CyberKnife in the Treatment of Prostate Cancer: A Revolutionary System

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The CyberKnife is a frameless advanced robotic system that uses image-guided radiotherapy (IGRT) and adaptive radiotherapy (ART) for stereotactic radiosurgery technique in intra- and extracranial lesions. The CyberKnife has also revolutionised the use of radiosurgery to treat tumours in different parts of the body. This system represents, after three-dimensional conformal radiotherapy (3DCRT), a new frontier in the treatment of prostate cancer, applying the same dosimetric and biologic considerations as with high-dose-rate (HDR) brachytherapy.

The CyberKnife combines three different advanced technologies to deliver frameless conformal radiosurgical doses. The first is a miniature linear accelerator (Linac X-6 MV) mounted on a robot arm (KUKA, Augsburg, Germany). The autonomous robot allows multiple positions and angles to deliver a series of up to 1560 different directions. The second innovation is real-time image guidance during treatment, using body landmarks or gold fiducials, to mark the target position to perform frameless radiosurgery in intracranial, spinal, and body sites. The registered image has been used to determine the treatment site’s coordinates with respect to the Linac robot and the target coordinates to the robot, with the beams to the tumour site. The third innovation is amorphous silicon detectors to establish patient position and orientation through body skeleton or gold fiducials. During treatment, two silicon cameras provide the actual image in real time, and they are compared with digitally reconstructed radiographs (DRR) obtained from computed tomography (CT) scan.

The biologic rationale for hypofractioned radiotherapy is that the proliferation of prostate cancer cells is low, and these cells are sensitive to high doses. The data indicate that the \(\alpha/\beta\) relationship of prostate neoplastic cells is around 1.5 Gy (CI 95%: 1.3–1.8 Gy), unlike the classic \(\alpha/\beta\) relationship of 10 Gy of other tumours [1]. From this, it follows that radiotherapy schemes of 20 fractions of 3 Gy, 10 fractions of 4.7 Gy, or 5 fractions of 7 Gy are all biologically equivalent to a dose of between 80 and 90 Gy. All this is also linked to the fact that the best results in treatment of prostate tumours are obtained with dose escalation to high doses. Therefore, it becomes necessary to distribute high doses along the prostate gland without provoking serious adverse side-effects in neighbouring organs. In practice, hypofractioned radiotherapy would be the best radiotherapy approach for prostate tumours [2]. HDR brachytherapy is the method that guarantees the best results [3]. However, this is an invasive procedure that requires anaesthetic, use of a catheter for 1–2 d, and hospitalisation. It is also an operator-dependent procedure.

Another attribute of the CyberKnife also represents the cutting edge of technologic progress. It gives the user the ability to track and correct for movements of the prostate in real time. In one study, intrafraction prostate motion was detected, with movements of 2.6–7 mm in the left–right, anterior–posterior, and cranio–caudal directions [4]. A second study reported measuring intrafraction prostate motions of \(<1\ cm\) over an 8-min period, with some motions lasting \(>1\ min\) [5]. Larger planning treatment volumes are required when using external-beam radiation therapy (EBRT) to compensate for this large intrafraction prostate motion, and this increases the risk that higher doses of radiation will be delivered to adjacent structures such as the bladder and rectum [6].

There are three phases of treatment when CyberKnife is used: transrectal ultrasound (TRUS) for the gold fiducial markers (GFMs), planning, and treatment.
The first step is ultrasound-guided implant of 4–6 gold-seed fiducial markers inside the prostate gland by the urologist about 1–10 d before treatment (Fig. 1).

The GFMs must be positioned at the apex, in the intermediate lateral zone, and at the base of the prostate. There must be a minimum distance of 2 cm between them, and, theoretically, they should not be farther than 5–6 cm from the tumoural lesions. Finally, the angle between the different groups of fiducials should not be <15°.

The second step is to carry out a CT scan about 1 wk after implanting the fiducials. It is very important that the CT scan is almost the same as that used in the treatment. The CT scan is fused with the magnetic resonance imaging (MRI) sequence to show prostate capsular and apical definition, the neurovascular bundle, and the GFMs.

At this point, the radiotherapist defines the volumes of interest (VOIs) and treatment planning, which determine the doses prescribed for the prostate (PTV) and the critical organs (bladder, rectum, rectal mucosa, and urethra). The PTV for favourable-prognosis patients corresponds to the prostate volume, up to 2 cm of contiguous seminal vesicle, and a 2-mm volume expansion in all directions except posteriorly. The volume expansion in intermediate-prognosis patients is 5 mm dorsolateral from the prostate and seminal vesicle (Fig. 2). The third step in the procedure is hypofractionated radiation treatment. At present, more than one treatment schedule is used: five fractions of 7 Gy (for a total of 35 Gy), four fractions of 9.5 Gy (for a total of 38 Gy; we use this schedule), or five fractions of 7.25 Gy (for a total of 36.25 Gy).

The CyberKnife treatment is indicated for localised cancer prostate in stage cT1/T2a-b N0 M0 with a Gleason score ≤6 and a prostate-specific antigen (PSA) level <10 ng/ml (low risk) or, in selected patients, with a Gleason score of 7 and PSA 10.1–20 ng/ml (intermediate risk). Obviously, there is no information on this system in the international guidelines, but one must bear in mind that the CyberKnife can be integrated completely into all methods of interstitial brachytherapy; thus, the indications for these systems can be considered valid, should the initial results be confirmed over time.

Contraindications for the use of this method are a prostate volume of >80 cm³ (although, naturally, hormonal downsizing of the gland is possible), while related contraindications that still have to be verified might be a severe level of obstruction or previous prostatic surgery.
At present, we have very few works in the literature on the first results of using this robotised system, even though it has been used for about 1000 patients with prostate cancer since it came on the market in 2003. At this moment, there are 94 CyberKnife platforms in the United States, and these have naturally been widely used, particularly for endocranial tumours as well as for pancreatic, pulmonary, and hepatic tumours. In addition, there is a real possibility of using CyberKnife for maxillofacial surgery. Unfortunately, in Europe, the apparatus is only available at ten centres. There are three each in Italy and France and one each in Germany, Greece, Spain and Holland. This means that the number of cases treated is many fewer than in the United States. Consequently, the little data available come from certain single-centre nonrandomised pilot studies, with results that have not been compared with other therapeutic options and, thus, have little scientific validity.

The Freeman group in Florida treated 40 patients with CyberKnife, 27 with radiosurgery only and 13 with radiosurgery and adjunctive hormonal therapy (ADH). All of the patients had localised tumours (only T1c), and the median PSA was 5.78. The scheme used was five hypofractions of 7 Gy (total 35 Gy), and a 12-mo follow-up found that PSA was lower in all but one of the patients. The PSA was 1.2 for the group treated only with CyberKnife and was 0.05 for the group treated with CyberKnife and ADH [7].

Another pioneering centre for treating prostate tumours is the San Diego CyberKnife Centre, which has recently published a report on 10 patients, again, all with localised tumours. The scheme used was five hypofractions of 7 Gy, for a total of 35 Gy. The results of a 4-mo follow-up were that PSA had fallen by 86% compared with the baseline.

Finally, there is our experience with six assessable patients. To better understand our experience we have treated 3 patients and we have implanted 3 more patients who are currently undergoing treatment. The average age was 74.8 yr of age (patients of >70 yr of age were deliberately chosen for the study), with an average International Prostate Symptom Score (IPSS) of 15.1 and average five-item International Index of Erectile Function (IIEF-5) score of 23. The scheme used was four hypofractions of 9.5 Gy, for a total of 38 Gy. The average PSA 6 mo after treatment was 0.8 ng/ml and had fallen in all the patients. The IPSS after about 2.5 mo had returned to normal, while the score for erectile function remained almost unchanged.

The side-effects of this treatment fall into two groups. Urinary irritative symptoms such as urgency and frequency and mild burning with urination and rectal irritative symptoms only lasted between 2 and 4 mo. The second group of side-effects are those that could be said to result from the treatment itself, and these are connected in particular to the incidence of erectile dysfunction. At present, we do not have data on this topic, as we simply do not have enough cases to perform a statistical analysis; we also lack information on the long-term effects. No cases of posttreatment incontinence have been reported when CyberKnife was used.

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.

Conflicts of interest: The authors have nothing to disclose.

References