



Brachytherapy for Penile Cancer: Indication, Technique, Dose, Efficacy and Safety

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SUMMARY

Penile cancer, which is a very rare neoplasm, is a malignancy that causes devastating physical and psychosocial effects in patients. The aim in penile cancer treatment is to provide optimal organ preservation without decreasing the oncologic control rate. Cure rates are very high in early stage disease. Brachytherapy can be applied in organ-sparing approach in early stage disease. In the majority of the studies, brachytherapy is applied with an interstitial implant. In the studies in which brachytherapy was applied with mold, similar results were obtained as in the studies in which implants were applied. Although LDR was mostly used as the dose rate, successful results were also obtained in studies using PDR and HDR techniques. It is seen that the Paris system was mostly preferred as dosimeter system. In most of the studies, a median dose of 60 Gy was applied. In recurrences after brachytherapy, which is a treatment with a high local control rate, control rates with amputation are quite high. Most of the treatment-related toxicities can be managed with conservative treatment. Considering literature data, brachytherapy is an effective and tolerable treatment option in organ-preserving approach in early penile cancer.

Keywords: Brachytherapy; organ preservation penile cancer.

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INTRODUCTION

Penile cancer, which is a very rare neoplasm, is a malignancy that causes devastating physical and psychosocial effects in patients.[1,2] The disease is most commonly seen in men aged 50–70 years. While squamous cell carcinoma constitutes the majority of penile cancers, sarcoma, melanoma and basal cell carcinoma can be observed more rarely.[2,3] Non-circumcision, phimosis, obesity, poor penile hygiene, lichen sclerosis, balanitis, smoking, psoralen UV-A (PUVA) treatment, human papillomavirus (HPV) infection, and having a low income level are defined risk factors for the disease.[2–5] HPV positivity has been found to be seen in approximately 40–50% of penile cancer cases. In HPV positive cases, types 16

and 18 are observed to be prominent.[2,3,6,7] The aim in penile cancer treatment is to provide optimal organ preservation without decreasing the oncologic control rate.[8,9] The latest TNM staging of penile cancer is shown in Table 1.[10] Early diagnosis and lymph node metastasis status are the main factors determining survival. Cure rates are very high in early stage disease. Radiotherapy can also be applied in organ-sparing approach in early stage disease. External radiotherapy or brachytherapy may be preferred as radiotherapy modality. Brachytherapy, as an invasive procedure, has a very important place in the management of the disease as it is a treatment with a high local control rate in early stage disease. The aim of this study is to review the place, technique, doses and side effects of brachytherapy in penile cancer.

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Table 1 TNM clinical classification of penile cancer

T - Primary Tumour		N - Regional Lymph Nodes	
Tx	Primary tumour cannot be assessed	Nx	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumour	N0	No palpable or visibly enlarged inguinal lymph nodes
Tis	Carcinoma in situ	N1	Palpable mobile unilateral inguinal lymph node
Ta	Non-invasive verrucous carcinoma	N2	Palpable mobile multiple or bilateral inguinal lymph nodes
T1	Tumour invades subepithelial connective tissue	N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
	T1a: Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated		M - Distant Metastasis
	T1b: Tumour invades subepithelial connective tissue with lymphovascular invasion or perineural invasion or is poorly differentiated		
T2	Tumour invades corpus spongiosum with or without invasion of the urethra	M0	No distant metastasis
T3	Tumour invades corpus cavernosum with or without invasion of the urethra	M1	Distant Metastasis
T4	Tumour invades other adjacent structures		

DIAGNOSIS, STAGING AND TREATMENT OF PENILE CANCER

Penile cancer often presents as a skin elevated or ulcerated lesion. If there is a penile lesion suggestive of penile cancer, a detailed anamnesis should be taken from the patient. Obtaining histologic confirmation with biopsy is important for planning appropriate treatment. A detailed physical examination of the penis and penile lesion should be performed. The location, size, morphology and extension of the lesion should be recorded. In patients with penile cancer, inguinal examination should also be performed. In inguinal lymph node examination, the number, nature and laterality of palpable or suspicious lymph nodes should be noted. MRI is useful to determine the T stage of the tumor and to understand whether the disease is suitable for organ-sparing surgery; ultrasound can also be performed in patients who cannot undergo MRI.[8,9,11,12] 20–25% of cN0 patients have occult metastasis. Detection of lymph node metastasis is important both for determining the prognosis of the disease and for determining the appropriate treatment approach. Although PET/CT is a very valuable imaging method in the detection of lymph node metastasis, due to the possibility of missing micrometastatic disease, the approach of surgical lymph node evaluation according to the determined risk groups has been accepted.[9,13,14] Patients in pTa, pTis and pT1a G1 stage were classified as low risk and

no surgical staging of the lymph node was necessary in this group. Patients in pT1a G2 stage were classified as intermediate risk and the probability of micrometastatic lymph node involvement in this group was found to be 6–8%. Patients at ≥ pT1b stage are classified as high risk and surgical staging is recommended for this group of patients. In addition to T stage, histologic grade and lymphovascular invasion (LVI) were found to be factors associated with occult lymph node involvement.[9,15] In cN0 patients with indication for surgical staging, dynamic sentinel lymph node biopsy (DSNB) should be recommended first. It is reported that the diagnostic accuracy rate is quite high with inguinal US and biopsy of sonographically pathologic lymph nodes prior to DSNB. In patients who cannot undergo DSNB, inguinal lymph node dissection should be performed.[9,16,17] In cN+ patients, a biopsy should be taken from the suspected lymph node to confirm nodal metastasis. In addition, FDG PET/CT or thoracoabdominal CT should be ordered to screen for distant metastasis.

The aim of the treatment is to ensure that the patient has a functional penis in addition to complete removal of the tumor without impairing oncologic control. An organ-sparing approach is recommended for penile cancers located in the Ta, T1-T2 glans or prepuce. Penile-sparing surgery, radiotherapy (external radiotherapy/brachytherapy) or laser ablation techniques are the treatment approaches that can be chosen in this patient group. In the patient with invasion of

the corpus cavernosum (T3), partial penectomy is recommended. Total penectomy is recommended for the patient whose tumor is not suitable for partial amputation. In patients who do not want surgery or whose tumors are not suitable for surgery, surgery may be preferred after chemoradiotherapy or induction chemotherapy.[9,11,18] Brachytherapy appears to have a place in the treatment of penile cancer. We aim to review the indications, efficacy, technique, dose-fraction regimens and safety of brachytherapy in this disease.

BRACHYTHERAPY FOR PENILE CANCER: INDICATION, TECHNIQUE, DOSE, EFFICACY AND SAFETY

In a study of 53 patients, patients who underwent interstitial brachytherapy with Ir-192 source were evaluated. [19] Fifteen of the patients were in T3 stage and 16 were N+. Forty eight patients received brachytherapy alone and 5 patients received a combination of brachytherapy + external radiotherapy. Eleven patients had local recurrence and control was achieved with penile amputation except 1 patient. Fifteen patients developed serious complications (necrosis, surgical urethral stenosis) and 10 of them underwent partial or total penile amputation. Complications were found to be associated with the irradiated area and doses above 65 Gy. Brachytherapy was reported to be the first choice in the treatment of T1-2 penile cancer and it was recommended to keep the dose below 65 Gy to reduce the complication rate. In a study of 51 patients, patients who underwent interstitial brachytherapy with Ir-192 source were evaluated. [20] Six of the patients were in T3 stage and 8 were N+. Brachytherapy dose ranged between 50–65 Gy (mean 60 Gy). Lymph node positive patients underwent external radiotherapy to the lymph nodes after surgery. Following treatment, nodal and/or distant metastasis developed in 6 patients (12%), 5 of whom were primarily clinical lymph node positive patients. In 7 patients (14%), only local recurrence was observed and partial or total penectomy was performed. It was observed that 6 of these patients continued their lives disease-free with a mean follow-up of 5.5 years. Nine patients developed local necrosis and 8 of them underwent partial or total amputation. Seventeen patients developed partial urethral stenosis. It was interpreted that interstitial brachytherapy is a treatment that provides a high local control rate in T1-2 penile cancer. In addition, it has been reported that recurrences can be successfully treated with surgery. In another study, treatment results

of 15 patients who underwent brachytherapy were evaluated.[21] Eight patients had T1, 5 patients had T2, 2 patients had T3 stage and 4 patients had inguinal lymph node metastasis. Brachytherapy was applied with a silicon made mold. Total brachytherapy dose ranged from 32–74 Gy / 1–3 fractions. Local control was achieved in 12 patients (80%). Local control rates by stage were 100% for T1, 80% for T2 and 0% for T3. Amputation was performed in 3 patients who could not achieve local control. One patient had local recurrence and was salvaged by surgery. In total, penile preservation was achieved in 11 of 15 patients (73%). In the study with a median follow-up period of 7 years, there were no serious complications requiring surgery during the follow-up period and satisfactory urinary function was achieved in all patients with preserved penis. It is concluded that brachytherapy with mold is an ideal treatment option in organ-sparing approach in patients with T1-2 penile cancer. In a study, 23 patients who underwent brachytherapy with Ir-192 source and temporary interstitial implant were evaluated.[22] In 7 patients, the primary lesion was in T1 stage and in 7 patients in T2 stage and 9 patients were treated for recurrence. In the study where the median dose was 50 Gy (40–60), low dose rate (LDR) afterloading system was used and the Paris dosimetry system was followed dosimetrically. In the study with a median follow-up period of 2 years, complete response was observed in 18 of 23 patients at the evaluation 2 weeks after treatment. During follow-up, 3 patients had local recurrence, 2 patients had locoregional recurrence and 1 patient had only groin recurrence. The 8-year local control rate was found to be 70%. Local control was achieved with partial amputation surgery in 4 of 5 patients with local recurrence. In 1 of 3 patients with groin recurrence, control was achieved with bilateral groin dissection + external radiotherapy. Local control was achieved in 21 of 23 patients at the last follow-up. Most of the recurrences occurred within the first year after implantation. Cosmetic and functional results were reported to be excellent and meatal stenosis was seen in only 2 patients. All 2 patients with meatal stenosis were treated endoscopically. No skin or soft tissue necrosis was observed in any patient. It was concluded that interstitial brachytherapy with Ir-192 is a treatment modality that provides organ and function preservation as well as high local control rate in early penile cancer. In a study by Kiltie et al.[23] the results of brachytherapy applied to 31 node-negative patients were evaluated. The median prescribed dose was 63.5 Gy. It was observed that the primary tumor was controlled in 80.6% of the pa-

tients. Except for 1 of the patients with recurrence, control was achieved with salvage surgery in the others. 5-year disease-free survival was 85.4%, recurrence-free survival was 57.8%, and local recurrence-free survival was 75.6%. 1 patient underwent amputation due to necrosis. Urethral stenosis was seen in 44% of patients with preserved penis and these patients were treated with dilatation. As a result of the study, it was emphasized that Ir-192 implantation treatment in penile cancer is a treatment with a high local control rate and salvage surgery may be possible in recurrences. Crook et al.[24] evaluated the results of interstitial brachytherapy applied to 30 patients. In 90% of the patients, the primary tumor was in T1 and T2 stage, 1 patient was in T3 stage and 2 patients were in Tx stage. The majority of tumors were located in the glans. Treatment was performed with Ir-192 source, LDR in 22 patients and pulsed dose rate brachytherapy in 8 patients. Planning was made according to the Paris dosimetry system. The median prescribed dose was 60 Gy. In the study with a median follow-up of 34 months, local recurrence was observed in 4 patients. The 2-year local failure free rate was 85% and the 5-year rate was 76%. Patients with local recurrence were salvaged by penectomy (2 partial). Four patients with isolated regional recurrence were salvaged by groin dissection. 2 patients died of metastatic disease, both patients had moderately differentiated tumors. The rate of regional and/or distant recurrence was found to be 50% in patients with intermediate and poorly differentiated tumors, while none of the patients with well-differentiated tumors had regional or distant recurrence. Tumor grade was found to be an important factor in terms of disease-free survival. Cosmetic and functional results were reported as good. 2 patients had loss of potency, 3 patients underwent partial penectomy due to dilatation of meatal stenosis and 1 patient underwent partial penectomy due to radiation necrosis. As a result of the study, it was emphasized that local control rates of T1 and T2 penile cancer brachytherapy were excellent, and considering the risk of regional and distant recurrence of intermediate and poorly differentiated patients, inguinal lymph node dissection was recommended for these patients after brachytherapy. In a multicenter study by Crook et al.[25] the results of interstitial brachytherapy applied to 49 patients were evaluated. 8% of the patients were in T3 stage and 23 patients received brachytherapy with PDR technique and 26 patients received brachytherapy with LDR technique. Four patients had a single plane implant with a plastic tube technique, and all others had a volume implant with predrilled acrylic templates

and two or three parallel planes of needles. The prescribed dose was in the range of 55–65 Gy. 5-year actuarial overall survival was 78.3% and cause-specific survival was 90.0%. The cumulative incidence rate for never having experienced any type of failure at 5 years was 64.4% and for local failure was 85.3%. All 5 patients with local failure were successfully salvaged by surgery; 2 other men required penectomy for necrosis. The soft tissue necrosis rate was 16% and the urethral stenosis rate 12%. Of 49 men, 42 had an intact and tumor-free penis at last follow-up or death. The actuarial penile preservation rate at 5 years was 86.5%. Brachytherapy was found to be an effective treatment modality for T1, T2 and selected T3s. The importance of close follow-up of these patients is emphasized, since recurrences can be successfully salvage with surgery. In a study of 144 patients, the results of interstitial brachytherapy applied to patients with glans localized SCC were evaluated. [26] Hypodermic or lumbar puncture needles were implanted through the glans. Gerbaulet's glans applicator was used in the study. This system consists of two square plates of transparent plastic, 50 mm wide and 2 mm thick. Treatment was performed with LDR technique and the median brachytherapy dose was 65 Gy (37–75). The 10-year penile recurrence rate was 20% and inguinal recurrence rate was 11%. After salvage treatment, 86% of patients with local recurrence were in complete remission at the last follow-up. The 10-year probability of avoiding penile surgery (due to complications or recurrence) was 72%. The 10-year cancer-specific survival rate was 92%. Tumor diameters were found to be associated with the risk of recurrence. The 10-year painful ulceration rate was 26% and stenosis rate was 29%. Seven patients underwent excision due to necrosis. Treated volume and reference isodose rate (≤ 0.6 Gy/h and >0.6 Gy/h) were found to be associated with complications. It was concluded that attention should be paid to the dose rate in order not to increase the complication rate. Makarewicz et al.[27] evaluated the results of brachytherapy applied to 33 patients. In this study in which 3 patients were in T3 stage and the remaining patients were in T1 and 2 stages, brachytherapy was applied with high dose rate (HDR) technique. Patients were assigned a dose between 48–54 Gy. In the study with a mean follow-up of 5 years, 72.7% of patients achieved complete remission. Five-year disease-free survival was 75.4% and locoregional control rate was 78.8%. In this study evaluating the results of brachytherapy with the HDR technique, the effectiveness of the treatment in the disease has been proven once again. In a multicenter study, the efficacy of

brachytherapy and its effect on sexual function were investigated.[28] In the study of 47 patients, a mean dose of 60 Gy was administered to the patients. Five-year disease-free survival rate was 84% and penile preservation rate was 66%. It was observed that 58.8% of the patients who were sexually active before treatment were sexually active after treatment. It was seen that 94.4% of the patients who had an erection before treatment also had an erection after treatment. The study found that brachytherapy had a low impact on sexual life. In a study of 76 patients, patients who underwent brachytherapy with HDR technique were evaluated.[29] In the study with a follow-up period of 76 months, 18.4% of the patients developed local recurrence and 10.5% had persistent disease after treatment. 5 and 10 year local control rate was 65.6% and 5–10 year penile protection rate was 69.5% and 66.9%. G3 and 4 toxicities were not detected. 1 patient developed urethral stenosis and was treated with dilatation. As a result of the study, HDR brachytherapy in penile cancer was found to be an effective treatment for penile protection. In the study by Martz et al.[30] the results of intersitial HDR brachytherapy applied to 29 patients were evaluated. Adjuvant or definitive brachytherapy was administered to the patients and a dose of 35 Gy/9 fractions was defined for those who received adjuvant treatment and 39 Gy/9 fr for those who received definitive treatment. T1–2 patients were included in the study. In the study with a median follow-up of 6 years, 5-year local recurrence-free survival was 82%, regional recurrence-free survival was 82%, metastasis-free survival was 89% and overall survival was 73%. Penile protection rate was 79.3%. grade 3 acute skin toxicity rate was 6%, while grade 1–2 acute skin toxicity developed in the remaining 94% patients. Late skin toxicity was telangiectasia in 17% of patients and grade 3 necrosis in 10.3% of patients; patients with necrosis were successfully treated with hyperbaric oxygen therapy. Skin appearance, International Prostate Symptom Score (IPSS) and International Index of Erectile Function 5-items (IIEF-5) scores did not differ significantly between pre and post treatment. HDR brachytherapy has been shown to be an effective and safe treatment in the conservative treatment of penile cancer. In a study of 259 patients by Rozan et al.[31] the LDR technique was used and local control rate was 85% and cause specific survival was 88% at 5 and 10 years. A study evaluated the results of brachytherapy applied with the PDR technique.[32] The efficacy and toxicity results of PDR brachytherapy in the treatment of penile cancer were comparable to those obtained with LDR brachytherapy in previous cohorts. A study

evaluated the long-term effects in patients who underwent brachytherapy.[19–36] The urinary scores showed moderate lower urinary tract symptoms. During the followup, a urethral dilation or self-catheterization had been necessary in 30% and 13%, respectively. The erectile dysfunction was mild and quality of life was good. Study's results showed the moderate impact of brachytherapy on functional outcomes. Studies on brachytherapy in penile cancer and the results obtained in these studies are shown in Appendix 1.

When the studies on brachytherapy in penile cancer are evaluated, the lack of randomized controlled trials draws attention. Studies have mostly included lesions located in the glans. Most patients in the studies underwent circumcision prior to brachytherapy. In the majority of the studies, brachytherapy is applied with an interstitial implant. Iridium wires are used in interstitial brachytherapy. The number and length of the wires and the volume of the implant were determined by the size and thickness of the lesion. In the studies in which brachytherapy was applied with mold, similar results were obtained as in the studies in which implants were applied. Although LDR was mostly used as the dose rate, successful results were also obtained in studies using PDR and HDR techniques. Paris system was mostly preferred as dosimeter system. In recurrences after brachytherapy, which is a treatment with a high local control rate, control rates with amputation are quite high. Most of the treatment-related toxicities can be managed with conservative treatment.

According to ESMO-EURACAN guideline, brachytherapy has a higher local relapse rate than penectomy but a lower local relapse rate than external radiotherapy in penile cancer.[37] Circumcision should be performed before brachytherapy. It is reported that the 5-year local control rate with brachytherapy is 70–90%. The 5-year penile protection rate was found to be 74%. It has been reported that patients with <4 cm tumors are suitable candidates for brachytherapy. In brachytherapy, HDR, PDR or LDR can be selected. If LDR or PDR is preferred, doses of 60–65 Gy, if HDR is to be applied, 42–45 Gy/12–14 fractions or 35 Gy/9 fraction regimens should be preferred. There is no difference between these techniques in terms of patient selection. Recently, HDR has come into favor due to patient convenience, less patient isolation due to lower risk of radiation exposure to staff, and adjustable source dwell time allowing for dose optimization of the target and normal tissue.[38] The most common late side effects after brachytherapy are urethral stenosis and necrosis with a mean occurrence rate of up to 33% in some series.

Considering all these data, brachytherapy is an effective and tolerable treatment option in organ-preserving approach in T1 or T2 and <4 cm penile cancer.

CONCLUSION

In early stage penile cancer, brachytherapy is a tolerable treatment option that can be applied with LDR, PDR or HDR techniques and has a high local control rate in an organ-sparing approach.

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Appendix 1 Studies on brachytherapy in penile cancer and the results

Studies	Study design	Patients	Stage	Localization	Source	Brachytherapy technique	Dose rate	Dose	Control	Penile conservation	Recurrence	Survival	Toxicity	Tx for recurrence
Suchaud [19]	Retrospective	53	T1:7, T2:31, T3:15; N0:37, N1:7, N2:6, N3:3	Ir-192	Interstitial	LDR	50-65 Gy (mean 60 Gy)	T1-2: 91% T1-2: 75%	Local Recurrence Rate: 20%	Local Recurrence Rate: 20%	5 y OS: 69%, DSS: 85.4%, RFS: 57.8%, LRFs: 75.6%	Serious complication rate: 28% (Dose must be <65 Gy)	Eleven pts Presented a Local Recurrence; All But One Were Controlled by Penile Amputation	
Delannes [20]	Retrospective	51	T1s:3, T1:14, T2:28, T3:6; N0:43, N1:7, N2:1	Ir-192	Interstitial	LDR	32-74 Gy/1-3 fr	73%	Nodal and/or metastatic disease: 12%, locoregional recurrence: 14%	Nodal and/or metastatic disease: 12%, locoregional recurrence: 14%	Amputation for 8 pts; Partial Urethral Stenosis: 17 pts No severe comp requiring surgery	Local Recurrence Only pts (7)		
Akimoto [21]	Retrospective	15	T1:8, T2:5, T3:2	Ra-226, Cs-137, Ir-192	Silicon Mold	LDR	40-60 Gy (median 50 Gy)	80% 8 y Local Control: 70%	Local Only Failure:3, Locoregionally Failure:2, Groin Only Failure:1	Local Only Failure:3, Locoregionally Failure:2, Groin Only Failure:1	Excellent Cosmetic and Functional Outcome	5 pts Who Failed Locally, 4 Were Successfully Salvaged with Partial Penectomy		
Chaudhary [22]	Retrospective	23	T1:7, T2:7, Recurrent:9	Glans:16, Corona only:1, Prepuce:2, Glans and Corona:3, Glans Extended to Involve The Urethral Meatus:1	Ir-192	Interstitial	63.5 Gy median	74.80%	Primary Tumor Control: 80.6%	5 y OS: 69%, DSS: 85.4%, RFS: 57.8%, LRFs: 75.6%	Amputation for Necrosis:1 Patient, Dilatation for Urethral Stenosis:11 pts	6 pts with Primary Relapse, 5 Were Successfully Salvaged with Amputation		
Crook [24]	Retrospective	30	T1:20, T2:7, T3:1, Tx:2	Glans:28, Shaft:2	Ir-192	Interstitial	55-65 Gy PDR	Complete Remission: 72.7%	Local Failure Free Rate: 85% (2 y)	Local Failure Free Rate: 85% (2 y)	Cause Specific Survival: 95% (2 y)	Loss of Potency:2, Dilatation for Meatal Stenosis:3, Partial Penectomy for Radiation Necrosis:1	Local Failures were Salvaged with Penectomy	
Crook [25]	Retrospective	49	T1:51%, T2:33%, T3:8%, Tx:4%	Interstitial (45) and Plastic Tube (4)	Ir-192	LDR, PDR	55-65 Gy	5y: 86.5%	5y Freedom From Local Failure: 85.3%, Freedom From Any Failure: 64.4%	5y OS: 78.3%, Cause Specific Survival: 90%	2 pts Penectomy for Necrosis:1	5 pts with Local Failure Were Successfully Salvaged by Surgery		

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De Crevoisier [26]	Retrospective	144	All Stage 1	Glans or Prepuce	Ir-192	Interstitial	LDR	65 Gy Median		10 y Probability of Avoiding Penile Surgery: 72%	10 y Penile Recurrence: 20%	10 y Cancer Specific Survival Rate: 92%	10 y Painful Ulceration Rate: 26%, Stenosis Rate: 29%, 7 pts Required Excision for Necrosis	Among 21 pts: Partial Penectomy: 12 pts, Total Penectomy: 6 pts, Second Brachytherapy: 2 pts, and Local Excision for 1 Patient
Makarewicz [27]	Retrospective	33	T1: 23, T2: 7, T3: 3 pts	Mostly Glans	Ir-192	Interstitial	HDR	48-54 Gy	Complete Remission: 72.7%		Locoregional and Distant Recurrences: 27.3%	5 y OS: 84.9%, DFS: 75.4%	Soft Tissue Necrosis: 3 pts	Salvage Penectomy was Performed in 5 Cases with Local or Locoregional Failure. 4 of Them Were Successfully Treated with Surgery.
Delaunay [28]	Retrospective	47	T1: 33, T2: 5, Unknown: 9	Glans: 43, Body: 4	Ir-192	Interstitial	LDR	60 Gy Mean		66%	Local Recurrence: 34%, Regional and/or Distant Recurrence: 17%	5 y Specific Survival: 87.6%, DFS: 84%	Of the 18 pts Who Had Erections Before Brachytherapy, 17 Still Had Them After Tx (94.4%)	16 pts with Local Failure Were Amputated (15 partial, 1 total)
Kellas-Sięczka [29]	Retrospective	76	Tis: 9, T1: 35, T2: 16, T3: 7, Tx: 9, N1: 5	Glans: 33, Prepuce: 20, Glans and Prepuce: 7, Retroglanular Sulcus: 16	Ir-192	Interstitial (70) and Mold (6)	HDR	Tumorectomy pts (Median): 25 Gy (Mold), 42.8 Gy (Interstitial). Biopsy Only or Local Recurrence pts: 47 Gy (mold), 48.2 Gy (Interstitial)	10.5% Persistent Disease	5-10 y: 69.5%, 66.9%	Local Recurrence: 18.4%	5, 10 Cause Specific Survival: 85.0%, 77.8%	No G3 or G4 Toxicity	Pts with Local Recurrence and Persistent Disease Underwent Salvage Penectomies, Except 4

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Martz [30]	Retrospective	29	T1: 22, T2: 6, Tis: 1	Glans/Coronal Sulcus: 17, Periarethral Meatus: 12	Ir-192	Interstitial	HDR	35 Gy/9 fr (adjuvant), 39 Gy/9 fr (definitive)		79.30%	LR: 20.7%, 5y LRF5: 82%, RRF5: 82%	5 y Specific Survival: 88% OS: 73%	Late Skin Complications: Telangiectasia: 5 pts (17%), Necrosis: 3 pts (10.3%) Requiring Hyperbaric Oxygen Therapy)	Six pts with (20.7%) Local Relapse Underwent Salvage Penectomy
Rozan [31]	Retrospective	259	T1: 96, T2: 97, T3: 25, Tis: 16	Glans: 125, Prepuce: 41, Shaft or Shaft and Prepuce: 3, Glans and Prepuce: 74, Glans and Shaft: 5, Glans and Prepuce and Shaft: 9	Ir-192	Interstitial	LDR	59 Gy Mean		74%	Overall Local Control Rate: 85%	5, 10 y Cause Specific Survival: 88%-88%, DFS: 78%-67%, Survival: 66%-52%	Late Side Effect: 53%	31 pts Accepted Salvage Surgery (3 Local Excisions, 16 Partial Penectomies, 12 Total Penectomies); 25 (81%) were salvaged. 6 pts Developed a Second Recurrence
Kamsu-Korn [32]	Retrospective	27	T1: 1, T2: 26	Glans: 23, Glans and/or Prepuce: 4	Ir-192	Interstitial	PDR	60 Gy Median			3 y Local Control: 88%	3 y OS: 95%	No G3 or More Acute Reaction. Delayed Ulcerations: 2 pts (9%) Stenoses Requiring at Least One Meatal Dilatation: 5 pts (22%)	All pts with Only Local Relapse (3) Were Successfully Salvaged with Partial Amputation
Pimenta [33]	Retrospective	25	T1-2	Glans or Prepuce	Ir-192	Interstitial	LDR, PDR, HDR	60 Gy Median		5 y: 86.1%	1 Local Progression, 1 Regional Progression	5, 10 y Cancer Specific Survival: 91.3%, OS: 82%	Two pts Underwent Partial Phallectomy for Toxicity	Patient with Local Progression Underwent Partial Penectomy
Cordoba [34]	Retrospective	73	T1: 55, T2: 11, Tis: 6, Tx: 1	Glans: 67, Shaft: 6	Ir-192	Interstitial	LDR	60 Gy Median		5 y Total or Partial Penile Preservation: 87.9%	Relapse Free Survival: 64.4%, Local Relapse Free Survival: 74%	5 y OS: 82%	5 pts (6.8%) Required Penile Amputation for Necrosis.	15 pts with Failure, Were Salvaged with Amputation (5 Total, 10 Partial)

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Escande [35]	Retrospective	201	T1, T2 and Selected T3	Glans	Ir-192	Interstitial	LDR, PDR	65 Gy Median		5 y: 85%	Local Control Rate: 82%	5y OS: 79%	50 patients (24.8%) Presented Urethral Stenosis Requiring at Least 1 Dilatation, and 14 (7%) Required Limited Surgeries for Toxicities	24/31 (77.4%) pts with Local Relapse as Only Site of Relapse Were in Complete Remission After Salvage Treatment (Surgery: 21, Second Brachytherapy: 2, Local Chemotherapy: 1)
Gambachidze [36]	Retrospective	39	T1-2	Glans	Ir-192	Interstitial	LDR, PDR	65 Gy Median					Sixteen (70%) pts Continued to Maintain a Sexual Activity and the Erectile Dysfunction Was Mild. Quality of Life Was Good	