ADAPTIVE INTELLIGENCE™ CONSORTIUM

Best Practices White Paper: Cervix Adaptive Radiotherapy with Ethos

Disease site: Cervix

Ethos version: Ethos Treatment Management 2.0 (Version 02.00.10) & Ethos Treatment Planning 1.0 (Version 01.00.10)

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Introduction

Despite advances in recent times with HPV vaccination and screening, cervical cancer still represents a significant burden in society, being the 4th most common cancer diagnosed in women globally. In 2018, an estimated 570,000 women were diagnosed worldwide, with an average age of 53 years at diagnosis, resulting in the deaths of 311,000 women[1].

The current standard of care for treatment of locally advanced cervical cancer is concurrent chemo-radiotherapy (RT). This consists of weekly cisplatin, external beam RT with a dose prescription of 45-55 Gy in 25 fractions, followed by an HDR brachytherapy (BT) boost of 24-30 Gy in 3-5 fractions[2]. This treatment management plan is suitable for a range of tumour types, including: squamous cell carcinoma, adenocarcinoma and adeno-squamous carcinoma of the uterine cervix.

Advanced RT techniques, such as intensity-modulated RT (IMRT), for cervical cancer RT treatment have been proven to reduce normal tissue toxicity whilst maintaining tumor control[3]. To account for variation in organ motion, appropriate Planning Target Volume (PTV) margins, as well as utilizing an Internal Target Volume (ITV) to account for cervix-uterine motion, ensures dose coverage to the Clinical Target Volume (CTV). Lim et al. [4] demonstrated, however, there still remains a potential of under-dosing to the target with unpredictable and excessive movement.

The use of adaptive radiotherapy (ART) to re-optimize and account for any inter-fractional changes to a patient's anatomy, presents itself as a solution to this problem. Through the use of auto-segmentation, deformable registration and auto-planning, the treatment can be customized and tailored for each fraction. The purpose of this document is to support the rapid and safe implementation of the Ethos system for online adaption of cervix cancer patients. This report is based on the early adopter experiences of the authors' institutions and testing valid for v1.1. In general, the recommendations in this document endorse the guidelines outlined in the EMBRACE II clinical trial [5], which follow the framework outlined in the Gyn GEC ESTRO Recommendations I-IV [6-9], as well as ICRU report 89[10].

Initial Planning

Patient cohort demographics and description

Patient inclusion/exclusion criteria are recommended to follow the EMBRACE II study[5] and Australian eviQ guidelines[2].

a. Inclusion
   i. Tumor types: squamous cell carcinoma (SCC), adenocarcinoma (AC) and adeno-squamous carcinoma (ASC) of the uterine cervix
   ii. Tumor and clinical staging: FIGO (International Federation of Gynecology and Obstetrics) stage IB-IVA. Nodal status according to TNM classification, para-aortic nodes to L2 included (M0), however extensive nodal involvement outside this region would be a contraindication
   iii. Performance status: ECOG 0-2

b. Cautions
   i. Non-rheumatoid collagen vascular disorders
   ii. Inflammatory bowel disease or history of bowel obstruction
   iii. Renal transplant or horseshoe kidney
   iv. Prior radiotherapy to the pelvis
   v. Hip prostheses

c. Exclusions
   a. Pregnancy

Treatment management and intent

Informed by patient workup and staging, usually definitive radio-chemotherapy with curative intent, inclusive of external beam radiotherapy (EBRT), brachytherapy boost and cisplatin.

Prescription dose and fractionation: EBRT is designed to be delivered dynamically (IMRT or VMAT), with 45 Gy to be delivered in 25 fractions to the whole pelvis and elective nodal region, and involved nodes boosted (simultaneous integrated boost- SIB) with an additional 10-15 Gy, as per the EMBRACE II protocol[11].

a. 45 Gy in 25 fractions (1.8 Gy per fraction) to CTV-T and CTV-E
b. 55-60 Gy in 25 fractions (2.2-2.4 Gy per fraction) to CTV-N

Characteristics of patients more likely to benefit from adaptive radiotherapy (ART)

Whilst all patients who fit the criteria for definitive EBRT in the setting of cervical cancer may potentially benefit from the use ART there may be patients who can be prioritized[12].

a. Rapidly progressing tumors, or conversely, rapidly responding or radiosensitive tumors, such as SCC
b. Patients who have undergone ovarian stimulation
c. Patients exhibiting incontinence or suggestive of bladder compliance issues, preventing them from being simulated/treated with a full bladder

d. Contraindications for IV/oral contrast
e. Pelvic sidewall invasion

Supporting imaging

Multi-modality imaging can be used to aid delineation of target volumes for initial planning. The utility of supporting imaging is limited by the image registration accuracy. The pertinent supporting imaging for this patient cohort includes;

a. MRI: the superior soft tissue contrast can be used to help define regions not so clearly identified on CT imaging as a result of lower contrast resolution.
b. PET/CT: where known or potential regional or distant disease is present, PET avidity is assessed and compared to features on planning CT images for consideration and inclusion in target volumes.

Outline recommended template used and capture physician's intent with target dose and OAR constraints for this disease site

Target coverage and OAR tolerance DVH metrics from EMBRACE 2[11] can be used as a starting point for template development, inclusive of RO clinical objectives and preferences for treatment, as well as informed by the template commissioning and development process. The Varian sponsored adaptive cervix study clinical trial protocol also provides more information on recommended templates to be used[13]. Example Ethos adaptive cervix planning templates are given in Appendix 1.

The template development process should utilize recommended templates and standard cervix radiotherapy planning constraints initially, however templates can be refined based on local testing in the emulator environment with local patient datasets and processes. Local users may consider making DVH comparisons to Eclipse plans, RapidPlan or other gold standards. Templates for single dose level and integrated boost nodal plans should be considered. Note that template development is a highly iterative process.

An important relationship to remember in planning template development is how it will impact the adaptive plan generation process on treatment. For example, any structures to be seen on treatment for editing and evaluation in the "Edit Contours" workspace must have at least one objective defined in Priority 1 or 2.

RapidPlan model in Ethos planning

RapidPlan has been applied to Ethos plans in the Ethos environment with mixed success, noting that it is dependent on how the RapidPlan model has been built. Inclusion of RapidPlan may not benefit target coverage, but may benefit OAR metrics with the basis that RapidPlan operates using a line objective across the full length of the DVH.

Ethos generated plans (using the Intelligent Optimization Engine- IOE) were compared to Eclipse generated plans (using RapidPlan), while controlling variables such as field number and geometry. These were compared using specified dose metrics, isodose comparison and full DVH comparison.

This comparison highlighted the following key differences;

1. Target volume coverage has a greater homogeneity i.e. steeper DVH gradient
2. OAR (e.g. bladder, bowel) lower dose regions were superior with use of RapidPlan

The utility of RapidPlan can vary from application in the Ethos environment directly to Ethos plans or in template development as a commissioning tool for benchmarking with Eclipse. It is common that OAR objectives are predominantly based at higher dose limiting objectives and therefore reliant on normal tissue objective (NTO) approaches implemented within the IOE. These comparisons have shown that we need to define more points along the length of the DVH curve to further optimize plan quality. Review of existing RapidPlan models or current planning methods enable the user to understand these additional metrics. There are a number of published journal articles describing the utility and benefit of knowledge-based planning in the setting of cervix cancer RT, which may guide the user in development and implementation of a RapidPlan model for commissioning or treatment purposes in the Eclipse environment[14, 15].

Planning CT Simulation

a. Patient preparation

   It is important to consider patient preparation in CT simulation to minimize uncertainties in patient treatment. Considerations, such as bladder filling and rectal filling, should be assessed to minimize uncertainties in synthetic CT (sCT) generation and ensure stability throughout treatment, particularly with respect to intrafraction motion. Margins should be tailored to account for these uncertainties.

   There are various methods to proceed, general consensus as per EMBRACE 2 guidelines is rectum/sigmoid empty (rectum <4cm max extension in any direction). Bladder may be empty, full, or neutral and voluming/planning technique changed accordingly. EMBRACE 2 recommend bladder empty/full simulation to create an ITV structure and proceed with bladder full at treatment, which reduces small bowel dose and increases the total irradiated volume[11]. Bladder empty simulation and treatment reduces the total irradiated volume, however increases small bowel dose. Of most concern for adaptive radiotherapy is stability throughout treatment, literature suggests that the smaller the bladder volume is on treatment the lower the inflow rate and consequently less intrafraction motion[16]. Studies have shown that on average 2-3mm of intrafraction variation in bladder/rectal volumes may be expected in cervix patients simulated with comfortably full bladder volumes over a 30 minute time period, which would need to be accounted for in the PTV margin employed[17, 18]. Therefore, the choice of bladder preparation and volume is a trade-off between small bowel dose, total irradiated volume of tissue, and intrafraction motion.

   A balanced approach may be to consider a neutral state, where by the patient empties their bladder 1-2 hours prior to simulation, voids fluids during this period and is allowed to fill naturally in the lead-up to planning scan and treatment each day, this is the recommended approach in the Varian sponsored adaptive cervix trial protocol[13]. Departments should evaluate the pros and cons of each approach, their margins and treatment technique in choosing which method to proceed with. A pre/post CBCT study may help inform intrafraction motion margins to be employed.

b. Immobilization and setup

   Patient setup and immobilization should follow standard radiotherapy[2, 11].

Site specific setup accuracy and precision should be assessed, including an evaluation of intrafraction motion uncertainties, informing appropriate margins to be applied to target volume. Additional immobilization measures may be considered and adopted following this evaluation.

Common setup and immobilization measures include supine patient positioning and use of patient comfort aids such as head rest/neck support, knee and ankle supports, or a wingboard. A vacuum bag may also be used as an alternative and may improve setup reproducibility.

c. Image acquisition
The image quality/dose relationship should be considered in the protocol used for scanning and will be specific to the department CT configuration. Use of a relatively large kV/mAs pelvis-type scan would be appropriate, with slice thickness <3 mm. Scan FOV and sup-inf extent should be large enough to encompass all targets (primary and nodal) and OARs for planning purposes. The use of IV, vaginal and oral contrast is optional and will aid in structure delineation, however will represent a systematic dosimetric and target propagation uncertainty in the sCT. Departments should evaluate the impact of this, although preliminary testing has shown these effects to be minimal and potentially outweighed by the benefits. A workaround for this, or intermediate implementation measure, is to consider acquiring 2 CT scans with and without contrast, with the non-contrast scan being identified as the primary reference image.

Segmentation

Organs contoured according to EMBRACE 2 guidelines for anatomical boundary conditions[11], and target volumes defined in accordance with ICRU 50[19], ICRU 62[20], ICRU 83[21] and ICRU 89[10].

a. Targets
    i. CTV-N (PTV-N)
    ii. CTV-E (PTV-E)
    iii. HR and LR CTV-T (PTV-T): given both of these structures are in close proximity and prescribed to the same dose level it can be more practical to combine them into a single CTV-T structure to minimize the amount of editing required in the on-couch adaptation process
b. Influencers
    i. Bladder
    ii. Uterus
    iii. Rectum
    iv. Bowel: note here the AI defined Bowel contour represents small and large bowel loops. Additionally, it is listed as an influencer, however in the current version of Ethos it does not act as an influencer for target propagation
c. OARs
    i. Sigmoid
    ii. Femoral heads
    iii. Bowel bag or bowel space: the definition of the structure needs to be considered here. Bowel bag is defined according to RTOG contouring guidelines [22], and in this sense crops out the uterus and bladder from the contour. Bowel space is defined differently again, cropping out CTV targets, although not the OARs listed previously. In both cases the structure is pre-processed and propagated according to the deformation vector field (DVF)[23]. Departments should evaluate the correct definition and use of the small bowel structure to maximize efficiency of workflow. Another option is to

consider a Bowel PRV, to be used as a surrogate for the cavity if the influencer Bowel loops are chosen as the planning structure.

Margins

a. Derived structures should be used to minimize the amount of contour modification required throughout the adaptive process. The downstream effects of initial planning contours and template setup on the reference CT and plan should always be considered. Structure margins and derivation can not only allow for increased efficiency in the on-couch adaptive process, but also increase the consistency of contours. In general, the recommendation is to apply derived structures to any contour that is created as a result of an expansion or Boolean operation performed on one or more other structures.
b. Departments should evaluate their technique in consideration of PTV margins to be applied. In particular, this would involve accuracy of patient setup/treatment, intrafraction motion and stability, contour accuracy (especially given the use of CBCT vs. CT), treatment time, machine tolerances and plan deliverability. The benefits of ART are that the interfraction uncertainty components of the PTV margin are minimized. A local pre/post CBCT study on a suitable cohort of cervix patients may help inform decision making. Although there is literature available on the topic (see "Planning CT simulation" section), the amount of intrafraction motion evident is highly dependent on patient preparation, simulation procedure, treatment time and local workflow. Dependent on the procedure followed and uncertainty evaluation performed PTV setup margins of 3-10 mm may be employed. The Varian sponsored adaptive cervix study trial protocol recommends 3-5 mm uniform PTV margins for all targets[13], while EMBRACE 2 recommends a minimum 5 mm margin be applied, however up to 10 mm depending on the uncertainty involved[11].

N.b. If voluming as per Embrace II is not currently implemented within your department, modifications to this process using similar principals to suit local or other internationally-recommended contouring guidelines can be considered. For example, deriving the CTV from the uterus influencer may assist with time saving on treatment in editing the propagated target structure, if the CTV definition is directly equivalent to uterus-cervix. There has also been evidence to suggest that avoiding cross-over of target structures (primary and nodal) can assist in propagation, however these definitions would contradict with the volume definitions proposed in EMBRACE II.

Dose Preview

This workspace provides an estimate of the structure DVHs and plan metrics according to the Ethos planning template and optimization applied. There is the ability to explore trade-offs in the plan optimization by adjusting the template order, e.g., moving an OAR D2cc constraint above a target D95% objective.

Plan optimization and DVH estimation is accomplished assuming a 9-field IMRT beam arrangement and technique to generate optimal fluences, not inclusive of leaf motion constraints. Photon Optimizer (PO), IOE and Fourier Transform Dose Calculation (FTDC) algorithms are used for optimization and dose calculation, which differs from the Acuros XB dose calculation algorithm used in final plan dose calculation[24].

The differences observed in DVH estimation and plan quality metric calculation between Dose Preview and the final plan calculation can often be significant, therefore it is important to follow through to final dose calculation for full plan evaluation when changes are made. Dose Preview does provide a good relative measure for exploring trade-offs and making patient-specific changes to the template/plan

following initial application of the commissioned template. Clinical experience has shown that small changes to the template on a per-patient basis are expected and that plan quality does benefit from these patient specific changes being applied.

Plan Generation and Review

Plan quality metrics

a. Evaluate all clinical target coverage objectives and OAR constraints as per EMBRACE 2 and template (scorecard system).
b. Evaluate dose distribution in terms of hot spots (D2cc or near-max dose), cold spots and low dose wash across targets and OARs.
c. Compare treatment plans generated for each beam arrangement, however during the template testing and commissioning phase it should be possible to identify a suitable beam arrangement and technique that best suits the patient cohort. The 12-field IMRT beam arrangement was found to give the highest plan quality based on testing completed within the AIC cervix group, however other factors such as treatment time may factor into the decision.

During the commissioning phase it can be useful to generate plans in Eclipse according to the accepted standard of care or local departmental protocol. This allows for benchmarking of Ethos-generated plans against the current standard Eclipse plans for template validation and refinement. Once the technique is established and Ethos plan quality proven to be equivalent or superior for a retrospective patient cohort and the first N (for example 5-10) clinical patients, there has been no evidence to suggest that generating plans in Eclipse is necessary for these patients. Commonly, Eclipse-generated plans for optimization and dose calculation in Ethos may be used for specific beam arrangements (for example 13 field IMRT) or for enforcing collimator rotation to increase degrees of freedom in plan optimization, however based on testing performed within the AIC group there was minimal benefit found when performing daily plan adaptation. If treating with IGRT plans and the Ethos-generated plan is considered highly complex and less robust to intrafraction anatomical changes, an Eclipse plan may be another alternative.

Pre-treatment patient specific QA

The design of pre-treatment patient specific QA for Ethos adaptive plans should consider existing guidelines and recommendations for treatment planning QA[25, 26], implementation of automated treatment planning in the clinic[27] and development of robust safety checklists[28]. Additional considerations specific to the Ethos adaptive process in the pre-treatment setting includes:

- Patient factors which may conflict with inclusion/exclusion criteria e.g. large metallic implants.
- Configuration/setup of technical structures (automatic/manual density corrections), simulation isocentre and couch plane.
- Review suitability of multi-modality image registration to aid contouring on subsequent treatment sessions.
- Review RT Intent configuration, noting that this applies to all treatment sessions (e.g., correct anatomical site and influencers)
- Ensure plan enabled for adaptive treatment, or as appropriate.
- Treatment frequency set as per prescription.
- Plan normalization, DVH estimation model and bolus set correctly.
- Contouring, activation and definition of derived structures set as per protocol (includes margin and Boolean operations).

- Correct clinical template and associated dose preview order (used in IOE) applied i.e. RO clinical priorities reflected in plan optimization and generation.
- All contours to be visualized/edited in on-couch adaptation have an objective in P1/2
- Assess beam arrangements and their suitability for the patient of interest.
- Evaluate Monitor Unit (MU) for each field and total against normal clinical range.
- Review plan quality using isodose distribution/homogeneity, hot spot locations/magnitude and DVH limits are within site protocol.
- Dose calculation (Mobius) and/or phantom measurement (suitable detector array) to independently validate the TPS dose prediction and deliverability of the RT Plan.

Implementation of a rigorous pre-treatment QA process is expected to optimize the quality of subsequent adaptive treatment sessions through ensuring all aspects that may have downstream impacts have been reviewed and adjusted where required.

Documentation

All documentation should follow standard treatment plan reporting requirements[19-21] and pre-treatment QA requirements[26, 28, 29]. Additional attention relevant to the Ethos adaptive process may include:

- CT checklist (inclusion/exclusion criteria, patient preparation instructions)
- RT intent report, clinical plan report and technical plan report.
- Independent dose calculation and plan deliverability reports (Mobius)
- Patient specific QA results (e.g., phantom- for plan verification or deliverability measurements)
- Physics/RT plan checklists

Team member roles and workflow

Roles and workflows may differ according to departmental workflows and credentialing/assessment programs in place. An example workflow is provided capturing the major steps in the initial planning process and typical tasks performed by various clinical staff. Table 1 provides one example implementation where the tasks required to conduct individual steps in the Ethos process are identified and associated with clinical team member roles. Clinical roles and responsibilities may vary in different clinical implementations.

a. Dosimetrist/RTT/RT
    i. Add RT intent based on RT prescription, planning directive template, review CT simulation document and specify setup instructions
    ii. Import planning and diagnostic imaging, including registration of images and assigning accuracy level
    iii. Contour OARs (note this step could involve performing contouring in other systems and importing the RT structure set)
    iv. Conduct preliminary manipulation of directive in Dose Preview
    v. Assess calculated treatment plan options against clinical protocol
    vi. Prepare plan reporting documentation
b. Physician/RO
    i. Prescribe treatment for RT intent

ii. Contour targets
iii. Review/edit directive in Dose Preview and authorize RT intent
iv. Review calculated plan options and select clinical treatment plan
v. Perform clinical approval

c. Physicist/ROMP
i. Review clinical treatment plan
ii. Sign off Technical Plan Report
iii. Perform independent dose check (e.g., Mobius)
iv. Perform phantom-based PSQA
v. Complete QA documentation

Table 1: The rows outline the chronological sequence of tasks to prepare a plan in Ethos. The columns list various abilities required for the tasks. Tasks and abilities have been linked to the classical roles to outline options for workflow.

	Navigate Initial Planning interface	Contour normal tissues	Perform image registration	Contour target	Create treatment plans	Evaluate treatment plans	Approve clinical aspects of treatment plans	Approve technical aspects of treatment plans	Perform plan QA	Approve plan QA	Navigate On-Couch Session interface	Use LINAC Clinically	Assess CBCT image quality
ROLES													
Dosimetrist	X	X	X		X	X							X
Physician	X	X	X	X		X	X				X		X
Physicist	X	X	X		X	X		X	X	X	X		X
Therapist		X	X								X	X	X
INITIAL PLANNING													
Add intent based on prescription, intent templates, and additional documentation.	X												
Contour normal tissues.	X	X											
Import normal tissue contours (if not created in Ethos).	X												
Register planning image with available supporting images.	X		X										
Contour targets.	X			X									
Import target contours (if not created in Ethos).	X												
Conduct preliminary manipulation of directive in Dose Preview.	X				X	X							
Review and edit the directive in Dose Preview, and approve the RT Intent.	X					X	X						
Preview calculated treatment plan options.	X				X	X							
Review calculated treatment plan options and select plan.	X					X	X						
Sign off Clinical Plan Report	X												

Create treatment plan documentation.	X												
Send plan to Mobius and plan QA phantom.	X												
Sign off Technical Plan Report.								X					
Review MobiusCalc results.								X					
Perform plan QA measurement.									X				
Create QA documentation.	X												
Perform treatment plan double check and complete documentation.								X					

Best practice recommendations for initial planning

- Protocol follows EMBRACE 2
- Evaluate margins with scope for reduction
- Shift in target voluming and margin methodology
- Patient preparation for CT simulation and treatment important
- Derived structures should be used carefully for optimizing efficiency and accuracy
- Commissioned and standardized Ethos templates recommended
- Multiple templates required for single and multi-dose level plans
- Additional clinical objectives to EMBRACE 2 may be required for plan optimization
- The 12-field IMRT beam arrangement is beneficial for plan quality

On-couch Adaptation

Patient setup and initial CBCT

a. Immobilization device(s) used for patient setup
See "Planning CT Simulation" section.

b. Description of image acquisition
Daily CBCT is performed as per the default workflow. Use of the Pelvis and Pelvis Large CBCT modes are recommended to optimize image contrast and resolution, which should improve the accuracy of sCT generation, AI segmentation, target/OAR propagation and volume delineation. It is important to consider the use of extended CBCT, particularly for patients with high-risk nodal volumes (CTV-N) where the treatment fields will extend outside the maximum standard CBCT length. The impact of discontinuities introduced in the sCT at the bounding limits of the acquired CBCT should be evaluated during implementation. Ideally the initial CBCT acquisition length should encompass all target and OAR volumes.

The initial CBCT should be evaluated for image quality, bladder/rectal filling, the presence of rectal/bowel gas or artefacts that may adversely affect contour propagation or represent a significant dosimetric uncertainty in sCT generation.

Contour evaluation and modification

a. AI segmentation
The influencers for the anatomical site "Cervix" are bladder, bowel, uterus and rectum. These influencers are AI segmented, which is achieved in less than a minute. The bladder and rectum segmentation typically requires no contour modifications. The uterus performs well for the majority of cases where anatomical boundaries are well defined, however can be an issue in the presence of image artefacts or the post-surgical setting. The bowel AI contour is defined as loops of small bowel and in the cohort of patients tested was found to require major edits in most cases.

b. Target and OAR propagation
All targets (CTV-N, CTV-E and CTV-T) and OARs (bowel bag or sigmoid) propagate in 2-3 minutes. The accuracy of target propagation and required editing was found to vary from no edits to major edits across the patient cohort tested. The bowel bag, comprising the small bowel, large bowel and sigmoid within a single structure, required the least edits across the patient cohort tested of all bowel definitions. Use of the Bowel Bag as a replacement for this structure is recommended.

c. Pattern of segmentation errors
More significant errors were associated with poor CBCT image quality (such as patients with large separation), artefacts (due to bowel or rectal gas), large variations in anatomy (bladder size variation, changes in rectal filling or bowel contents/position) and the presence of contrast in the planning CT.

The issues listed above would often be the reason for poor influencer AI segmentation for all structures. Bladder, uterus and rectum would often generate well and were robust to small issues in CBCT images, however the bowel would always be poorly generated and was the most

susceptible to any image quality issues. Removal of the bowel as an influencer would reduce the influencer evaluation time from 10min on average to <5min.

The sigmoid was added as an OAR, propagated by the deformable registration DVF alone, and would often require major edits similarly to the bowel contour. If the Bowel Bag definition is used, the small bowel, large bowel and sigmoid can all be encompassed in this structure for contour evaluation and plan optimization.

Plan generation and selection

Plan generation and selection is dependent on a number of technical and clinical factors, including:

a. Plan calculation time is approximately 1-3 min, varying dependent on the complexity of the template design.

b. Decision criteria for scheduled plan selection (relative to adapted):
    i. Patient movement or large intrafraction internal anatomical changes since adapted plan generation, however given the current workflow for performing verification CBCTs after plan selection this is logistically difficult to accomplish
    ii. Suspected issues with sCT generation as seen in Mobius, or indicated by Bones/Body agreement with CBCT, or poor contour propagation
    iii. Poor quality CBCT (e.g., artefact, gas)
    iv. Sub-optimal adapted dose distribution
    v. If selecting the scheduled plan, review scheduled plan couch shifts, in addition to plan quality comparisons. Large couch shifts may be indicative of significant inter or intra-fraction setup uncertainties that are difficult to fully account for or assess with 3DoF corrections. Users should evaluate the scheduled couch shifts applied offline to understand how the automatic 3 DoF match is executed during the template development process.

c. Adaptive plan QA processes
    i. Mobius: adaptive plan dosimetric verification
    ii. Mobius: review sCT, compare with Bones/Body agreement on CBCT
    iii. Technical plan report: review MU variation vs reference plan per field, and total MU against commissioned clinical thresholds/acceptable ranges
    iv. Plan meets target objectives and OAR constraints as per DVH metrics
    v. Dose distribution acceptable, reviewed for hot/cold spots, coverage/conformality and low dose spill
    vi. Although not specific to the on-couch QA for adaptive plans, it should be noted that adaptive plans should be validated by measurement (e.g., array or phantom) for at least a subset of patients and fractions to validate plan deliverability in an adaptive setting for any given planning template/technique.

Treatment delivery

Setup verification post planning
A second CBCT performed just prior to treatment delivery, after adapted plan generation on the first CBCT, with image matching and rigid shifts performed relative to the first CBCT, is recommended.

The magnitude of couch shifts performed should be evaluated as an indicator of patient movement, and the user should also check for intrafraction changes in bladder filling, rectal filling and external contour/body variation.

A post-treatment CBCT may be performed to evaluate any intrafractional geometric changes, where subsequent dosimetric assessment may be performed. This would also help with evaluating margins for future scope of reduction, note this can be done on either the pre or post-CBCT, with the post-CBCT including any variations that may occur during beam-on time. Low-dose imaging modes, such as Pelvis-Fast, may be considered for verification CBCTs to reduce patient imaging dose, however it must be noted that the degradation in image quality increases the uncertainty in any dosimetric evaluations performed on those CBCTs.

Patient monitoring during treatment
CCTV is the primary means for visually assessing the patient for any intrafraction movement externally.
Note that in the current TDS version there is no option for surface guidance, respiratory monitoring or beam-level imaging (MV or kV).

Treatment delivery time
This varies from 3-5 min depending on plan complexity and treatment technique.

Team member roles and workflow

Roles and workflows may differ according to departmental workflows and credentialing/assessment programs in place. An example workflow is provided capturing the major steps in the on-couch adaptation process and typical tasks performed by various clinical staff. Table 2 provides one example implementation where the tasks required to conduct individual steps in the Ethos process are identified and associated with clinical team member roles. Clinical roles and responsibilities may vary in different clinical implementations.

a. Dosimetrist/RTT/RT
    i. Review setup instructions
    ii. Operates Ethos interface at treatment console
    iii. Acquires and review CBCTs, with image matching where relevant
    iv. Monitors patient for movement
    v. Reviews and edits influencers and OARs
    vi. Review generated treatment plans
    vii. Deliver treatment and monitor for movement
    viii. Complete on-couch adaptation QA checklist

b. Physician/RO
    i. Review imaging
    ii. Review and edit target structures
    iii. Check all OAR/influencer structures
    iv. Review and select treatment plan
    v. Perform clinical approval

c. Physicist/ROMP
    i. Provide technical support throughout workflow

ii. Review imaging, provide advice on geometric/dosimetric impact of anatomical changes (inter/intra-fraction)
iii. Review clinical treatment plan
iv. Sign off Technical Plan Report
v. Review MobiusAdapt QA results
    i. Independent dose calculation
    ii. sCT accuracy and agreement with CBCT contouring

Table 2: The chronological sequence of tasks, skills and roles involved in the on-couch adaptation process. The columns indicate necessary skills and the rows tasks to be completed in the adaptive treatment process, where by the skills can be matched to roles and identify who may be involved in each step of the workflow.

	Navigate Initial Planning interface	Contour normal tissues	Perform image registration	Contour target	Create treatment plans	Evaluate treatment plans	Approve clinical aspects of treatment plans	Approve technical aspects of treatment plans	Perform plan QA	Approve plan QA	Navigate On-Couch Session interface	Use LINAC Clinically	Assess CBCT image quality
ROLES													
Dosimetrist	X	X	X		X	X							X
Physician	X	X	X	X		X	X				X		X
Physicist	X	X	X		X	X		X	X	X	X		X
Therapist		X	X								X	X	X
ON-COUCH SESSION													
Acquire CBCT												X	
Review CBCT													X
Review, edit, and approve influencer structures		X									X		
Review, edit, and approve target contours				X							X		
Review clinical aspects of scheduled and adaptive treatment plans, and select plan.							X				X		
Sign off Clinical Plan Report.							X				X		
Review technical aspects of the adaptive plan.								X			X		
Review MobiusAdapt results.								X					
Sign off Technical Plan Report.								X			X		
Deliver treatment.												X	

Documentation

Documentation largely follows recommendations detailed in the "Initial Planning- Documentation" section. In addition to these documents, an on-couch adaptation QA checklist is recommended. This should include:

- Reference plan name for comparative purposes (e.g., in Eclipse or Ethos)
- Comments on CBCT image quality or artefacts
- Influencer agreement with CBCT
- Target/OAR agreement with CBCT
- Notable regions for editing of all structures
- Timings for each step
- Body/Bones agreement with CBCT
- Clinically relevant isodose levels (per fraction) for plan dose distribution assessment
- Total MU variation between reference and adapted plans
- Scheduled and/or applied couch shifts

Final best practice recommendations for on-couch adaptation

- Use high quality CBCT image acquisition mode (e.g., Pelvis), ensuring all targets and OARs are covered in the scan length. Consider extended CBCT for long structure sets.
- Ensure target and OAR contouring is consistent (i.e., by protocol) between the reference plan and adaptive fractions.
- Consider structure definitions (e.g., Bowel bag) and the use of derived structures for minimizing user input in contouring and maximizing workflow efficiency
- Ensure patient preparation followed as per the planning CT simulation session to minimize intrafraction variation and reduce uncertainty in the anatomical changes observed
- Use of an additional computer/monitor at the treatment console for viewing the pCT image, plan and structure set is useful to aid in target/OAR contouring for adaptive fractions (Eclipse or Ethos)
- On-couch adaptive treatment QA checklist recommended to identify high priority items for checking and allow for handover between adaptive fractions
- Recommend use of a pre-treatment CBCT to verify patient position and anatomy relative to the initial CBCT/adaptive plan
- Consideration should be given for formal handover to occur between staff over the full course of an adaptive treatment to facilitate continuity in patient care and the adaptive treatment process

Treatment monitoring

Monitoring is a workspace in Ethos that provides the ability to evaluate aspects of the adaptive treatment course, including workspaces for: Sessions, Accumulation, Cine and Trends. This allows the user to evaluate session activity, accumulated dose distribution for delivered treatments, longitudinal imaging comparisons, and evaluate dose/volume trends for structures with clinical goals.

a. Sessions
   This workspace is useful for reviewing the timeline of each treatment fraction, including decisions made for scheduled vs adapted plan selection, imaging performed (initial, pre or post CBCTs), and adaptive plan information (plan report).

b. Accumulation
   Dose accumulation is helpful for ensuring the spatial distribution of dose remains consistent with the clinical intent and goals.
c. Cine
   Cine allows the user to qualitatively assess anatomical changes in chain-registered images across the full treatment course, informing expected target/OAR variation and adaptive plan changes.
d. Trends
   Provides a summary of the dose accumulated clinical goals and structure volume changes across adaptive fractions. This can be used to evaluate the likelihood of the prescribed clinical objectives and constraints being achieved based on the accumulated delivered dose distribution. This review may prompt a revised intent whereby the dose preview objectives or priorities are modified for subsequent adaptive fractions to better achieve the clinical goals.
e. Best practice recommendations for treatment monitoring and off-line adaptation
   It is important to note that there is insufficient clinical information on full treatment course adaptation and subsequent dose accumulation to make informed recommendations regarding clinical implementation and interpretation of these results. The primary issues to be considered in future studies include: validation of deformed dose accumulation, mixing adaptive and non-adaptive treatments/intents in a single course for assessment, and subsequent decision-making processes/thresholds for revising adaptive intents based on the information provided in monitoring.

   Tools within monitoring lend themselves useful for review across different workspaces. These tools can support review of previously treated fractions for incorporation into a staff handover process between adaptive treatments. They can also be used to investigate unexpected or significant adaptive changes during a treatment session retrospectively to inform steps moving forward (e.g., bladder filling, bowel gas or tumor response).

Conclusion

The Ethos platform is a novel system capable of providing fully adaptive radiotherapy treatment courses. This white paper outlines the recommendations and considerations for implementation in the setting of cervix radiotherapy.

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Appendix 1- Example Ethos adaptive cervix planning template

SIB Nodal Boost TEMPLATE 55Gy/25fx

Priority 1

1	**CTV LR N**	**V98% ≥ 98%**
2	CTV LR P	V98% ≥ 98%
3	PTV LR P	V95% ≥ 95%
4	PTV LR N	V95% ≥ 95%
5	Bowel	Dmax (0.5cm^3) ≤ 56Gy
6	Bowel PRV 0.3cm	Dmax (0.5cm^3) ≤ 57Gy
7	Rectum	Dmax (0.5cm^3) ≤ 57.25Gy
8	CTV HR N	V99.5% ≥ 98%
9	PTV HR N	V98% ≥ 90%
10	Rectum	V47Gy ≤ 1cm^3
11	Bowel PRV 0.3cm	V47Gy ≤ 2cm^3
12	Bladder	Dmax (0.5cm^3) ≤ 47.25Gy
13	PTV LR N	V105% ≤ 0.5cm^3
14	PTV LR P	V105% ≤ 0.5cm^3
15	PTV HR N	Dmax (0.5cm^3) ≤ 107%

Priority 2

16	Rectum	Dmean ≤ 35Gy
17	Bowel PRV 0.3cm	V30Gy ≤ 350 cm^3
18	Bowel PRV 0.3cm	V40Gy ≤ 100 cm^3
19	Rectum	V30Gy ≤ 60%
20	Rectum	V40Gy ≤ 75%
21	Sigmoid	V40Gy ≤ 85%
22	Sigmoid	Dmax (0.5cm^3) ≤ 57Gy
23	Bladder	V40Gy ≤ 75%
24	Bladder	V30Gy ≤ 85%
25	Bowel PRV 0.3cm	V15Gy ≤ 120 cm^3

Priority 3

26	Femoral Head & Neck LT	V30Gy ≤ 15%
27	Femoral Head & Neck Rt	V30Gy ≤ 15%
28	Kidney RT	Dmean ≤ 10Gy
29	Kidney LT	Dmean ≤ 10Gy
30	Ext Genitalia	V30Gy ≤ 30%
31	Cauda Equina	Dmax ≤ 45Gy
32	Sacrum	D50% ≤ 35Gy

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