IMRT Guidance Document for Intact Cervix

A report developed by the Gynecological Cancers Community of Practice (CoP) of the Radiation Treatment Program of Cancer Care Ontario (CCO) for circulation to Regional Cancer Programs

Chair: Jennifer Croke, Princess Margaret Cancer Centre
Chair: Kathleen Surry, London Regional Cancer Program
Donna Murrell, London Regional Cancer Program
Melanie Davidson, Odette Cancer Centre
Kitty Chan, Princess Margaret Cancer Centre
Laura D'Alimonte, Odette Cancer Centre
Krystine Lupe, The Ottawa Hospital Cancer Centre
Quinn Benwell, London Regional Cancer Program
Raxa Sankreacha, Carlo Fidani Peel Regional Cancer
CCO Advisor: Julie Himmelman

June 2018

1. Preamble

Cervical cancer is a leading causing of death for women worldwide.[1] Radiotherapy (RT) plays a fundamental and curative role in the management of patients diagnosed with locally advanced cervical cancer. Unfortunately, a significant proportion of long-term survivors suffer from long-term treatment-related toxicities impairing their quality of life.[2,3,4] Recent technologic innovations, including intensity-modulated radiotherapy (IMRT) and image-guided brachytherapy (BT) provide opportunities to reduce toxicity and improve quality of life, while maintaining high rates of local control.

Definitive RT for locally advanced cervical cancer has historically used a 4-field box using 3D conformal radiation techniques. There is a potential for IMRT to reduce doses to the organs at risk (OARs) and subsequent treatment related toxicity, while maintaining adequate target coverage and dose to the target. IMRT guidelines delineating the clinical target volume (CTV) in the definitive setting for patients with locally advanced cervix cancer have been published.[5] Locally advanced cervical cancer patients are often cured with definitive chemo-RT; however, chronic, low grade gastrointestinal (GI) side effects, such as food intolerance, cramping and diarrhea, occur in up to 90% of patients during treatment[6] and persists in 50% afterwards.[7] Previous studies have shown that IMRT is feasible in the treatment of cervix cancer and decreases dose to OARs compared to standard 3D conformal RT in these patients[8,9]. IMRT has been shown to decrease doses to the small bowel and the use of anti-diarrheal medications during treatment by 50%.[6,8]

Although the results of IMRT are promising, there is still reluctance within the gynecological radiation oncology community to adopt it as standard of care. Adopting a strategy of IMRT to increase conformity has been impeded by concerns of inter- and intra-fraction target motion, especially in the anterior posterior directions and uncertainty of planning target volume (PTV) margins required to encompass this motion.[10,11] Recent patient-reported toxicity results from the NRG Oncology/RTOG 1203 found less acute toxicity (risk of soiling and bowel bother) in post-operative endometrial/cervix cancer patients treated with IMRT compared to standard pelvic radiation. These results should translate into long-term improvements in quality of life.[12]

With advancements in radiation therapy delivery, on-line 3D image guidance and availability of MRI fusion, there has been a shift towards developing standard cervical cancer IMRT protocols around the world. Currently, two international clinical trials (EMBRACE II[13] and NRG GY006[14]) include IMRT techniques in their protocol. This document pulls data and processes from ongoing trials and recent publications regarding the use of IMRT in cervical cancer. It acts to guide IMRT implementation and use in Ontario. Should centres participate in EMBRACE II we encourage the use of the source protocol.

The Community of Practice (CoP) for gynecological cancers, hosted by Cancer Care Ontario (CCO) and representing all treating hospitals in Ontario, identified a need for a guidance document for IMRT programs treating intact cervical cancer. This fits with CCO's mandate to coordinate and harmonize practice across regional centres in Ontario. At the general meeting of the CoP in June 2017, a call was made for volunteers for a working group who would draft a document for adoption in Ontario. A multi-site, multi-disciplinary group was struck for this project. A radiation oncologist and a medical physicist volunteered to be co-chairs, and this balance of discipline representation was continued with ensuring membership from radiation oncology, physics and radiation therapy (2, 4 and 3, respectively). We also ensured a multi-site experience, with five hospitals being represented. The group met through regular teleconference discussions

and worked on the document through email correspondence. The first teleconference call was December 5, 2017 and the draft document was presented to the GYN CoP on May 11, 2018. The CoP guided the final version.

The following constitutes a recommendation document for guidance when developing, implementing and maintaining an IMRT program for treating intact cervical cancer. This document is supported by the CCO GYN CoP. These recommendations should help participating centres in developing and implementing their own local procedures and supporting documentation to be used during training as well as during operations. We also suggest that creation of "Mentor Centres" may be a helpful guide for a new centre when implementing IMRT treatment for cervix cancer. The CCO GYN CoP can assist participating centres in making these connections.

2. Simulation

It is recommended that simulation for radiation treatment of intact cervix consist of the following:

- MRI (either diagnostic or MR-simulation) (see Appendix B for the Draft Diagnostic MRI for Cervical Staging Protocol)
  - T2-weighted MRI, ideally in three orthogonal planes
- Treatment planning CT Scan
- FDG PET-CT (where indicated as per CCO) and other diagnostic scans (if applicable)
  - PET has been recently approved for locally advanced cervix cancer for the following indications. (Please refer to Gynecologic Oncology Requisition to PET Centre form in Appendix A)
    - CT/MRI shows positive or indeterminate pelvic nodes
    - CT/MRI shows borderline or suspicious para-aortic lymph nodes
    - CT/MRI shows indeterminate or suspicious distant metastases (ex. Chest nodules)

Some suggested possibilities for the combination of CT and MR imaging include (but are not limited to) the following.

Table 1. Possible options for combining CT and MR imaging when only diagnostic MR image set is available.

Imaging Criterion	**Details/Rationale**
Scans required	1) CT scan (with contrast†), with bladder comfortably full – this will be the primary image set for planning 2) CT scan, with bladder empty † IV contrast (optional) may be used to aid in delineating the nodal targets
Scan limits	Dependent upon the intended target volume: - Pelvis only: L3 vertebral body to 3cm below the ischial tuberosities - Pelvis + para-aortic lymph nodes: T10 vertebral body to 3cm below the ischial tuberosities
Slice thickness	<=3mm[13]

Immobilization	Dependent upon the intended target volume: • Pelvis only: device(s) to ensure reproducible leg positions and pelvis rotation (e.g. knee and / or ankle supports) per current institutional practice. Some examples may include: VacLok, knee wedge + foot support, foam leg support, foot straps • Pelvis + para-aortic lymph nodes: device(s) to ensure both reproducible leg position and a straight torso position per current institutional practice. Some examples may include: full body VacLok, upper body support (wing board, breast board in flat position) + lower leg support (outlined above)

Special instructions	Bladder filling:
	• A water drinking protocol should be used, outlining timing of voiding and intake, as well as amount of intake – e.g. void 1 hour before simulation and each treatment fraction, then drink 300-500 mL of water before treatment delivery (and try not to void).[13]
	
	Rectum filling:
	• Rectal preparation protocol should consist of voiding stools and gas before simulation and treatment.[13]
	
	Bladder and rectal filling should be assessed on each CT scan. In particular:
	• Bladder should be sufficiently full on full bladder scan and essentially empty on empty bladder scan. If either scan is felt to be inadequate, consideration to re-acquire images should be done.
	• Rectum <4cm in diameter (or other, per institutional protocol). If diameter > threshold, patient should be asked to empty the rectum (the use of a rectal tube to evacuate rectal gas may be considered), and scan re-acquired.[13] Bladder re-filling may be necessary.
	• It is recommended that the number of repeat scans per simulation appointment be limited to 1 (beyond the full + empty bladder scans). If adequate images cannot be obtained:
	  ○ Consider treating using a 4 field box, or substantially increasing the margins to account for possibility of inconsistent setup on treatment
	  OR
	  ○ Consider scheduling a repeat simulation appointment on a different day. If adequate images cannot be obtained following 2 separate simulation appointments, consider treating using a 4 field box, or substantially increasing the margins to account for possibility of inconsistent setup on treatment.
	
	Tattooing:
	For pelvis + para-aortics, additional tattoo at level between L2-L4 is required to ensure proper positioning / straightening on treatment.

Fusion required	Required: CT scan (full), CT scan (empty), Diagnostic MR scan Optional: FDG PET-CT, other diagnostic scans Fuse diagnostic images to CT simulation scan on bony anatomy as much as possible (particularly at the level of the lower pelvis that includes the pubis and femoral heads). Where bone position between diagnostic and simulation scans differ significantly, fine-tune the match to soft tissue in the cervix region.

Table 2. Possible options for combining CT and MR imaging when MR Simulation is available.

Imaging Criterion	**Details/Rationale**
Scans required	1) CT simulation (with contrast†) , with bladder comfortably full – this will be the primary image set for planning 2) MR simulation, with bladder full (in treatment position as much as possible, depending on MR-compatibility of immobilization devices used) 3) Bladder empty scan, use either: a. Ideally, where possible, MR simulation with bladder empty (in treatment position as much as possible, depending on MR-compatibility of immobilization devices used) b. CT simulation, with bladder empty † IV contrast (optional) may be used to aid in delineating the nodal targets
Scan limits	MR scan limits may be constrained by the local MR acquisition protocol used : - At minimum, it is recommended that scan limits include the pelvic anatomy containing the CTV-T CT scan limits dependent upon the intended target volume: - Pelvis only: L3 vertebral body to 3cm below the ischial tuberosities - Pelvis + para-aortic lymph nodes: T10 vertebral body to 3cm below the ischial tuberosities
Slice thickness	<=3mm (CT) and <=5mm (MR)[13]
Immobilization	Dependent upon the intended target volume: - Pelvis only: device(s) to ensure reproducible leg positions and pelvis rotation (e.g. nee and / or ankle supports) per current institutional practice. Some examples may include: VacLok, knee wedge + foot support, foam leg support, foot straps - Pelvis + para-aortic lymph nodes: device(s) to ensure both reproducible leg position and a straight torso position per current institutional practice. Some examples may include: full body VacLok, upper body support (wing board, breast board in flat position) + lower leg support (outlined above)

	• Consider MR-compatibility of immobilization devices (or alternative positioning required to reproduce treatment position as much as possible for non-MR-compatible devices)

Special instructions	Bladder filling:
	• A water drinking protocol should be used, outlining timing of voiding and intake, as well as amount of intake – e.g. void 1 hour before simulation and each treatment fraction, then drink 300-500 mL of water before treatment delivery (and try not to void).[13]
	
	Rectum filling:
	• Rectal preparation protocol should consist of voiding stools and gas before simulation and treatment.[13]
	
	Bladder and rectal filling should be assessed on each CT scan. In particular:
	• Bladder should be sufficiently full on full bladder scan and essentially empty on empty bladder scan. If either scan is deemed to be inadequate, consideration for re-acquiring images should be done.
	• Rectum <4cm in diameter. If >4cm, patient should be asked to empty the rectum (the use of a rectal tube to evacuate rectal gas may be considered), and scan re-acquired.[13] Bladder re-filling may be necessary.
	• It is recommended that the number of repeat scans per simulation appointment be limited to 1 (beyond the full + empty bladder scans). If adequate images cannot be obtained:
	  ○ Consider treating using a 4 field box, or substantially increasing the margins to account for possibility of inconsistent setup on treatment
	  OR
	  ○ Consider scheduling a repeat simulation appointment on a different day. If adequate images cannot be obtained following 2 separate simulation appointments, consider treating using a 4-field box, or substantially increasing the margins to account for possibility of inconsistent setup on treatment.
	
	Tattooing:
	For pelvis + para-aortics, additional tattoo at level between L2-L4 is required to ensure proper positioning / straightening on treatment.

Fusion required	Required: CT scan (full +/- empty), MR simulation (full +/- empty) – Fuse to bony anatomy Fuse diagnostic images to CT simulation scan on bony anatomy as much as possible (particularly at the level of the lower pelvis that includes the pubis and femoral heads). Where bone position between diagnostic and simulation scans differ significantly, fine-tune the match to soft tissue in the cervix region.

3. Nomenclature

Table 3. Overview of Contouring Nomenclature.

Definition	Description	EMBRACE[13] Nomenclature	AAPM TG 263[15] Nomenclature
Initial Gross Tumour Volume of the primary tumour	Extension of the primary cervix tumour (inside and outside of the cervix) defined by: [5,13] - T2w MRI, supported by clinical investigation, FDG PET-CT - intermediate/high signal seen on T2-weighted MR images	GTV-T	GTVp GTVp_MRfull GTVp_MRempty (where applicable)
Initial High Risk Clinical Target Volume of the primary tumour	Gross tumour volume + any remaining cervix not infiltrated by tumour	CTV-T HR	CTVp^HR CTVp^HR_MRfull CTVp^HR_MRempty (where applicable)
Initial Low Risk Clinical Target Volume of the primary tumour	the complete parametria bilaterally; the entire uterus; uninvolved vagina with a 20 mm margin measured from the most inferior position of the initial HR CTV-T along the vaginal axis (not starting in the fornix); CTV-T HR plus a margin of about 5 mm ant and post towards the bladder and rectum (excluding the non-involved walls); in case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum, or other involved structures a 20 mm margin around the initial HR-CTV-T will be extended into these structures; any pathological lymph nodes in the parametrium may be included	CTV-T LR	CTVp^LR_MRfull CTVp^LR_MRempty CTVp^LR_CTfull CTVp^LR_CTempty (depending on what scans were done with full and empty bladder)
Initial Internal Target Volume of the Primary Tumour		ITV-T LR	ITVp

Definition	Description	EMBRACE[13] Nomenclature	AAPM TG 263[15] Nomenclature
Internal target volume for 45Gy		ITV45	ITV
Gross tumour volume of individual pathologic lymph nodes; numbered as GTVN1, GTVN2, etc.	Individual GTV-N for each pathological lymph node is contoured; the outer contour and visible extra capusular extension on MRI or CT. PET should be used for guidance and not for precise delineation. In case of nodes beyond the FOV of pelvic MRI, contours should be based on PET-CT and planning CT appearance. Definition on volumetric imaging: short axis ≥1cm on CT or MRI and/or short axis between 0.5-1.0 cm on MRI with pathological morphology: irregular border, high signal intensity and/or round shape	GTV-N	GTVn#
Clinical target volume of individual pathologic lymph nodes numbered at CTVN1, CTVN2, etc.	In principle is equal to GTV-N; however, an individualized margin may be considered taking into account extra-capsular extension and possible progression during treatment planning interval, avoiding bones and muscles. Typically 0-3 mm.[13,16]	CTV-N	CTVn#
Planning target volume of individual pathologic lymph nodes numbered as PTVN1, PTVN2, etc.		PTV-N	PTVn#

Definition	Description	EMBRACE[13] Nomenclature	AAPM TG 263[15] Nomenclature
Clinical target volume of the elective nodal regions, including pathologic lymph nodes if present		CTV-E	CTVn (if pelvis and para-aortic nodes were contoured separately some suggested names could be: CTVn^Pelvis and CTVn^PA
Planning target volume for 45Gy for Primary Tumour		PTV45-T	PTVp
Planning target volume for 45 Gy for Elective Nodal Regions		PTV45-N	PTVn
Planning target volume for individual pathologic gross node volumes		PTV-N	PTVn#
Planning target volume for 45Gy		PTV45	PTV

4. Contouring and Margins

The contouring guide outlined below follows the paper by Lim et al, in general.[5]

4.1. Targets

Table 4. Targets where only a diagnostic MR is available.

Target	EMBRACE Nomenclature[13]	TG-263 Nomenclature[15]
Contour on Diagnostic MRI	GTV-T, CTV-T-HR	GTVp, CTVp^HR
Contour on CT (full bladder)	CTV-T LR (full), GTV-N, CTV-E, CTV-N, OAR	CTVp^LR_CTfull, GTVn#, CTVn#, CTVn, OAR
Contour on CT (empty bladder)	CTV-T LR (empty)	CTV^LR_CTempty
Generate (on Full bladder CT)	ITV-T LR = [CTV-T HR+ CTV-T LR(full) + CTV-T LR (empty)] ITV45 = ITV-T LR + CTV-E PTV45-T =ITV-T LR + 7-10mm Sup-Inf and Ant-Post, and 5-7mm laterally[4,5,8] PTV45-E = CTV-E + 5-7mm[5,13] PTV-N = GTV-N + 5-7mm PTV45 = PTV45-T + PTV45-E + PTV-N	ITVp = CTVp^HR+CTVp^LR_CTfull+CTVp^LR_CTempty ITV = ITVp+CTVn+GTVn#/CTVn# PTVp= ITVp+7-10mm Sup-Inf and Ant-Post, and 5-7mm laterally PTVn = CTVn+5-7mm PTVn#=GTVn# (or CTVn#) + 5-7mm PTV = PTVp + PTVn + PTVn#

Table 5. Where a MR simulation is available.

Target	EMBRACE Nomenclature[13]	TG-263 Nomenclature[15]
Contour on MRI sim	GTV-T, CTV-T HR, CTV-T LR (on both full and empty bladder scans if available) May contour GTV-N, CTV-N on MRI instead of CT	GTVp_MRfull, GTVp_MRempty CTVp^HR_MRfull, GTVp_MRempty GTVn#, CTVn# (either on MR or CT)
Contour on CT (full bladder)	CTV-T LR (full), GTV-N, CTV-E, CTV-N, OAR	CTVp^LR_CTfull, GTVn#, CTVn#, CTVn, OAR
Contour on CT (empty bladder)	CTV-T LR (empty) * if this scan was done	CTV^LR_CTempty (may not be done if MR sim was done with full and empty bladder)

Target	EMBRACE Nomenclature[13]	TG-263 Nomenclature[15]
Generate (on Full bladder CT)	ITV-T LR = [CTV-T-HR (full +/- empty)+ CTV-T-LR(full, MR and CT) + CTV-T LR (empty, MR or CT)] ITV45 = ITV-T LR + CTV-E PTV45-T =ITV-T LR + 7-10mm Sup-Inf and Ant-Post, and 5-7mm laterally[13,17] PTV45-E = CTV-E + 5-7mm[5,13] PTV-N = GTV-N + 5-7mm PTV45 = PTV45-T + PTV45-E + PTV-N	ITVp = CTVp^HR_MRfull + CTVp^HR_MRempty+CTVp^LR_MRfull+ CTVp^LR_MRempty+ CTVp^LR_CTfull+CTVp^LR_CTempty ITV = ITVp+CTVn+GTVn#/CTVn# PTVp= ITVp+7-10mm Sup-Inf and Ant-Post, and 5-7mm laterally PTVn = CTVn+5-7mm PTVn#=GTVn# (or CTVn#) + 5-7mm PTV = PTVp + PTVn + PTVn#

4.2. OARs

Table 6. The outer contour of the following organs should be delineated separately.

EMBRACE nomenclature[13]	TG-263 nomenclature[15]	Contour Definition
Bladder	Bladder	Whole organ including the bladder neck
Rectum	Rectum	From the ano-rectal sphincter to the recto-sigmoid junction
Sigmoid	Sigmoid	From the recto-sigmoid junction to the left iliac fossa
Bowel	Spc_Bowel	Superior limit: 1cm superior to superior-most slice containing PTV (if no bowel at this level, start from its most superior extent) Inferior limit: most inferior extent of bowel in the pelvis. Include bowel loops and any space within the abdominal cavity the bowel may occupy.
Femoral heads	Femur_L, Femur_R **or** Femur_Head_L, Femur_Head_R	Both femoral head and neck to the level of the trochanter minor
In case of ovarian transposition: Ovary	Ovary_L, Ovary_R, Ovaries	Outer contour

4.3. Reference points

Table 7. Reference points

EMBRACE nomenclature[13]	TG-263 nomenclature[15]	Contour Definition
Vagina	Vagina	Lower and mid-vagina doses (at the level of the Posterior-Inferior Border of Symphysis (PIBS), as well as PIBS ± 2 cm)

4.4. For para-aortic nodal irradiation

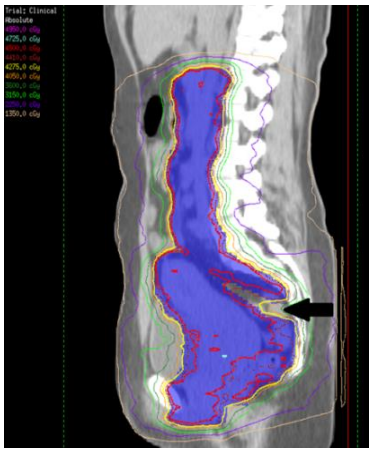
Table 8. Reference points for para-aortic nodal irradiation

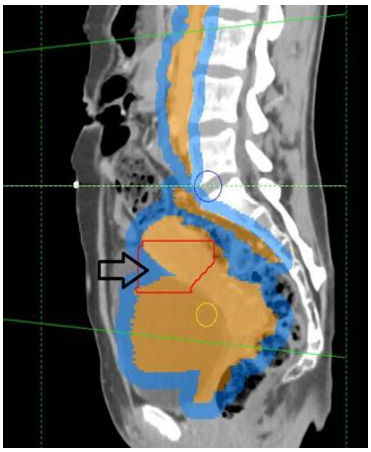
EMBRACE nomenclature[13]	TG-263 nomenclature[15]	Contour Definition
Kidneys	Kidney_L, Kidney_R, Kidneys	Outer contour excluding renal pelvis
Spinal canal	SpinalCanal	contour canal
Ovaries (in case of ovarian transposition)	Ovary_L, Ovary_R, Ovaries	Outer contour
Optional (if para-aortic RT above L1 is applied): Duodenum	Duodenum	Whole organ

4.5. Considerations

- Once PTV45 is generated, the contours should be reviewed (particularly areas between the PTV45-T and PTV45-E). Identify gaps between the contours that may not require avoidance (consider joining the volumes together for planning) – see Figure 1 and 2 for examples.
- If treating both pelvic and para-aortic nodes, consider the upper extent of suggested PTV45-E margins (7mm) since it is more difficult to provide a good match of both pelvic and vertebral bones in combination. In addition, many imaging systems available will likely only be able to image a portion of the treated volume, and the daily focus will be the primary tumour area (for example, if the maximum field of view is 20cm sup-inf on CBCT, the treatment isocentre should be placed in a sup-inf location that allows visualization of the entire ITVp. This may result in an inability to visualize portions of the field >10cm superior to the isocentre on treatment such as some of the para-aortic nodal regions).
- It is suggested that the more generous of the recommended PTV margins be used when starting this program, until the clinical team has gained experience and expertise with the patient setup, preparation and IGRT matching, since they will be more forgiving and reduce the likelihood of multiple setup attempts or suspended treatments.
- Consider larger PTVs for a larger patient, due to poorer image quality on CBCT.[18]
- When converting to the more stringent of the recommended PTV margins, be sure to combine this with following strict and clear IGRT procedures after a period of time in which local experience is gained.
- It is recommended that an AP and lateral field be placed on the initial simulation CT at the time of contouring by the radiation oncologist. This is in anticipation of the possibility for the need to re-plan the patient based on inadequate CTV coverage. It is proposed that instead of putting the patient on hold for a few days while a new IMRT plan is developed, that treatment could revert to a 4-field 3DCRT plan in the meantime. Having the fields already on the original CT allows for an expedited simple plan to be provided for treatment. See section 7.
- It is important to ensure communication is clear and frequent between the treating physician and the Medical Radiation Technologist (Therapist) (MRT(T)s) delivering the treatment.
- Consider using the 95% isodose line as a contour in some cases where matching could be challenging. As this volume is often a little bit more generous, it can give the treating team confidence that the target volume is well covered. As it is not an anatomical structure, however, it should be used with due consideration.

Figure 1 and 2: Example of plan for IMRT Intact Cervix: please note some gaps in target coverage which may require review.





5. Planning

- 45 Gy in 25 fractions to PTV
- Dose to PTV45 should be homogeneous with at least 95% of PTV covered by 95% prescription isodose and dose maximum less than 107% of the prescribed dose
- Ensure treatment isocentre is placed appropriately so that daily image guidance offers the best visualization of key anatomy.

5.1. Boost

- Lymph node boosting: simultaneous integrated boost (SIB)[13] vs. sequential to be at institutional discretion (EMBRACE II[13] guidelines stipulate SIB)
- Individual nodal boost prescriptions may be required for the various PTV-N. While the dose for each PTV-N will be at the discretion of the treating radiation oncologist, it is suggested that doses include estimated contributions from brachytherapy. According to EMBRACE II, a total dose of ~60Gy EQD2 to each PTV-N should be achieved.[13] Some examples are given below for reference based on examples given in the EMBRACE-II protocol[13] (*Note: SIB only is suggested in EMBRACE-II and sequential boost options were calculated to give similar EQD2):
    - In the lower pelvis:
        - SIB boost: EBRT with SIB 25 x 2.2Gy = 55Gy physical dose. This schedule is equivalent to 56Gy EQD2 EBRT + 4Gy EQD2 from brachytherapy = ~60Gy EQD2
        - Sequential boost: 44.25Gy EQD2 from phase 1 EBRT + 4Gy EQD2 from brachytherapy + EBRT sequential boost of 6-7 fractions (1.8Gy/fraction) = ~58.9-60.6Gy EQD2
    - In the high pelvis or para-aortic:
        - SIB boost: EBRT with SIB 25 x 2.3 Gy = 57.5Gy physical dose. This schedule is equivalent to ~59 Gy EQD2 and 0 Gy brachytherapy dose = ~59Gy EQD2

- Sequential boost: 44.25Gy EQD2 from phase 1 EBRT + 0Gy EQD2 from brachytherapy + EBRT sequential boost of 8-9 fractions (1.8Gy/fraction) = ~58.4 – 60.2Gy EQD2

5.2. Summary of planning aims

Table 9. Summary of planning target aims

Summary of Planning Target Aims	**No boost (or ph1 in the case of a sequential boost)**	**SIB (*OAR values only also applicable to composite plan in the case of a sequential boost)**
Targets		
PTV	V4275cGy > 95%[13] Dmax < 4815cGy[13]	V4275cGy > 95%[13]
ITV	Dmin > 4275cGy[13]	Dmin > 4275cGy[13]
PTV-N	NA	D98% > 90% of prescribed LN dose[13] Dmax < 107% of prescribed LN dose[13]
GTV-N or CTV-N	NA	D98% > 100% of prescribed LN dose (optional: D50% > 102%)[13]
PTV - (PTV-N+10mm)	NA	Recommend limiting V4815cGy < 5% (or limiting V4725cGy) to control hot spot in 45Gy volume
ITV – (PTV-N+10mm)	NA	Recommend limiting Dmax < 90% prescribed LN dose (to maintain reasonable conformity around SIB volumes)
OAR		

Bowel space	Dmax < 4725cGy[13] If no lymph node boost: • V4000cGy < 100cc[13] • V3000cGy < 350cc[13] If para-aortic irradiation: • V4000cGy < 250cc[13] • V3000cGy < 500cc[13]	Dmax < 5750cGy[13] • V5000cGy < 20cc[19] • V4000cGy < 250cc[13] • V3000cGy < 500cc[13]
Sigmoid	Dmax < 4725cGy[13]	Dmax < 5750cGy[13]
Bladder	Dmax < 4725cGy[13] Optional: V4500cGy < 50%[14] V4000cGy < 75%[13] V3000cGy < 85%[13]	Dmax < 5750 cGy[13] Optional: V5750cGy < 50%[14] V4000cGy < 75%[13] V3000cGy < 85%[13]
Rectum	Dmax < 4725cGy[13] Optional: V4500cGy < 50%[14] V4000cGy < 85%[13] V3000cGy < 95%[13]	Dmax < 5750cGy Optional: V5400cGy < 50%[14] V4000cGy < 85%[13] V3000cGy < 95%[13]
Femurs	Dmax < 4725cGy[13]	Dmax < 5000cGy[13]
Spinal Canal	Dmax < 4725cGy[13]	Dmax < 4800cGy[13]
Kidneys	Dmean < 1500cGy (ideally < 1000cGy)[13] V2000cGy < 32%[20]	Dmean < 1500cGy (ideally < 1000cGy)[13] V2000cGy < 32%[20]
Ovaries	Dmax < 500 – 800cGy[13]	Dmax < 500 – 800cGy[13]
Duodenum	V4500cGy < 15cc	V5500cGy < 15cc20

The optional dose constraints, as described in the EMBRACE II protocol,[13] can be used as optimization constraints; however, they are not based on clinical evidence. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients. The recommended dose constraints are also meant to guide the optimization (and prevent distributions from becoming too “hot” in the SIB scenario).

If the treating team deems it necessary to exceed the required dose limits, the clinical reasoning for this, along with the implications, should be discussed with the patient.

6. Image guidance

Daily 3D (CBCT or MVCT) IGRT is required. The treatment isocentre should be selected to be central to the treatment volume that maximizes visualization of relevant anatomy.

6.1. Recommendations upon initiation of a cervix IMRT program

- Complete a few dry runs to finalize technical protocol:
  - Perform simulation protocol as required for IMRT
  - Complete contouring as required for IMRT
  - Choose appropriate treatment isocentre for given target volumes
  - Complete planning as per current 3DCRT guidelines (e.g. 4 field box)
  - Complete basic training with RTs on one chosen treatment unit for these dry runs. Perform daily CBCT, matching to bone only. Conduct image matching assessment using the contoured target volumes as per intended protocol outlined below. This will help identify the following issues prior to starting IMRT delivery for similar cases:
    - image quality issues (and give an opportunity to adjust CBCT acquisition protocol as required to enhance visualization)
    - areas of weakness in the image matching protocol (is anything unclear or misunderstood?)
    - challenges that might appear on treatment: are the troubleshooting guidelines adequate? Have troubleshooting mechanisms been provided to deal with these scenarios?
    - suitability of chosen PTV margins: instances where the image match would have been unsuitable for treatment with IMRT can be noted (as well as magnitude of offset).
  - These dry runs will also allow teams to collect planning CTs and CBCT image sets in a database to use for IGRT training purposes with RTs prior to launching IMRT technique. Interesting cases flagged during these dry runs should be used to discuss CBCT match review and troubleshooting during the training sessions.

- Provide IGRT training for intact female pelvis for RTs prior to starting, to ensure that protocol is understood, and to clarify guidelines based on feedback gained during training sessions. Training should include the clinical and technical teams (radiation oncologists, physicists, radiation therapists and educators) and should ideally include:
  - An overview of the clinical scenario and new proposed treatment protocol for cervix patients
    - why the switch to IMRT? What is the importance of IGRT in this context?
    - the role of the external beam treatment in the context of the brachytherapy boost
    - how this differs from IMRT treatments for post-op GYN
  - Review anatomy and contours relevant to this protocol, and discuss the importance and significance of each contour; particularly how to use the 95% isodose line as a matching contour, if that should arise.
  - An overview of the IGRT protocol, and image matching workflow, including a decision tree

- Demo / walk-through of one image matching example on a set of patient images
- A discussion of what might lead to unsuitable matches, and how to troubleshoot these issues
- Practical examples for RTs to attempt, with some discussion about image matching specifics that apply to each case. A variety of cases is key for this training- include cases with good and bad target matches, and also cases where OAR are different from the plan.

- Due to the complexity of image matching (and repercussions of missing targets in cervix treatments), it is recommended that:
  - Cervix IMRT treatments be limited to specific treatment units to maintain an expertise in image matching amongst a fixed team
  - Consistency and continuity of staff reviewing a patient's images over the course of treatment be maintained (this includes treating RTs as well as radiation oncologists)
  - Participating centres find a practice for scheduling Day 1 treatments, such that the treating physicians (or their delegate) are able to attend.
  - A group of experts is developed, who could be called upon to give opinion in a difficult case. This can be members of the technical team, such as an on-call GYN RO, physicists, therapy educators and/or specialist therapists.

6.2. Technical IGRT guidelines

- kV CBCT 3D images prior to treatment
- bone match with clipbox
- a specific directive from Radiation Oncologist regarding the PTV coverage and avoiding specific avoidance structures (e.g. bowel) must be present

Criterion for IGRT	**Description**
Basis of image verification	Bony anatomy only.[13] * Corrections based on soft tissue match should not be done (as it may move nodal and elective targets outside the treated volume)
Clipbox	The clipbox in which to focus the registration should encompass: Ant-Post: include the pubic bone to Sacrum Lateral: Mid-point of femoral heads Superior-inferior: Superior extent of nodal targets to pubic bone (superior extent will depend on patient risk category) * Ensure this clip box is contained within the IGRT scan volume for more optimal automatic registration.
Scan settings	Largest imaging field available (in superior-inferior dimension) should be used (with kV, mA, and ms optimized for the pelvis site).
Contours to assist in verifying image match	Targets: CTV-HR, ITV45, PTV45, GTV-N, PTV-N, 95% isodose OAR: Bladder, rectum, kidneys and spinal cord/canal (for pelvis+para-aortics)

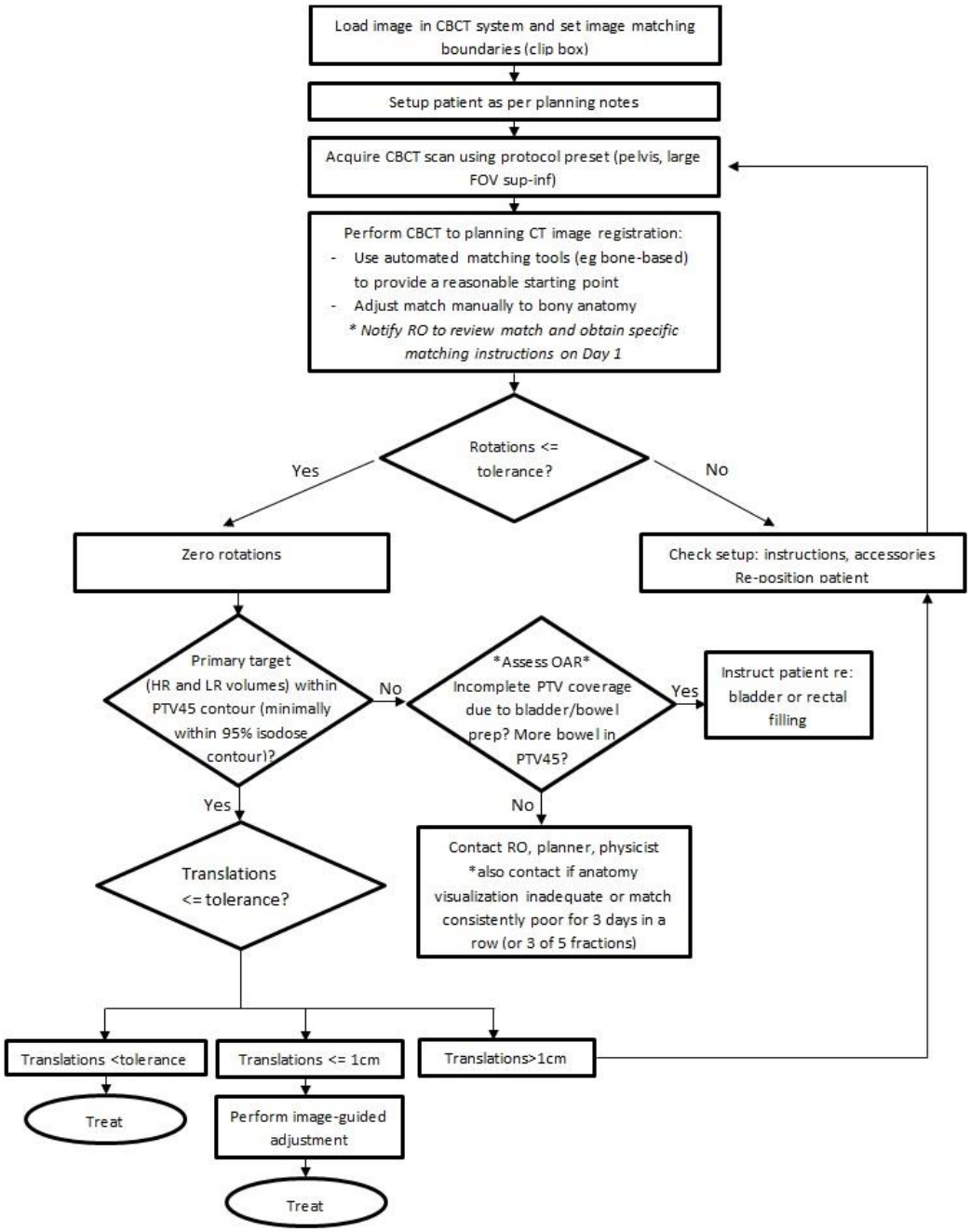
Assessing image match	<u>1) Assess shifts</u> Rotational shifts: • Omit rotational shifts < 3-5 degrees (per institutional guidelines), i.e. zero any rotational shifts identified during image matching – particularly the large volumes that include para-aortic nodes (recommended) Translational shifts: • Apply translational shifts >=1-2mm, but <=1cm (per institutional guidelines) If translational shifts>1cm or rotational shifts>=3-5 degrees (per institutional guidelines), repeat setup (and check all parameters, including accessories) and repeat CBCT. <u>2) Assess soft tissues</u> • Verify rectal diameter < 4cm and bladder filling adequate (and not much beyond the CT simulation bladder size). • Inspect the position of bowel and other OAR relative to PTV45 volume (is there significantly more bowel (or other OAR) than seen on planning scan?) – document this in the R+V system, and alert Radonc if this occurs on a regular basis (e.g. 3 days in a row, or 3 of 5 days in 1 week) • Verify bone match particularly: o At the superior portion of the scan if para-aortic nodes are being treated and scan doesn't encompass entire treatment volume o Around the areas receiving SIB (GTV-N, PTV-N). A review of soft tissues in these areas should also be done (coronal images often helpful). • Verify position of cervix (CTV-HR) and uterus relative to the ITV45 and PTV45 contours: portions of the CTV should fall within the PTV45 contour, and minimally within the 95% isodose contour. o Considerations about the non-involved uterus should be at the discretion of the treating oncologist.

Physician review	The physician, or their delegate, is required to be present at minimum for Day 1 IGRT to review the images and to provide specific matching instructions, where necessary (what is important in this case? what are the things to look out for?). Ideally, the physician will attend the first few fractions to get a sense of daily variation for each patient prior to providing matching instructions for that patient. For unusual cases, the physician may request to review images on treatment more frequently (e.g. once weekly). It is recommended (but not necessary) that the physician review other images offline at the start of the IMRT program (some options might include a weekly offline review at the treatment unit, or review during weekly QA rounds). This might allow the team to flag potential issues with the IGRT protocol upfront and provide some assurance that the matching is done as expected. Treating therapists will consult with the physician (or member of the technical team) if the CTV-HR and uterus are not contained within the PTV contour, or if bone match is poor on a regular basis (e.g. 3 days in a row, or 3 of 5 days in 1 week).
Troubleshooting	Rectal diameter: • If rectal diameter>4cm, patient should be asked to empty the rectum. Consideration for the use of a tube to evacuate rectal gas can be made at the discretion of the treating physician Bladder refilling may be necessary. Bladder filling: • If bladder volume on treatment is larger than simulation CT, counsel patient to drink less or change timing of fluid intake prior to appointment. If this is not successful (bladder consistently larger than on planning CT), a re-simulation with FULL bladder only should be considered to re-capture a more realistic extreme of non-nodal target position with full bladder. • If bladder volume on treatment is smaller than simulation CT, document in R+V if more bowel is falling into the treatment area (particularly for pelvis only treatments). If this occurs on a regular basis (e.g. 3 days in a row, or 3 of 5 days in 1 week), consult with physician. If a re-scan is required: • A patient should not have more than 2 scans per day. If an adequate image match is unsuccessful after 2 attempts, contact the physician or a member of the technical team to review and decide how to proceed. • It is advisable to document the number of rescans (and reason for rescan) in the Record and Verify system to track poor setups.

6.3. IGRT decision tree example

In addition to technical protocol given, providing RTs with a decision tree when performing the CBCT image matching may be useful. An example is provided below for reference.
Figure IGRT decision tree example when performing the CBCT image matching.

Figure 3. IGRT decision tree example when performing the CBCT image matching.



7. Plan adaptation / Re-planning

Potential scenarios where re-planning is indicated include:

If patient setup/image matching is poor on a regular basis (e.g. 3 days in a row, or 3 of 5 days in 1 week), contact the physician and/or member of the technical team to assess whether or not the patient should be re-planned (according to one of the options outlined below). Unacceptable setup conditions may include:

- Poor matching of non-nodal targets (CTVs falling outside PTV or 95% isodose contour)
  - may be due to changes in target size (regression/progression)
  - may be due to bladder or rectal filling differences
- Poor bone match on 3 consecutive days
  - May be due to inadequate tattoos for alignment or inadequate immobilization
  - May be due to patient position at the time of simulation not representative of daily position (patient may have been tense at sim, etc.)

When motion is an issue:

- Hold radiation for that day.
- Re-simulate the patient same day/next day, with full and empty bladder CT (+/-MR simulation where possible where significant changes in the target volumes are identified/suspected). If this is not possible, PTV margins may be increased where needed for replanning.
- Restart radiation the following day with a 4-field box until new plan is ready to avoid missing treatments.
- If this scenario occurs a second time, consider treating the remaining fractions with a 4-field box to avoid excess time and resource demands on oncologists, planners and physicists

Tools to help decide when re-planning is necessary:

- Export CBCT images to treatment planning system to review :
  - May look at maximum excursion of targets to determine more adequate PTV expansions (or may consider contouring additional volumes seen on CBCT, adding these to the ITV45 and re-expanding the standard PTV).
  - May look at dosimetric calculations to determine if target covered

8. References

1. Ferlay J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374-403 (2013).
2. Eifel PJ et al. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 32:1289-300 (1995).
3. Perez CA et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. Cancer 54:235-46 (1984).
4. Roeske JC et al. Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix: a dosimetric analysis. Int J Radiat Oncol Biol Phys 37:351-8 (1997).
5. Lim, K. et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int. J. Radiat. Oncol. Biol. Phys. 79, 348–355 (2011).
6. Mundt AJ et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 52:1330-7 (2002).
7. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. Int J Radiat Oncol Biol Phys 56:1354-60 (2003).
8. Roeske JC et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys 48:1613-21 (2000).
9. Forrest J et al. A dosimetric planning study comparing intensity-modulated radiotherapy with four-field conformal pelvic radiotherapy for the definitive treatment of cervical carcinoma. Clin Oncol (R Coll Radiol) 24:e63-70 (2012).
10. van de Bunt, L. et al. Motion and deformation of the target volumes during IMRT for cervical cancer: What margins do we need? Radiother. Oncol. 88, 233–240 (2008).
11. Taylor, A. & Powell, M. E. B. An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer. Radiother. Oncol. 88, 250–257 (2008).
12. Klopp, A. H. et al. Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018 Jul 10.
13. Tanderup, K. et al. Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer EMBRACE-II. EMBRACE II study protocol v.1.0 (2016).

14. NRG-GY006. Radiation therapy and cisplatin with or without Triapine in treating patients with newly diagnosed stage IB2, II, or IIIB-IVA cervical cancer or stage II-IVA vaginal cancer. NCT02466971 (2015).

15. Mayo, C. S. & Moran, J. M. Standardizing Nomenclatures in Radiation Oncology: The Report of AAPM Task Group 263. (2018).

16. Cheng, J. Y., Huang, E. Y., Hsu, S. N. & Wang, C. J. Simultaneous integrated boost (SIB) of the parametrium and cervix in radiotherapy for uterine cervical carcinoma: A dosimetric study using a new alternative approach. Br. J. Radiol. 89, (2016).

17. Bondar, M. L. et al. Individualized nonadaptive and online-adaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans. Int. J. Radiat. Oncol. Biol. Phys. 83, 1617–1623 (2012).

18. Bray, T. S., Kaczynski, A., Albuquerque, K., Cozzi, F. & Roeske, J. C. Role of image guided radiation therapy in obese patients with gynecologic malignancies. Pract. Radiat. Oncol. 3, 249–255 (2013).

19. Stanic, S. & Mayadev, J. S. Tolerance of the small bowel to therapeutic irradiation: A focus on late toxicity in patients receiving para-aortic nodal irradiation for gynecologic malignancies. Int. J. Gynecol. Cancer 23, 592–597 (2013).

Cancer Care Ontario

9. Appendices

Appendix A: Gynecology Oncology Requisition to PET Centre Form

Gynecology Oncology Requisition to PET Centre

TO BE COMPLETED BY THE REFERRING PHYSICIAN

Referring Physician Name: _____

Physician Phone: (____) _____ **ext.** _____ **Fax:** (____) _____ **CPSO No:** _____

Patient Name: _____

_____

_____

SURNAME FIRST NAME MIDDLE

OHIP Number: _____

_____

Telephone: (____) _____ **Postal Code:** _____

Date of birth: _____/_____/_____ **Gender:** ☐ M ☐ F

YYYY / MM / DD

Fax Instructions

Please fax the completed request form, (page 1 and 2), along with the required supporting documentation to the PET Centre of choice for appointment.

	Fax no.
• Hamilton – McMaster University Medical Centre	(905) 521-2358
• Hamilton – St. Joseph's Healthcare Hamilton	(905) 308-7215
• Ottawa – Ottawa General	(613) 737-8752
• Windsor – Precision Diagnostic Imaging Inc.	(519) 252-5000
• London – St. Joseph's Health Care London	(519) 646-6135
• Mississauga – KMH Cardiology Centres Inc.	(905) 855-1863
• Mississauga – MyHealth Centre	(888) 761-9156
• Toronto – Princess Margaret Cancer Centre	(416) 946-2144
• Toronto – Sunnybrook Health Sciences Centre	(416) 480-5218
• Toronto – Hospital for Sick Children	(416) 813-6043
• Thunder Bay – Regional Health Sciences Centre	(807) 684-5907

☐ **STAGING CERVICAL CANCER – PET for the staging of patients with locally advanced cervical cancer.**

Complete Sections A, B, and C

A) Reason for PET *(choose only one)*:
☐ CT/MRI shows positive or indeterminate pelvic nodes (>7mm, and/or suspicious morphology), **OR**

☐ CT/MRI shows borderline or suspicious para-aortic nodes, **OR**

☐ CT/MRI shows indeterminate or suspicious distant metastases (e.g., chest nodules)

B) Histology: ☐ Squamous Cell Carcinoma ☐ Adenocarcinoma ☐ Other (specify): _____

C) Clinical Stage: ☐ IA ☐ IB ☐ IIA ☐ IIB ☐ IIIA ☐ IIIB ☐ IVA ☐ IVB

Attach the CT/MRI reports & provide images to the PET Centre.

Other information regarding eligibility:_____

☐ **RECURRENT GYNECOLOGIC CANCER – PET for the re-staging of patients with recurrent gynecologic malignancies under consideration for radical salvage therapy (e.g., pelvic exenteration).**

Complete Sections A, B, C, and D

A) Reason for PET *(choose all that apply)*:
☐ PET after failed attempt at biopsy to establish a diagnosis of recurrence, **OR**

☐ PET to guide biopsy, **OR**

☐ PET to exclude extra-pelvic metastatic disease prior to salvage therapy

B) Primary Disease Site: ☐ Endometrial ☐ Cervical ☐ Vaginal ☐ Vulvar

Histologic confirmation of recurrence: ☐ Yes ☐ No

C) ☐ Patient has **no** significant comorbidities that would preclude surgery (pelvic exenteration) if clinically indicated.

D) ☐ Patient must have no metastases in chest and abdomen (negative or equivocal CT chest **and** abdomen)

Attach CT/MRI/US reports & provide images to the PET Centre.

Other information regarding eligibility:_____

Physician Signature:_____

Date: _____

Version Date: April 26, 2018
PET Scans Ontario Info Line Toll Free Phone Number: 1-877-473-8411

Appendix B: DRAFT - Diagnostic MRI for Cervical Staging Protocol

General Comments

- Exam must be MD supervised to advise on the appropriate anatomical plane orientation
- Buscopan must be administered for the diffusion weighted imaging
- Sat band must be used unless otherwise specified
- FOV: Use smallest field of view as appropriate. Imaging of the whole pelvis is not needed (patient will have a staging CT)

	Draft MRI for Cervical Staging Protocol	Additional Notes
T1 weighted	AX T1 no fat sat	• Orientation is at discretion of the centre or supervising MD
Standard anatomic T2 weighted	AX T2	• Fat sat on axial or coronal planes only • No fat sat on sagittal plane
	COR T2	
	SAG T2 no fat sat	
High res T2 weighted imaging	High res T2	• 1 plane must be done perpendicular to cervical canal • At least one other plane must be done at the discretion of the MD monitoring the test

DWI	AX DWI – 3 b values (b100-150, b300-500, b600-900)	• Must be done with buscopan
		• Select three b values in the following ranges, as appropriate:
		  ○ b100 – 150
		  ○ b300 – 500
		  ○ b600 – 900

Contrast enhanced	AX or AX/OBL T1w fat sat – pre- and post Gd	• Early dynamic acquisition • Ideally in same plane identified on T2w • Note – delayed acquisition post gad not recommended; nodal measurement can be performed on T2w