NOWOTWORY Journal of Oncology • 2005 • volume 55
Number 1 • 58–65

Three-dimensional (3D) real-time conformal brachytherapy – a novel solution for prostate cancer treatment Part I. Rationale and method

Marek Fijałkowski[1], Brygida Białas[1], Bogusław Maciejewski[2], Joanna Bystrzycka[3], Krzysztof Ślosarek[3]

Introduction. Recently, the system for conformal „real-time" high-dose-rate brachytherapy has been developed and dedicated in general for the treatment of prostate cancer. The aim of this paper is to present the 3D- conformal "real-time" brachytherapy technique introduced to clinical practice at the Institute of Oncology in Gliwice.
Material and methods. Equipment and technique of 3D-conformal "real time" brachytherapy (3D-CBRT) is presented in detail and compared with conventional high-dose-rate brachytherapy. Step-by-step procedures of treatment planning are described, including own modifications.
Results. The 3D-CBRT offers the following advantages: (1) on-line continuous visualization of the prostate and acquisition of the series of NS images during the entire procedure of planning and treatment; (2) high precision of definition and contouring the target volume and the healthy organs at risk (urethra, rectum, bladder) based on 3D transrectal continuous ultrasound images; (3) interactive on-line dose optimization with real-time corrections of the dose-volume histograms (DVHs) till optimal dose distribution is achieved; (4) possibility to overcome internal prostate motion and set-up inaccuracies by stable positioning of the prostate with needles fixed to the template; (5) significant shortening of overall treatment time; (6) cost reduction – the treatment can be provided as an outpatient procedure.
Conclusion. The 3D- real time CBRT can be advertised as an ideal conformal boost dose technique integrated or interdigitated with pelvic conformal external beam radiotherapy or as a monotherapy for prostate cancer.

Trójwymiarowa brachyterapia w „czasie rzeczywistym" - nowa metoda leczenia chorych na raka gruczołu krokowego Część I. Założenia i opis metody

Wprowadzenie. W ciągu ostatnich kilku lat dostępny jest system konformalnej brachyterapii w „czasie rzeczywistym", z użyciem źródeł promieniowania o wysokiej mocy dawki (3D-CBRT), dedykowany dla leczenia chorych na raka gruczołu krokowego. Celem opracowania jest prezentacja tej metody i techniki wdrożonej do praktyki w Instytucie Onkologii w Gliwicach od 2003 roku.
Materiał i metodyka. Przedstawiono i omówiono wymagane wyposażenie aparaturowe oraz technikę 3D-CBRT, w porównaniu do standardowej brachyterapii HDR. Omówiono kolejne etapy planowania i realizacji leczenia przy użyciu tej metody.
Wyniki. Stosowanie metody 3D-CBRT wnosi następujące korzyści: (1) ciągłą trójwymiarową wizualizację „on-line" gruczołu krokowego podczas wszystkich etapów planowania i realizacji leczenia; (2) wysoką precyzję definiowania i konturowania objętości tarczowej i narządów krytycznych (cewka moczowa, odbytnica, pęcherz moczowy), w oparciu o serię obrazów uzyskanych dzięki przezrektalnej ultrasonografii; (3) optymalizację „on-line" planu leczenia i ciągłą korektę „histogramów dawki w objętości" w czasie rzeczywistym, aż do uzyskania optymalnego rozkładu dawki promieniowania; (4) eliminację ruchomości gruczołu krokowego i niedokładności pozycjonowania pacjenta poprzez pełną stabilizację położenia gruczołu krokowego za pomocą igieł umocowanych w płycie aplikacyjnej; (5) znaczące skrócenie czasu leczenia; (6) obniżenie kosztów leczenia w wyniku możliwości stosowania leczenia w trybie ambulatoryjnym.

[1] Department of Brachytherapy
[2] Department of Radiotherapy
[3] Department of Radiotherapy and Brachytherapy Planning
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Gliwice Branch, Poland

Wnioski. Konformalna brachyterapia w „czasie rzeczywistym" zasługuje na rekomendację jako wysoce precyzyjna technika podania dawki uzupełniającej (boost), zintegrowanej lub stosowanej naprzemiennie z konformalną radioterapią, przy użyciu zewnętrznych wiązek promieniowania lub jako samodzielna metoda leczenia chorych na raka gruczołu krokowego.

Key words: 3D-conformal real-time brachytherapy, method and its advantages, practical applicability
Słowa kluczowe: trójwymiarowa, konformalna brachyterapia w czasie rzeczywistym, metodyka i korzyści, zastosowanie w praktyce

Introduction

For over 30 years brachytherapy (BRT) has been well established and documented method of treatment of patients with prostate cancer. The BRT can be used as a sole treatment modality or in combination with external irradiation. In case of the latter it is often used as a boost to escalate the dose to the selected subvolume or whole target, without significant extension of overall treatment time. An important physical and radiobiological advantage of BRT is the concentration of a relatively high dose within a well-defined target volume, and with the large dose (dose rate) gradient within short distance out of the target. Short treatment time allows to minimize, or even exclude, the negative impact of the time factor on treatment outcome.

BRT for prostate cancer with Iodine – 125 seeds was developed in the early seventies. However, this method was not widely popular because of unprecise dosimetry with a relatively high local failure rate and late complications. Development of transperineal techniques under transrectal ultrasound (TRUS) guidance has led to the widespread popularity of permanent ^{125}I prostate implants, and it was recognized as an effective and safe treatment method [1]. Although the technique of temporary removable ^{125}I plastic tube implants solved the problem of patient comfort, there were some dosimetric uncertainties and there existed a risk of cold spots in the target volume. To meet all clinical situations and expectations modern techniques involving computer-controlled remote afterloading machines allowing for the delivery of the LDR, HDR or the PDR have opened new possibilities for brachytherapy [2-4].

Treatment planning is undertaken using a 3D-computer system based on three-dimensional reconstruction of the target and surrounding critical organs from series of cross-section images of CT, MRI or US. A variety of templates have been designed in an attempt to render the placement of interstitial sources easier and to obtain more homogenous dose distribution. C-arm fluoroscopy offers step-by-step seed positioning during and on completion of the planned implant. These technological innovations have allowed to develop a full therapeutic line for brachytherapy, conceptually similar to that for external beam therapy. MSC Memorial Cancer Center and Institute of Oncology in Gliwice has Nucletron devices including LDR, HRD, PDR selectrons connected on line with the 3D- PLATO planning system and CT, MRI and US and C-arm fluoroscopy. Treatment planning is connected with 3D-planning stations for external RT through the VARIS directory.

In brachytherapy it is extremely important to follow carefully quality assurance procedures concerning planning and verification of treatment parameters, applicators positioning, loading time and treatment delivery. It is obvious that an error in brachytherapy can be corrected, but it is more difficult to correct it than in external-beam irradiation. However, from the first step till the last step of treatment planning until the sources are loaded, brachytherapy is virtual in its nature (Figure 1A). Although there is an intension and belief that dose distribution and delivery during treatment session(s) reflects precisely all physical and technical parameters planned and prescribed, optimal choice of applicators geometry and dose distribution still remains a matter of subjectivity.

Recently a new system (SWIFT) has been designed and released for real-time brachytherapy for prostate cancer. In 2002 the Institute in Gliwice was one of three world-centers where this system has been installed and since 2003 it is used in clinical practice. The aim of this paper is to present the method of "real-time brachytherapy" (3D-CBRT).

Real-time brachytherapy

Equipment

Real-time BRT calls for two major elements, i.e. Sure-Point Stepping and Stabilization System and SWIFT™ v 1.0 System (Figure 2). The Sure-Point (Figure 2A) is a device which includes an Ultrasound Transducer (US-T) and a Needle Template (NT) fixed on the probe cradle. The Sure-Point is designed to securely hold the US-T and it allows for precise manual rotation and stepwise movement of the US-T only along the longitudinal axis and provides 3-dimmensional orthogonal positioning. Each axis (x,y,z) can be adjusted perpendicularly and independent of each other. After the US-T is in the transrectal position the NT position is adjusted. To perform calibration a needle is inserted through one of the holes in the NT, while the US-T is on and both the NT and the US-T are fixed on the probe cradle. A series of transverse images 5 mm apart from the base to apex of the prostate can be obtained. The location of the urethra at each of these sections is measured and stored.

The SWIFT™ 0 v 1.0 (Figures 2B, C) is a moveable unit of software applied for Real-Time – BRT planning and consists of the real-time US images capture, real-

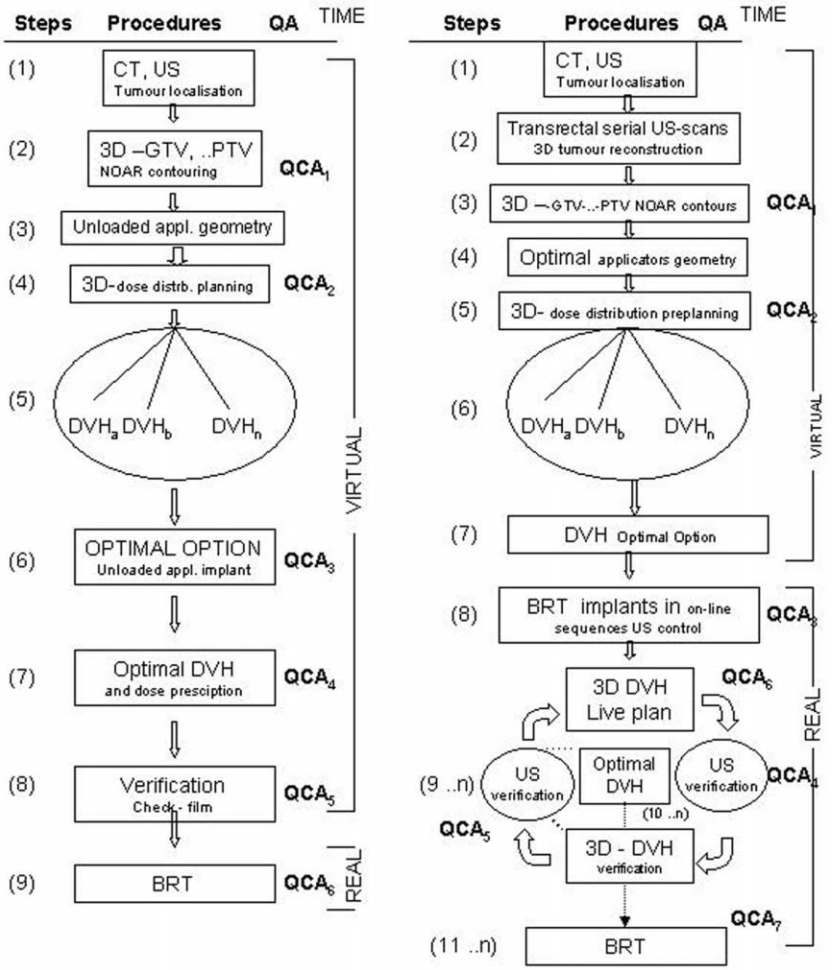

Figure 1. Scheme of step-by-step procedures in (A) conventional and (B) 3D-real time-conformal brachytherapy (US – ultrasound, NOAR – normal organ at risk, DVH – dose volume histogram, BRT – brachytherapy, QCA – quality control audit)

Figure 2. Equipment of the SWIFT System for 3D-real time conformal brachytherapy: (A) Ultra Sound Transducer and Needle Template fixed on the probe cradle, (B/C) SWIFT™ v. 1.0 System with the real-time US images acquisition, and US-3D treatment planning, (D) microselectron-HDR

time 3D ultrasound visualization of the prostate and of the SWIFT treatment planning software. It is connected on-line with Sure-Point to collect series of transversal, transrectal US images and implant positioning.

The SWIFT-System is a "real-time" treatment planning system especially designed for the treatment of prostate cancer. Series of direct 3D ultrasound imaging of the implant allow to update the treatment plan during the insertion of the catheters to the prostate. Before treatment, the software provides anatomical and dosimetric information, which allows to determine the positioning and loading of radioactive sources. The software also provides a variety of plan evolution tools to assist in the optimization of dose distribution (e.g. dose verification at a point and dose volume histograms).

Although SWIFT has its own database software, in Gliwice the entire system is connected on-line via the VARIS DIRECTORY data base with the 3D-ECLIPSE planning system for external beam radiotherapy. In Gliwice the VARIS is a central data base for radiotherapy. Connection of the SWIFT with the central data base is especially important if brachytherapy is planned as a boost or as a part of treatment combined with external irradiation. Direct flow of images and brachytherapy dose-volume histograms (DVHBr) through the VARIS to the 3D-planning stations for external irradiation increases the precision of combined planning, especially when conformal or IMRT techniques are used.

Real-time Step-by-Step procedures

Real-time planning and delivery of brachytherapy for prostate cancer is realized using an integrated 3D-CBRT therapeutic line which consists of a US transrectal probe, a stopper to fix the probe and the needle template, the 3D-treatment planning SWIFT system and HDR micro-selectron.

Procedures (Figure 1B)

1. Positioning and imaging

The patient is placed in a dorsal lithotomy position under spinal or general anesthesia with greatest possible pelvic flexion. A Foley catheter is placed with a balloon containing 7cc of contrast, and the bladder is filled with 150 cc of sterile water. A biplaner TransRectal US probe is connected to and fixed to the template/stepper cradle to allow only for longitudinal motion. The template has 12 columns and 12 rows of needle holes spaced at 5 mm intervals and a large hole for the TRUS probe. The TRUS probe is positioned and coordinated parallel to the urethra. Both the US-T and the NT template are displayed in the acquisition window and both must match each other. The TRUS probe is inserted into the rectum and moved in such a way as to place the template in contact with the perineum. To minimize prostate motion during imaging and implantation two stabilizing needles are implanted into the prostate (Figure 3).

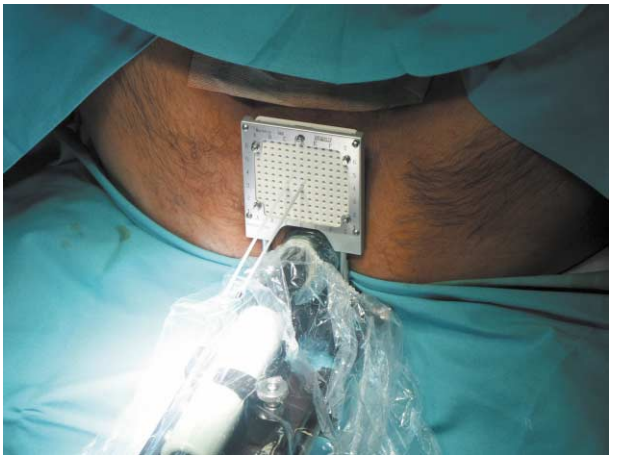

Figure 3. Two stabilizing needles implanted into the prostate. The TRUS probe is inserted into the rectum

The next step is the acquisition of the transversal US images. The stepper moves in the longitudinal direction with the US scan density of 1-5 mm distance between two consecutive frames to identify and to mark the base and apex of the prostate, and urethra, rectum and bladder. After acquiring all the necessary frames the positions of anatomic planes (base, reference and apex) are defined for treatment (Figure 4). The reference plane

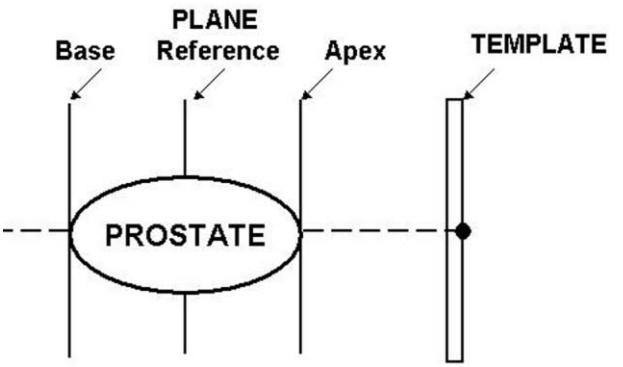

Figure 4. Scheme of anatomic plane definitions

is the largest crass-section of the prostate. The difference in depth between the base plane and the apex plane is called the active length. The location of the urethra is measured and marked at each section.

2. 3D volume reconstruction and contouring

From the acquired images a 3D volume called an Image Set is reconstructed. Each volume of interest (VOI), that is prostate, urethra, bladder, rectum, and tumour, must consist of at least a few contours taken from different transversal slices. The more contours are taken – the more precise is the 3D reconstruction. The 3D contours are recorded, visualized and can be corrected any time (Figure 5-A).

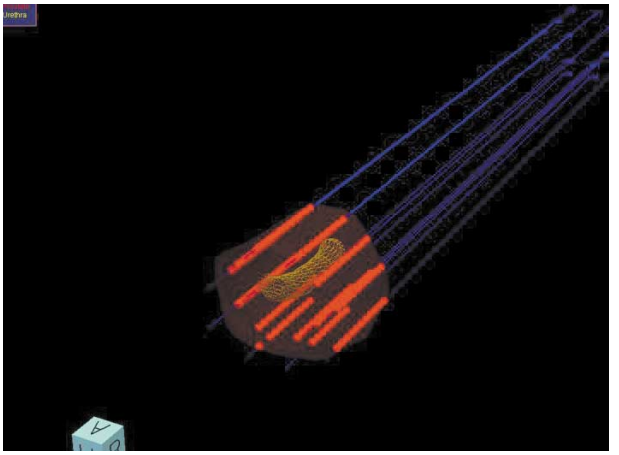

Figure 5A

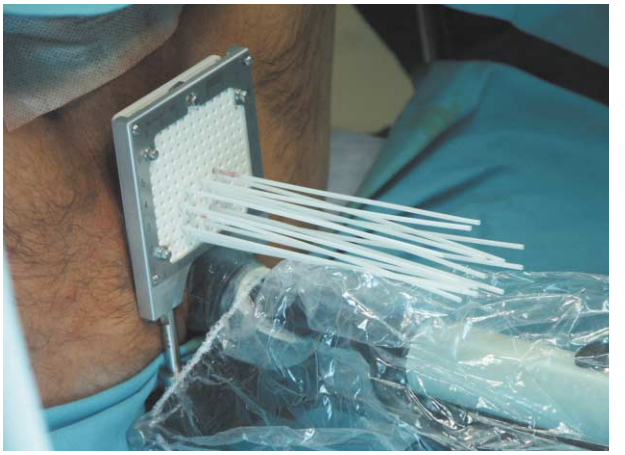

Figure 5B

Figure 5. (A) Three-dimensional visualization of the needles inserted into the prostate including position of the urethra, (B) Template with the all inserted needles and the TRUS probe positioned in the rectum

3. Normalization and prescription

After defining the PTV and OAR (organ at risk) the optimal needle position within the reference plane is determined using a real time, interactive optimization program. The location of each needle is measured and the implant is automatically reconstructed, dwell weights optimized, reference dose determined, rectal dose calculated and displayed on the live US image. Dose prescription is normalized either by the mean dose on PTV or the minimum peripheral dose on PTV. Placement of the needles is visualized continuously. This "live" method allows to control needle positioning "one-by-one" (Figure 5-B). Prescribing the number of needles the system can warn the planner if this number is too low or too high to achieve the prescribed dose in the selected volumes.

4. 3D dose distribution (DVH) and optimization (Figure 6)

For a given dose prescription the system (Figure 7-A) visualizes the isodose distribution and the respective DVH with corresponding dwell positions and dwell times for the sources. If the isodose distribution and the respective DVH do not reach the assumed and prescribed optimal conditions the system allows for real-time corrections. By manual or automatic corrections of isodose distribution the system automatically provides the respective corrections in DVH and in dwell times and in dwell positions of the sources. Therefore, the geometric anatomy related dose point optimization is performed in real-time until the optimal level is achieved. Each step of the optimization and its results are immediately

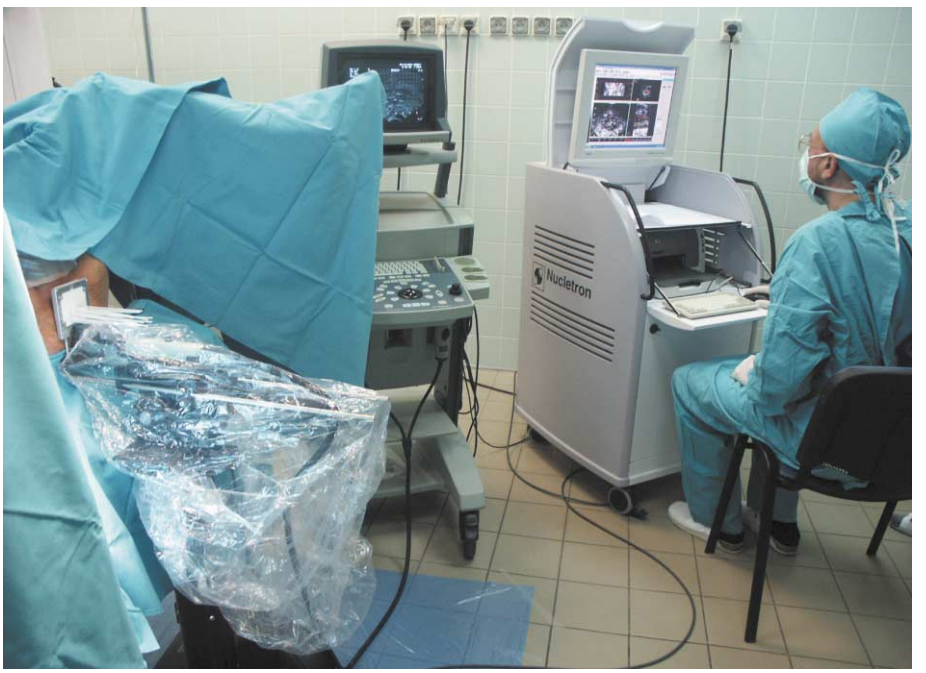

Figure 6. Procedure of the 3D-treatment planning – live optimalization

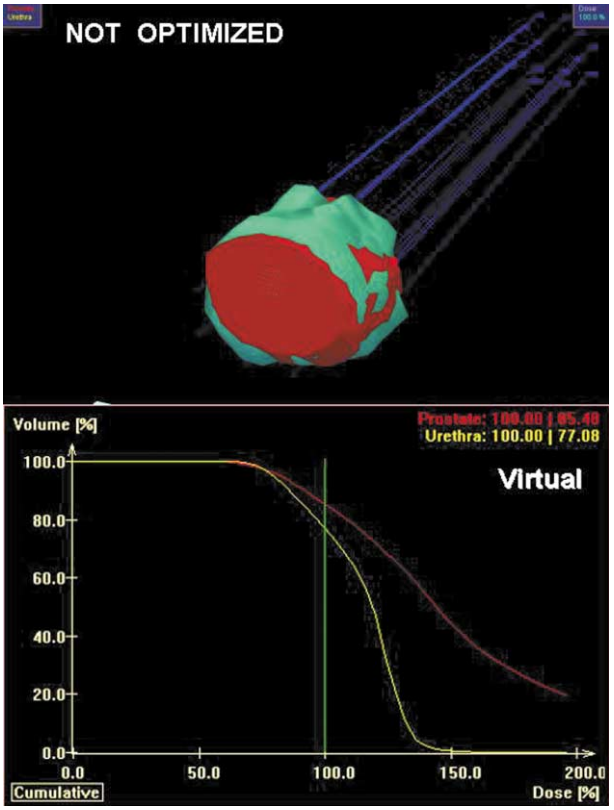

Figure 7A

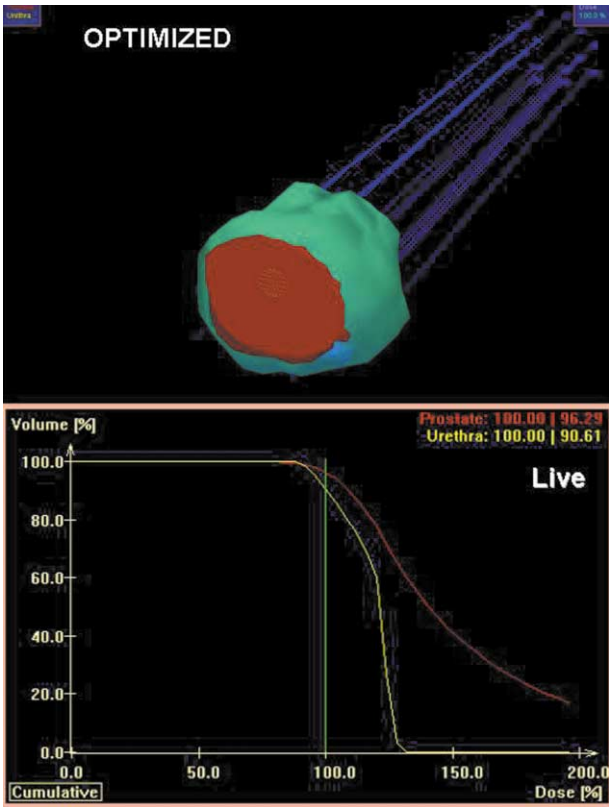

Figure 7B

Figure 7. (A-upper part) 3D-reference isodose distribution (green) which does not optimally cover the whole prostate (red). Part of prostate volume is out of the volume of the reference dose. (A-lower part) the respective virtual DVH showing non-optimal dose distribution (B-upper part) Image (A) after 3D-real time optimalization. Reference isodose (green) covers whole prostate (red). (B-lower part) the respective "Live" optimal DVH

displayed and the dwell weights are always given as normalized in the range between 0 to 1.

The DVH mode allows to select the cumulative or differential mode and it can be changed interactively. The DVH_s graphs are updated in real-time. Finally DVH curves are displayed for all selected VOI and OAR (Figure 7-B).

The SWIFT real-time planning is a continuous process of step-by-step corrections displayed on each step of correction until optimal physical and technical parameters are achieved. After accepting the final resolution the treatment session begins (Figure 8).

5. Dosimetric analysis

All dosimetric calculations are performed using real-time optimization software. On each transverse TRUS image, the 100% isodose line encompasses the contour of prostate volume. The urethral dose is calculated on each transverse image and is limited to ≤125% of the treatment dose. The rectal dose is calculated at the anterior edge within the reference plane and is limited to ≤75%. The needle positions from TRUS are captured and optimal DVH is generated from a dose distribution. Following the American Brachytherapy Society (ABS) recommendations, the values of D_{90} and D_{80} (dose delivered to at least 90% and 80% of the target volume respectively) are defined. To assess the level and range of urethral

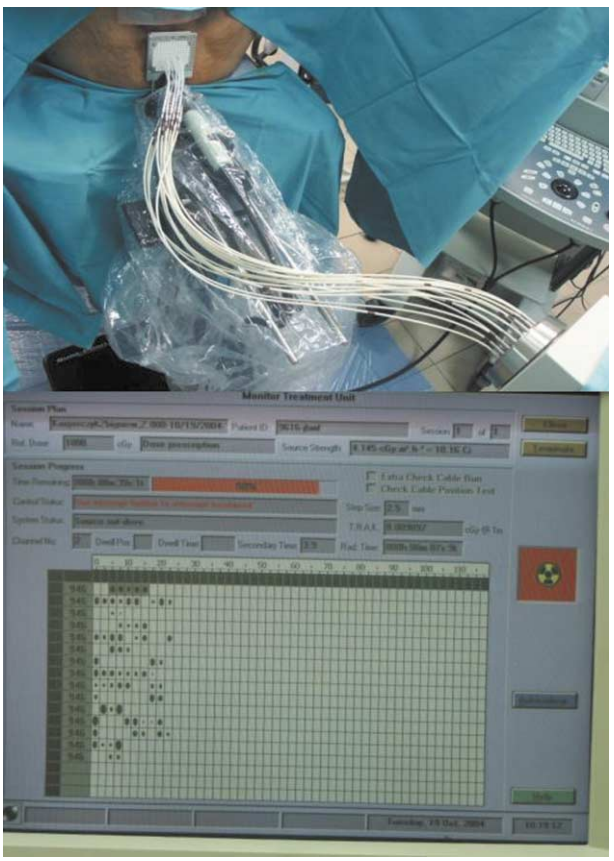

Figure 8. 3D-real time conformal BRT session (upper) with the recording of dwell positions of the sources (lower)

doses the D_{10} (dose delivered to 10% volume of the urethra) is recorded.

Discussion

The optimal therapy for patients with prostate cancer, mainly for those within the moderate and high risk groups, still remains undefined. Standard EBRT alone or combined with standard BRT does not allow to reach the expected therapeutic gain. A relatively large target may not receive the prescribed dose and subvolumes of lower doses might likely explain suboptimal results. Development of 3D conformal EBRT became an important step forward to more accurate and precise covering of the target volume while decreasing the dose to normal tissue [5, 6]. This method allows to escalate the dose within the tumour and recently published preliminary studies show promising results [7, 8]. However, it is not always easy to fully cover the target volume even in early disease, and dose escalation may not be safe or possible, due to geometrically unfavourable lesions. Systemic and volume set-up errors, internal organ motion, deformation and organ changes related to daily treatment can limit the efficacy of the 3D – conformal EBRT [7, 9].

Computerized HDR brachytherapy (BRT) using remote after-loading techniques is widely used in practice. This is still useful and effective method to boost the dose delivered by external irradiation. Stepping-source-type HDR-BRT allows to manipulate the dose distribution by controlling the dwell time used at each dwell position of the sources. Optimization of treatment is the process of determining the dwell times. This process is based on mathematical formulas used prior to the treatment, and it produces a number of options. Dose-point and geometric optimization are evaluated by a physicist and a radiation oncologist. Despite the precision and accuracy all multistep procedures remain virtual and optimalization is the result of subjective choices.

At the time when conformal external beam therapy had been introduced into clinical practice, significant progress has also been made in transrectal ultrasound imaging of the prostate and computer – based dose specification in brachytherapy. These technological advances have led to the development of a new real-time (3D-real-time CBRT), conformal, ultrasound-guided brachytherapy dedicated for treatment of prostate cancer. Martinez referred to this method as *"the HDR-smart seed technique"* [10]. The 3D-real time CBRT presented in this paper offers several important advantages as compared with standard BRT and/or conformal EBRT. First of all, it provides on-line continuous visualization of the prostate during the whole procedure of planning and dose delivery. Therefore, accurate definition and contouring of the target volume and surrounding normal organs (urethra, rectum) can be performed with high precision. Secondly, the program allows to select and to visualize ideal needle positions and correlate the anatomic relationship of the organs with the needle placements and their spatial distribution. The interactive on-line dose optimization program allows for the visualization of isodose curves and dose-volume histograms (DVH) in relation to the prostate, as well as rectal and urethral boundaries. By modification dwell positions and dwell times in real-time the DVH can be optimized. Actual doses at multiple prostate levels with corresponding doses to the rectal wall and urethra are visualized and documented during whole procedure.

Furthermore, the 3D-real time – CBRT overcomes internal prostate motion and set-up inaccuracies found in conformal EBRT by stable positioning of the prostate with needles fixed by the template. There are a few other advantages over conformal EBRT: it is much simpler and less costly in terms of CT-based planning, simulation, physicist and physician time, high geometric precision, significantly shorter overall treatment time and its ability to account and correct internal organ motion prior to dose delivery. Martinez et al. have demonstrated no shifting or displacement of the prostate just before and immediately after the treatment [11].

Finally, important advantages of the 3D- real time CBRT are (a) complete radiation protection for the staff, (b) increased applicability because general anesthesia and abdominal surgery are not required and (c) significant reduction of costs, as the treatment is short and can be performed on an outpatient basis.

Summarizing, the 3D- real time CBRT appears to be an ideal conformal boost dose technique and when integrated or interdigitated with pelvic conformal EBRT it forms an effective treatment modality for patients with prostate cancer, especially those with a large target volume.

Professor Bogusław Maciejewski Md, PhD
Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Gliwice Branch
Wybrzeże Armii Krajowej 15
44-101 Gliwice, Poland
e-mail: bmaciejewski@io.gliwice.pl

References

1. Martinez-Monge R, Nag S, Martin EW. 125 Iodine brachytherapy for colorectal adenocarcinoma recurrent in the pelvis and paraortics. *Int J Radiat Oncol Biol Phys* 1998; 42: 545-50.
2. Martinez A, Edmundson GK, Cox RS et al. Combination of external beam irradiation and multiple-site perineal applicator (MULDIT) for treatment of locally advances or recurrent prostate, anorectal and gynecological malignances. *Int J Radiat Oncol Biol Phys* 1985; 11: 391-8.
3. Perez CA, Grigsby W, Williamson J. Clinical applications of brachytherapy. In: Perez CA, Brady LW. *Principles and Practice of Radiation Oncology*. Ed. III. Lippincot-Raven; 1998, 487-560.
4. Nag S. Brachytherapy for prostate cancer: summary of American Brachytherapy Society recommendations. *Sem Urol Oncol* 2000; 18: 133-6.
5. Leibel SA, Ling CC, Kuteller GS et al. The biological basis for conformal three-dimensional radiation therapy. *Int J Radiat Oncol Biol Phys* 1991; 21: 805-12.
6. Liehler AS. Three-dimensional conformal radiation therapy: A testable hypothesis. *Int J Radiat Oncol Biol Phys* 1991; 21: 853-6.

7. Hanks GE. Conformal radiation in prostate cancer: Reduced morbidity with hope of increased local control. *Int J Radiat Oncol Biol Phys* 1993; 25: 377-8.
8. Zelefsky MJ, Leibel SA, Burman CM et al Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostate cancer treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1994; 29: 755-61.
9. Melian E, Mageras GS, Fuks Z et al. Variation in prostate position quantitation and implications for three-dimensional conformal treatment planning. *Int J Radiat Oncol Biol Phys* 1997; 38: 73-81.
10. Martinez AA, Yan D, Lockman D et al. Improvement in dose escalation using the process of adaptive radiotherapy combined with 3D – conformal or intensity modulated beams for prostate cancer. *Int. J Radiat Oncol Biol Phys* 2001; 50: 1226-34.
11. Martinez AA, Gustafson G, Gonzalez J et al. Dose escalation using conformal High-Dose-Rate brachytherapy improves outcome in unfavourable prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; 53: 316-27.

Paper received: 14 November 2004
Accepted: 30 November 2004