CASE REPORT

Innovative image-guided CyberKnife® stereotactic radiotherapy for bladder cancer

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ABSTRACT. CyberKnife® stereotactic body radiation therapy is used to treat extracranial tumour sites that move with respiration. It has also been employed for the successful treatment of prostate cancer, using the image-tracking CyberKnife® system to compensate for intrafraction movements resulting from peristaltic motion and bladder filling. Large sporadic motions can be compensated for using an online target motion monitoring and cybernetic correction strategy. Radio-opaque gold markers can be implanted in the bladder during transurethral resection and used for online image-tracking during radiation to compensate for bladder filling and target movements. Transurethral bladder resection followed by chemoradiation and a stereotactic CyberKnife® radiotherapy boost seems a promising approach for the treatment of invasive bladder cancer in heavily pre-treated patients or patients eligible for preservation strategies. In this case study of a patient with a previously irradiated pelvis, CyberKnife® radiotherapy was feasible and well tolerated, with disease control and non-altered functional results two years after treatment completion. CyberKnife® irradiation may also be considered for the conservative treatment of locally advanced T2–T4a N₀ M₀ bladder cancer with incomplete or uncertain transurethral resection.

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Chemoradiation can be used to treat selected cases of localised invasive bladder cancer in an attempt to preserve the bladder without compromising survival [1, 2]. Selection is based on tumour stage and grade of differentiation after transurethral bladder resection (TUR), TNM (tumour, node, metastasis) staging, comorbidities and the patient's wishes. The benefits must be balanced against the risk of local failure, gastrointestinal/genitourinary toxicity and quality of life.

Different radiation techniques (e.g. brachytherapy and external beam concomitant boost) have been used to limit the high-dose regions and to improve local control rates. By contrast, improving the accuracy of delivery of highly conformal radiotherapy relies upon accurate target organ localisation systems, including transabdominal ultrasound, the use of fiducial markers in conjunction with electronic portal imaging devices and/or cone beam CT. CyberKnife® (Accuray Inc., Sunnyvale, CA) is a 6 MV linear accelerator (linac) mounted on a computer-controlled robotic arm that is capable of stereotactic irradiation of extra-cranial tumours. This technology has been approved by the Food and Drug Administration (FDA) and by the European Community since 2002. More than 100 CyberKnife® instruments have been installed worldwide and more than 60 000 patients have

been treated with this technique over the past seven years. CyberKnife® is the only integrated system designed to use real-time image guidance during radiotherapy delivery. It improves upon other irradiation techniques in several ways. Firstly, CyberKnife® allows for real-time organ position and motion corrections during a course of radiotherapy and, secondly, it allows for inverse optimisation solutions and delivery with multiple non-isocentric, non-coplanar arcs. These capabilities can produce improved conformal isodose profiles and dose-volume histograms (DVHs), as compared with other currently available irradiation techniques. Hypofractionation (*i.e.* the use of dose-per-fraction sizes >2.5 Gy) might increase the therapeutic ratio of some tumours, provided that particular caution and accuracy is given to limiting high-dose volumes (*i.e.* tumour size) while delineating and minimising the dose to organs at risk. CyberKnife® stereotactic irradiation has proved clinically beneficial for extra-cranial tumours that move with respiration and allows for a precision of <0.5 mm and a tracking error of ≤1 mm resulting in a global error of about 1.5 mm [3]. The high degree of accuracy in target coverage and the steep dose gradients allow planning target volume (PTV) margins to be reduced. The resulting target coverage with the prescription isodose is usually within 3–5 mm from the contoured target, which might resemble brachytherapy isodoses.

As for urological tumours, robotic stereotactic CyberKnife® radiotherapy (RSR) has been used for the

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Figure 1. Orthogonal oblique (45°) views obtained from digital reconstructed radiographs to track fiducials (radio-opaque markers shown by crosses).

successful treatment of prostate cancer [4]. In this case, a fiducial-based image-tracking CyberKnife® system was used to account for intrafraction movement [5] resulting from peristaltic motion and bladder filling. Radio-opaque gold markers (Figure 1) can be implanted in the bladder during transurethral resection; these markers are then used for online image-tracking during radiation delivery to compensate for bladder filling and target movements [6]. The integrated tracking system detects and adapts the beams according to a clinically determined relevant threshold in terms of target translations/rotations and distances between fiducials. Large sporadic motions can be compensated for using online offset corrections, while motions below the clinical threshold can be compensated for automatically by the machine online.

There are no data in the literature regarding the use of RSR for the treatment of bladder cancer. In the case study reported here, CyberKnife® technology was used to treat a patient with bladder cancer who had undergone previous radiation treatment for pelvic cancer. With CyberKnife®, real-time correction to compensate for daily positional changes in the target bladder wall during radiation delivery was accomplished using an orthogonal pair of digital X-ray imaging devices to monitor the position of fiducial markers (gold “seeds”). These markers were placed around the tumour bed under transcystoscopy guidance by the urologist. The planning CT scan was obtained with these seeds in place and their relative position with respect to the contoured organ served as a reference point. To our knowledge, this is the first reported use of this innovative and accurate four-dimensional irradiation technique to treat bladder cancer.

Illustrative case and technical aspects

A 75-year-old woman presented in August 2007 complaining of painless haematuria. Her medical history was significant for carcinoma of the pT4pN0M0 lower rectum treated with chemoradiation up to 45 Gy followed by radical surgery in 1994. She also had atrial fibrillation, a 40-year smoking history and prolonged professional contact with chloroethylene. On physical examination, she was 75 kg in weight, 170 cm in height and had stable vital signs. She had colorectal derivation in the left iliac fossa and moderate abdominal wall dehiscence. The patient had difficulty eliminating urine and experienced

nocturnal overflow incontinence. Urinary symptoms required twice-daily mini-catheterisation to prevent discomfort and cystitis. On pelvic examination and bimanual palpation, her vaginal stump revealed numerous adhesions. There was no palpable tumour. Laboratory studies showed mild normocytic anaemia with a normal coagulation profile. Urinary samples showed neoplastic urothelial cells. A contrast CT scan revealed a thickened left posterolateral bladder wall $\geq$ pT2 and N0. A bone scan and complete diagnostic work-up were otherwise negative. Cystoscopy showed an infiltrating tumour of the left lateral bladder wall with surrounding erythematous lesions of *in situ* carcinoma. Complete transurethral resection of the bladder tumour was performed in August 2007. Histology showed urothelial transitional cell carcinoma invading the muscularis mucosa (pT2 World Health Organization [WHO] Grade 3). On urodynamic testing, initial filling sensation appeared at 240 ml with a strong desire to void at 340 ml. Spontaneous voiding was limited to 100 ml. These results were consistent with motor neurogenic bladder, possibly owing to damaged sacral nerve roots with overall limited bladder compliance and detrusor dysreflexia secondary to previous irradiation and abdominoperineal resection. The patient was judged unfit for partial and total cystectomy, owing to her past medical history and the presence of numerous surgical adhesions from previous radiotherapy and surgery; she was medically unfit for chemotherapy. Following a multidisciplinary team consultation to seek a curative alternative, hypofractionated accelerated stereotactic radiotherapy with a curative intent was proposed. Patient informed consent was obtained. In September 2007, the patient underwent uncomplicated flexible urethrocystoscopy for the placement of fiducials under topical anaesthesia in the department of urology. Four non-coplanar fiducials were placed around the TUR area (Figure 1). The patient was discharged the following day. The patient underwent highly conformal RSR using the CyberKnife® system equipped with a real-time tracking tumour system and a personalised vacuum mattress designed for optimal comfort. The patient was asked not to drink for 3 h preceding irradiation and underwent mini-catheterisation 30 min to 1 h before each treatment fraction. The prescribed dose was determined on the expected normal tissue complication probability established from the linear quadratic model extrapolated to hypofractionated therapy using fractions $\leq$ 8 Gy. A contrast-enhanced millimetric CT scan was performed and

Figure 2. Axial view showing dose distribution around the target transurethral bladder resection area.

the fiducials used to delineate the target TUR area; a 1 cm security margin was included along the bladder wall that also covered the full wall thickness (Figure 2). The patient received 24 Gy in 4 Gy fractions over a period of 10 days for a radiobiological 2 Gy equivalent of 53 Gy to normal tissues with an estimated α/β ratio for healthy tissues of 2 Gy using the linear quadratic formula. Dosimetric planning was performed to minimise the dose to normal tissues in close vicinity of the bladder. Isodoses conformed very well to the tumour bed (Figure 2). The healthy bladder and other tissues including the femoral heads and small intestine received <6 Gy using a 220-collimated beam plan (Figure 3); 96% of the non-spherical PTV (16 609 mm³) was enclosed in the 80% prescription isodose. The patient was aligned, positions of the fiducials were registered and the effect of abdominal respiration was studied. The patient was observed throughout the treatment using closed-circuit television. Projections of the fiducials on bony structures were easily identifiable on intrafraction radiographs obtained every 10–20 s online (Figure 1). Differences in scalar distances between the original alignment plan and online centroid (the barycentre defined by the four fiducials) position were <3 mm

Figure 3. Three-dimensional visualisation of beams and isodose distribution centred on the transurethral bladder resection area.

(mean 1.4 mm). Changes in tumour bed position were corrected online for adequate tumour coverage. The mean centroid respiratory amplitudes were <0.25 mm. Set-up errors could be corrected for by performing real-time translations and rotations using the fiducials. Bladder filling was minimised, as demonstrated by bladder surface deformation measures, by voiding 30 min before irradiation and by not allowing the patient to drink beforehand. The patient was well, without haematuria, diarrhoea or pain and disease, 2 years after completion of the treatment. Urinary samples showed neither tumour cells nor infection. Control cystoscopy showed a limited area of scar tissue with no sign of tumour, and abdominopelvic CT scan was normal. The patient's voiding perceptions and related symptoms partially improved.

Discussion

Dose escalation is a promising approach for localised bladder cancer radiotherapy [7]; however, the tolerance dose to organs at risk limits the potential to increase the therapeutic ratio. RSR for localised bladder cancer in a patient who was denied standard treatment owing to previous treatment for pelvic cancer yielded good immediate tolerance. Further follow-up is warranted to provide long-term results on local control and side-effects. RSR uses a miniaturised linear accelerator driven by a robotic arm. It yields excellent dose distribution, delivering maximally conformal isodoses with high accuracy using non-coplanar non-isocentric beams. It is the only integrated system capable of extra-cranial target position verification and real-time tumour-tracking during treatment. Fiducial markers within the bladder wall [8] can be used to verify organ position and to track organ motion by means of an orthogonal pair of silicon X-ray imagers to provide real-time feedback correction to the robotic arm. The real-time RSR tracking system has the potential for designing a precise course of radiotherapy for mobile tumours, including localised bladder and prostate cancer [9]. The RSR circular collimators yield sharp dose fall-off in ellipsoidal tumours; thus, organs at risk close to the target receive only very low doses (Figure 4). During conventional radiotherapy, margins must be applied around the clinical target volume to account for set-up uncertainties and internal organ motion. Such margins are between 1 and 1.5 cm for the bladder. RSR offers an ideal means of decreasing margins around the tumour, therefore limiting volumes that receive significant doses and optimising DVHs. Compared with three-dimensional radiotherapy, RSR yields superior DVHs on the healthy bladder and provides excellent coverage for moving targets. These characteristics hold the potential for dose escalation and shortening of overall treatment times, making RSR convenient for patients. It is of note that, because each fraction duration is quite long (1–1.5 h), bladder surface deformations and volume changes (*i.e.* the filling rate) must be minimised. The normal filling rate is around 1.5 ml min⁻¹, but can be minimised using precise voiding and drinking rules or through the use of a urinary catheter during irradiation. Urodynamic evaluation can be used to estimate the minimal steady bladder volume that best allows minimised irradiation of

Figure 4. Organs at risk delineated for radiotherapy planning on coronal view. Orange, femoral heads; red, right kidney; purple, left kidney; green, bladder wall; dark orange, TUR area.

surrounding organs and to assess the bladder filling capacity and voiding perceptions. Owing to the long fraction durations, urodynamic studies might be useful before treatment. The need for medications should be assessed by the urologist to reduce hazardous movements in cases of unstable bladder, a disorder that might be underestimated in bladder cancer. Moreover, any diarrhoea and stool problems should be reported to the physician. RSR for bladder cancer appears feasible and accurate. Nevertheless, more data on its feasibility are needed for bladder tumours and, in particular, for tumours of the mobile portion of the bladder in non-heavily pre-treated patients.

In conclusion, stereotactic CyberKnife® radiotherapy was used safely and provided prolonged disease control in a patient with bladder cancer and a previously irradiated pelvis. Further to this preliminary case study, a Phase I/II clinical trial is at the Centre Lacassagne for

bladder cancer patients eligible for an organ preservation approach. A stereotactic boost (plus chemotherapy) is delivered after 46 Gy of conformal chemoradiation to the pelvis may be an alternative to consider instead of conventional chemoradiation for the conservative treatment of locally advanced T2–T4a N₀ M₀ bladder cancer with incomplete or uncertain transurethral resection.

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