DESCRIPTION AND FEATURES OF A TECHNIQUE OF SEEDS IMPLANTATION WITH 3D REAL TIME PLANNING CONNECTED TO AN AUTOMATIC AFTERLOADING AND QUALITY CONTROL DEVICE

M. Ortiz Seidel (1), C. Cantera de Frutos (1)

(1) Nucletron S.A.

1. INTRODUCTION: SEEDS IMPLANTATION AS A TREATMENT METHOD FOR PROSTATE CANCER

According to statistics, 9% of males older than 50 years will develop prostate cancer and 33% of them will finally die of their disease. Detection can be based on digital rectal examination, tumoral markers measurements as PSA (Prostate Specific Antigen), CT/MR or Ultra Sound imaging. Treatments may be radical prostectomy (usually combined with chemotherapy), external radiation therapy, brachytherapy, or a combination of the former two techniques.

In the last few years permanent seed implantation is becoming an attractive alternative for treatment of prostate cancer at early stages, either as monotherapy (total prescribed dose of 145Gy) or as an additional boost after external beam irradiation (95-100Gy after external beam delivery of 50Gy). But not all cases are suitable for seed treatment. Tumors must be at an early state and not very active (low tumoral markers values), without extra-capsular spreading and no metastasis in surrounding area. There must be no trans-urethral resection, no calcifications nor pubic arc interference and, finally, the volume should not be bigger than 50 cm$^3$.

The technique consists on the permanent implantation of radioactive seeds into the prostate that, while decaying, will deliver the prescribed dose to the tumor. Isotopes mostly used are I-125 and Pd-103. Procedures for seed implantation vary but traditional ones generally imply two stages. The first one is the manual pre-loading of needles which can be performed either by composing loose seeds and spacers, either by cutting off strands of seeds and reabsorbable spacers. This process can be done according to a previously approved preplan or based on the accumulated experience about the number of needles and loading usually needed. Second stage consist on the implantation of these preloaded needles on the operation room.

2. DESCRIPTION OF NUCLETRON FIRST SYSTEM

Nucletron FIRST system, Fully Integrated Real-time Seed Treatment system, is a complete, safe and reliable method for seed implantation. It allows an integrated work-flow from preparation and planning to treatment delivery, with integrated verification and quality assurance, and the ability to adapt seed configuration up to the very last moment to actual treatment situation. As it will be later explained, the whole system is designed so as to provide the maximum accuracy and flexibility on the planning and delivery of the treatment, but the essential component of FIRST system, responsible for the benefits relative to radiation protection is the automatic seed loader called seedSelectron.

Opposite to traditional methods for seed implantation, Nucletron seedSelectron system is designed as a remote afterloading device, allowing hospital personnel to perform a seed implantation in an automatic, safe, accurate and reliable manner, minimizing the handling of radioactive material and subsequently the radiation exposure. Nucletron seedSelectron System uses Iodine-125, which is an isotope which has modest half life (59.4d) and emits a low-energy gamma ray and x-rays with energies below 0.0355 MeV. This low energy facilitates local shielding with metal foils only a few tenths of a millimeter thick and allows numerous applications not available with other isotopes.

Nucletron FIRST system is manufactured by Nucletron and seeds are produced by the daughter company Isotron. Both posses the ISO 9001 / EN 46001 certificate, which represents a warranty of its reliability. Installation may only be performed by Nucletron qualified personnel. This equipment is classified as IEC 601-1, Class 1, Type B. Certain parts are classified as Type BF.

FIRST System can be installed in any standard hospital operating rooms (OR) and a normal distribution for the complete setup is displayed on the diagram bellow.
The physician works on the sterile area around the patient, near the stepper that holds and allows the control of the ultrasound probe. Afterward it will also support the template—to guide the needle insertion—and finally the seed loader. Sterility applies to all those components of the seed loader to be assembled on the OR that will be in contact with the patient (disposables).

On the non sterile area, where physicist works, there are the ultrasound unit connected to the probe and the cart containing the Nucletron Planning System for seeds called SPOT (Sonoagraphic Planning on Oncology Treatments) that will transfer the final plan to the Treatment Control Panel for the ultimate delivery of the treatment.

Being the main scope of this article the improvements on radiation protection represented by an automatic and remote device for seed implant, a more detailed description of the seedSelectron is needed. Its main components are: seeds and spacer cartridges, seedSelectron unit itself and disposables. Careful attention deserves as well the description of the emergency tool designed to finish the treatment in case an error happen that prevents the unit to complete it normally.

### 2.1 Seeds and spacer cartridges

The seed cartridge contains a minimum of 10 and a maximum of 100 SelectSeeds, in steps of 5. The cartridge is made of nickelled brass and provides the shielding for the radioactive seeds (thickness of the brass walls: 1.2 mm), has a shape for one-way insertion into the seedSelectron and it is sterile and for single use only.

The source consists of two component parts: a biocompatible titanium tube capsule (ASTM F67-95, grade-2) and a silver bar where the iodine-125 (AgI) is deposited on and that also serves as a radiopaque marker for evaluating source position via radiography. The seamless titanium tube has a wall thickness of 0.05mm and is laser end welded. The design has also been improved to decrease the anisotropy. The activity can be chosen from an Isotron list of 14 different nominal activities, ranging from 0.375 µGy/hr m² to 1.174 µGy/hr m². The shipped activity will be in a range of ±4% around the nominal activity.
The Source type is a sealed source according ISO 2919 and classification is C63211. It has recently also been included on the AAPM/RPC Registry for Low Energy Brachytherapy Seeds.

Manufacturing and Quality Assurance concerning sources is performed by Isotron, company based in Berlin and full daughter of Nucletron. The production of seeds is highly automated and includes several automated inspections of the activity and anisotropy of the seeds versus NIST calibrated seeds, additional checks on the activity of the batch, several automated checks on the quantity of seeds, automatic CCD–aided geometric inspection and automated leak tests. Seed cartridges are finally double packaged and sterile. Careful labelling as package type A is done, adding source certificates and shipping documents.

The final inspection and QA Release consist on the verification of dose rate of packaging < 5µSv/h, verification on trace-ability and on required labeling and documents. Much effort has been put forth to avoid mislabeling, such as: the use of barcodes and color codes, strict separation of production batches, computer aided storage, etc.

Before delivering seeds to any hospital, Isotron requests the following documentation: copy of the import license for seeds from the hospital, copy of the hospital license indicating the maximum amount of I-125 that they are allow to keep and validity period for this license, and a copy of the re-export license that will allow the return of disposed seed to Isotron.

The spacer cartridge contains 100 spacers made of bio-degradable polymer. It has a unique shape for one-way placement on the Basic Unit and it is sterile and for single use only.

2.2 SeedSelectron

Before treatment, the SeedSelectron is partly assembled in the operation room with the sterile parts. The fittings for these sterile parts can be cleaned and disinfected. For the delivery of the treatment, the seedSelectron will be attached to the stepper device with a fixation mechanism.

The seedSelectron contains Electronic Control circuit boards, Power Supply, Radiation Sensors (Diode Array), and 4 motors, respectively the Seeds Cartridge Motor, the Spacers Cartridge Motor, the Delivery Drive Motor, and the Needle Extraction Motor. Each motor meets different requirements, and per motor different control logic parameters are used. System posses indicators of Power On, Normal Operation, Test Runs, Seeds out of Cartridge, Error Status and Interrupt Status.

The Radiation Sensors check every building and step of the delivery of the seeds/spacers train. If the Radiation Sensors detect a deviation between the planned seed activity and the actual seed activity, they will provide a warning. Insertion of wrong cartridges or wrong seed calibration values, are also detected in this way. Besides, during treatment a watchdog will detect the malfunctioning of the system. In case of a power interruption, the treatment status is saved and the UPS takes over the power supply.
2.3 Disposables

Some description is necessary of the set of disposables that, together with seed and spacer cartridges will be used for each single treatment. It includes the following elements: Delivery Compose Element, Delivery Drive, Adjust Knob, Fixation Needles and set of Interstitial Needles with their Obturators.

Delivery Compose Element consists of a Compose Element and a Delivery Tube. The part is sterile and for single use only to prevent malfunctions through contamination of body fluids. The Compose Element is suitable to measure and build a seed/spacer train with a length up to 8 cm and it can only be fastened in one way onto the seedSelectron. It is designed so that in case of removal from the seedSelectron seeds and/or spacers can not fall out of it. The Delivery Tube is inserted into the Compose Element and assembled onto the seedSelectron. The needle connector fits onto the Nucletron prostate needles and in case they are not connected, it will block the path to the Delivery Drive.

The Delivery Drive is used to compose and deliver the seed/spacer train. It has a one-way fastening to the seed and spacer cartridge. The delivery drive must be placed onto the seedSelectron together with the seed and spacer cartridges. The part is sterile and for single use only to prevent malfunctions through contamination of body fluids.
The Extractor Adjustment Knob is used to calibrate the needle position relative to the Basic Unit. It is sterile and for single use only.

Finally, the part of the Interstitial Needle that will be implanted and the Obturator are made of stainless steel. The Obturator is inside the Needle during implantation, to prevent Needle bending. After removal of the Obturator, the Needle is connected to the Compose Element through the delivery tube and by means of the quick-fit connection. The part is sterile and for single use only. To fixate the Prostate position before the insertion of the Interstitial Needles, two anchor Needles are included, also made of stainless steel, sterile and for single use only.

The seedSelectron has a click fit system for assembling the cartridges and sterile disposables. The seedSelectron itself is designed to minimize the entry of dirt, water and other foreign matter. The device can be readily and safely cleaned. Temperatures normally encountered in use will have no adverse effect on the device. The materials in close proximity to the sources will not be adversely affected by radiation. It is also very important to notice that every element of the set is designed to ensure that in no case, seeds will fall out.

2.4. Emergency tool (manual loading device)

The Emergency Tool is designed to finish treatments in case of failure of the automatic procedure. It is a mechanical tool to manually load seeds and spacers from cartridges into a needle. The Emergency Tool has a click fit system for assembling the cartridges. The cartridges have to be unblocked, while in the Emergency Tool, to prevent unintentional rotation of the cartridges. A wire is used to build the seeds/spacers train in the Build Tube which has a transparent window of lead glass to visualize the seeds/spacers train while shielding properly. The Emergency Tool is reusable and its sterility, according to manufacturer instructions, is the responsibility of the hospital. Before reuse, it has to be checked on damage and proper functioning.

3. DESCRIPTION OF THE PROCEDURE FOR SEED IMPLANTATION WITH FIRST SYSTEM

The general procedure that implies the use of FIRST system at its full extend will be described, though there are some details that may vary between institutions.

At least one week before the treatment, hospital must order the seeds through the form specially designed for that, specifying the number of them and the nominal activity. The required number of seeds, usually estimated from a study previously made, should include a margin of approximately 10% to account for possible changes of prostate size -that might make necessary adding more seeds- or seed trains disposed during treatment due to some problem.

Before the procedure starts, the patient is prepared on the operation room (OR) with epidural anesthesia to immobilize him hip downwards. Patient is placed in gynecological position to allow the use of US rectal probe.
The probe is introduced on the patient controlling the longitudinal movement with the aid of the stepper. On the ultrasound screen, transversal and longitudinal views will allow right localization of what is called the base plane -the most inner plane where prostate can still be seen-. Study will be made starting usually 10mm beyond the base plane, ensuring the prostate is completely covered on the longitudinal view. To acquire images, the SPOT system is connected to a ECRM (endo-cavity rotation movement) device that rotates the probe a predefined arc, acquiring longitudinal images every predefined step. The acquired images will be used by the system to generate a 3D reconstruction where contouring of prostate and other organs of interest (urethra, rectum wall...) will be performed for posterior planning.

After the contouring is done on the transversal reconstructed images, physicist will produce a preplan aimed to cover with the right isodose the target volume while sparing the urethra as much as possible. SPOT will superpose a template onto the transversal image that has been previously calibrated to the physical one assembled on the stepper to ensure a perfect reproducibility of the plan. A number of needles with certain coordinates will be placed, some of them reaching the most inner plane (base plane) and others at a certain distance from it, called retraction distance. It is general practice trying to avoid trespassing the urethra. Trains of seeds and spacers will be defined for each needle. Final evaluation of the implant by means of dose-volume histograms is necessary to asses that the objectives are achieved.

When the preplan is complete, surgical act begins. As a initial step, anchor needles may be placed on free positions on the template in order to limit prostate movement during insertion of treatment needles. After prostate has been fixed, physicist will communicate the position of every needle to the physician performing the insertion. Some institutes prefer to insert all needles at a time and do a later delivery while other like better to insert and deliver needle by needle. The choice depends on the experience and preferences of the medical staff. All needles insertion allows the use of the system at its full extent but presents the inconvenience that the procedure is much more traumatic and if not done quickly may lead to undesirable prostate swelling. Needle by needle procedure is less traumatic but very time consuming.

Nucletron FIRST system offers the possibility to use a life-planning module to update the needle position. Therefore, a new scan has to be made and real position of needles updated on the system with immediate updating of isodoses. Therefore, preplan can be adapted at the very last moment according to possible changes between the theoretical position of needles and the real one.

When the final plan has been approved, it is transferred to the Treatment Console Panel that will ultimately control the seedSelectron performance during treatment. SeedSelectron has been switched on previously to ensure by means of the initial tests that the device is working fine. SeedSelectron is assembled to the stepper on an adjustable bracket and disposables placed by the physician paying very much attention to the fact that while they are sterile, the seedSelectron is not, making the collaboration from a second non-sterile person necessary.

Once all elements are on place, the process begins on the treatment console with the definition of seeds and spacer cartridges and the source calibration process. The first seed of the cartridge is deposited on a sterile container for calibration. Dosimetry of such sources is usually done in well ionization chambers of $4\pi$ measurement geometry and sensible enough to small activities. Ideally, the well chamber should be calibrated by an authorized calibration laboratory for the specific type of source to be used on the implant. If this is not possible, the constants provided by the chamber manufacturer for this type of seeds or similar, will have to be used. Once the seed has been measured, the obtained value is entered into the program and compared with the reading provided by the device detectors in order to establish an absolute calibration. During composition of trains, the seedSelectron will compare the activity of each seed with the nominal one and indicate any case in which there may be a discrepancy. User will decided on these cases whether to carry on or dispose the train.

Before the delivery starts, calibration of base plane is also necessary. During this last process, the system will know exactly which is the distance to the base plane for the central deepest needle and will therefore be able to deposit all trains taking into consideration retraction distances. During this calibration procedure and the previous one, the system will perform a number of checks oriented to detect the presence of all necessary disposables and verify that they are working fine.

The delivery process implies interaction and fluent communication between physicist, controlling the Treatment Console, and physician responsible for the assembly of the delivery tube to each needle. For each of them the system will perform the following actions: test run (if activated) to detect any possible obstruction on the path; composition of the train of seeds and spacers; delivery to the right position by the delivery wire and final retraction of the needle one cm beyond the deposited train while the delivery wire keeps the train in place and
finally retracts to its zero position, ensuring in this way that no suction effect will take place. After needle retraction, the physician disconnects it from the delivery tube and extract it completely from the patient, doing a final check with the obturator to verify no seed remains on the needle. Process continues until the last needle is done. A film of the patient is finally made to check seeds positions and count them.

The final step of the procedure is the disposal of remaining seeds in the cartridges to a dispose container to be counted afterward. The number of remaining seeds, together with the seeds on the patient, the one used for calibration and any others that may have been disposed during treatment, must match the original number on the cartridges (otherwise, it would mean a seed is lost).

4. RADIATION PROTECTION ASPECTS

It is interesting to analyze in more depth some aspects of radiation protection related to exposure of personnel, patient and relatives and how they are minimized in order to fulfill the ALARA criterion (As Low As Reasonably Achievable).

4.1 Related to patient during the implant

The application of the ALARA criterion to the patient undergoing seed implantation implies that the procedure has to be performed in such way that the patient will only receive the prescribed dose to the target volume (prostate) and as low as possible to the rest of the organs. To ensure this, the FIRST system has unique features.

On one hand, a high accuracy on the physical placement of the radioactive seeds. This is due to the possibility of updating the needle position on the SPOT system and to the procedure of delivery of radioactive trains which is very accurate. During this procedure, in case that one seed or spacer were missing (which is very unlikely due to the numerous automated tests performed during cartridges manufacturing), the system would detect this difference in length and provide a warning indicating that the real length of the train differs from the planned one. Such situation forces to dispose immediately the train because, otherwise, the final dose distribution would be different from the originally intended one.

On the other hand, there is an exhaustive quality control on the activity of each seed. As it was shortly mentioned during the procedure description, the calibration process involves the measuring of the first seed and entering the apparent activity into the Treatment Control Panel in such a way that a direct comparison with the lecture given by the seedSelectron sensors will establish an absolute calibration. During the train composition, each seed out of the seed cartridge will be measured on the radiation sensors and the lecture will be compared internally with the calibrated activity of the first seed. The user may customize the value of the acceptance range which is usually around ±5%. If the measured activity is the same as the reference one, the indicator displayed on the Treatment Console Panel beneath the seed will appear green. If it is different but still inside the accepted range, the indicator will be yellow. And if it is outside range, indicator will appear red. In case the system shows any of the seeds outside range, the user may chose whether to dispose the complete train, whether to continue if the decision is taken that such difference will not significantly change the final dosimetry.

The control of the activity of each seed represents a real innovation. Even if the procedure used for the manufacturing of seeds is highly automated and safe, there is always a small possibility of a seed having a different activity than the specified for the whole cartridge. Only the previous check could detect such discrepancies that otherwise would lead to differences between the plan and the final dose delivery.

4.2 Related to exposure of involved personnel during automatic and manual delivery of seeds

As it has been described in previous sections, every element of the seedSelectron system is specially designed to minimize the radiation exposure: seeds come in a brass cartridge that shields conveniently and during the process of composition of the train—which is done inside the plastic compose element-, the more active part will always be covered by a plate of stainless steel that protects against radiation.

The only step where seeds are not properly shielded is during its path through the delivery tube but this process is performed so quickly than it is generally accepted as enough protection to step back to a minimum distance of 50cm from the tube during the process. Assuming a maximum train of 5 seeds of maximum activity of 1.1mCi, dose rate at 50cm distance would be no higher than 0.01mSv/hr. Just to give an idea of the total dose rate, the average number of needles per treatment is around 20.
Even in case the treatment can not be completed in the normal way and the emergency tool is needed, and assuming once more the longest possible train of 5 seeds with the maximum possible activity (1.1mCi), the resultant dose rate produced during composition and insertion would be only 0.002mSv/hr on the surface (made of 2mm of lead glass) of the build tube and negligible at 1m distance.

4.3 Related to exposure of involved personnel during possible emergency situations

In case of problems during seedSelectron operation, there is a set of action protocols especially designed to cover all possible emergency situations. They will be displayed adequately by the Treatment Console Panel as the error happens. Nucletron training on FIRST (usually one week long and performed immediately before the first treatment) is aimed to that each person involved on the treatment is perfectly trained on the procedure and knows exactly what to do and how to react in case abnormal situations happen. Moreover, a Nucletron qualified person is present during at least the first 10 treatments on the institute during the learning period.

In general, problems can be caused by abnormal function of the seedSelectron itself or by obstruction of any part of the disposable due to body fluids entry.

Problems involving malfunction of any mechanical or electronic component of the seedSelectron (motors, detectors, etc) must be communicated immediately to Nucletron. In no circumstance the hospital personnel will open the unit and manipulate switches that may affect the radiation detectors.

Obstructions may happen due to blood entry on compose and delivery elements. The seedSelectron system has an additional security feature called test run. In case of activation of this option on the Treatment Console Panel, a test will be performed for each needle before the train composition, to ensure the path to the end of the needle is free. In this way, if there is any obstruction, the obstructed element can be replaced without handling of radioactive material. As this additional check can be deactivated, there is a possibility that the obstruction occurs while seeds are on compose elements or delivery tube. The presence of radiation on any of the former elements will always indicated by a blinking LED on the seedSelectron. In this case, protocols usually involve retrying the action and, in case the obstruction persists, replacement of the damaged element which has to be removed carefully and deposited for later disposal of remaining seeds on it. The two situations described before are easily solved but, as time is crucial, in case of necessity there is always the possibility to use the emergency tool to complete the treatment.

Seed lost may also occur when a needle perforates a vessel and the resultant blood flow trail it outside, or by inappropriate seed handling. In these cases it is necessary to quickly localize the seed using a suitable dosimeter, and collect it using tweezers to deposit it immediately on the dispose container. During this procedure, neighboring area must be closed and access will not be permitted until the seed is found.

Other type of emergency situations include seed cartridge damaged or contaminated. I-125 can not escape in normal conditions from seed cartridge. In case of filtration or contamination, cartridge must be dispose immediately and all equipment that may have been in contact with it must be checked and cleaned. Neighboring areas must be closed and affected persons checked for possible contamination. After the damaged cartridge has been transferred to a container and sealed, and the area cleaned, the person responsible for radiation protection may allow the access again.

4.3. Related to exposure of patient and relatives after the implant

There is a number of possible situations after the implant that require that the patient and his relatives are sufficiently informed and trained to handle them.

Emergency procedures on the post-implant period relate to the possibility of biological expulsion of one seed in the days after the treatment. To handle correctly these situations, the patient must be informed about the type of treatment he has undergone, risks and related safety measures. Particularly, in case of excretion of one seed, he has to be trained on the right handling of this seed which will be collected with tweezers, deposited on a container and kept as far as possible from populated areas until hospital staff is informed and proceed to the collection.

Finally, for the sake of protection to radiation exposure of patient relatives, direct contact must be avoided until 8 weeks after the implant, while pregnant women and persons below 18 years must keep a safety distance of at least 2m during this period.
In case of death of the patient on the 2 years after the implant, relatives must consult the responsible physician or the competent authority about the modality of burying.

5. DISPOSE PROCEDURES

As it has been said on the previous section, disposed seeds will be finally stored on a dispose container. Final disposal of seeds should be carried out in compliance with the regulations as laid down by the hospital concerned, which must conform to the rulings of the respective supervisory authority.

If the hospital is not in the position to dispose seeds, they will be returned to the manufacturer, according to the instructions. These instructions include: use of official Nucletron Dispose Container, which has the required shielding to qualify the package as type A; determination of seeds and total activity; obliteration of the labeling of the empty package materials; complete labels and shipping documents and final measure of the radiation from the package to verify that it meets the requirements.

It is important to note that the maximum number of seeds, estimating the maximum activity of 1.1mCi, that the Dispose Container may hold is 500. Subsequent dose rate on the surface of the container would be 0.5mSv/hr and dose rate at 1m would be negligible.

6. CONCLUSIONS

Due to the increasing complexity of brachytherapy treatments, of which seed implants are just an example, the responsibility for the team in charge has also grown. It starts from the design and implementation of the facility that meets all the clinical needs (technical support personnel, treatment planning and delivery equipment, and dedicated space) and the management of required licenses. In case of Spain, licenses for importing, handling and storing radioactive sources are provided by the Ministry of Industry advised by C.S.N. (Nuclear Security Counsel). Following the installation, acceptance tests and commissioning of the equipment are required. A careful quality control process must finally ensure the accuracy and safety of each individual brachytherapy treatment through review of calculations and monitoring treatment team compliance to established procedures. Quality control procedures may include sets of redundant performance checks, physical measurements, documentation standards, training and experience standards, and guidelines for the development of treatment procedures, and they are designed to minimize the frequency of human errors, miscommunication, misunderstandings and equipment malfunctions.

Nucletron global system for planning and performing seed implantation has the goal of making the previously described process as simple and safe as possible. Installation is extremely easy and flexible and adequate training of personnel in charge ensures a fast learning curve during the implementation period. The ability that the planning system SPOT has to do preplanning and life planning during the same surgical session, ensure that the implanted needle configuration will finally correspond to the originally planned and that any needle deviation will be corrected. The remote afterloading device seedSelectron performs the composition and delivery of the radioactive train in a safe, fast and reliable manner. The numerous quality control checks during composition and delivery, of which the most important by far is the control of the activity for each delivered seed, ensure that the final seed distribution on the patient will produce the intended dose coverage of the tumor, while sparing organs at risk. All the same, the seedSelectron design and operation ensure that the exposure of the personnel involved on the procedure will be almost negligible, according to the ALARA criterion. The whole procedure can be done in approximately 60 to 90 minutes and any emergency situation, as the ones previously explained, can easily be faced and solved by an adequately trained personnel without increasing significantly the radiation exposure.

Forms are created for the following processes: source receipt, calibration and disposal. The careful management of these forms together with the detailed inventory the system stores of all used and disposed seeds, allows maintaining a complete coherent information always available.

Therefore, Nucletron FIRST system represents a step forward for the seed implantation technique. The implementation of this system fulfill the following requirements: realize the clinical intent of the radiation oncologist, protect the patient from treatment delivery errors and maximize safety of the patient and staff.