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High Dose Rate prostate brachytherapy with ^{192}Iridium: the Seattle experience

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Introduction. The aim of this paper is to describe our experience with high dose rate (HDR) ^{192}Iridium brachytherapy for prostate cancer and the advantage of this HDR technique.
Methods and material. Afterloading needles are directly inserted via TRUS guidance into the prostate, transperineally, using a special template. The dose fractionation scheme is described. HDR brachytherapy as a monotherapy is discussed.
Results. Outcomes of a series of 104 patients are given, including survival to 10 years where the bNED is 77%.
Conclusions. HDR brachytherapy has proceeded cautiously since its start-up in the mid-1980s. Now, maturing studies indicate that multifractionated HDR brachytherapy combined with external beam radiotherapy is a well tolerated and effective treatment for localised prostate cancer. Early reports also indicate that monotherapy HDR brachytherapy of early disease is feasible.

Brachyterapia z zastosowaniem wysokiej mocy dawki (irydem 192) w leczeniu raka prostaty – doświadczenia grupy z Seattle

Wstęp. Celem pracy jest opisanie naszych doświadczeń w zakresie brachyterapii wysoką mocą dawki (HDR) z zastsosowaniem irydu 192 w leczeniu raka prostaty, ze szczególnym uwzględnieniem zalet takiego postępowania.
Materiał i metody. Prowadnice do brachyterapii wprowadza sie bezpośrednio przez krocze pod kontrolą TRUS, z zastosowaniem specjalnej płytki. Praca zawiera również opis metod obliczania dawek promieniowania oraz omówienie brachyterapii z zastosowaniem wysokiej mocy dawki jako monoterapii.
Wyniki. Praca przedstawia wyniki leczenia 104 chorych, wśród których obserwuje się nawet 10-letnie przeżycia.
Wnioski. Brachyterapia z zastosowaniem wysokiej mocy dawki rozwijała się ostrożnie od czasu swoich początków, to jest od połowy lat osiemdziesiątych. Obecnie itnieją doniesienia dowodzące, że brachyterapia wielokrotnie frakcjonowana w połączeniu z dawkami promieniowania zewnętrznego, stanowi dobrze tolerowaną i skuteczną metodę leczenia ograniczonego raka prostaty. Ponadto istnieją pierwsze doniesienia sugerujące, że możliwa jest monoterapia HDR z zastosowaniem izotopów irydu 192.

Key words: prostate cancer, high dose rate, brachytherapy
Słowa kluczowe: rak prostaty, wysoka moc dawki, brachyterapia

Rationale for HDR brachytherapy

The development of the high dose rate (HDR) ^{192}Ir remote afterloader has provided new avenues for performing precise genitourinary brachytherapy. A remote afterloading machine can precisely place a single high activity ^{192}Ir source (5-10 Curie) into each needle of a needle array at predetermined points. The source can be kept at a desired target position along an individual needle for a specified time period: known as the dwell time.

This imparts a great deal of positive control on the radiation delivery, while target motion and seed shifting issues are eliminated. With HDR, highly conformal and reliable comprehensive radiation coverage is delivered to the prostate, while undesirable "cold" and "hot" spots are significantly reduced. The peripheral prostate zones, where typically bulky portions of tumours reside and extracapsular tumor penetration occurs, can reliably be targeted.

Lastly, HDR brachytherapy can provide better sparing of rectum and bladder while delivering a higher dose to the prostate than even seven-field conformal beam radiotherapy boost [1].

Radiobiology

Emerging radiobiological data from human prostate cancer cell lines and from clinical data suggests that prostate cancer may have an α/β ratio as low as 1.5, much like a late responding tissue [2, 3]. This is probably due to

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the fact that prostate cancer contains a high proportion of non-proliferating cells.

A tumour with a low α/β ratio such as 1.5 would be predicted to be a particularly responsive tumour to hypofractionation with larger fraction size as compared to a conventionally fractionated approach. As such, tumour cell kill will be relatively higher when fractionated HDR brachytherapy is employed than with low dose rate treatment (LDR) [4].

In order to keep the potential for adverse late effects equal, the overall total radiation dose must be lowered when hypofractionated doses are used. Thus there is a reasonable radiobiological argument for the use of HDR in the treatment of prostate cancer.

Technique

With the advent of transrectal ultrasound (TRUS), most institutions performing HDR ^{192}Ir prostate brachytherapy ultrasonically direct needles transperineally into the prostate. Various templates to guide needle insertion are available, examples being the Seattle, Martinez and Syed templates [5, 6]. Needle counts range from about 12 to 22.

In contradistinction to permanent LDR seed implants, the planning of the radiation delivery is performed after needle insertion. Institutions use various imaging techniques, such as CT, orthogonal filming or intraoperative ultrasound for the planning process [5, 6]. The objective is to identify actual needle locations within the prostate tissue, the degree of needle deflection, the relation to known tumour locales and radiation sensitive tissues such as the urethra, bladder, and rectum. This combined information is used to devise an optimal HDR ^{192}Ir source pattern for the individual patient prior to actual insertion of the ^{192}Ir.

However, the resultant dose distributions from any of the above techniques are quite similar. Prescribed target volumes (PTV) are typically 1-3 mm beyond the clinical edge of the prostate, except over the rectum. A minimum peripheral dose (MPD) is prescribed to the PTV. Doses to the urethra are generally kept to 1.10-1.20 X MPD and doses of 1.20-1.50 X MPD exist in those regions between the periphery and the urethra [1, 5].

Once a preplan has been approved, the computer-controlled HDR afterloading machine precisely places and moves the ^{192}Ir source within the implanted needle array according to the plan specifications. Typically, the prescribed dose, defined by the 100% isodose curve, covers 90% or more of the target volume [1, 5].

Dose Fractionation Schedules

As with every new radiation therapy modality, knowledge of appropriate dose fraction has evolved with time. Initial trials investigating the potential usefulness of HDR were in the form of an HDR boost with external beam to the prostate, generally in the range of 45-50 Gy.

Early European investigators began with a schedule of two implants with one HDR fraction rendered per implant. This had the advantage of outpatient treatment, but necessitated two implants. Doses per HDR fraction were in the range of 12-15 Gy. Early North American users were initially more cautious, choosing a single implant with 3-4 HDR fractions rendered per implant, delivering 3.0-4.0 Gy per HDR fraction separated by six hours or more. This had the advantage of a single implant, but necessitated that the patient be hospitalised one or two days to receive the HDR brachytherapy.

Martinez et al have conducted a methodical dose escalation trial spanning several years [7]. The study validates that very high dose of HDR brachytherapy dose can be rendered safe, as long as the total dose is adjusted accordingly. The American Brachytherapy Society (ABS) in 1998 convened a consensus panel to draft guidelines for the use of HDR ^{192}Ir prostate brachytherapy as a boost to external beam irradiation, Table I.

Table I. American Brachytherapy Society Consensus Panel: example external beam + HDR dose fractionation schedules. EBRT: external beam radiotherapy. CET: California Endocurietherapy Cancer Center, Oakland. LBMMC: Long Beach Memorial Medical Center, Long Beach. MMC: Memorial Medical Center, New Orleans. SPI: Seattle Prostate Institute, Seattle. SC: Scripps Clinic, La Jolla. WBH: William Beaumont Hospital, Royal Oak

Institution	EBRT dose (cGy)	HDR fractionation (cGy x no. of fractions)
CET	3600	600 x 4 in 2 implants
LBMMC	3960	550-650 x 4 in 1 implant
MMC	4500	550 x 4 in 1 implant
SPI	5040	400 x 4 in 1 implant (1st series)
	4500	550 x 3 in 1 implant (2st series)
	4500	600 x 3 in 1 implant
SC	5040	550 x 3 in 1 implant
WBH	4600	950 x 2 in 2 implants

Outcomes

The first use of HDR ^{192}Ir for prostate brachytherapy was begun in 1985 at the University of Kiel in Germany by Bertermann et al [8]. Early reports from this institution subsequently led others [5, 9, 10] to initiate HDR-IR^{192} prostate brachytherapy programmes in the late 1980s.

Information regarding long-term efficacy is beginning to emerge as these early feasibility studies mature. The Kiel group recently reported the eight-year results of their initial protocol involving 131 patients [11]. A total of 90 patients had T1-T2 disease, 40 had T3 disease, and for the entire group the initial mean PSA was 25 ng/ml. With a mean follow-up of eight years, the biochemical no evidence of disease rate (bNED) was 74.8%. The grade 3 late radiation toxicity, according to the RTOG/EORTC scoring scheme, was 2.3% for the genitourinary and 3.8% for the gastrointestinal system respectively. No grade 4 or 5 genitourinary/ gastrointestinal morbidity occurred.

The Seattle group recently reported extended follow-up of its initial group of 104 patients of varying stages and grades, none of which had hormone therapy [12], Figure 1. With a mean follow-up of 76 months (median of 75 months and maximum of 124 months) the bNED at five years and 10 years was respectively 83% and 77%. Patients grouped by PSA <10, PSA 10-20, and PSA >20 demonstrated a bNED of 95%, 80% and 42% at 10 years. Multivariate analysis revealed three independent risk factors: PSA >15, Gleason score >6, and tumour stage >T2b. Patients with no risk factors had a bNED of 100% at five years and 97% at 10 years. Patients with one risk factor had a bNED of 78% at five years and 69% at 10 years. Patients with 2-3 risk factors showed a bNED of 44% at five years and 33% at 10 years. Long-term toxicity included a 6.7% rate of grade 3 urethral strictures, but no other significant genitourinary or gastrointestinal morbidity occurred. Changes in the implant technique appear to have significantly lowered the stricture rate in subsequently treated patients.

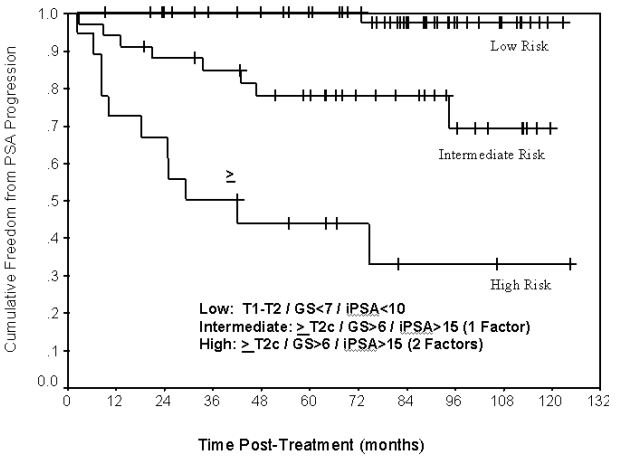

Figure 1. Seattle Prostate Institute (SPI) results at 10 years. IPSA: initial PSA. EB: external beam radiotherapy

Several other institutions are reporting five-year outcomes with similar early results as was seen in the more mature studies, see Table II. For a group of 136 patients treated with EBRT and HDR with a mean follow-up of 57 months (range 24-98 months), Quackenbush et al [13] reported a biochemical control of 92%. No patient received androgen suppression. The median PSA nadir was 0.2 ng/ml. According to PSA, the bNED control was PSA ≤10: 83/86 (97%), PSA >10-20: 32/36 (89%), and PSA >20: 10/14 (71%). No late Grade 3 or 4 gastrointestinal morbidity was observed. There were six cases (4%) of Grade 3 genitourinary morbidity, all being bulbar urethral strictures, but no Grade 4 toxicity was observed.

Martinez et al [6] provided an interim report on 142 patients with unfavorable prostate cancer that were prospectively treated in a dose-escalating trial with pelvic EBRT in combination with HDR, with no androgen suppression. Patient's with any of the following characteristics were eligible: PSA ≥10.0 ng/ml, Gleason's score ≥7, or clinical stage T2b or higher. The median follow-up was 2.1 years (range 0.2-7.2 years). Despite the high frequency of poor prognostic factors, the five-year actuarial bNED was 63%. The 5-year actuarial rate of RTOG Grade 3 late complications was 9% with no patient experiencing Grade 4 or 5 acute or late toxicity.

In most series 2-4% of the patients experienced persistent dysuria or urinary frequency up to one year post-treatment [5, 6, 9]. Potency appears to be preserved in the majority of patients with intact erectile ability before treatment [5, 6, 9]. However, no prospective quality of life studies are available for critical review.

Direct comparison with the results achieved with permanent LDR seed implants is difficult due to different patient selection criteria and the absence of comparable outcome data.

Monotherapy

In the above reports, HDR was used as a boost prior to, during or following external beam. Monotherapy prostate HDR would be attractive for a variety of reasons. The foremost being the ability to deliver all the treatment with a highly optimised, conformal and controlled dose while sparing the adjacent structures due to rapid fall-off outside the prostate.

Other reasons include eliminating concerns that organ motion may occur during external beam, and the variable degree of prostate edema that follows seed implants which may affect delivered dose. Furthermore, there are no radiation safety concerns for the patient and his immediate family as with permanent LDR seed implants. Lastly, patients would have a significantly shortened course of treatment without the external beam component.

Early in the history of prostate HDR brachytherapy, were concerns over potential late effects predicted by the

Table II. PSA control rates with HDR brachytherapy and external beam radiotherapy

Reference	Number of patients	Median PSA	Follow-up (months)	PSA control (%)	End point (ng/ml)
Stromberg [6]	58	14.0	26	85[a]	>1.5 & 2 rises
Eulau [12]	104	12.9	78	77[c]	3 rises
Galalae [11]	131	25	96	74[c]	3 rises
Borghede [9]	50	4-10	45	78[b]	>1.0

NR = not reported. [a] 3-year actuarial. [b] actual biochemical control during follow-up period. [c] 10-year actuarial

prevailing radiobiological theory at the time, and the absence of any clinical trials prevented any monotherapy studies. Now, many years later into the HDR prostate experience, several clinical trials have established the safety of prostate HDR as a boost. These trials, coupled with the recent revised thinking over the α/β ratio for prostate cancer has prompted much interest in using HDR as a monotherapy treatment.

Several feasible monotherapy studies are now being reported. The group from Osaka has recently published preliminary results of a phase I/II clinical trial of HDR interstitial brachytherapy as a monotherapy for localised prostate cancer [14]. A total of 22 patients with localised prostate cancer were treated with either 48 Gy in eight fractions over five days,7/22 cases, or either 54 Gy in nine fractions over five days, 15/22 cases. During treatment lumbar pain due to prolonged bed rest was the primary complaint. As scored by RTOG criteria, 11 patients reported some acute toxicity, but none reported any grade 3 symptoms. With a median follow-up time of 31 months and a range of 19-58 months, chronic toxicity appears quite acceptable. One patient experienced a grade 2 rectal ulcer 22 months post-brachytherapy and another had occasional grade I rectal bleeding. No significant late urethral or bladder symptoms were reported. PSA response is satisfactory given the rather advanced stages being treated.

Martinez et al treated 41 patients with conformal monotherapy HDR brachytherapy alone with a single implant of 38 Gy total dose in four fractions of 9.5 Gy each, delivered twice a day over two days [15]. No patient experienced any grade 3 or greater acute toxicity.

Similarly, Rodriquez et al at the California Endocurietherapy Cancer Center started treating early stage prostate cancer patients with an HDR monotherapy protocol in April 1996, with 40 patients treated as of February 2001 (*Personal Communication*). The fractionation schedule was two implants, one week apart, of three fractions each. The prescription dose per fraction was either 6.75 or 7.0 Gy, delivered to a 4.5-6.0 mm margin beyond the prostatic capsule. Of 14 patients with at least a two-year follow-up, no biochemical failures have been observed. Patients achieved a mean and median PSA of 0.2 ng/ml. Morbidity was low with no grade 3 or 4 acute or late toxicity.

Conclusions

HDR brachytherapy was begun in the mid-1980s and has proceeded cautiously due to initial concerns over late effects. Today, maturing studies indicate that multi-fractionated HDR ^{192}Ir brachytherapy combined with moderate dose external beam radiotherapy is a well tolerated and effective treatment for localised prostate cancer.

Early reports also indicate that monotherapy HDR treatment of early prostate cancer is feasible. Though the adoption of HDR prostate brachytherapy has been slower than LDR seed implants it is now accelerating. Longer follow-up and comparative studies are needed to ascertain its position among the various definitive irradiation schemes for prostate cancer.

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