HANDS ON WORKSHOP

BT BRACHYTHERAPY

EVIDENCE AND CASE-BASED REVIEW IN PROSTATE AND GYNECOLOGIC BRACHYTHERAPY

London Health Sciences Centre
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PROSTATE BRACHYTHERAPY

CASE 1: PROSTATE LDR BRACHYTHERAPY

Case: A 63-year-old man diagnosed with prostate adenocarcinoma, overall ISUP grade group 2, 4 of 12 cores involved bilaterally, 10% prostate tissue involved, PSA at presentation of 5.2, clinical T1c. The patient underwent an MRI of his prostate indicating an 18 cc volume gland and a PIRADS 3 lesion located in the lateral right peripheral zone apex. There are no signs of extraprostatic extension or seminal vesicle involvement. No clinically concerning lesions were detected in the left lobe.

IPSS score: 6/35. SHIM questionnaire: 20/25 points. No comorbidities. No previous history of TURP.

LDR brachytherapy was discussed among other options and recommended to the patient as monotherapy. During the discussion, it was mentioned that LDR BT is a day procedure that requires general anesthesia and takes approximately 1-2 hours. In terms of toxicities and quality of life impact, we discussed that this is a well-tolerated treatment compared to other modalities.

WHEN IS LDR BRACHYTHERAPY INDICATED AS MONOTHERAPY?

LDR brachytherapy is typically recommended as monotherapy for patients with low-risk disease, declining active surveillance, and favorable intermediate-risk disease. Some patients with unfavorable intermediate-risk diseases, such as those with one unfavorable feature and organ-confined disease on MRI, could benefit from this treatment modality (ref).

WHAT CRITERIA DETERMINE A PATIENT'S SUITABILITY FOR PROSTATE BRACHYTHERAPY?

1. Favorable urinary tract function: This can be documented using the International Prostate Symptom Score (IPSS), which assesses the severity of obstructive and irritative urinary symptoms and their impact on quality of life. Additionally, metrics accessed through a urodynamics study could objectively measure indicators of an existing obstructive symptom including post-voiding residue and peak urinary flow. This comprehensive evaluation ensures urinary issues are identified and potentially managed before proceeding with brachytherapy as patients with IPSS scores ≥ 15-18 have a greater risk of acute urinary retention and catheterization post implant. crook ref (urodynamics)

2. Prostate volume - shape: Patients with an enlarged prostate (>50-60 cc) are less suitable candidates for LDR brachytherapy due to technical difficulties in seed placement, including higher chance for pubic arch interference. Additionally, prostate shape can play an important role in the final dosimetry and clinic outcome. For example, a significant median lobe enlargement can result in poor post-implant dosimetry and/or lead to unsatisfactory rates of acute toxicity.

3. TURP defect: A history of TURP can present challenges for brachytherapy, especially if there is a significant defect. It is essential to evaluate the relationship between the size of the TURP defect and the prostate, utilizing pre-procedural ultrasound and/or MRI to assess whether the patient is a suitable candidate for brachytherapy. Large TURP defects that prevent proper seed placement and compromise acceptable dosimetry are considered an absolute contraindication for the procedure.

4. Inflammatory bowel disease: patients with inflammatory bowel diseases like Crohn's disease or ulcerative colitis have increased risks of radiation-induced gastrointestinal toxicities, making them less suitable candidates for radiotherapy. In this clinical setting, due to its tighter dose conformality, prostate brachytherapy is preferred when compared to external radiotherapy options

5. Absolute contraindications per ABS Guidelines, such as limited life expectancy, unacceptable operative risks, distant metastasis, absence of rectum, large TURP defects, and ataxia telangiectasia.

WHAT ARE THE SEED TYPES, AND HOW DO YOU CHOOSE THEM?

The choice of radionuclides (iodine-125, palladium-103, or cesium-131) mainly depends on availability, although there are differences in the expected radiation distribution, isotopes' half-life, which can influence the duration and intensity of the radiation delivered. There is no clear evidence of clinical superiority between different radioisotope..

- Iodine-125: The most commonly used isotope, with a half-life of 59.4 days, provides a slow and continuous radiation dose. The suggested dose is 144-145 Gy.
- Palladium-103 has shorter half-life of 17 days and delivers a quicker radiation dose resulting in higher peaks of urinary toxicity that are shorter in duration.. The suggested dose is 125 Gy.
- Cesium-131: FDA approved in 2003, and to date, there are just a few reports describing long-term outcomes, a shorter half-life of 9.7 days, and higher energy (30.4KeV). The suggested dose is 115 Gy.

WHAT ARE THE ACUTE AND LONG-TERM TOXICITIES ASSOCIATED WITH LDR BRACHYTHERAPY?

Short-term morbidity associated with brachytherapy is primarily marked by urinary irritative and obstructive symptoms that typically peak within the first 3 months after treatment with I-125. However, symptom resolution occurs within a median of 1 year for I-125 and 6 months for Pd-103.

Brachytherapy monotherapy has been shown to result in low rates of late toxicities, with only 3% of patients experiencing Grade 3+ genitourinary toxicity and 2% experiencing Grade 3+ gastrointestinal toxicity, as reported in the RTOG 0232 trial. Urethral D5 and rectal V100 values were correlated with increased rates of urinary and gastrointestinal toxicities. Erectile dysfunction is commonly seen in 30-50% of patients (ref).

HOW TO CONDUCT PATIENT FOLLOW-UP AND WHAT TO ANTICIPATE REGARDING BIOCHEMICAL RESPONSE?

Patients should be closely monitored up to 5 years post implant. Recommended PSA measurement intervals are every 6 months until 2 years, and then annually until 5 years. Patients reaching a PSA level below 0.2 post-IDR brachytherapy are considered to have very low risk of PSA increase and prostate cancer relapse and are considered to have reached the biochemical definition of cure <Cite the biochemical definition of cure below 0.2>

Unlike undetectable PSA levels post-radical prostatectomy, patients who undergo radiation therapy continue to produce PSA with a gradual drop in PSA levels with time. Typically, a period of multiple years takes place between the prostate brachytherapy procedure and PSA nadir. The Phoenix/Houston criteria, revised in 2005, is the standard criteria to define biochemical failure post radiotherapy (including brachytherapy) and is defined by a PSA rise of 2 ng/mL or more above the nadir, regardless of androgen deprivation therapy.

A continuous rise in PSA levels post radiotherapy can indicate early signs of cancer recurrence. PSA benign bounces are common post prostate brachytherapy and are defined retrospectively by a rise and decline of PSA levels post radiotherapy. Benign bounces affect 30-50% of prostate brachytherapy patients.

PROSTATE BRACHYTHERAPY

CASE 2: PROSTATE HDR BRACHYTHERAPY BOOST

A 72-year-old man was diagnosed with prostate adenocarcinoma, overall ISUP grade group 3, with 6 out of 12 biopsy cores involved, primarily on the left side, with 50% of prostate tissue involvement. He presented with a PSA of 12 ng/mL and was staged as clinical T2b. The patient underwent a multiparametric MRI of the prostate, which revealed a suspicious lesion in the left peripheral zone at the mid-gland level, classified as PI-RADS 4. The prostate gland volume was measured at 32 cc. There was no evidence of extraprostatic extension or seminal vesicle involvement. The right lobe of the prostate showed no suspicious lesions on imaging.

His International Prostate Symptom Score (IPSS) was 8/35, indicating moderate lower urinary tract symptoms. His medical history includes well-controlled hypertension and type 2 diabetes, both managed with medication. He has no prior history of transurethral resection of the prostate (TURP) or other prostate surgeries.

Given his unfavorable intermediate-risk prostate cancer, multiple treatment options were discussed, including external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT), radical prostatectomy, and HDR brachytherapy combined with EBRT +- ADT. After a detailed discussion with the multidisciplinary team, he has chosen for HDR brachytherapy as a boost followed by EBRT.

WHEN BRACHYTHERAPY IS INDICATED AS A BOOST?

For candidates with intermediate-risk prostate cancer undergoing EBRT, with or without androgen deprivation therapy (ADT), brachytherapy boost should be offered. In selected cases of low-intermediate risk prostate cancer, with a single unfavorable intermediate-risk factor, LDR brachytherapy may be offered as a standalone treatment. For high-risk prostate cancer patients receiving EBRT and ADT, a brachytherapy boost should also be considered for eligible individuals. Randomized trials have shown that brachytherapy as a boost to EBRT results in improved biochemical disease-free survival when compared to EBRT alone. Brachytherapy as a boost, results in increased biological dose resulting in better local control within the prostate when compared to EBRT. This has the potential to future reduce metastatic events (due to second wave of metastasis) associated with an uncontrolled primary.

WHAT ARE THE SEED TYPES, AND HOW DO YOU CHOOSE THEM?

There is a large variety of dose-fractionations associated with HDR brachytherapy as a boost to the prostate. Frequent DR regimens include 15 Gy administered in 3 fractions, 11–22 Gy in 2 fractions, or 12–15 Gy in a single fraction. According to the latest GEC-ESTRO ACROP prostate brachytherapy guidelines, 15 Gy in a single fraction is the recommended prescription dose.

WHAT ARE THE ACUTE AND LONG-TERM TOXICITIES ASSOCIATED WITH HDR BRACHYTHERAPY?

SHDR brachytherapy combined with EBRT can result in both acute and long-term toxicities, particularly affecting the urinary and sexual systems. Acute side effects, such as urinary frequency, urgency are common but typically resolve within a weeks to months after treatment. Alpha-adrenergic blockers can enhance short-term urinary quality of life by relieving mostly obstructive symptoms.

HOW TO CONDUCT PATIENT FOLLOW-UP AND WHAT TO ANTICIPATE REGARDING BIOCHEMICAL RESPONSE?

Patients should be closely monitored during the first five years after primary curative treatment, as this is when the risk of treatment failure is highest. PSA levels should be measured semesterly until 2 years, and annually up to 5 years. Additionally, patients should be regularly assessed for both acute and late toxicities, with appropriate management to ensure comprehensive and individualized follow-up care.

A PSA bounce, similar to what is observed after LDR brachytherapy, is a common occurrence after HDR brachytherapy, affecting more than a third of patients.

Understanding this phenomenon is key to avoiding unnecessary interventions. Patients who experience rising PSA levels after an HDR brachytherapy boost should be reassured and closely monitored rather than subjected to immediate investigations or treatments.

GYNE BRACHYTHERAPY

CASE 3: CERVICAL CANCER BRACHYTHERAPY

A 42-year-old woman was diagnosed with squamous cell carcinoma of the cervix, FIGO stage IIB, with a tumor size measuring 5 cm in diameter. Her pelvic MRI showed a hyperintense lesion in T2 involving the cervix with proximal parametrial involvement on the right side. There was no evidence of lymph node metastasis or distant spread. The tumor had no signs of bladder or rectum involvement. The patient's general condition was good, with an ECOG performance status of 0.

Given the tumor size and the involvement of parametria, the patient was planned for treatment with radiotherapy (EBRT with 45 Gy in 25 fractions) with radiosensitizing weekly cisplatin. EBRT was followed by image-guided brachytherapy as a boost with prescribed dose given to the cervix and remaining gross tumour as per GEC-ESTRO Guidelines (ref). The whole radiotherapy treatment was completed in less than 50 day, as recommended by guidelines to counteract repopulation factors(ref).

WHEN IS BRACHYTHERAPY INDICATED IN CERVICAL CANCERS?

Brachytherapy can be used as monotherapy for select early-stage cervical cancer cases (e.g., stage IA1). In the postoperative setting, brachytherapy can be used as a boost to EBRT to escalate dose to the vaginal apex and surrounding tissues in the event of close or positive margins.

However, brachytherapy is more commonly applied after pelvic EBRT, as part of the definitive treatment, to escalate dose to the gross residual primary tumor and cervix. Brachytherapy is an essential component of treatment resulting in increased local and pelvic control () that result in approximately a 12% improvement in survival outcomes compared when compared to strategies without brachytherapy as a boost. In the context of cervical cancer boost therapy, image-guided adaptive brachytherapy (IGABT) is the gold standard, endorsed by the GEC-ESTRO GYN Working Group, the American Brachytherapy Society (ABS) and supported by the EMBRACE I/II and retroEMBRACE studies.

There are different strategies that are encompassed within the terminology of IGABT, but ultimately all of them involve acquisition of 3D axial images that are used to define 3D volumes (organs at risk and targets), to reconstruct applicators and for planning. T2 MR series have better soft tissue definition in the female pelvis and, whenever available, should be utilized to assist target definition (+- registered CT scan).

MRI-based target volume definition and dose optimization in IGABT have significantly improved clinical outcomes by enhancing treatment precision and reducing toxicity. MRI allows for individualized treatment planning by accurately determining tumor extent, growth patterns, and regression, ensuring the appropriate selection of brachytherapy techniques and more accurate target and organ contouring that ultimately improves the effectiveness of brachytherapy while reducing its side effects.

This approach allows for dose escalation in large tumors through combined interstitial and intracavitary (IC/IS) brachytherapy, widening the therapeutic window by 5-10 Gy. For smaller tumors, IGABT allows for dose de-escalation, reducing morbidity without compromising local control. A gynecological physical exam is mandatory before the start of EBRT and before determining the timing and execution of brachytherapy. If available, pre-brachytherapy MRI is recommended.

WHAT IS THE RECOMMENDED TIMING FOR BRACHYTHERAPY?

As previously mentioned, the total treatment duration from the start of EBRT to the end of brachytherapy should be less than 50 days. To maximize tumor regression and improve tumor geometry for the brachytherapy component while treating micrometastatic disease, treatment typically starts with EBRT and concurrent chemotherapy (typically Cisplatin). For small tumors and/or those with a good response, BT may be initiated during EBRT to shorten the total treatment time. For larger tumors or with reduced tumor response, BT could be delivered on weeks 6 and 7 to allow for maximum tumor response and better brachytherapy implant quality.

WHAT IS THE RECOMMENDED TIMING FOR BRACHYTHERAPY?

Tumor volumes and OARs should be contoured on T2-weighted MRI images. The residual GTV is defined as the macroscopic residual tumor present during brachytherapy, detected by clinical examination and as visualized on MRI. The Adaptive High-Risk CTV includes the residual GTV, the entire cervix, and any adjacent pathological tissue, if present, and is determined through clinical and radiological examination at the time of brachytherapy, taking into account tumor spread at diagnosis as indicated on clinical examination and initial MRI for staging. The Intermediate-Risk CTV always encompasses the Adaptive High-Risk CTV along with appropriate margins that can be individualized and usually vary from 5-15 mm, accounting for potential microscopic disease spread.

OARs in brachytherapy include the bladder, rectum, sigmoid, and bowel. These organs are contoured from at least 2 cm below the IR-CTV to 2 cm above the uterus. The bladder is contoured by outlining the outer bladder wall, including the bladder neck. The rectum is contoured by defining the outer rectal wall, extending from the anal sphincter to the point where it transitions into the sigmoid. The sigmoid is contoured starting from the recto-sigmoid flexure and extending at least 2 cm above the parametria and the uterus. Finally, bowel loops positioned within 3-4 cm of the uterus and the applicator are also contoured by outlining their outer contours to ensure precise dose delivery while minimizing risk to these critical organs.

If MRI is unavailable, CT-based contouring guidelines, as outlined by Mahantshetty U et al. in Radiotherapy and Oncology (2021), should be followed.

WHAT IS THE RECOMMENDED APPROACH FOR TREATMENT PLANNING IN BRACHYTHERAPY?

In terms of dose prescription and planning goals, according to GEC-ESTRO recommendations validated by EMBRACE and RetroEMBRACE, the D90 for the High-Risk CTV should be ≥ 85 Gy EQD2, with the more updated EMBRACE II recommending a D90 between 90-95 Gy EQD2. The residual GTV-T D98 should be ≥ 95 Gy, while the Intermediate-Risk CTV-T D98 should be ≥ 60 Gy. For OARs, the bladder D2cm³ should be kept below 80 Gy, the rectum D2cm³ below 65 Gy, the recto-vaginal point dose below 65 Gy, and the sigmoid/bowel D2cm³ below 70 Gy. Vaginal stenosis risk associates with dose to the recto-vaginal point. This point rectovaginal reference point is defined by the intersection between the tandem and the source positions (ovoids or ring) and 5mm dorsal of the posterior vaginal wall and dose reduction to this point can typically be achieved by decreasing dwell times in the ovoid/ring applicators and increasing tandem or needle loading.

WHAT ARE THE ACUTE AND LONG-TERM TOXICITIES ASSOCIATED WITH HDR BRACHYTHERAPY?

During the 5-6 week course of EBRT, adverse effects manifest gradually, peaking towards the end of treatment. Common side effects include proctitis, characterized by rectal irritation leading to diarrhea, cramping, and urgency; cystitis, presenting with increased urinary frequency, dysuria, and urgency; and vaginal mucositis, which results in vaginal irritation, discomfort, or discharge. Brachytherapy can cause additional vaginal soreness and/or bleeding. Long-term effects of brachytherapy may include vaginal narrowing, dryness, and loss of elasticity, which can impact sexual function. Vaginal dilators are recommended to alleviate these effects, as they help maintain vaginal patency by stretching the tissue, reducing fibrosis, and promoting healing by encouraging blood flow and flexibility. Consistent use of dilators can prevent or minimize long-term vaginal shortening, narrowing, and sexual dysfunction, improving post-treatment quality of life.

HOW TO CONDUCT PATIENT FOLLOW-UP?

In the follow-up protocol for patients who have undergone treatment for cervical cancer, visits are typically scheduled every 3-4 months during the first year, every 6 months during the second and third years, and annually up to five years post-treatment. Imaging to assess complete cancer response with either MRI or FDG PET-Scan is typically performed 4-6 months after radiotherapy completion and additional imaging or biopsies are performed as clinically indicated. Each visit includes a thorough gynecological examination to assess local control and detect potential recurrence.

Education on recurrence symptoms, lifestyle modifications, sexual health, and long-term treatment effects is also provided to patients.

GYNE BRACHYTHERAPY

CASE 4: ENDOMETRIAL VAGINAL RECURRANCE BRACHYTHERAPY

A 68-year-old woman with a history of stage IA G1 endometrial cancer, treated 3-years ago with surgery alone and no adjuvant therapy, presented more recently with vaginal bleeding. A gynecologic examination revealed a firm 2..5 cm mass on the posterior upper vaginal wall with no fixation to paravaginal tissues or pelvic sidewall. On direct visualization, the lesion was friable and no other lesions were appreciated in the vagina or external genitalia.

Pelvic MRI revealed a 2.5 cm hyperintense lesion confined to the vaginal wall, with no involvement of adjacent organs, nodes or distant metastasis. Her ECOG performance status is 1, and her medical history includes well-controlled type 2 diabetes. A biopsy was performed, and the pathology confirmed recurrent endometrial carcinoma, grade 2. As a salvage strategy, the patient was planned for EBRT at a dose of 45 Gy in 25 fractions, followed by intesrtitial vaginal brachytherapy.

WHAT IS THE RECOMMENDED TREATMENT FOR A LOCAL ENDOMETRIAL RECURRANCE?

A thorough disease evaluation should include a pelvic examination, along with a diagram that accurately depicts the tumor's characteristics, including size, location (upper, mid, or lower vagina), paravaginal involvement, and potential extension to the pelvic sidewall. The diagram should illustrate the precise location of the tumor, such as the anterior or posterior vaginal wall and lateral involvement (left or right). Endometrial cancer recurrences typically occur at the site of the posthysterectomy surgical scar but can also develop in other areas of the vaginal wall.

Before initiating treatment, it is crucial to obtain biopsy confirmation of the recurrence to guide appropriate therapeutic decisions. A pelvic MRI is valuable because it offers superior soft tissue resolution compared to CT, allowing for more detailed visualization of the local extent of disease, including tumor invasion, lesion thickness and involvement of surrounding tissue involvement.

Since this patient has not previously undergone pelvic radiotherapy, the treatment plan should include EBRT with doses of 45-50 Gy in 25-28 fractions to the pelvis. This approach serves two key purposes: first, to target microscopic disease potentially located in lymph nodes, vagina and paravaginal tissues and also to downsize the gross disease located in the vaginal cuff. Downsizing allows for reduction of brachytherapy treated volumes thereby reducing radiation doses to surrounding organs at risk and toxicity.

Before treatment simulation, it is helpful to mark the most distal extent to ensures that an adequate margin is maintained around the full extent of the tumor for accurate treatment planning. Elective doses of EBRT should be considered for tumors involving the lower vagina.

After EBRT, an additional boost to any residual disease is typically delivered via brachytherapy, which can be either intracavitary or interstitial. Image-guided interstitial brachytherapy is preferred to lesions that are thicker than 7mm due to its ability to better minimize exposure to surrounding healthy tissue including vaginal mucosa. Thinner lesions that, especially not involving the vaginal cuff, can be safely boosted by intracavitary brachytherapy techniques (ie. multichannel cylinder).

WHAT IS THE RECOMMENDED CONTOURING PROTOCOL FOR IMAGE-GUIDED VOLUME-BASED PRESCRIPTION AND PLANNING?

Recently, representatives from the Gynecologic GEC-ESTRO, ABS, and CBG published a comprehensive set of guidelines titled GEC-ESTRO (ACROP)-ABS-CBG Consensus Brachytherapy Target Definition Guidelines for recurrent endometrial and cervical tumors in the vagina. These guidelines offer standardized recommendations on target definition, aiming to improve precision in brachytherapy treatment for vaginal recurrences.

For contouring recommendations in vaginal recurrences, the GTV-T residual is the macroscopic tumor that remains after EBRT. This is identified by clinical examination and T2-weighted MRI, which typically shows as an hyperintense signal. The CTV-T high-risk includes GTV-T residual and surrounding tissues that may harbor macroscopic disease. This encompasses thickened, irregular vaginal mucosa on clinical exam and hypointense fibrotic areas on MRI. If there was prior involvement of paravaginal or parametrial spaces, regressed areas, termed “gray zones,” should also be included. The CTV-T intermediate-risk addresses potential microscopic disease adjacent to CTV-T high risk and includes the initial extent of disease with a 0.5 cm safety margin while respecting anatomic boundaries such as the bladder, rectum, pelvic floor, and pelvic walls. In cases of high-risk histology, such as serous carcinoma or known lymphovascular space invasion, a larger safety margin may be considered. However, this should be carefully balanced to avoid unnecessary damage to vulnerable areas, such as the vulva or vaginal introitus, which are at risk for necrosis.

The normal vagina outside of the CTV-T high-risk should be treated as an OAR to minimize excessive radiation exposure to healthy tissues. In cases of complete response to EBRT with no detectable macroscopic disease, only the CTV-T intermediate risk should be delineated, covering the original extent of the disease. OARs in brachytherapy include the bladder, rectum, sigmoid, and bowel.

WHAT TOTAL DOSE OF EXTERNAL BEAM RADIATION AND BRACHYTHERAPY SHOULD BE PRESCRIBED IN PATIENTS WITHOUT A PREVIOUS HISTORY OF RADIATION THERAPY?

There are no prospective trials that establish the optimal dose for treating vaginal recurrences of endometrial cancer. However, several studies suggest that higher radiation doses improve local control. More recent image-guided brachytherapy series have demonstrated excellent local control rates with D90 doses between 74.8, 76, and 83 Gy. Current practice is to aim for 75–80 EQD2Gy when no prior radiation therapy has been administered.

HOW TO CONDUCT PATIENT FOLLOW-UP?

For follow-up after treatment of vaginal recurrence of endometrial cancer, a physical examination every 3-6 months for the first 2-3 years, then every 6 months to annually thereafter. Imaging, such as PET or MRI, should be performed based on clinical indications, with the first post-treatment imaging typically occurring at 4-6 months. Regular follow-up is essential to monitor for local recurrence and treatment-related adverse effects. The use of a vaginal dilator is recommended to reduce the risk of vaginal stenosis and maintain tissue elasticity.

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