the obstructive disturbance was about 2 to 3%. Most importantly, these studies did not report any cases of urorectal fistulas.

In an extensive review published in 2009, Ritch and Katz [32] compared the results of cryotherapy with other options available for treating localised forms of the prostatic cancer (surgery, brachytherapy, external radiotherapy, 3D-radiotherapy). According to this review, open surgery was found the most efficacious for treating low risk patients, whereas cryotherapy was the most efficacious for treating medium and high risk patients [33]. Morbidity in cryotherapy treated patients was low, the rate of incontinence reduced as compared to brachytherapy, although percentage of previously potent patients maintaining their sexual functions was very limited. Only 15-20% of the patients retained sexual potency after cryotherapy, which was comparable with only the worst results reported for the other techniques. However, as mentioned above, the main limitation of that review and of similar studies was that the number of patients treated with cryotherapy was at that time very small and the follow-up period very brief (Table 1). As far as the near future is concerned, recent experimentations on laboratory animals seem very promising. In these studies, a type of cryotherapy based on heating the neurovascular bundle is applied, which may be defined as novel "nerve sparing".

Radiotherapy by CyberKnife

In recent years CyberKnife, a novel method of radiotherapy intended for better and more accurate targeting of the tumor compared to standard radiotherapy techniques, has been proposed. CyberKnife is a frameless robotic radiosurgery system consisting of a 6 MV compact linear accelerator (Linac) mounted on the robot (Gantry) [34]. In CyberKnife, radiation energy is generated within the Linac. Thereafter, the produced radioactive energy is dispatched via a robotic hand at any part of the body, and from any chosen direction. The autonomous hand of the robot can deliver radiation at up to 1248 different directions via its multiple positions and angles, making CyberKnife an excellent non-invasive alternative way of treating various neoplasms. At present, CyberKnife has been tried on operating the benign tumors, malignant tumors and some other medical conditions [35].

There are four distinct working phases of treatment when using

Author	Year	No. of pts.	PSA	BDFS	Follow up	Fistula %	Incontinence %	Obstruction %	Impotence %
Ellis	2002	75	0.4	84	12 mo	0	5.3	5.3	82.3
Bahn	2002	590	ASTRO	89	68 mo	2.4	9	3	41
Han MCS	2003	104	0.4	75	12 mo	0	11	0	89
Cytron	2003	20	0.5	80	12 mo	0	0	0	80
Prepelica	2005	65	ASTRO	83.3	35 mo	0	3.1	3.1	NR
Cresswell	2006	31	0.5	60	12 mo	0	4	7.8	100
Garcia	2006	20	0.5	50	33 mo	0	0	0	80/100
Ellis	2007	416	ASTRO	78.3	48 mo	0	2.9	0	49
Polascik	2007	50	0.5	90	18 mo	0	3.7	0	50
Bjerklund	2007	90	ASTRO	98	21 mo	NR	0	NR	86
Hubosky	2007	89	0.4/ASTRO	70/94	11 mo	0	NR	NR	80
El Hayek	2008	44	1	61.4	41 mo	0	13	NR	NR
Witzsch	2009	228	ASTRO	84.1	36 mo	NR	4.3	11.1	66
Cheetham	2010	25	ASTRO	87%	10 yr	--	--	--	--

Legend:
*Efficacy-survival rate of patients free of biochemical tumour markers.
*Year-the year when the report was published.
*No. of pts.-the number of patients enrolled in the study.
*BDFS-biochemical disease-free survival.
*PSA-prostate specific antigen.
*NR-no response

Table 1: Cumulative report on the efficacy of cryotherapy in different medical institutions.

the CyberKnife: TRUS guided fiducial marker implantation phase; planning phase; treatment phase and post-planning phase [36].

The first step constitutes the echo-graphically guided implantation of 4-6 gold seed fiducial markers (GFM) inside the prostate gland by the operating urologist. This step must be performed about one week before starting the treatment phase. GFM, the already mentioned fiducial markers, are small gold seeds about 0.8 mm in diameter and about 5 mm long. Prior to implantation, these seeds are loaded into the 19 gauge, 15-20 cm long needles. GFM must be positioned at the apex, in the intermediate lateral zone, and at the base of the prostate. A minimum distance between the implanted GFM groups must be 2 cm. The problem is that at the time of the procedure, one does not necessarily have the evidence of the exact location of neoplastic lesions [37]. Yet, at least in theory, the implant must be close to the target, i.e., the tumoral lesions, not less than by 5-6 cm. Finally the angle between the different groups of fiducials should not be less than 15°.

The planning step comprises carrying out CT a week after implantation of the fiducials. It is very important that the CT scan device is the same that will be used during the treatment. In other words, the prostate must be seen during the pre-planning exactly the same way as during the treatment. In this respect, the state and the position of the surrounding organs is also important: thus, the bladder must be empty (either through spontaneous urination or by means of a catheter), the intestine must be emptied, and, finally, a ball must be inserted into the rectum in order to immobilise the latter. Most unfortunately, not all surgeons follow this procedure. The CT scanning must be performed so as to cover the whole prostate gland as well as the GFM. At this point the radiotherapist defines the treatment plan, which determines the doses prescribed for the prostate (PTV) and the critical organs (bladder, rectum and urethra). Looking at this planning, one can easily see that the highest concentrations of radiation must be received by the peripheral zones of the prostate. Since the CyberKnife can achieve a very high degree of accuracy in target coverage, the effective PTV margins are significantly reduced in every direction and coverage with the 100% prescription iso-dose is within 3-5 mm from the contoured target. CyberKnife® can also preserve the relative nerve structure at an accuracy of 0.7 mm, targeting which has never been achieved before.

The third step of the CyberKnife procedure would be the hypo-fractionated radiation treatment per se. At present, more than one treatment schedule are possible: either five fractions of 7 Gy, for a total of 35 Gy, or four fractions of 9.5 Gy, for a total of 38 Gy (in our medical centre, we apply this schedule), or five fractions of 7.25 Gy for a total of 36.25 Gy. It is important that not more than one day passes between the CT scan and the treatment, and that the conditions of treatment planning are reproduced during the treatment phase as faithfully as possible. Normally, the treatment course can be completed in one week.

The last step of the CyberKnife procedure is the post-planning phase, which usually takes place four weeks after the end of the treatment [36]. This phase consists of an additional CT scan or in an "image fusion" procedure using both CT and NMR, in order to make an appropriate quality control evaluation of the dose administered.

The best indications for treatment with CyberKnife are the early detected localised neoplasia, or cT1/T2a-b N0M0, Gleason score less than 7 and pre-operative PSA less than 10 ng/ml. Thus, this method may be proposed as a substitute to high-dose rate brachytherapy (HDR), low-dose rate brachytherapy (HDR), intensity modulated radiation therapy (IMRT), 3D-conformal radiotherapy or external beam radiation therapy (EBRT). The international guidelines have not yet provided sufficient information on this system, but one must bear in mind that CyberKnife technique can be integrated completely into all existing methods of brachytherapy, so indications for the latter may be considered valid for CyberKnife, provided the initial, preliminary results are confirmed over time [38].

The major contraindication for CyberKnife application is a prostate volume of more than 80cc, although for most cases a hormonal downsizing of the gland prior to using CyberKnife is possible. The volume-related contraindications may be severe obstruction of prostate, evident from the high Gleason score or previous, pre-obstructive, prostate surgery.

The information on the results of CyberKnife applications is scarce, despite the fact that the methodology is on the market since 2003. Thus far, there are 94 CyberKnife® platforms in USA only; they have been used on more than 1000 patients, mainly with endocranial, pancreatic, pulmonary and hepatic tumours. In addition, a possibility of using CyberKnife® for maxilla-facial surgery has been reported. Unfortunately, at present this apparatus in only available at ten medical centres in Europe. Three of them are in Italy and three more - in France; one apparatus is available in Germany, Greece, Spain and Holland, respectively. Thus, it is not surprising the experience in using CyberKnife is much less that in Europe than it is in the USA.

The Debra Freeman group from Florida reported the results of a study wherein 40 patients were treated with CyberKnife®, 27 were subjected to radiosurgery only, and 13 participants received radiosurgery combined with adjunctive hormonal therapy (ADH). All the patients had the localised form of the disease (T1c only), and their median PSA was 5.78 ng/ml prior to starting the study. The scheme used for radiotherapy was five hypo-fractions of 7Gy, for a total of 35 Gy. Following 12 months of follow-up, PSA was found significantly decreased in all but one of the patients. The resultant median PSA values were 1.2 ng/ml for the group treated only with CyberKnife® and 0.05 ng/ml for the group treated with CyberKnife® and ADH [39].

Another pioneering medical centre treating prostate tumours with CyberKnife® is the San Diego CyberKnife Center. They have recently published a report on ten such patients with localised tumours. The scheme used was five hypo-fractions of 7Gy, for a total of 35Gy. The results of a four month follow-up were extremely promising: the patients' PSA dropped by 86% compared to their pre-treatment baseline values.

In our medical center, we had an experience with six assessable patients (4T2a and 2T2b). Their average age was 74.8 years (we have deliberately chosen the patients over seventy years old for this study); with an average IPSS of 15.1 and average IEEF-5 of 23 (i.e. all were potent before treatment). The scheme used was four hypo-fractions of 9.5 Gy, for a total of 38 Gy. In all our patients the average PSA dropped to 0.8 ng/ml six months after treatment. Their IPSS values, also decreased post-treatment, returned to normal about 2.5 months later, whereas their score for erectile function remained almost unchanged throughout the entire treatment [15].

At present, there are two ongoing clinical studies on CyberKnife applications, conducted at the medical centers of Boston and Seattle. The first study is aimed at evaluation of genital-urinary (GU) and gastro-intestinal (GI) tolerability of the treatment, as well as the evaluation of overall survival (OS), biochemical disease-free survival (BDFS), quality of life (QOL) and the necessary costs. This study comprises the low and intermediate risk patients, all of them treated with a scheme of 5 hypo-fractions of 7.25 Gy, for a total of 36.25 Gy [40].

The future of this frameless robotic radiosurgery system may,

indeed, be to use it not only as monotherapy but also in conjunction with other boosters after radiotherapy.

Conclusion

1. Whereas the open external beam radical prostatectomy, ERBT, remains the gold standard for treatment of organ-confined prostatic carcinoma, there is always space for novel, daring and challenging therapy methods to be proposed, thoroughly investigated and introduced in clinical practice.

2. The recently proposed novel therapeutic approaches to cancer treatment are predominantly based on research and development of exclusive technologies. Robotic arms and CyberKnife are the last but, most hopefully, not the least examples of such technologies.

3. Application of various additional methodologies, such as radiotherapy, MRI, CT scan, that have been "borrowed" from the adjacent medical fields, is extremely welcome. Such fusion of knowledge, research and experience is always beneficiary both for the patients and the medical professionals.

References

1. Walz J, Graefen M, Michl UH, Heinzer H, Friedrich MG, et al. (2007) [Technical aspects of nerve sparing during retropubic prostatectomy]. Ann Urol (Paris) 41: 23-30.
2. Walsh PC, Marschke P, Ricker D, Burnett AL (2000) Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 55: 58-61.
3. Menon M, Tewari A, Peabody JO, Shrivastava A, Kaul S, et al. (2004) Vattikuti Institute prostatectomy, a technique of robotic radical prostatectomy for management of localized carcinoma of the prostate: experience of over 1100 cases. Urol Clin North Am 31: 701-717.
4. Russo GI, Cimino S, Salamone C, Madonia M, Favilla V, et al. (2013) Potential efficacy of some african plants in benign prostatic hyperplasia and prostate cancer. Mini Rev Med Chem 13: 1564-1571.
5. Morgia G, Cimino S, Favilla V, Russo GI, Squadrito F, et al. (2013) Effects of Serenoa repens, selenium and lycopene (Profluss®) on chronic inflammation associated with benign prostatic hyperplasia: results of "FLOG" (Flogosis and Profluss in Prostatic and Genital Disease), a multicentre Italian study. Int Braz J Urol 39: 214-221.
6. Cimino S, Sortino G, Favilla V, Castelli T, Madonia M, et al. (2012) Polyphenols: key issues involved in chemoprevention of prostate cancer. Oxid Med Cell Longev 2012: 632959.
7. Sebastiano C, Vincenzo F, Tommaso C, Giuseppe S, Marco R, et al. (2012) Dietary patterns and prostatic diseases. Front Biosci (Elite Ed) 4: 195-204.
8. Rassweiler J, Schulze M, Teber D, Seemann O, Frede T (2004) Laparoscopic radical prostatectomy: functional and oncological outcomes. Curr Opin Urol 14: 75-82.
9. Danila DC, Anand A, Sung CC, Heller G, Leversha MA, et al. (2011) TMPRSS2-ERG status in circulating tumor cells as a predictive biomarker of sensitivity in castration-resistant prostate cancer patients treated with abiraterone acetate. Eur Urol 60: 897-904.
10. Heidenreich A, Varga Z, Von Knobloch R (2002) Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol 167: 1681-1686.
11. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, et al. (2012) Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 366: 981-990.
12. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, et al. (2010) Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 11: 725-732.
13. Bhavsar T, McCue P, Birbe R (2013) Molecular diagnosis of prostate cancer: are we up to age? Semin Oncol 40: 259-275.
14. Ridout AJ, Kasivisvanathan V, Emberton M, Moore CM (2013) Role of magnetic resonance imaging in defining a biopsy strategy for detection of prostate cancer. Int J Urol.
15. Morgia G, Russo GI, Berretta M, Privitera S, Kirkali Z (2013) Genito-Urological Cancers in Elderly Patients. Anti-Cancer Agents in Medicinal Chemistry 13.
16. Burkhard FC, Schumacher MC, Studer UE (2006) An extended pelvic lymph-node dissection should be performed in most patients if radical prostatectomy is truly indicated. Nat Clin Pract Urol 3: 454-455.
17. Kim ED, Nath R, Slawin KM, Kadmon D, Miles BJ, et al. (2001) Bilateral nerve grafting during radical retropubic prostatectomy: extended follow-up. Urology 58: 983-987.
18. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, et al. (2011) EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 59: 61-71.
19. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, et al. (2012) Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 62: 418-430.
20. Savera AT, Kaul S, Badani K, Stark AT, Shah NL, et al. (2006) Robotic radical prostatectomy with the "Veil of Aphrodite" technique: histologic evidence of enhanced nerve sparing. Eur Urol 49: 1065-1073.
21. Lei Y, Alemozaffar M, Williams SB, Hevelone N, Lipsitz SR, et al. (2011) Athermal division and selective suture ligation of the dorsal vein complex during robot-assisted laparoscopic radical prostatectomy: description of technique and outcomes. Eur Urol 59: 235-243.
22. Novara G, Ficarra V, Rosen RC, Artibani W, Costello A, et al. (2012) Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol 62: 431-452.
23. Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W (2001) 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125) I brachytherapy. Int J Radiat Oncol Biol Phys 51: 31-40.
24. Blasko JC, Ragde H, Luse RW, Sylvester JE, Cavanagh W, et al. (1996) Should brachytherapy be considered a therapeutic option in localized prostate cancer? Urol Clin North Am 23: 633-650.
25. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, et al. (2013) Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol 63: 618-622.
26. Alblin RJ, Soanes WA, Gonder MJ (1971) Prospects for cryo-immunotherapy in cases of metastasizing carcinoma of the prostate. Cryobiology 8: 271-279.
27. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, et al. (2011) EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 59: 572-583.
28. de la Taille A, Hayek O, Benson MC, Bagiella E, Olsson CA, et al. (2000) Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. Urology 55: 79-84.
29. Nguyen HD, Allen BJ, Pow-Sang JM (2013) Focal cryotherapy in the treatment of localized prostate cancer. Cancer Control 20: 177-180.
30. Baust JG, Gage AA (2005) The molecular basis of cryosurgery. BJU Int 95: 1187-1191.
31. Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ, Sartor O, et al. (2007) Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 178: 2260-2267.
32. Ritch CR, Katz AE (2009) Prostate cryotherapy: current status. Curr Opin Urol 19: 177-181.
33. Theodorescu D (2008) Cryotherapy for prostate cancer: what we know, what we need to know. J Urol 180: 437-438.
34. King CR, Lehmann J, Adler JR, Hai J (2003) CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. Technol Cancer Res Treat 2: 25-30.
35. Hannoun-Levi JM, Benezery K, Bondiau PY, Chamorey E, Marcié S, et al. (2007) Robotic radiotherapy for prostate cancer with CyberKnife. Cancer Radiother 11: 476-482.
36. Morgia G, De Renzis C (2009) CyberKnife in the treatment of prostate cancer: a revolutionary system. Eur Urol 56: 40-42.
37. Pawlicki T, Cotrutz C, King C (2007) Prostate cancer therapy with stereotactic body radiation therapy. Front Radiat Ther Oncol 40: 395-406.
38. Fuller DB, Naitoh J, Lee C, Hardy S, Jin H (2008) Virtual HDR CyberKnife

treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. Int J Radiat Oncol Biol Phys 70: 1588-1597.

39. Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM (2009) Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technol Cancer Res Treat 8: 387-392.

40. Katz AJ, Santoro M, Diblasio F, Ashley R (2013) Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. Radiat Oncol 8: 118.