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UROONCOLOGY

Review

Salvage therapies for radiorecurrent prostate cancer

Radiorekürren prostat kanseri için salvage terapiler

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ABSTRACT

Locally recurrent prostate cancer after radiation therapy, also known as radiorecurrent prostate cancer, has an unfavorable prognosis. Two-thirds of patients with radiorecurrent prostate cancer have an advanced pathological disease status by the time they undergo salvage therapy. Several salvage therapies for radiorecurrent prostate cancer are available. Salvage radical prostatectomy (SRP) and salvage cryoablation are the most feasible and effective therapies for radiorecurrent prostate cancer. Although SRP is technically more difficult and has a higher complication rate than do other salvage therapies, the procedure provides a long-term survival benefit. Preliminary studies of salvage robot-assisted radical prostatectomy (SRARP) suggest that SRARP may be similar to or at least as effective as SRP. The intermediate oncological efficacy and morbidity of salvage cryoablation are similar to those of SRP. Prognostic factors for successful salvage therapy include serum prostate-specific antigen level ≤10 ng/mL, Gleason score ≤8, and a clinical disease stage T1c or T2. Assessing the comparative oncological efficacy and complications of the available salvage therapies for radiorecurrent prostate cancer requires strict guidelines, including universal patient selection criteria and an intergrade definition of biochemical failure.

Key words: Prostate; prostate cancer; prostatectomy.

ÖZET

Radiorekürren prostat kanseri olarak da bilinen, radyasyon terapisi sonrası lokal rekürren prostat kanseri kötü prognoza sahiptir. Radiorekürren prostat kanserli hastaların üçte ikisinin, salvage terapi aldıkları sırada ileri patolojik evrede hastalıkları vardır. Radiorekürren prostat kanseri için birkaç salvage tedavi vardır. Salvage radikal prostatektomi (SRP) ve salvage kriyoablasyon, radiorekürren prostat kanseri için en uygulanabilir ve etkili tedavilerdir. SRP, öteki salvage terapilerden teknik olarak daha zor ve daha yüksek komplikasyon oranlarına sahip olsa da, uzun dönem sağkalım avantajı vardır. Salvage robot yardımlı radikal prostatektominin (SRARP) ilk sonuçları SRARP'nin en az SRP kadar veya benzer şekilde etkin olacağını göstermektedir. Salvage kriyoablasyonun orta dönem onkolojik etkinliği ve morbiditesi SRP'ninkine benzerdir. Başarılı salvage tedeavi için prognostik faktörler: prostat spesifik antijen seviyesi ≤10 ng/mL, a Gleason sckoru ≤8 ve T1c veya T2 klinik hastalık evresidir. Radiorekürrent prostat kanserinin mevcut salvage tedavilerinin karşılaştırmalı onkolojik etkinlik ve komplikasyonlarını değerlendirmek için evrensel hasta seçim kriterlerini içeren ve evreler arası biyokimyasal başarısızlık tanımını içeren katı kılavuzlara ihtiyaç vardır.

Anahtar sözcükler: Prostat; prostat kanseri; prostatektomi.

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Uncontrolled local disease is a significant risk factor for metastatic progression, cancer-specific mortality, and considerable morbidity. Biochemical recurrence (BCR) of prostate cancer occurs in 40-50% of patients who receive primary therapy with external beam radiation therapy or brachytherapy for localized disease.[1,2] Seventy-two percent of patients who have an increasing serum prostate-specific antigen (PSA) level and a negative metastatic evaluation after radiation therapy have local prostate cancer recurrence, as evidenced by positive rates of prostate biopsy.[3] Local salvage therapy, defined as further local treatment for clinically proven disease recurrence following initial local therapy, is the only approach that has curative potential in such patients. Salvage therapy is given in the context of a detectable PSA after initial surgery or a rising PSA profile after initial radiation therapy. No consensus on when and how to detect and cure radio recurrent prostate cancer exists, but strong evidence indicates that salvage therapies may improve survival rates in patients with prostate cancer.

Table 1. Findings of studies on salvage radical prostatectomy

Studies	Patients (n)	Follow-up (years)	BCR definition (PSA, ng/mL)	BDFS (%)	10-year CSS (%)
Pisters et al.[8]	42	7.8	≥0.4	61%	NR
Ward et al.[5]	138	7	≥0.4	58%	77%
Bianco et al.[4]	100	5	≥0.2	55%	73%
Amling et al.[6]	108	Ns	≥0.2	44%	70%

BCR: biochemical recurrence, BDFS: biochemical disease-free survival, CSS: cancer-specific survival, PSA: prostate-specific antigen, NR: not reported.

Table 2. Complications of salvage radical prostatectomy [n (%)]

	Studies (years)		
	Amling et al.[6] (1992-1996)	Stephenson et al.[9] (1993-2003)	Heidenreich et al.[11] (2004-2008)
Number of patients	60	60	55
Incontinence	30 (50%)	61%[a]	25 (45%)
Anastomotic stricture	16 (27%)	19 (32%)	6 (11%)
Blood transfusion	10 (17%)	17 (29%)	2 (4%)
Rectal injury	3 (5%)	1 (2%)	2 (4%)
Urinary fistula	0	1 (2%)	1 (2%)

[a]reported at 5-years and includes years 1984-2003.

Four whole-gland salvage therapies are available for radiorecurrent prostate cancer: salvage radical prostatectomy (SRP), salvage cryoablation (SCA), salvage brachytherapy (SBT), and salvage high-intensity focused ultrasound (SHIFU). Although these therapies offer benefit to patients with radiorecurrent prostate cancer, few oncologists are familiar with their applications and outcomes. Herein, we discuss the efficacy and safety of each approach.

Salvage radical prostatectomy

SRP is the most effective treatments for locally recurrent prostate cancer after initial radiation therapy. Of the available salvage therapies for radiorecurrent prostate cancer, only SRP results in cancer control for 10 years or more in a substantial proportion of patients.[4-7] Among reported patients who have undergone SRP for radiorecurrent prostate cancer, the 5-year biochemical disease-free survival (BDFS) rates are 55-61%, and the 10-year BDFS rate is 44% (Table 1).[4,6-8] The 10-year cancer-specific survival rate after SRP is 70-77% (Table 1). SRP also provides intermediate cancer control in patients at high-risk for disease progression. An estimated 51% of patients with radiorecurrent prostate cancer who have Gleason scores of 8-10 and/or rapid PSA doubling times are free of BCR at 5 years after SRP alone. Pisters et al.[8] performed a stratified control comparison of BDFS after SRP and SCA in patients with a presalvage PSA level <10 ng/mL and a Gleason score ≤8 who previously received radiation therapy alone without pre- or post-salvage hormonal treatment. They found that the 5-year BDFS rate of patients who underwent SRP (61%) was

Table 3. Salvage robotic-assisted radical prostatectomy series

	Studies				
	Kaouk et al.[16]	Eandi et al.[17]	Ahallal et al.[15]	Boris et al.[18]	MDACC
Patients (n)	4	18	15[a]	11	19
Age (year, mean)	NR	67	62.3	64.9	66
PSA (ng/mL, mean)	20	6.8	5.5	5.2	6.3
Gleason score (mean)	7.5	7.5	7	7	7
Patients with lymph node involvement (%)	0	6	6	18	19
Lymph node yield (n)	NR	NR	NR	5.6	10
Positive margins (%)	50	28	20	27.3	16.2
BCR rate	25	33	20	27	23
Stricture (n, %)	0	3 (18%)	0	1 (9%)	0
Continence (%)	75%	33%	46.7%	80%	62.5%
Rectal injury (n, %)	0	0	1 (7%)	0	1 (5%)
Hospitalization (days, mean)	2.7	2	2	1.4	3
Operative period (min, mean)	125	156	235	183	295
Follow-up (months, mean)	1	18	8	21	6

MDACC: MD Anderson Cancer Center, PSA: prostate-specific antigen, BCR: biochemical recurrence, NR: not reported.
[a]Only 4 patients underwent salvage robotic radical prostatectomy while the remaining 11 patients underwent laparoscopic salvage radical prostatectomy.

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Table 4. Series of salvage cryoablation

Studies	Patients (n)	Cryogen	Follow-up (months)	BDFS definition (PSA ng/mL)	BDFS (%)
Pisters et al.[25]	79	N	10	Phoenix	65
Chin et al.[35]	118	Ar	18.6	<0.5 <2 <4	34 55 68
Bahn et al.[27]	59	N	82	<0.5 <1	59 59
Katz et al.[34]	157	Ar	37	ASTRO criteria	73
Ismail et al.[36]	100	Ar	33.5	<0.5	73 low risk 45 intermediate risk 11 high risk
Donelly et al.[29]	46	Ar	20	<0.3 <1	44 59
Pisters et al.[22]	279	N+Ar	21.6	ASTRO criteria Phoenix criteria	59 55

BDFS: biochemical disease-free survival, PSA: prostate-specific antigen, ASTRO (American Society for Therapeutic Radiation and Oncology) criteria: three successive rises in PSA level above nadir, Phoenix criteria: the nadir PSA level plus 2 ng/mL, cryogen: N-liquid nitrogen, Ar-Argon.

Table 5. Oncological outcomes and complications of salvage brachytherapy

	Studies		
	Grado et al.[37]	Nguyen et al.[39]	Koutrouvelis et al.[38]
Patients (n)	49	25	31
Follow-up (months, mean)	64	47	30
BDFS [years, n (%)]	34 (5%)	70 (4%)	87 (5%)
Failure definition	Phoenix	Phoenix	ASTRO
Incontinence (%)	6	0	0
Patients with GU toxicity (%)			
Grade 1-2	12	NR	NR
Grade 3-4	14	16	NR
Patients with GI toxicity (%)			
Grade 1-2	4	NR	NR
Grade 3-4	2	24	5

BDFS: biochemical disease-free survival, ASRTO: American Society for Therapeutic Radiation and Oncology, GU: genitourinary, GI: gastrointestinal, NR: not reported.

significantly higher than that of patients who underwent SCA (21%, p<0.001). Pisters et al.[8] concluded that young patients with radiorecurrent prostate cancer should be considered for SRP because the surgery offers a superior BDFS benefit and offers the best chance for a cure. SCA may be considered in older patients who decline to undergo SRP.

The major complications of SRP are summarized in Table 2. Urinary incontinence occurs in 46-61% of patients, and 23% of these patients require an artificial sphincter.[9] Urethral stricture occurs in 11-32% of patients. A Memorial Sloan-Kettering Cancer Center series revealed that the rates of rectal injury and incontinence among patients with radiorecurrent prostate cancer who underwent SRP were 6% and 57%, respectively, before 1990 and 3% and 44%, respectively, from 1990 onward. However, that series also revealed that the rate of bladder neck contraction due to SRP increased from 14% in the years prior to 1990 to 26% from 1990 onward.[5] This increase in the rate of bladder neck contraction may be related, in part, to radiation-induced sphincter dysfunction, as continence rates have not risen markedly despite improved techniques for selecting patients, preventing pelvic fibrosis, and performing the surgery. Rectal injury and urinary fistula due to SRP are very uncommon, occurring in only 2-5% and about 2% of patients, respectively. Patients with a urinary fistula are at risk for deep venous thrombosis and should undergo routine thromboprophylaxis. Erectile dysfunction (ED) was previously thought to be an inevitable consequence of SRP; however, selecting patients with good preoperative erectile function who undergo SRP with cavernous nerve preservation and bilateral nerve sparing may recover erectile function.[10,11]

Twenty-five percent of surveyed urologists and radiation oncologists would recommend SRP to patients aged 45-65 years who have a definite local recurrence after radiotherapy.[10] Patients who develop BCR after radiation therapy typically do not undergo SRP; only 2% of men who develop BCR after radiation therapy undergo SRP, whereas 92% of these patients receive hormonal therapy, largely because of the historical impact of

SRP and the high surgical complication rate in this patient population.[10] A few centers have presented data on salvage laparoscopic and robotic radical prostatectomy, and the outcomes were comparable to those for open SRP. To our knowledge, only four studies have reported experience with conventional salvage laparoscopic radical prostatectomy.[12-15] The series included only 9, 9, 7, and 15 patients, respectively; nevertheless, patient functional and oncological outcomes were comparable to those in patients who underwent open SRP. Rectal injury occurred in only 1 patient, and no anastomosis strictures were observed. The four series reported BCR-free rates of 71%, 89%, 55%, and 73% at median follow-up times of 27, 12, 11, and 8 months, respectively.[12-15]

The promising outcomes reported for laparoscopic SRP encouraged surgeons to begin using salvage robot-assisted radical prostatectomy (SRARP) (Table 3).[16-18] Kaouk et al.[16] recounted their experience with SRARP in 4 patients, the first of such reports. Kaouk et al.[16] were unable to detect PSA levels following SRP throughout the follow-up period in all but one patient. Eandi et al.[17] have published the largest series of patients who underwent SRARP for radiorecurrent prostate cancer. Of the 18 patients included in that series, 12 (67%) did not develop BCR; of the 6 patients in whom BCR did develop, 2 had a preoperative PSA level >10 ng/mL, 2 had multifocal positive surgical margins, and 2 had unifocal margin involvement. Eandi et al.[17] also reported promising functional results, noting that 6 patients (33%) regained continence after SRP. Boris et al.[18] reported on 11 patients whose median follow-up time was 21 months. BCR was detected in just 3 patients, at 1, 2, and 43 months, respectively. Of the contemporary SRARP series authors, Boris et al.[18] reported the highest continence rate (80%), likely because they defined incontinent patients as those who used more than 1 pad daily. The preliminary report of the SRARP experience at MD Anderson Cancer Center is also encouraging. In the MD Anderson series, continent patients were defined as those who did not need pads, and the continence rate was 53%. Of the 5 series, 3 reported no urethrovesical strictures, and 2 reported stricture rates of 9% and 18%, respectively.[17,18] These series indicate that SRARP is feasible and safe in patients with locally recurrent prostate cancer after failure of radiation therapy and/or cryotherapy and suggest that the oncological and functional outcomes are comparable to those of open surgery. However, larger studies with longer follow-up periods are necessary to confirm these results.

Salvage cryoablation

SCA of the prostate gland for radiorecurrent prostate cancer is less invasive and may have less morbidity than does SRP. Because SCA is much less technically demanding than SRP, it is performed four times as often as SRP, which is performed at only a limited number of academic centers. However, both procedures are underutilized to treat patients with radio recurrent prostate cancer.[19,20] Recent improvements in SCA include advances in argon- and helium-based cytotechnology and the development of small-caliber cryoablation probes, pinpoint thermocouples, effective urethral warming devices, and software packages that facilitate optimal placement of cryoablation probes and thermocouples.[21]

Although no randomized SCA studies have been performed, single-center studies and pooled retrospective series demonstrate its effectiveness. The largest SCA multicenter series examined outcomes recorded in the Cryo On-Line Data Registry, a secure online database that tracks outcomes after cryoablation in academic and community settings.[22] Among the 279 patients with radiorecurrent prostate cancer who underwent SCA, the 5-year actuarial BCDF rates according to the American Society of Therapeutic Radiation Oncology (ASTRO) criteria (three successive rises in PSA level) and Phoenix criteria (the nadir PSA level plus 2 ng/dL) were 58.9% and 54.5%, respectively.[22] The outcomes reported in selected SCA series are summarized in Table 4. Patient PSA level, Gleason score, and androgen status before SCA convey prognostic information and have been associated with disease-free and disease-specific survival. A PSA doubling time of <16 months following radiation therapy may be associated with a higher risk of relapse.[23] No cut-off value exists for PSA doubling times after radiation therapy. Gleason score is highly prognostic of disease-specific survival following SCA. One study found that the 5-year disease-specific survival rates for patients with a Gleason score ≤8 before SCA and patients with Gleason score of 9 or 10 before SCA were 87% and 63%, respectively.[24] Patient androgen status also has profound prognostic value, particularly in patients who have androgen-independent disease progression (defined as a rising PSA profile despite radiation therapy and hormonal therapy and medical castration levels of testosterone). Izawa et al.[24] found that patients who had clinical stage T1 or T2 prostate cancer before radiation therapy had a significantly higher 5-year disease-specific survival rate than did patients who had clinical stage T3 or T4 prostate cancer before radiation therapy (94% and 72%, respectively; p=0.004). Patients who had a PSA level >10 ng/mL before SCA had a higher BCR rate than did patients who had a PSA level ≤10 ng/mL before SCA.[25,26] Patients who had received only radiation therapy before SCA had a significantly higher 5-year disease-specific survival rate than did patients who had received both radiation therapy and hormonal therapy before SCA (89% and 50%, respectively; p<0.001).[25] Although SCA can be used to treat androgen-independent local recurrence, androgen-independent progression carries a serious risk for distant metastasis and death. Finally, Spiess et al.[26] recently developed a nomogram that predicts which patients are most likely to develop a biochemical relapse following SCA. This nomogram is useful for counseling patients who have radiorecurrent prostate cancer.

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Urinary incontinence, defined as any urinary pad usage, occurs in 4-10% of patients who undergo SCA.[23,27-29] The use of an external sphincter temperature probe has decreased severe incontinence rates to <5%.[30] Additionally, the use of a warming catheter and improved catheterization techniques have reduced urethral sloughing and stricture rates from 10-15% to as low as 0%.[31,32] Impotence remains an accepted side effect of whole-prostate SCA. Focal subtotal SCA can be offered to the rare patient who is potent and has a limited number of positive biopsy cores. In a study of SCA outcomes, two of five patients for whom follow-up sexual health data were available maintained erectile function; however, three of the five patients developed ED.[33] The risk of rectal fistula is low, ranging from 0% to 3%.[23,28,29,34] Table 4 summarizes select SCA series.[22,25,27,29,34-36]

Salvage brachytherapy

Memorial Sloan-Kettering Cancer Center reported their experience with SBT in 1990. Grado et al.[37] from the Mayo Clinic reported the largest SBT series, presenting data on 49 patients who underwent SBT (120 Gy with Pd^{103} seeds or 160 Gy with I^{125} seeds) after primary external beam radiotherapy had failed. Patient 3- and 5-year BDFS rates were 48% and 34%, respectively. Oncological outcomes and complications in select SBT series are summarized in Table 5.[37-39] Koutrouvlies et al.[38] reported a 5-year BDFS rate of 87% in 31 patients using the ASTRO criteria; the median follow-up time was 30 months. However, all but one patient had received 3 months of neoadjuvant androgen ablation, which may have led to the high BDFS rate. Lee et al.[40] retrospectively reviewed outcomes in 21 patients with radiorecurrent prostate cancer who underwent high-dose SBT in which 36 Gy was delivered in 6 weekly fractions via transrectal ultrasonography-guided high-dose radiation (HDR) prostate implants. Lee et al.[40] concluded that HDR SBT is feasible and effective; the 2-year BDFS rate (based on ASTRO criteria) was 89%, and the median follow-up time was 18.7 months.

SBT complications are defined using common terminology criteria or the Radiation Therapy Oncology Group criteria for adverse events.[41] The most common complications of SBT are of genitourinary (GU) (e.g., frequency, urgency, incontinence, hesitancy, nocturia) or gastrointestinal origin (e.g., rectal bleeding, frequent bowel movement). In their literature review, Nguyen et al.[31] reported that the mean rates of grade 3 or 4 GU toxicity as an early or late complication of SBT were 5.6% (range 0-24%) and 17% (range 0-47%), respectively. Toxicity as an early complication of SBT included rectal injury. The most serious complication was rectal fistula with a mean rate of 3.4% (range 0-12.9%). Incontinence was reported in 6% of patients who underwent transurethral resection of the prostate after SBT.[37] Lee et al.[40] reported that 9 patients had grade 1 or 2 ED before SBT, and all but 1 patient had ED after SBT. Most of the patients who had ED after SBT had grade 2 ED; however, 2 patients had grade 3 ED, which did not improve despite treatment with a phosphodiesterase inhibitor.

Salvage high-intensity focused ultrasound

Four studies have investigated the oncological outcomes of SHIFU.[42-45] The median follow-up times in these studies were 7, 4, 18.1, and 14.8 months, respectively. The study definitions of PSA failure and follow-up were not uniform, and the reported BDFS rates ranged broadly, from 25% to 71%. Moreover, 30-58% of the patients in these studies received hormonal therapy before SHIFU, and the patient follow-up periods were shorter than those of other patients who underwent minimally invasive salvage methods, thereby hindering the comparison of SHIFU with other salvage treatments. The most serious complication was rectovesical fistula, which occurred in 3-7% of patients.[46] The most common complications included incontinence (range 7-49.5%), stricture (range 17-20%), and bladder neck contracture and retention (range 8.5-36%). SHIFU has a higher complication rate, and particularly a higher incontinence rate, than does SCA or SBT. Because of the limited experience with SHIFU and the lack of available data, longer and more detailed studies are required to assess the feasibility of this procedure in patients with radiorecurrent prostate cancer.

As a conclusion, the BCR of prostate cancer after primary radiation therapy presents a diagnostic and therapeutic challenge. Two-thirds of patients have an advanced pathological disease status by the time salvage treatment is offered. SRP offers a long-term survival benefit in such patients, and the findings of initial studies indicate that SRARP outcomes are promising. The intermediate-term oncological efficacy and morbidity of SCA are comparable to those of SRP. To ensure that appropriate salvage therapy is offered, researchers must establish a more comprehensive definition of BCR that considers new molecular markers, imaging studies, and prostate-mapping biopsy findings to identify locally recurrent early-stage disease after radiation therapy has failed. Strict guidelines, including universal patient-selection criteria and an intergrade definition of BCR, are required to accurately compare the oncological efficacy and complications of salvage therapy for radiorecurrent prostate cancer.

Conflict of interest

No conflict of interest was declared by the authors.

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