Chapter 6

Radiation Therapy for Prostate Cancer

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Additional information is available at the end of the chapter

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1. Introduction

Public concern on the radiation therapy for prostate cancer has increased recently. The leading causes of this phenomenon are thought of as popularization of prostate-specific antigen (PSA) measurement and having been able to tell the curable patients apart by means of the accomplished risk classifications. Massive development of radiation therapy technology also seems to be one of the leading causes. This chapter focuses on the variety of curative radiation therapy for clinically localized prostate cancer.

2. External beam radiation therapy

2.1. Conventional External Beam Radiation Therapy (EBRT)

In the 1970s, the treatment field size and portal configuration for radiation therapy were based on estimations of the anatomic boundaries of the prostate defined by plain-film radiography and by the digital rectal examination. At that time, a variety of treatment techniques were used. In general, four fields were used to treat the pelvis and prostate to an initial dose of 45 Gy, with a boost to 70 Gy to the prostate only [1, 2]. Early conventional external beam radiation therapy used total doses in the range of 60 to 70 Gy, because it was believed that this dose was close to the maximum dose allowed by the surrounding normal tissues, especially rectum. Today, it is obvious that this dose is not sufficient to get an adequate local control rate.

2.2. Three-Dimensional Conformal Radiation Therapy (3D-CRT)

In the early to mid-1908s, three-dimensional conformal treatment techniques became increasingly available. Although these techniques vary in some aspects, they share certain

common principles that offer significant advantages over conventional external beam radiation therapy techniques. CT-based images referenced to a reproducible patient position are used to localize the prostate and normal organs and to generate high resolution 3D reconstructions of the patient. Treatment field directions are selected using beam`s-eye-view techniques and the fields are shaped to conform to the patient`s CT-defined target volume, thereby minimizing the volume of normal tissue irradiated. Compared with treating a patient by conventional external beam radiation therapy technique, 3D-CRT is associated with a nearly 30% reduction in the dose received by 50% of the rectum. Based on this kind of analysis, it greater than or equal to 10% should be possible without an increase in acute or chronic toxicity [3].

2.3. Intensity Modulated Radiation Therapy (IMRT)

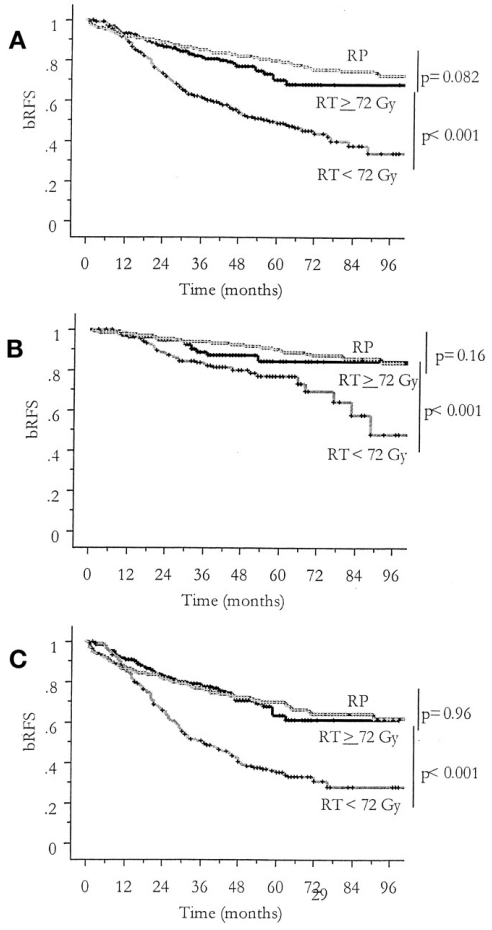
IMRT is a relatively recent refinement of three-dimensional conformal techniques that uses treatment fields with highly irregular radiation intensity patterns to deliver exquisitely conformal radiation distributions. These intensity patterns are created using special inverse and optimization computer planning systems. Rather than define each shape and weight as is done in conventional treatment planning, planners of IMRT treatment specify the desired dose to the target and normal tissues using mathematical descriptions referred to as constraints or objectives [4]. Sophisticated optimization methods are then used to determine the intensity pattern for each treatment field that results in a dose distribution as close to the user-defined constraints as possible. IMRT delivery is significantly more complex than conformal delivery as well. Delivery of an IMRT intensity pattern requires a computer-controlled beam-shaping apparatus on the linear accelerator known as a multi-leaf collimator (MLC). The MLC consists of many small individually moving leaves or fingers that can create arbitrary beam shapes. The MLC is used for IMRT delivery in either a static mode referred to as step and shoot, which consists of multiple small, irregularly shaped fields delivered in sequence, or a dynamic mode with the leaves moving during treatment to create the required irregular intensity patterns [5]. Since its inception, IMRT has become a common and important method for treating prostate cancer and has facilitated an escalation in dose.

2.4. Clinical results of EBRT

2.4.1. Clinical results of conventional EBRT

The results of several large single-institution comparison between radical prostatectomy (RP) and EBRT were reported.

Investigators from Cleveland Clinic Foundation, USA analyzed 1,682 patients with clinical stage T1 and T2 disease treated with either RP or RT. They reported that the 8-year biochemical relapse free survival (bRFS) rates for RP and conventional EBRT less than 72 Gy were 72% and 34%, respectively, and conventional EBRT less than 72 Gy was inferior to RP in the 8-year bRFS rate (Fig 1)[6].



(Cited from Kupelian PA et al.[5])

Figure 1. Biochemical relapse-free survival by treatment modality: RT to doses < 72 Gy, RT to doses > or = 72 Gy, and RP for all (A), favorable (B), and unfavorable patients(C).

D'Amico et al. reported a retrospective cohort study of 2635 patients with either RP or RT of median dose to 70.4 Gy (95% CI, 69.3-70.4 Gy) [7]. Eight-year bRFS rates for low-risk (T1c, T2a, PSA < or = 10 ng/ml, and Gleason score (GS) < or = 6) patients were 88% and 78% for RP and RT, respectively. Eight-year bRFS rates for intermediate-risk (T2b or GS 7 or PSA > 10 and < or = 20 ng/ml) patients with < 34% positive prostate biopsies were 79% and 65% for PR and RT, respectively. Eight-year bRFS rates were 36% versus 35% for intermediate-risk patients with at least 34% positive prostate biopsies and 33% versus 40% for high-risk (T2c or PSA > 20ng/ml or GS > or = 8) patients treated with RP versus those treated with RT, respectively. In conclusion, in their retrospective cohort study, intermediate-risk and low-risk patients with a

low biopsy tumor volume who were treated with RP appeared to fare significantly better compared with patients who were treated using conventional-dose RT. For the meanwhile, Intermediate-risk and high-risk patients with a high biopsy tumor volume who were treated with RP or RT had long-term estimates of bRFS that were not found to be significantly different.

2.4.2. Clinical results of 3D-CRT

Above-mentioned investigators from Cleveland Clinic Foundation reported that 3D-CRT more than 72 Gy was superior to Conventional EBRT less than 72 Gy and very similar to RP in the 8-year bRFS (6). Eight-year bRFS rate were 86% versus 86% ($p = 0.16$) for favorable-risk (T1 to T2a, GS < or = 6, PSA < or = 10 ng/ml) patients and 62% versus 61% ($p = 0.96$) for unfavorable-risk (T2b to T2c, GS > or = 7, PSA > 10 ng/ml) patients with RP versus those treated with RT > or = 72 Gy (Fig 1). Several study also have demonstrated that doses in excess of 70 to 72 Gy are associated with a reduction in the risk of recurrence compared with lower doses [8-12].

2.4.3. Clinical results of IMRT

Investigators from Memorial Sloan Kettering Cancer Center (MSKCC) reported their experience in 1002 patients treated with IMRT of 86.4 Gy [13]. They reported 7-year bRFS rates for low, intermediate, and unfavorable risk group patients as 98.8%, 85.6%, and 67.9%, respectively. In this report, they concluded that high dose IMRT to 86.4 Gy for localized prostate cancer resulted in excellent clinical outcomes with acceptable toxicity.

2.4.4. Clinical results of combined with Androgen Deprivation Therapy (ADT) and EBRT

Thus far, there have been five phase III randomized controlled trials for high-risk prostate cancer that compared radiotherapy alone with radiotherapy and ADT [14-18]. In all of these trials, ADT improved bRFS. In three of these four trials, ADT improved both overall survival (OS) and cause-specific survival (CSS).

From above-mentioned results, combining ADT with radiotherapy should be recommended in the high-risk group.

For intermediate-risk prostate cancer, two studies were published. Investigators from Brigham and Women's Hospital reported their randomized trial that consisted of 206 patients [19]. Two months each of total androgen blockade given before, during, and after radiotherapy for a total of 6 months. After a median follow-up of 4.52 years, ADT had improved 5-year bRFS, CSS, and OS. The Trans-Tasman Radiation Oncology Group (TROG) 96.01 study consisted of 802 patients, who were randomized to radiotherapy alone, 3 months, or 6 months of neoadjuvant hormones with radiotherapy. Five-year bRFS was significantly improved in the 3-month and 6-month arms as compared to the control arm. Although the 6-months arm showed significantly improved 5-year CSS, the 3-month arm was not significantly improved.

The thing to note is that these trials used doses less than 72 Gy that would be considered suboptimal by today's standard. Whether the benefit of ADT remains in the current era of dose escalation is currently unclear.

2.5. Acute and late adverse events

2.5.1. Acute and late adverse events of conventional EBRT

EBRT delivered with conventional techniques is fairly well tolerated, although grade 2 or higher acute rectal morbidity (discomfort, tenesmus, diarrhea) or urinary symptoms (frequency, nocturia, urgency, dysuria) requiring medication occur in approximately 60% of patients. Symptoms usually appear during the third week of treatment and resolve within days to weeks after treatment is completed. The incidence of late complications that develop > or = 6 months after completion of treatment is significantly lower, whereas serious complications that require corrective surgical intervention are rare. An analysis of 1,020 patients treated in two large Radiation Therapy Oncology Group (RTOG) trials 7506 and 7706 demonstrated an incidence of chronic urinary sequelae, such as cystitis, hematuria, urethral stricture, or bladder contracture, requiring hospitalization in 7.7% of cases, but the incidence of urinary toxicities requiring major surgical interventions such as laparotomy, cystectomy, or prolonged hospitalization was only 0.5% [20]. More than half of chronic urinary complications were urethral strictures, occurring mostly in patients who had undergone a previous transurethral resection of the prostate (TURP). The incidence of chronic intestinal sequelae, such as chronic diarrhea, proctitis, rectal and anal stricture, rectal bleeding or ulcer, requiring hospitalization for diagnosis and minor intervention was 3.3%, with 0.6% of patients experiencing bowel obstruction or perforation. Fatal complications were rare (0.2%). Most complications attributed to radiation therapy are observed within the first 3 to 4 years after treatment, and the likelihood of complications developing after 5 years in low. The risk of complications is increased when radiation doses exceed 70 Gy. The risk of rectal toxicity has been correlated with the volume of the anterior wall exposed to the higher doses of irradiation

2.5.2. Acute and late adverse events of CRT

Michalski et al. reported the toxicity outcomes of Stages T1-T2 prostate cancer in RTOG 9406, a phase I-II dose escalation study [21]. Two hundred twenty five patients were treated to 78 Gy (2 Gy fractions). The median follow-up was 2.2 years. Only 3% of patients had grade 3 acute toxicity. No grade 4 or 5 acute toxicity was reported. The late grade 2 and 3 bowel toxicity rates were 18% and 2%, respectively. 2 had grade 4 bowel toxicity. The late grade 2 and 3 bladder toxicity rates were 17% and 4%, respectively. No grade 4 or 5 late bladder toxicity was reported.

Zietman et al. reported acute and late genitourinary (GU) and gastrointestinal (GI) toxicity among patients treated on a randomized controlled trial [22]. The median follow-up was 5.5 years. The acute GU grade 3 toxicity for both the 70.2 Gy (1.8 Gy fractions) and 79.2 Gy dose arms in 2 Gy per fraction were 1%. The acute GI grade 3 toxicity for the 70.2 Gy and 79.2 Gy dose arms were 1% and 0%, respectively. The late GU grade 2 and 3 toxicity were 18% and 2%, respectively, for the 70.2 Gy dose arm, and 20% and 1%, respectively, for the 79.2 Gy dose arm (difference not significant between two arms). The late GI grade 2 for the 70.2 Gy and 79.2 Gy arms were 8% and 17%, respectively ($p = 0.005$). The late GI grade 3 toxicity, however, was 1% for both arms.

Zelefsky et al. reported the long-term tolerance of high-dose 3D-CRT at MSKCC [23]. The 5-year actuarial rate of grade 2 rectal toxicity for patients receiving 64.8 to 70.2 Gy was 7%,

compared with 16% for those treated to 75.6 Gy and 15% for those who treated to 81 Gy (70.2 vs. 75.6 or 81 Gy, p <0.001). The 5-year actuarial rate of grade 3 or higher rectal toxicity was 0.85%, and no correlation between dose and the development of grade 3 complications was found within the range of 64.8 to 81 Gy. Multivariable analysis demonstrated the following variables as predictors of late grade 2 or higher GI toxicity: prescription doses >75.6 Gy ($p < 0.001$), history of diabetes mellitus ($p = 0.01$), and the presence of acute GI symptoms during treatment ($p = 0.02$). The 5-year actuarial likelihood of Grade 2 or higher late GU toxicity for patients who receiving 75.6 to 81 Gy was 15%, compared with 8% for those treated to 64.8 to 70.2 Gy ($p = 0.008$). The 5-year actuarial likelihood of the development of a urethral stricture (Grade 3 toxicity) for patients who had a prior TURP was 4%, compared with 1% for those who did not have a prior TURP ($p = 0.03$). No correlation was observed between higher radiation doses and the development of a urethral stricture. Multivariable analysis demonstrated the following variables as predictors of late Grade 2 or higher GU toxicity: prescription doses >75.6 Gy ($p = 0.008$) and the presence of acute GU symptoms during treatment ($p <0.001$).

Peeters et al. reported on the incidence of acute and late complications in a multicenter randomized trial comparing 68 Gy to 78 Gy 3D-CRT [24]. The median follow-up was 31 months. For acute toxicity, no significant differences were seen between the two arms. GI toxicity Grade 2 and 3 was reported as the maximum acute toxicity in 44% and 5%, respectively. For acute GU toxicity, these figures were 41% and 13%. The 3-year in incidence of grade 2 and higher GI and GU toxicities for the 68 Gy dose arm was 23.2% and 28.5%, respectively. The 3-year incidence of grade 2 and higher GI and GU toxicities for the 78 Gy dose arm was 26.5% and 30.2%, respectively. The differences were not significant. However, the authors did note a significant increase in grade 3 rectal bleeding at 3 years was 10% for the 78 Gy arm, compared to 2% for the 68 Gy arm ($p = 0.007$), and in nocturia ($p = 0.05$). The factors related to acute GI toxicity were hormone therapy (HT) ($p < 0.001$), a higher dose-volume group ($p = 0.01$), and pretreatment GI symptoms ($p = 0.04$). For acute GU toxicity, prognostic factors were: pretreatment GU symptoms ($p < 0.001$), ADT ($p = 0.003$), and prior TURP ($p = 0.02$). The following variables were found to be predictive of late GI toxicity: a history of abdominal surgery ($p <0.001$), and the presence of pretreatment GI symptoms ($p = 0.001$). The following variables were predictive of late GU toxicity: pretreatment urinary symptoms ($p <0.001$), the use of neoadjuvant ADT ($p <0.001$), and prior TURP ($p = 0.006$).

Sabdhu et al. reported that urethral strictures for 1,100 patients treated with 3D-CRT [25]. The 5-year actuarial likelihood of developing urethral stricture was 4% for 120 patients with a prior history or TURP compared to 1% for 980 patients with no history of TURP ($p = 0.01$). Other late urinary toxicities were not observed among patients with a prior history of a TURP. Lee et al. observed a 2% incontinence rate among patients with a prior history of TURP who were treated with EBRT compared with a 0.2% rate in patients without a prior TURP[26].

2.5.3. Acute and late adverse events of IMRT

In an attempt to improve further the conformality of the high-dose therapy plans and decrease the rate of grade 2 and higher toxicity, an IMRT approach was introduced for the treatment of clinically localized disease.

Zelefsky et al. reported their experience in 1571 patients treated with 3D-CRT or IMRT with dose raging from 66 to 81 Gy [27]. The median follow-up was 10 years. In this experience, IMRT significantly reduced the risk of grade 2 and higher late GI toxicities compared with conventional 3D-CRT (5% vs. 13%, $p < 0.001$), although IMRT delivered higher dose than 3D-CRT. However, IMRT increased the risk of acute and late grade 2 and higher GU toxicities and acute grade 2 and higher GI toxicities compared with conventional 3D-CRT (37% vs. 22%, $p = 0.001$, 20% vs. 12%, $p = 0.01$, and 3% vs. 1%, $p = 0.04$, respectively).

According to the latest report from MSKCC, actuarial 7-year grade 2 or higher late GI and GU toxicities with the use of IMRT to 86.4 Gy were 4.4% and 21.1%, respectively. Late grade 3 GI and GU toxicities were 0.7% and 2.2%, respectively [13].

Mamgani et al. compared the toxicity of 41 prostate cancer patients treated with IMRT to 78 Gy with that of 37 patients treated with the 3D-CRT approach at the same dose level within the Dutch dose-escalation trial [28]. They reported that IMRT significantly reduced the incidence of acute grade 2 or higher GI toxicity compared with 3D-CRT (20% vs. 61%, $p = 0.001$). For acute GU toxicity and late GI and GU toxicities, the incidence was lower after IMRT, although these differences were not statistically significant (53% vs. 69%, $p = 0.3$, 21% vs. 37%, $p = 0.16$, and 43% vs. 45%, $p = 1.0$, respectively).

3. Low-Dose-Rate (LDR) brachytherapy (Permanent implants)

3.1. Introduction to permanent implants

Interstitial prostate brachytherapy was first performed by Barringer in 1915 [29-31]. Its first widespread adoption occurred in the 1970s, when the retropubic method was popularized [32]. A laparotomy was done for lymph node dissection and exposure of the prostate. Iodine-125 sources were implanted under direct visualization. The procedure was technically difficult to perform, in part because of limited working space in the pelvis. As a result, retropubic implantation lost popularity in the 1980s [33]. Instead, ultrasound-guided permanent prostatic implantation emerged in the early 1980s and has spread all over the world. The ultrasound-guided transperineal technique was initially described by Holm and coworkers in 1983 [34]. Transrectal ultrasound (TRUS) allowed visualization of the needle location within the prostate, facilitating real-time read-justments of needle position as necessary. Implants could be computer preplanned using transverse ultrasound images. Transperineal implants also could be done percutaneously on an outpatient basis, without laparotomy. Combined with modern, computer-based treatment planning, technological advances allowed for higher quality outpatient prostate brachytherapy [35].

Brachytherapy offers substantial biologic advantages over EBRT in terms of dose localization and higher biologic doses. A modification of the time, dose, and fractionation tables has been made to allow interconvertability between beam radiation and low-dose-rate brachytherapy [36]. There are also substantial practical advantages of brachytherapy, including vastly shorter treatment times and lower costs. These practical advantages have helped maintain widespread

interest in brachytherapy, despite continuous improvements in beam radiation. Although enthusiasm remains high in some quarters, there are still vexing discrepancies in reported cure rates and morbidities. It is becoming clearer that such discrepancies result partly from different technical expertise and patient management policies [37]. Brachytherapy, like surgery, is operator-dependent and outcomes vary with skill and experience.

3.2. Patient selection

Contraindications to brachytherapy include metastatic disease (including lymph node involvement), gross seminal vesicle involvement because that radioactive seeds are unlikely to be capable of sterilizing more than the most proximal 1 cm of seminal vesicle tissue, or large T3 disease that cannot be adequately implanted because of geometrical impediments to adequate tumor mass implantation (an unusual presentation).

Large prostate size can be often contraindication to brachytherapy because that the anterior and lateral portion of the gland may be inadequately covered because of pubic arch interference of needle placement. When a patient has a prostate > 60 cc, and pubic arch interference is a concern, a short course of ADT will reduce prostate volume by an average of approximately 30% in 3-4 months [38, 39]

Patients with a high International Prostate Symptom Score (IPSS) for urinary irritative and obstructive symptoms are at increased risk of developing postimplant urinary retention [40-43]. Terk et al. [44] and Gutman et al. [45] reported that patients with IPSS had a high risk of urinary retention.

Patients with prior pelvic radiotherapy may be at increased risk of developing late GI or GU toxicity. In such patients, the dose delivered to the prostate, rectum, and bladder should be considered.

In patients with prior TURP, a large TURP defect may disturb implantation of seed throughout the entire gland, resulting in unacceptable dosimetry.

Early-stage prostate cancer with T < or = 2a, initial PSA < or = 10ng/ml, and GS < or = 6 is suitable for brachytherapy without supplemental EBRT. Meanwhile, the generally accepted policy has been to add EBRT for the prostate cancer with T > 2a, initial PSA > 10ng/ml, or GS > 6. However, patients with intermediate-risk disease (T = 2b, GS = 7, or PSA > 10 and < or = 20 ng/ml) represent a heterogeneous patient population some of whom may benefit from monotherapy. Some investigators reported their experiences to perform monotherapy for patients with intermediate- and high-risk disease [46 – 51].

3.3. Treatment techniques

3.3.1. Preplanned transperineal implantation techniques

First of all, TRUS imaging is obtained before planned procedure to assess the prostate volume. A computerized plan is generated from the ultrasound images, producing isodose distributions and the ideal location of seeds within the gland to deliver the prescription dose to the

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prostate. Several days to weeks later, the implantation procedure is performed. Needles are then placed under ultrasonographic guidance through a perineal template according to the coordinates determined by the preplan. Radioactive seeds are individually deposited in the needle with the aid of an applicator or with preloaded seeds on a semirigid strand containing the preplanned number of seeds. In the latter case, this is accomplished by stabilizing the needle obturator that holds the seed column in a fixed position while the needle is withdrawn slowly, depositing a row or series of seeds within the gland.

In general most brachytherapists use a modified peripheral loading technique for permanent interstitial implantation. This approach can reduce the urethral doses more than a homogenous loading technique. The portion of the urethra receiving 150% dose (UV_{150}) should be limited [52]. Likewise, the volume of the rectum (RV_{100}) receiving the prescription dose ideally should be < 1 cc [53].

3.3.2. Intraoperative planning techniques

Intraoperative planning takes advantage of the opportunity of using real-time measurements of the prostate during the procedure while preplanning is often preformed several weeks before implantation, frequently under different conditions than the actual operative procedure. Subtle changes in the position of the ultrasound probe as well as the distortion of the prostate associated with needle placement and subsequent edema can result in profound changes in the shape of the gland compared with the preplanned prostatic contour.

3.4. Dose selection

Numerous studies have confirmed D_{90} (the minimum dose received by 90% of the prostate volume) and V_{100} (percentage of the prostate volume receiving 100% of the prescribed dose) are correlated with outcome [54-56].

Prescription doses for I-125 or palladium-103 (^{103}Pd) are typically 140 to 160 Gy or 110 to 130 Gy, respectively. In practice, many brachytherapists plan a dose higher than the above mentioned doses to compensate for edema, seed misplacement, and so on. Merrick et al. [57] examined variability in permanent prostate brachytherapy preimplant dosimetry among eight experienced brachytherapy teams. A range of D_{90} values from 112% to 151% of the prescription dose was planned. Several investigations suggest that an acceptable dose range for postimplant D_{90} for I-125 may be 130 to 180 Gy as long as normal structures are not overdosed. Zelefsky et al. [58] reported that D_{90} < 130 Gy was associated with and increased risk of failure. Meanwhile, Gomez-Iturriaga Pina et al. [59] reported that D_{90} from 180 Gy to 200 Gy was associated with excellent biochemical disease-free survival and acceptable toxicity.

When combined EBRT and brachytherapy, a wide variety of implant and beam radiation dose combinations are used. Implant prescription doses area generally dropped to approximately 70% to 80% of monotherapy doses, ranging from 110 to 120 Gy with I-125 and 90 to 100 Gy with Pd-103. External beam doses of 40 to 50 Gy area typically used. No studies have investigated either the sequencing of EBRT and brachytherapy, or the time interval between the two.

A wide variety of seed activities, seed numbers, or total activities have been used because of no clinical evidence of any effect outcome. Seed activities typically vary from 0.3 to 0.6 mCi for I-125 and 1.2 to 2.2 mCi for Pd-103.

3.5. Clinical results

3.5.1. Clinical results of LDR brachytherapy as monotherapy

It is generally accepted that patients with low-risk disease are excellent candidate for LDR monotherapy. There is no randomized data comparing therapeutic outcomes between LDR monotherapy, surgery, and EBRT. However, multiple reports of low-risk patients treated with LDR monotherapy have demonstrated excellent long-term biochemical control rates of 80 – 95% (Table 1).

Patients with intermediate-risk disease represent a heterogeneous patient population. Some of them seem to benefit from LDR monotherapy, whereas others may require combined modality approaches with EBRT and/or ADT. D'Amico et al [65] reported that percentage of positive prostate biopsy cores is a predicting factor of biochemical outcome following EBRT, particularly for intermediate-risk patients. In their report, patients with > 50% of biopsy cores positive had PSA relapse rates comparable to those of high-risk patients, whereas patients with < 34% of biopsy cores positive had favorable biochemical outcomes similar to those of low risk patients. Long-term biochemical control rate for intermediate-risk patients treated with LDR monotherapy is also favorable, ranging from 70% to 90% (Table 1).

Authors	N	Mean/Median Follow-up	Adjuvant Hormone Therapy	bRFS rate		
				Low-risk	Intermediate-risk	High-risk
Sylvester et al [60]	215	11.7 years	NO	15-year		
				85.90%	79.90%	62.20%
Prade et al [61]	734	55 months	YES	10-year		
				92.00%	84%	65%
Henry et al [62]	1298	4.9 years	YES	10-year		
				86.40%	76.70%	60.60%
Zelefsky et al [63]	2693	63 months	NO	8-year		
				82%	70%	48%
Zelefsky et al [64]	367	63 months	YES	5-year		
				96%	89%	-

Table 1. LDR brachytherapy as monotherapy

For patients with high-risk disease, the use of supplemental beam radiation to cover the periprostatic prostate tissue has been widely practiced. However, LDR monotherapy has been good results comparable to combination of monotherapy and EBRT even in patients with high-risk disease.

3.5.2. Clinical results of combination of LDR brachytherapy and EBRT

Outcomes (bRFS rates) for a combination of LDR brachytherapy and EBRT are shown in Table 2.

Authors	N	Mean/Median Follow-up	Adjuvant Hormone Therapy	bRFS rate		
				Low-risk	Intermediate-risk	High-risk
Critz et al [66]	1469	6 years	NO		10-year	
				93%	80%	61%
Merrick et al [67]	204	7 years	YES		10-year	
						86.60%
Sylvester et al [68]	223	9.43 years	NO		15-year	
				85.60%	80.30%	67.80%
Stock et al [69]	181	65 months	YES		8-year	
						73%
Wernicke et al [70]	242	10 years	NO		10-year	
					77.30%	-

Table 2. Combination of LDR brachytherapy and EBRT

3.6. Acute and late adverse events of LDR brachytherapy

3.6.1. Urinary toxicity

Almost all patients after LDR brachytherapy develop some kind of acute urinary symptoms, for example, urinary frequency, urgency, and occasional urge incontinence. These symptoms often peak at about 3 months after brachytherapy, subsequently gradually decline over the ensuing 3 to 6 months, and resolve with in 1 year (71). Most patients benefit with the use of an

α-blocker. However, Brown et al [71] reported that 22% of patients experienced persistent urinary symptoms even after 12 months.

Acute urinary retention (AUR) is a common complication of modern brachytherapy, but can occur immediately after LDR brachytherapy. Crook et al. [72] demonstrated on the basis of a multivariate analysis that larger prostate volumes and prior hormone therapy were each independent predictors of AUR. AUR should be managed by intermittent or continuous bladder drainage. If AUR persists more than a few days, clean intermittent self-catheterization is preferred to continuous drainage by a Foley catheter. The use of transurethral incision of prostate should be avoided in the first 6 months, but if retention persists, transurethral incision of prostate or minimal TURP may be considered, recognizing the risk of urinary incontinence after these procedures [73-75].

3.6.2. Rectal toxicity

Grade 2 rectal toxicity symptoms, which manifest as rectal bleeding or increased mucous discharge, occur in 2 to 10% of patients, nearly always manifests between 6 and 18 months of implantation [76]. It is partly related to rectal dose and its volume exposed to a particular dose. The incidence of grade 3 or 4 rectal toxicity, which symptoms manifest rectal ulceration or fistula, is unusual (< 1.0%), providing that the volume of rectal wall receiving the prescription dose is kept below 0.5 cc on day 0 or 1 cc on day 30 dosimetry [77]. Most cases of rectal bleeding do not progress to rectal ulceration or fistula and are self-limited in nature. However, healing is typically slow. With the ineffectiveness of medical therapies, more invasive therapies with argon plasma coagulation or topical formalin have been highly effective therapy for rectal bleeding [78]. Invasive therapies, however, might exacerbate radiation damage, so they should be undertaken with caution. Rectal wall biopsy in the course of evaluation for rectal toxicity should avoid as much as possible because it may result in the development of rectal ulceration or fistula.

3.6.3. Sexual dysfunction

Erectile impotence occurs from 20% to 80% after implantation. According to Zelefsky et al [79], whereas the incidence of impotence at 2 years after implantation was 21%, the rate increased to 42% at 5 years after. Merrick et al. [80] reported that there is a strong correlation between radiation-induced impotence and the dose to the penile bulb and proximal penis. They recommend that with day 0 dosimetric evaluation, the minimum dose delivered to 50% and 25% of the bulb should be maintained below 40% and 60% of prescribed minimum peripheral dose, respectively, whereas the minimum dose delivered to 50% and 25% of the crura should be maintained below 40% and 28% of prescribed minimum peripheral dose, respectively, to maximize posttreatment potency.

Several reports suggest that sildenafil citrate have good response to impotence after implantation[81, 82]. Potters et al. [83] reported that the addition of neoadjuvant androgen deprivation had a significant impact on the potency preservation rate after implantation.

The response to sildenafil was significantly better in those patients not treated with neo-adjuvant ADT.

4. High-Dose-Rate (HDR) brachytherapy (Temporary implants)

4.1. Introduction to HDR brachytherapy

HDR brachytherapy has been used as the brachytherapy component in combination with EBRT for the treatment of prostate cancer [84-90]. In general, for this approach patients undergo transperineal placement of afterloading catheters in the prostate under ultrasonographic guidance. After CT-based treatment planning, several high-dose fractions are administered during an interval of 24 to 36 hours using ^{192}Ir. This treatment is followed by supplemental EBRT directed to the prostate and periprostatic tissues to a dose of 40 to 50.4 Gy using conventional fractionation. Recently, dose-escalation studies have been implemented to increase gradually the dose per fraction delivered with the HDR boost [91]. Improved outcomes with higher HDR boost doses were observed compared with outcomes achieved using lower dose level. Single higher dose fraction also becomes used for dealing with the issue of needle displacement between each fraction [92]. More recently, several institutes have used HDR brachytherapy as monotherapy without the addition of EBRT, largely for low-risk, but also for intermediate- and high-risk patients [93-99].

HDR brachytherapy offers several potential advantages over other techniques. Taking advantage of an afterloading approach, the radiation oncologist and physicist can more easily optimize the delivery of radiation therapy to the prostate and compensate for potential regions of underdosage that may be present with permanent interstitial implantation. Further, this technique reduces involved in the procedure compared with permanent interstitial implantation. Finally, HDR brachytherapy boosts may be radiobiologically more efficacious in terms of tumor cell kill for patients with increased tumor bulk or adverse prognostic features compared with low-dose-rate boost such as ^{125}I or ^{103}Pd.

4.2. Clinical results of HDR brachytherapy

The reported outcomes of combination of HDR brachytherapy and EBRT are favorable (Table 3). Multiple reports of low- and intermediate-risk patients treated with combination of HDR brachytherapy and EBRT have demonstrated excellent long-term biochemical control rates of 90-100% and 87-98%, respectively (Table 3). Long-term biochemical control rate for high-risk patients treated with combination of HDR brachytherapy and EBRT is also favorable.

Yoshioka et al. [99] have performed HDR brachytherapy as monotherapy for localized prostate cancer since 1996. The 5-year bRFS rate for low-, intermediate-, and high-risk patients was 85%, 93%, and 79%, respectively.

Authors	N	Mean/Median Follow-up	HDR dose	bRFS rate		
				Low-risk	Intermediate-risk	High-risk
			Boost			
Astrom et al. [100]	214	4 years	10 Gy x 2		5-year	
				92%	88%	61%
Bachand et al. [101]	153	44 months	9 Gy x 2/ 10 Gy x 2		5-year	
					95.9%	95.5%
Chen et al. [84]	85	40 months	5.5 Gy x 3		4-year	
				100%	91%	81%
Demanes et al. [85]	209	6.4 years	5.5 Gy x 4/ 6.0 Gy x 4		10-year	
				92%	87%	63%
Yamada et a.l [86]	105	44 months	5.5 Gy x 3/ 7.0 Gy x 3		5-year	
				100%	98%	92%
Phan et al. [89]	309	59 months	6 Gy x 4		5-year	
				98%	90%	78%
Prada et al. [102]	313	71 months	11.5 Gy x 2		10-year	
				100%	91%/88%	79%
			Monotherapy			
Yoshioka et al. [99]	112	5.4 years	6 Gy x 9		5-year	
				85%	93%	79%
Rogers CL et al. [103]	284	35.1 months	6.5 Gy x 6		5-year	
					94.40%	

Table 3. HDR brachytherapy

4.3. Acute and late adverse events of HDR brachytherapy

4.3.1. Urinary toxicity

Acute urinary symptoms such as urinary urgency and frequency are common and usually resolve within a few months. Urinary retention occurs in less than 5% of patients treated with combination of HDR brachytherapy and EBRT [89, 94, 104, 105]. Urinary strictures are reported in up to 15% of patients, and most commonly seen in the bulbomembranous urethra [106, 107]. Urinary incontinence is extremely rare, and seen in less than 2% of patients [107, 108].

4.3.2. Rectal toxicity

Transient rectal symptoms such as rectal urgency or frequency often occur. Late rectal bleeding may occur and is usually not clinically significant. Rectal fistula is extremely rare, and seen in less than 1% of patients[89].

4.3.3. Sexual toxicity

Erectile dysfunction has been reported in up to 40% of patients, but approximately 80% will respond to phosphodiesterase-5 inhibitors (86).

5. Particle beam radiation therapy

Particle beam radiation therapy is the cancer therapy to deliver the ions accelerated by means of a cyclotron or synchrotron. Nowadays, protons and carbon ions (heavy particles) are in clinical use.

For protons and heavy particles, unlike electrons or X-rays, the dose increases while the particle penetrates the tissue and loses energy continuously. Hence the dose increases with increasing thickness up to the Bragg peak that occurs near the end of the particle's range. Beyond the Bragg peak, the dose drops to zero (for protons) or almost zero (for heavy particles). The advantage of this energy deposition profile is that less energy is deposited into the healthy tissue surrounding the target tissue.

Although proton beams have approximately the same biological effectiveness as X-rays or electrons, carbon ions have 1.2 to 3.5 times as much effectiveness as X-rays. Carbon ions many other biological features, which X-rays don`t have, as follows; 1) having their reduced ability to repair damage DNA, 2) having smaller oxygen enhancement ratio, 3) effectiveness even against the hypoxic cancer cells, 4) effectiveness even against S-late phase cancer cells because of their being less of cell cycle dependence.

Investigators from National Institute of Radiological Sciences, Japan reported their experience in 927 patients treated with hypofractionated conformal carbon-ion radiation therapy between April 2000 and December 2010 [109]. Of 927 patients, 250, 216, and 461 patients were treated with 66 GyE (Gray equivalent (a measure of carbon-ion radiation dose base on an relative biological effectiveness (RBE) ratio of 3 with respect to photon radiation)) in 20 fractions (Fr), 63 GyE in 20 Fr, and 57.6 GyE in 16 Fr, respectively. Neoadjuvant ADT was given to the patients in the intermediate- and high-risk groups for 2 to 6 months. Adjuvant ADT was continued for a duration of 6 months for intermediate-risk patients and for 2 years for the high-risk patients. They reported the 5-year cause specific survival rates for the low-, intermediate-, and high-risk group patients as 100%, 100%, and 97.9%, respectively. The 5-year bRFS rates of the low-, intermediate-, and high-risk groups were 89.4%, 96.8%, and 88.4%, respectively. They reported that grade 2 rectal bleeding developed in 15 patients (1.6%), but no grade 3 or worse morbidities at the rectum were observed in all groups. They also reported that late grade 2 and grade 3 GU toxicities were observed in 57 (6.1%) and one (0.1%) of 927 patients, respectively. These

incidences of late morbidities, especially of rectal bleeding are favorable compared with other RT methods (Table. 4).

Authors	Method	Dose fractionation (Gy/Fr)	No. patients	Morbidity rate	
				GI	GU
Coote et al. [110]	IMRT	60.0/20	60	9.5%	4.0%
Martin et al. [111]	IMRT	60.0/20	92	6.3%	10.0%
Kupelian et al.[112]	IMRT	70.0/28	770	4.4%	5.2%
King et al. [113]	SRT	36.25/5	41	15.0%	29.0%
Madsen et al. [114]	SRT	33.5/5	40	7.5%	22.5%
Michalski JM et al. [115]	3DCRT	68.4-79.2/38-41	275	7-16%	18-29%
	3DCRT	78.0/39	118	25-26%	23-28%
Schulte RW [116]	Proton	75.0/39	901	3.5%	5.4%
Ishikawa et al. [109]	Carbon-ion	57.6-66.0/16-20	927	1.9%	6.3%

(Cited from Ishikawa et al [109])

Table 4. Comparison of Grade 2 or worse late morbidity rates according to RT method

6. Postoperative radiotherapy

6.1. Adjuvant radiotherapy (ART)

The results of three large phase III trials, which evaluated the merits of adjuvant versus expectant management in postoperative patients with positive surgical margins and/or pT3 disease, were reported.

EORTC 22911 confirmed the value of ART, which reduced the risk of biochemical failure and prolongs the time to clinical progression [117]. Patients eligible for this study had pT2-3N0M0 tumors and one or more pathologic risk factors (extracapsular extension (ECE), positive surgical margins (PSM), seminal vesicles invasion (SVI)). After a median follow-up of 5 years, biochemical and clinical progression-free survivals were significantly improved in the radiotherapy group ($P < 0.0001$ and $P = 0.0009$, respectively). The rate of local regional failure was also lower in the radiotherapy group ($P = 0.07$). Severe toxicity (grade 3 or higher) was similar, being 2.6% versus 4.2% at 5 years in the postoperative radiotherapy group ($P = 0.07$).

SWOG 8794 randomly assigned 473 node-negative patients initially treated with radical prostectomy, but found to have either PSM or pT3 (ECE and/or SVI) disease to ART or observation [118]. ART consisted of 60 to 64 Gy. ART resulted in an improvement in metastasis-free and overall survival compared with deferred therapy (HR 0.71; $P = 0.016$ and HR 0.72; $P = 0.023$, respectively). Although adverse effects were more common with radiotherapy versus

observation, by 5 years there were no differences in health-related QOL, and a subset analysis suggests that earlier treatment is better than delayed treatment [119].

From the German Cancer Society, ARO 96-02/AUO AP 09/95 randomized 385 patients with pT3 or PSM to either ART (60Gy in 2 Gy fractions) or observation [120]. Although this study had the short median follow-up of 40 months, ART significantly improved progression-free survival ($P < 0.0001$) with a low incidence of late complications from radiotherapy.

6.2. Salvage radiotherapy (SRT)

A multi-institutional study suggests that early intervention with radiotherapy is better than delayed intervention for patients with biochemical failure [121, 122]. This analysis included patients with pT3-4N0 disease who received either SRT or early ART. Early ART for pT3-4N0 disease significantly reduces the risk of long-term biochemical progression after radical prostatectomy compared with SRT.

Stephenson et al. [123] reported on the outcomes and prognostic factors of 501 men who had salvage radiotherapy after a biochemical recurrence. In the entire cohort, the 4-year progression-free survival (PFS) was 45%, and 67% attained a PSA nadir of <0.1 ng/mL. Multivariate analyses demonstrated that Gleason score of 8 to 10, preradiotherapy PSA >2 ng/mL, negative margins, PSA-doubling time <10 months, and seminal vesicle invasion were associated with PSA progression. Supporting earlier intervention, preradiotherapy PSA <0.6 ng/mL had significantly improved PFS than a PSA of 0.61 to 2 ng/mL ($P = 0.006$) and >2 ng/mL ($P = 0.001$).

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