Abstract. – Both low dose rate (LDR) permanent either 125I or 103Pd seed implant and high dose rate (HDR) 192Ir temporary implant are an excellent way to release high dose of ionizing radiations to cancerous lesions while significantly sparing the surrounding healthy tissues. Therefore, the radiation brachytherapy, among the established treatment options of organ-confined prostate carcinoma – interstitial radiofrequency, high intensity focused ultrasound, cryotherapy – has gained large acceptance in the last decades. The LDR permanent interstitial radioactive seed implantation is often used as monotherapy for low risk prostate carcinoma whereas the HDR temporary implant may useful to treat intermediate-to-high risk prostate tumors as a radiation boost to combined external beam radiation therapy (EBRT). On the other hand, with recent refinement of EBRT techniques – either three-dimensional conformal- or intensity-modulated radiotherapy, cyber-knife radiosurgery with even 4D-high resolution image-guided tracking – high doses of X-rays may be precisely delivered to prostate malignant lesions without increasing toxicity for surrounding normal structures. Also hadron therapy is an increasingly successful technique that allows the release of effective energy of protons (H\(^+\)), neutrons or carbon ions (\(^{12}\)C) to the limited extent of the cancerous target site, thus destroying malignant lesion with millimetric precision – just as bloodless surgery – while less damaging the neighbouring healthy tissues. Looking to the near future, even more effective oncotherapy modality appears to be the use of antiprotons because of their highly confined energy deposition at well defined body dept around the annihilation point in contact with protons of the ordinary matter, so targeting only a very limited body volume.

Introduction

Even though noteworthy progress has been most recently made in lowering frequency and mortality of prostate carcinoma – like lung and colon-rectal male cancers – however, prostate carcinoma, in the developed Western countries, remains the most common male tumor, mainly in men over age 65, although it might also occur in younger men, sometimes under fifty\(^1\).

Among the established treatment options against the organ-confined prostate tumor, the radiation brachytherapy has grown rapidly and gained large acceptance in the last decades, especially after the introduction of three-dimensional transrectal ultrasound-guided transperineal stereotactic implantation procedure and 3D-CT-guided posterior pararectal approach\(^2-5\).

The increasing use of focal approaches to prostate-localized carcinoma – including ablative technologies such as high-intensity focused ultrasound (HIFU), interstitial radiofrequency, cryotherapy – is because the proportion of patients with localized low- to intermediate-risk tumor – early-stage prostate cancer – is rising as a result of more and more wide both PSA (prostate specific antigen) -2proPSA test screening and use of suitable imaging techniques\(^6,7\).

Conceptual Background of Radiation Brachytherapy

The main aim of brachytherapy is to deliver a supraletal dose of ionizing radiations to the cancerous area together with sparing radiation exposure to surrounding healthy tissues, hence avoiding both radical prostatectomy- and external

Key Words:
Radiation therapy, Brachytherapy, Hadron therapy, Antiproton, Prostate carcinoma.
beam radiation therapy (EBRT)-related adverse side effects, the conventional EBRT unfortunately involving the whole prostate gland and neighbouring organs in higher proportion than individual cancerous targets7-9.

Besides the interstitial radioactive seed implantation as radical monotherapy for the organ-confined low risk prostate carcinoma, that one intermediate- or high-risk may be treated by combined EBRT and a radiation boost supplied by brachytherapy (Table I)10-12. Moreover, brachytherapy – like radical prostatectomy, cryotherapy, HIFU – is used as local salvage treatment for locally relapsed prostate carcinoma11. Indeed ultrasound-guided permanent radioactive source interstitial implantation, mainly of either 125I or 103Pd seeds, by delivering a radiation low dose rate (LDR), is usually considered as safe and curative treatment for patients affected by low-risk disease, whereas high dose rate (HDR) radiation fractions, most commonly by temporary radioactive implant of 192Ir, are proposed for patients affected by intermediate- to high-risk disease, sometimes as supplemental radiation dose to EBRT12-17. An intriguing enlargement-reversal of indications for these modalities has been recently pointed out, such as the temporary HDR with 192Ir for low risk carcinoma and, instead, the permanent LDR with 125I seed interstitial implantation, in combination with EBRT for intermediate-high-risk carcinoma (Table I)10,15.

### Outcomes
A large number of long-term radiation brachytherapy studies have shown recurrence-free survival rates of 77 to 93%. Although the brachytherapy, as first line monotherapy, might be usually prescribed to treat prostate carcinoma exhibiting precise characteristics – T1c÷T2a as clinical stage with digital rectal examination and diagnostic imaging suggesting no extension outside of gland, PSA level of 10 ng/mL or lower, Gleason score of 6 or less, gland volume below 60 cc or g thus excluding patients with severe benign prostatic hyperplasia – however, high rates of favorable biochemical (PSA) outcome and cause-specific survival have been reported even after brachytherapy of patients with several adverse pre-treatment risk factors – such as PSA levels of 10÷20 ng/mL or PSA velocity over 2 ng/mL/year, Gleason score equal to 7 or sometimes higher, clinical stage T2b÷T2c – whose the risk of post-treatment prostate cancer-specific mortality seems to be only slightly higher. Obviously, brachytherapy candidates with risk of most likely extraprostatic extension should be treated with supplementary intensity modulated radiotherapy5,6,10,13,16,21.

The brachytherapy, even for quite small prostate glands, appears to be effective, with a low treatment-related morbidity profile, particularly regarding the rectal complications, and with favorable biochemical outcome (post-brachytherapy PSA values)16.

### Table I. Brachytherapy: radioactive source options.

<table>
<thead>
<tr>
<th>Low dose rate (LDR): most commonly used permanent implants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>125I</td>
<td>γ emitter</td>
</tr>
<tr>
<td>103Pd</td>
<td>γ emitter</td>
</tr>
</tbody>
</table>

Also 131Cs is an attractive source, with average dose similar to that of 125I while a half-life of just 9.7 days

<table>
<thead>
<tr>
<th>High dose rate (HDR): most commonly used temporary implant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>192Ir</td>
<td>γ emitter</td>
</tr>
</tbody>
</table>

Monotherapy typical prescription dose: 145 Gy (1 gray = 1 J/kg), potentially ensuring a cytotoxic irradiation for 1 year
- Average dose: 13 Gy/wk
- Boost dose: 108÷110 Gy (added to EBRT)

Monotherapy typical prescription dose: 125 Gy
- Average dose: 10 Gy/wk
- Boost dose: 90÷100 Gy (added to EBRT)

High dose administered in one to three short fractions (only a few minutes), by using a computer-remote-controlled source loading machine (after loading technique)
- Mainly providing a dose addition (boost) to EBRT
Brachytherapy-Associated Morbidity

Just pointing out the today good outcomes of prostate cancer brachytherapy, one mustn’t disregard some its problematic issues, particularly those permanent radioactive seed implant-related\(^1,16,22-33\):

- the hard «pernickety job» of interstitial seed implantation, sometimes lasting out two hours, in order to achieve the proper both focal and peripheral radiation dosimetry;
- acute side effects due to needle-insertion in the gland: bleeding from needle holes, hematuria, hematospermia, periprostatic-perineal hematoma due to laceration of periprostatic veins, lymphocoele, seldom infection with prostatic abscess, pelvic cellulitis, thromboembolic disease;
- genitourinary radiation toxicity: sexual disorders such as erectile dysfunction and decreased semen volume, penile numbness, stress urinary incontinence, radiation cystitis-related boring symptoms (dysuria, frequency and urgency), urinary retention;
- intestinal radiation toxicity: painful bowel morbidity, proctitis, rectal ulcer, urethral-prostate-rectal fistula;
- errant seed deposition outside prostate gland; either extracapsular-pelvic seed shift into the bladder and periprostatic tissue or endovascular seed migration in several distant organs such as lung and heart, moreover it affecting the post-implant prostate dosimetry;
- accidentally irradiation to sanitary staff and persons in contact with patients carrying still radioactive permanent implants (it is advisable to restrict the contacts with children and pregnant women).

A separate-distinctive modality of brachytherapy is the IORT, intra-operative radiation therapy, carried out in operating theatre, by single administration, directly onto open tumoral area, of external ionizing radiations generated by linear accelerators (electron-energy range of 4÷12 MeV).

Photon- and Hadron-beam Radiation Therapy

Beyond the conventional EBRT, new external photon beam radiation therapy modalities have been recently developed – such as three dimensional conformal radiotherapy (3D-CRT)/volumetric modulated are therapy, helical tomotherapy, intensity modulated radiotherapy (IMRT), \(\gamma\)-rays (\(^{60}\)Co)-knife-therapy, cyber-knife-radiotherapy-radiosurgery with 4D-image-guided tracking furthermore improved in high-powered “True-Beam” machine and 6D-image-guided stereotactic-RT, that dynamically synchronize imaging, patient positioning and treatment delivery with a dose escalation – to obtain more and more conformal “radio-ablative” treatment of the cancerous lesion while at the same time minimizing the damage to nearby normal tissues\(^4,29,30,34-37\).

Hadron therapy is an increasingly successful radiation technique that uses a focused beam of quark-constituted particles, such as protons (H\(^+\)), carbon ions or neutrons, allowing a more precise delivery of high dose of effective energy at the cancerous target site to destroy malignant lesions with millimetric precision – bloodless surgery – while preserving the surrounding healthy tissues, hence avoiding the risk of secondary tumors together with overcoming the disadvantages of either conventional EBRT- or brachytherapy-associated morbidity\(^38-45\).

Compared to photons (X-rays, \(\gamma\)-emissions) of any energy, which induce roughly equal levels of cell lethality at the entrance- and exit-path besides the tumor, proton beams are characterized by a low entrance dose while a maximal dose at a user-defined dept (so-called “Bragg peak”) and almost no damage on the exit path, thus it making a significant reduction of integral dose delivered to healthy tissues\(^45\).

While protons, like high-energy photons, interact with cell structures by preliminary ionization process and, therefore, by ROS (reactive oxygen species, also called free oxygen radicals such as superoxide and hydrogen peroxide), the neutrons, instead, appear to directly damage DNA, less depending on the tissue presence of oxygen to induce cell-killing.

Carbon ions (\(^{12}\)C), that are much heavier than protons, are used to especially treat radioresistant deep tumors\(^36,43,46-48\) because of their higher linear energy transfer (LET) and the following greater relative biological effectiveness (RBE).

Anyway, RBE and penetration dept of hadrons are strongly influenced by their speed, that depends on the characteristics of either synchrotron/cyclotron or short pulse-laser accelerators\(^49\).

On the basis of above-mentioned hadron physical properties, the prostate carcinoma, together with other malignancies such as cerebral paraspinal-, pituitary-, esophageal-, lung- and pancreas-tumors, is an elective candidate to hadron therapy\(^51\).

Even a more effective oncotherapy modality appears to be the use of antiprotons because of
the intriguing physical antimatter-related characteristics. The antiproton is symmetric mirror antimatter particle of the proton, with the same mass and size as the proton while differing in its both negative charge of -1 and opposite magnetic sign; in contact with the ordinary matter, it straightaway annihilates converting its mass, together with that of proton, into subnuclear particle emission (particularly energetic pions/secondary neutrons) and high energy pion decay-derived $\gamma$-beams that are also able to create a real-time image of the site of delivered lethal radiation.\textsuperscript{50-53} Currently antiprotons are produced for research purposes only in a few subnuclear particle physics laboratories such as Fermi National Accelerator Center (Chicago, IL, USA), CERN (Geneva, Switzerland), GSI (Darmstadt, Germany).

In the near future, a possible antiproton cancer therapy, founded on the highly confined deposition of energy around the antimatter-ordinary matter annihilation point at well defined body dept (in the particular case, within the cancerous mass so destroying it) and on antiproton-related-EBR and -BEDR (biologically effective dose ratio as tumor/healthy tissue damage ratio), both significantly higher than protons and even carbon ions, could be an attractive option to effectively treat deep radio-resistant tumors.\textsuperscript{50-53}

\textbf{Concluding Remarks and Perspectives}

Among the established treatment options against the organ-confined prostate carcinoma – including ablative technologies such as HIFU, cryotherapy, interstitial radiofrequency – the radiation brachytherapy with either permanent seed interstitial implantation or temporary implant has gained large acceptance in the last decades, particularly because of the introduction of 3D-transrectal ultrasound-guided transperineal radioactive source implantation.\textsuperscript{2-5,54} Just appreciating the today good outcomes of prostate cancer brachytherapy, that are due to its peculiar release of a supraletal dose of ionizing radiations to the cancerous area together with sparing the surrounding healthy tissues, one mustn’t disregard its associated morbidity such as acute side-effects (hematuria, hemospermia, lymphocele) and both genitourinary and bowel toxicity, besides the possible endovascular seed migration in distant organs (lung, heart).\textsuperscript{18-33}

New external photon beam radiation therapy modalities have been recently developed – 3D-CRT, IMRT, $\gamma$-knife, cyber-computer-assisted-knife with 4D- high resolution images-guided tracking – to achieve a more selective treatment of malignant lesions while sparing the nearby healthy structures.\textsuperscript{34-37}

Also hadron (proton, neutron, carbon ion) therapy appear to be a successful particle beam technique, that allows a highly selective release of effective energy at the cancerous target site with less damage to surrounding normal tissues, thus avoiding both the induction of secondary tumors and foremost either EBRT- or brachytherapy-associated morbidity.\textsuperscript{38-47}

Whereas the protons, as well as high-energy photons, interact with cell structures by ionization products such as ROS, the neutrons, instead, are able to directly damage DNA and, therefore, to kill cells without free oxygen radical-mediated effects. Conformal proton beam radiotherapy of prostate carcinoma reaches excellent biochemical outcomes (PSA level values) with a very low treatment-associated morbidity profile.\textsuperscript{45} Current developments of the intensity-modulated proton therapy seem to indicate a further reduction of integral dose to healthy tissues by a factor 1.7 in comparison with IMRT.\textsuperscript{44,45,54} Carbon ions, as heavier than protons and therefore supplied with higher LET and RBE, may be used to treat radio-resistant deep tumors.\textsuperscript{43,46-48,55}

Looking to the near future, an intriguing highly effective oncotherapy modality appears to be the use of the antiprotons because of their confined delivery of annihilation-derived energy at well defined body dept, hence destroying only the cancerous lesions without any significant damage to nearby normal tissues.\textsuperscript{50-53}

The recently developed external either photon- or especially hadron-therapy technologies could become more and more competitive, as for precisely target locally-confined tumors, with brachytherapy modalities, as alternative options to anyhow carried out – open, laparoscopic, robot-assisted – surgical approaches.\textsuperscript{29,41,45,47,53,56-59}

\textbf{References}

Radiation brachytherapy vs external either photon- or hadron-beam radiation therapy

4) PLOWMAN PN. Radical radiation therapy options for organ-confined prostate cancer. BJU International 2001; 87: 431-440.


9) PIETERS BR, REZAE E, GEILSEN ED, KOEDOoker K, VAN DER GRIENT JN, DE REIJKE TM, KONING CC. Development of late toxicity and international prostate symptom score resolution after external-beam radiotherapy combined with pulsed dose rate brachytherapy for prostate Cancer. Int J Radiat Oncol Biol Phys 2010; [Epub ahead of print]


12) HINNEN KA, VAN VULPEN M. Predictors in the outcome of 125I brachytherapy as monotherapy for prostate cancer. Expert Rev Anticancer Ther 2011; 11: 115-123.


