Thames Valley and Wessex Radiotherapy Network

Radiotherapy Protocols

Brachytherapy – Cervix, Endometrium, Vagina

This document is the standardised Thames Valley and Wessex Radiotherapy Network Brachytherapy treatment protocol developed collaboratively by the Gynaecology Brachytherapy Protocol Working Group:

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Document History

Date of Issue	Version Number	Date Approved	Responsible for Change	Nature of Change	Ratification/ Approval
12.11.2024	1.0	12.11.2024	RTN Gynae Group	Network-wide protocol	Formal ratification by the NOG 13.12.24

Contents

1. Primary Objective and Scope

To summarise the planning and treatment of patients receiving adjuvant and radical High Dose Rate (HDR) Brachytherapy radiotherapy for gynaecological cancers for use in Radiotherapy Centres in the Thames Valley and Wessex Radiotherapy Network.

This protocol should be read in conjunction with the site-specific protocols for Cervix, Endometrium and Vulva.

2. Indications

Inclusion/Exclusion Criteria (including retreatment guidelines)

- Reference should be made to tumour site-specific protocols.

Clinical Indications

- Brachytherapy can be considered as the sole treatment for early stage cervical, uterine, vulval or vaginal cancer if the patient declines, or is unsuitable, for surgery.

- Intracavitary and interstitial brachytherapy is an integral part of radical radiotherapy management of gynaecological cancers. It is usually given after completion of external beam treatment. It is scheduled to complete all radiation treatment within 47 to maximum 56 days, as per RCR guidance. Some clinical situations may require a delay.

- Interstitial brachytherapy should be offered where clinically appropriate. A referral pathway should be in place to centres of expertise if not available locally.

- Interstitial brachytherapy can be delivered using interstitial needles within an applicator (Applicator interstitial) or as a sole interstitial implant (template interstitial), usually delivered for gynaecological brachytherapy using a perineal template. If centres with applicator interstitial expertise do not offer template interstitial brachytherapy, they should develop links with a specialist centre where they can refer appropriate patients if required.

Complex brachytherapy is defined as:

- Procedures requiring interstitial insertions either with or without intracavitary applicators.
- Reirradiation using brachytherapy requiring off-protocol planning.

Indications for interstitial brachytherapy include:

- Large or wide residual GTV or HRCTV that would not be covered by intracavitary applicators only.
- Patients whose OAR dose would be reduced by use of interstitial needles.
- Vaginal, vulval or perineal disease extending into vaginal or paravaginal spaces.
- Complex pelvic recurrences such as vaginal vault disease that would not be covered with an intravaginal applicator alone.

Re Irradiation

- Re-irradiation may be considered where clinically appropriate, and after MDT discussions where other treatment options such as surgery or SABR can be offered.

- Consider neoadjuvant chemotherapy to reduce the treatment volume if appropriate.

3. Pre-Radiotherapy Investigations

Reference should be made to tumour site-specific protocols.

Consider magnetic resonance imaging (MRI) within the week prior to first brachytherapy insertion to aid applicator selection including placement of interstitial needles.

4. Therapeutic Schema

Radiotherapy involves a combination of external beam pelvic (± para-aortic) radiotherapy plus brachytherapy, with the additional of weekly cisplatin chemotherapy if appropriate.

Interstitial brachytherapy insertions must be offered to patients where clinically appropriate, and referral to a brachytherapy centre within the network is recommended if interstitial brachytherapy cannot be offered locally.

For clarification, the doses stated below are intended to be prescribed to the 100% isodose, and therefore a different (usually higher) dose may be received by the HRCTV D90. The BED EQD2 is the dose received by the target, in most cases the HRCTV D90, and is the combined dose from EBRT (if used in combination) and brachytherapy.

Cervix

Cervix (primary)

- HR-CTV D90 >85Gy EQD2
- 45Gy/25# EBRT + 28Gy/4#
- 45Gy/25# EBRT + 3 fraction regimen if HR-CTV D90 of >85Gy can be achieved. This is useful for small tumours <30cc.
- Suggested fraction limit of 10Gy to reduce OAR doses.

Cervix (adjuvant)

- 45Gy/25# EBRT + VVBT if close or positive margins
- Suitable VVBT regimen following 45Gy/25# EBRT: 8Gy/2# (EQD2 53.6Gy), 10Gy/2# BT (EQD2 56.8Gy),
- 45Gy/25# EBRT + 12Gy/3# (EQD2 58.3Gy) is a suitable regime for positive margins.

Endometrial

Endometrial (radical – intact uterus with inoperable disease)

- 45Gy/25# + 28Gy/4#

In rare circumstances, brachytherapy alone may be considered.

- RCR suggests 36Gy/5# (EQD2 51.6Gy) or 37.5Gy/6# (EQD2 50.8Gy) prescribed to uterine serosa.

Endometrial (adjuvant):

Suitable regimens combined EBRT and VVBT

- 48.6Gy/27# EBRT + VVBT 8Gy/2# (EQD2 57.1Gy)

- 45Gy/25# EBRT + 10Gy/2# (EQD2 56.8Gy)
- 45Gy/25# EBRT + 8Gy/2# (EQD2 53.6Gy)- careful consideration as lower EBRT dose than PORTEC trial
- 45Gy/25# EBRT + 12Gy/3# (EQD2 58.3Gy) is a suitable regime for positive margins.

VVBT alone

- 21Gy/3# (EQD2 29.8Gy)

Vaginal vault brachytherapy - prescribed to 5mm treatment depth,
Typical length 3-5cm. Different lengths can be considered with evidence supporting good outcome.

Endometrial (Salvage):

Salvage cases vary on an individual basis, and any brachytherapy dose fractionation and applicators will be chosen as appropriate.

- Aim to give >60Gy EQD2 (including brachy, provided OAR constraints are met).

Suitable regimes would be:

- 45Gy/25# + 24Gy/4# (EQD2 76.3Gy) upper vagina

A high dose (macroscopic tumour) and low dose (microscopic spread) volume may be considered using a multichannel applicator.

- 45Gy/25# + 20Gy/4# (EQD2 69.3Gy) High dose
- 45Gy/25# + 12Gy/4# (EQD2 57.3Gy) Low dose

Brachytherapy alone:

- 42Gy/6# (EQD2 59.5Gy)

Vagina

There is currently a lack of evidence-based recommendations to guide target definition and planning aims for vagina cancer. The GEC-ESTRO (EMBRAVE) group are developing protocols. The current guidance is summarised below, with suggested dose fractionation regimes.

Current guidance:

- RCR guidance suggests 70-80Gy EQD2.
- retroEMBRAVE suggests increased local control EQD2 >80Gy.
- ABS suggests upper vagina 70-85Gy EQD2, distal vagina in close proximity to the vulva or rectovaginal septum 70-75Gy EQD2. Poor response to EBRT or large residual disease may benefit from 80-85Gy EQD2.

Suitable regimes include:

- 45Gy/25# + 24/4# (EQD 76.3Gy) or 28Gy/4# (EQD2 83.9Gy) Upper vagina
- 45Gy25# + 20Gy/4# (EQD2 69.3Gy) Lower vagina.

A high dose (macroscopic tumour) and low dose (microscopic spread) volume may be considered using a multichannel applicator.

- 45Gy/25# + 20Gy/4# (EQD2 69.3Gy) High dose
- 45Gy/25# + 12Gy/4# (EQD2 57.3Gy) Low dose

RCR suggested regimes

- 24-28Gy/4# to upper vagina
- 18.75-20Gy in 5# to lower vagina.

Vulva

Vulva (adjuvant)

- Brachytherapy not recommended for adjuvant vulva.

Vulva (inoperable):

- Most likely to treat with EBRT, but brachytherapy boost case be considered in selected patients.

RCR suggests 60-68Gy EQD2 to vulva. Minimum of 60Gy
RCR suggest if disease is more vulvo-vaginal in nature, doses of up 80Gy may be appropriate.

5. Tumour Motion

Consideration should be made to assess applicator movement and needle migration between imaging/treatment planning and treatment.

6. Treatment Planning

Integrating MRI into the imaging pathway is considered standard of care for intracavity and interstitial treatments. MRI planning is defined as an MRI scan done on the day of procedure with an MRI-compatible brachytherapy applicator in situ. Images are used to mark gross tumour

volume (GTV), high/ intermediate-risk clinical target volume (HRCTV/IRCTV) and OAR and to calculate doses on planning software. CT can also be used within the planning pathway.

Individual centres will develop their own techniques based on the planning software, applicator inventory, clinical findings and imaging modalities available. EMBRACE and retroEMBRAVE protocol guidance is available for planning aims.

Vault applicator treatments are based on standard library plans. CT imaging is required verify applicator positioning.

7. Volume Outlining

MRI imaging is recommended for delineation of the target volume, as per GEC/ESTRO guidelines. Imaging for planning will vary between centres and will follow local protocol, with suggested imaging modalities below.

OAR outlining can be performed on CT or MRI imaging depending on local imaging techniques. Consistency is required between imaging schedules (i.e., if outlining is performed on MRI at fraction 1, this imaging must be available for outlining and planning on fractions 2-4 to ensure consistency in reporting).

Fusion between CT and MR imaging is required to transfer volumes to a common dataset for treatment planning. Priority should be given to applicator registration (rather than bony anatomy) and reviewed on a patient basis, as there are clinical situations that require fusion based on needles (not applicators).

Fusion between MRI sequences can be performed based on DICOM however each centre must review the reliability of DICOM fusion and assess whether additional registration is required.

<u>Cervix (radical): as per EMBRACE guidelines</u>

- GTV-res: Gross tumour volume (residual disease after chemoradiotherapy, based on EUA and imaging).
- HR-CTV: High risk clinical target volume. Entire cervix plus GTV and extra-cervical spread including “grey zones” on MRI at the time of brachytherapy.
- IR-CTV: Intermediate risk clinical target volume

<u>Cervix/endometrial (adjuvant):</u>

- Vaginal vault (5mm depth)

<u>Endometrial (primary):</u>

- As per cervix protocol.

Vaginal (primary):

- GTV-res disease based on EUA and MRI.

Consideration to subclinical spread should be made when defining treatment volumes, dose, and fractionation. EMBRAVE are developing definitions for HR-CTV and IR-CTV.

OAR Outlining:

OAR outlining will be performed on organs in the brachytherapy treatment region, including:

- Bladder, rectum, sigmoid and small bowel.
- Vaginal wall: PIBS points are unsuitable for vaginal disease, and only applicable in cervix.
- Urethra (if inside treatment area):

8. Dose Calculation

Dose calculation should be performed using TG43 or equivalent.

- Consider TG186 or advanced algorithms for dose calculation when closer to air.
- In-vivo dosimetry could also be used to determine the scatter and lack of dose contribution from air at labia/vulva.

If TG43 algorithms are used, it may be appropriate to apply bolus material to help with backscatter or adjust dose prescription to account for the dose calculation difference.

Sum the EBRT dose with brachytherapy dose.

- Use α/β 3 for OAR and α/β 10 for HR-CTV to convert to EQD2.
- If dose received during EBRT >100% in OAR, confirm site of hotspots do not correspond to D2cc region and assess if SIB overlaps with Brachytherapy volume.

9. Organs at Risk (OARs) Limits

Plan evaluation based on EMBRACE hard limits (planning limits) and with consideration for soft constraints (planning aims).

EMBRACE planning aims for Cervix	**D90 HR-CTV $EQD2_{10}$**	**D98 HR-CTV $EQD2_{10}$**	**GTV D98 $EQD2_{10}$**	**D90 IR-CTV $EQD2_{10}$**	**D2cc bladder $EQD2_3$**	**D2cc rectum $EQD2_3$**	**D2cc Vagina (Rectal ICRU) $EQD2_3$**	**D2cc sigmoid/bowel $EQD2_3$**
Planning Aims	>90Gy	>75Gy	>95Gy	>60Gy	<80Gy	<65Gy	<65Gy	<70Gy
Planning Limits	>85Gy		>90Gy		<90Gy	<75Gy	<75Gy	<75Gy

If the planning aims or planning limits to the OAR are to be exceeded, the clinician will make the decision of whether to accept reduced HR-CTV coverage, or exceed the OAR tolerances, on an individual basis

Other OAR tolerances can be considered if appropriate.

- Urethra: D0.1cc <85Gy
- Vagina: D2cc <145Gy
- Anus: D2cc <70Gy

10. Treatment Delivery

Brachytherapy treatments will be performed on a remote HDR Afterloader using Ir-192 high dose rate source with a nominal activity of 370GBq (10Ci) using the vendor supplied equipment at each centre.

Cervix

The aim is to complete radiotherapy treatment within 56 days (from start of EBRT to last fraction of brachytherapy), however local protocols aim to treat within 47 days.

Typical treatment schedules will treat EBRT in weeks 1-5, and then brachytherapy in weeks 6-7. Overlap with brachytherapy and EBRT treatments can be considered if the brachytherapy regime means the overall treatment time is exceeded.

Brachytherapy treatment delivery will be performed in 3-4 fractions, with a minimum of 6 hours between fractions.

Brachytherapy regimes include:

- 4 fractions based on 1 theatre insertions
- 4 fractions based on 2 theatre insertions
- 4 theatre insertions with 1 fraction delivered on each insertion.

There is currently no evidence to suggest any clinical benefit to either regime, and brachytherapy treatments should be based on local resource. There are some practical advantages for 2 insertions which include the ability to optimise or adjust the second applicator insertion if required.

Consideration of a 3-fraction treatment regime is feasible in individual circumstances. Reasons for variation may include patient tolerance, or for small target volumes (HR-CTV <30cc)

Treatment delivery based on standard plans is not recommended and evidence shows image-based planning reduces OAR related toxicity.

Single fractions can be delivered based on a previously optimised plan (i.e., treat fraction 2 based on fraction 1), however careful review of imaging is recommended prior to treatment to ensure OAR status and applicator movement do not affect the plan integrity and treatment delivery. In cases where a previous fraction treatment plan is used, a retrospective plan must be generated to assess to the delivery and record DVH information for radiobiological calculation.

Endometrial Cancer

Adjuvant brachytherapy is delivered in combination with EBRT or as a sole treatment. The aim is to start adjuvant radiotherapy 6-12 weeks post op. If VVBT is given in combination with EBRT it is usually given towards the end of the EBRT treatment or in the week after completion. If VVBT is given alone, it is given as 2-3 fractions per week over 1-2 weeks.

11. Supportive care

Centres will develop protocols for care prior to and during the brachytherapy treatment. This will include safe blood count parameters for platelets and neutrophils prior to, during insertion, and in-patient stay.

- Anticoagulation protocol needs to be in place.

- Consider IV antibiotics during interstitial brachytherapy.
- Suitable analgesic regime required (e.g., epidural and/or PCA)
- Prior to removal of interstitial applicator, consider methoxyflurane and tranexamic acid.

12. Follow-up after treatment

As per site specific protocol.

13. References

1. EMBRACE-II study protocol. Available at: https://www.embracestudy.dk/UserUpload/PublicDocuments/EMBRACE%20II%20Protocol.pdf
2. Pötter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, Nout R, Tan LT, Haie-Meder C, Mahantshetty U, Segedin B, Hoskin P, Bruheim K, Rai B, Huang F, Van Limbergen E, Schmid M, Nesvacil N, Sturdza A, Fokdal L, Jensen NBK, Georg D, Assenholt M, Seppenwoolde Y, Nomden C, Fortin I, Chopra S, van der Heide U, Rumpold T, Lindegaard JC, Jürgenliemk-Schulz I; EMBRACE Collaborative Group. **The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies**. Clin Transl Radiat Oncol. 2018 Jan 11;9:48-60.
3. Westerveld H, Schmid MP, Nout RA, Chargari C, Pieters BR, Creutzberg CL, Sturdza A, Lindegaard JC, van Kesteren Z, Mazeron R, Nesvacil N, Fokdal LU. **Image-Guided Adaptive Brachytherapy (IGABT) for Primary Vaginal Cancer: Results of the International Multicenter RetroEMBRAVE Cohort Study**. Cancers (Basel). 2021 Mar 23;13(6):1459.
4. Beriwal S, Demanes DJ, Erickson B, Jones E, De Los Santos JF, Cormack RA, Yashar C, Rownd JJ, Viswanathan AN; American Brachytherapy Society**. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer**. Brachytherapy. 2012 Jan-Feb;11(1):68-75.
5. Schmid MP, Fokdal L, Westerveld H, Chargari C, Rohl L, Morice P, Nesvacil N, Mazeron R, Haie-Meder C, Pötter R, Nout RA; **GEC-ESTRO GYN Working Group. Recommendations from gynaecological (GYN) GEC-ESTRO working group - ACROP: Target concept for image guided adaptive brachytherapy in primary vaginal cancer**. Radiother Oncol. 2020 Apr;145:36-44.
6. Kamrava M, Leung E, Bachand F, Beriwal S, Chargari C, D'Souza D, Erickson B, Fokdal L, Han K, Harkenrider M, Lin L, Mahantshetty U, Nesvacil N, Ravi A, Schmid M, Vigneault E, Westerveld H, Yashar C, Nout R. **GEC-ESTRO (ACROP)-ABS-CBG Consensus Brachytherapy Target Definition Guidelines for Recurrent Endometrial and Cervical Tumors in the Vagina**. Int J Radiat Oncol Biol Phys. 2023 Mar 1;115(3):654-663.

7. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann J, Bosse T, Chargari C, Fagotti A, Fotopoulou C, Gonzalez Martin A, Lax S, Lorusso D, Marth C, Morice P, Nout RA, O'Donnell D, Querleu D, Raspollini MR, Sehouli J, Sturdza A, Taylor A, Westermann A, Wimberger P, Colombo N, Planchamp F, Creutzberg CL. **ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma**. Int J Gynecol Cancer. 2021 Jan;31(1):12-39. doi: 10.1136/ijgc-2020-002230. Epub 2020 Dec 18.
8. Rovirosa Á, Zhang Y, Tanderup K, Ascaso C, Chargari C, Van der Steen-Banasik E, Wojcieszek P, Stankiewicz M, Najjari-Jamal D, Hoskin P, Han K, Segedin B, Potter R, Van Limbergen E; Endometrial Task Group. **Stages I-III Inoperable Endometrial Carcinoma: A Retrospective Analysis by the Gynaecological Cancer GEC-ESTRO Working Group of Patients Treated with External Beam Irradiation and 3D-Image Guided Brachytherapy**. Cancers (Basel). 2023 Sep 27;15(19):4750.
9. RCR Radiotherapy dose fractionation, 4th Edition, 2024. Available at: https://www.rcr.ac.uk/our-services/all-our-publications/clinical-oncology-publications/radiotherapy-dose-fractionation-fourth-edition/
10. Clinical Oncology Gynaecological cancer: RCR consensus statements, 2024. Available at: https://www.rcr.ac.uk/media/5snbzz40/rcr-publication-gynaecological-consensus-statement.pdf