AN EVALUATION OF THE IMPACT OF MR IMAGE SLICE THICKNESS ON THE ACCURACY OF HIGH-DOSE-RATE BRACHYTHERAPY FOR GYNAECOLOGICAL CANCERS

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Abstract

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High-dose-rate (HDR) Magnetic Resonance (MR) guided brachytherapy (BT) is rapidly becoming the standard for treatment of locally advanced cervical cancer, globally. MR is an integral aspect of this treatment, enabling the level of soft tissue visualization required for precise delineation of organ and target contours with respect to the BT applicator or needles during treatment planning. The optimal slice thickness for MR datasets, and the role of super-resolved datasets are questions yet to be investigated. A digital phantom-based study assessed the impact of slice thickness on volumetric and geometric uncertainties in traditional MR datasets and estimated the resultant dosimetric uncertainty. Datasets with traditional slice thicknesses produced uncertainties up to 27% of the imaged structure volume, and contour uncertainty up to one third of the slice thickness This resulted in the exceeding of the American Association of Physicists in Medicine's (AAPM) recommended dosimetric uncertainty in HDR BT. Trilinearly interpolated datasets reduced these uncertainties substantially, allowing imaging with 2.7 mm coarser slices while conferring an imaging time reduction of 6 minutes. The results of this thesis demonstrate that the recommended range of slice thicknesses introduces uncertainties on a level known to impact dosimetry more than 9%. Trilinearly interpolated datasets may thus confer benefit in this clinical setting.

Acknowledgements

In the dance of dharma and karma, I have found myself frequently engulfed by the music – occasionally to the extent that I would lose my balance and fall to the ground. Somehow, I would always manage to fall to my knees, despite no desire to do so initially.

As if by some miracle, the embarrassment and disappointment this seemed to invoke within myself and others around me would dissipate – or at least my perception of it did. So much so that whatever wounds my mind and body acquired in the process would simply turn to nothing more than just scars to learn from and forget about. And so, each time, I would be granted the opportunity to stand back up and play catch-up with the routine I had missed.

But as the falls kept occurring, I began to question why I was dancing in the first place. As though balancing an elephant on a needle, wise cowardice anchored me to the dance floor long enough for reckless courage to settle.

It was only from this vantage point that I could live – and die – my own ignorance. And it was only from this vantage point that I could recognize the purpose of the dance – and take His hand.

I thank all those that have shown me forgiveness when I deserved it least – and support when I needed it most.

I am profoundly indebted to my supervisor, Dr. Ananth Ravi, for his invaluable pedagogy and unwavering patience. He taught me how to sharpen the blade of reason and the value of the question “why” repeatedly asked a healthy number of times.

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I pour out my love and thanks to my family and friends for reminding me to keep on dancing.

Dedicated to G. N.

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Acronyms

3D	Three-dimensional
3D-CRT	3D conformal radiotherapy
ABS	American Brachytherapy Society
ASC-H	Atypical squamous cells of undetermined significance, cannot rule out high-grade
AAPM	American Association of Physicists in Medicine
ASCUS	Atypical squamous cells of undetermined significance
ASIR	Age standardized incidence rate
ASMR	Age standardized mortality rate
AX	Axial dataset
BED	Biologically equivalent dose
BT	Brachytherapy
CCRT	Concurrent chemoradiation
CO	Coronal dataset
CT	Computer tomography
D1cc and D2cc	Minimum dose of most irradiation 1 and 2 cm^3
D90	% Dose to 90% of the volume
DFS	Disease-free survival
Dmean	Mean dose
DR	Direct reconstruction
DSC	Sørenson-Dice coefficient
EBRT	External beam radiotherapy
EQD2	Equieffective dose
FIGO	Federation of Gynecology and Obstetrics
FSE	Fast spin echo
Gy	Gray (1 J/kg, exposure unit)

GYN GEC-ESTRO	Gynaecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology
HD	Hausdorff Distance
HDR	High dose-rate
HPV	Human papillomavirus
HR CTV	High risk clinical target volume
hrHPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesions
ICRP	International Committee for Radiation Protection
IGABT	Image-guided brachytherapy
IGF-1	Insulin Growth Factor 1
IMRT	Intensity modulated radiotherapy
IR CTV	Intermediate risk clinical target volume
LBC	Liquid-based cytology
LIB	Library reconstruction
LNM	Lymph node metastasis
LSIL	Low-grade squamous intraepithelial lesion
LVSI	Lymphovascular space invasion
MIS	Minimally-invasive surgery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NAC	Neoadjuvant chemotherapy
OAR	Organ at risk
OS	Orifice
OS	Overall survival
PE	Pelvic exenteration
PET	Positron emission tomography
PI	Parametrial invasion
PLND	Pelvic lymph node dissection
PLNM	Pelvic lymph node metastasis
PTV	Planning target volume

REF	Reference dataset
RFI	Recurrence-free survival
RV	Percent relative volume
SA	Sagittal dataset
SBRT	Stereotactic body radiotherapy
SLND	Sentinel lymph node dissection
SNR	Signal to noise ratio
T2W	T2-weighted
TBS	The Bethesda System
TPS	Treatment planning system
TRI	Trilinearly interpolated dataset
TRUS	Transrectal ultrasound
V100	Volume irradiation by 100% of prescription dose
VMAT	Volumetric-modulated arc therapy
σ_{RV}	Standard deviation of the percent relative volume

CHAPTER 1: INTRODUCTION

1.1 Cervical Cancer

Cancer is the second leading cause of death worldwide according to the Global Health Data Exchange (GHDx) [1]. The International Agency for Research on Cancer (IARC) estimates that over 18.1 million new cases of cancer were diagnosed in the world in 2018, along with over 9.6 million deaths [2]. Approximately 44% of deaths are in women, and 7.5% of those deaths are from invasive cervical cancer, the most common gynecologic cancer in women. This puts current estimates of invasive cervical cancer deaths at over 310,000 worldwide [2]. While the cancer largely affects the developing world, more than 50,000 women develop the disease annually in the European Union and North America [3-5]. Trend analysis of epidemiological data suggests a reduction to the rate of disease prevention despite significant improvements to clinical screening, diagnostic strategy, and greater public awareness of the disease [6]. Data further indicates a high prevalence of oncogenic viral infection and concomitant lesions, the greatest risk factors for invasive cervical cancer, specifically among young women [7-9]. Promisingly, recent immunization efforts have been successful in substantially reducing the prevalence in test populations of teenage girls and young women [10]. As most women still remain at risk of cervical abnormalities that lead to invasive cervical cancer, the disease will decisively continue recruiting the focus of contemporary oncology in the future [5]. Present outcomes for women that develop the illness are favourable, with 5-year survival rates of nearly 90% for early-stage and 60% for advanced disease [11].

1.2 Epidemiology

The major decline that cervical cancer has undergone in the developed world is a testament to the persistent cooperation of researchers and policy makers. Despite a lack of data from most of the twentieth century, cohort analysis with extrapolation suggests that the invasive cervical cancer

age standardized incidence rate (ASIR) and mortality rate (ASMR) in Canadian women were as high as 35 and 15 per 100,000 after the Second World War [17]. These rates resemble those found presently in many developing nations, especially across Sub-Saharan Africa, where both rates can range between 15 to over 50 per 100,000 [2]. Early implementations of the Pap smear, a cervical abnormality screening test described by Papanicolaou et al. in 1941, were reported to significantly decrease mortality in select study populations in the 1960s [12, 13]. Some screening initiatives were conducted as early as that time in British Columbia, Canada and were highly successful, encouraging the rest of Canada and the United States to follow thereafter [14, 15]. Due to these efforts, the ASIR and ASMR for North American women were dropping steadily, and are presently less than half of those in 1975 [16, 18]. The 2015 Canadian ASIR and ASMR were 7.5 and 1.6 per 100,000; approximately 1550 Canadian women were diagnosed and 400 died from the disease in 2017 [18, 23]. Incidence was found to be highest in women between the ages of 35 to 49, and lowest in those that are under 20 years old [17, 21]. Figure 1 showcases the ASIR and AMSR data for Canadian women reported by the Canadian Cancer Registry and Statistics Canada.

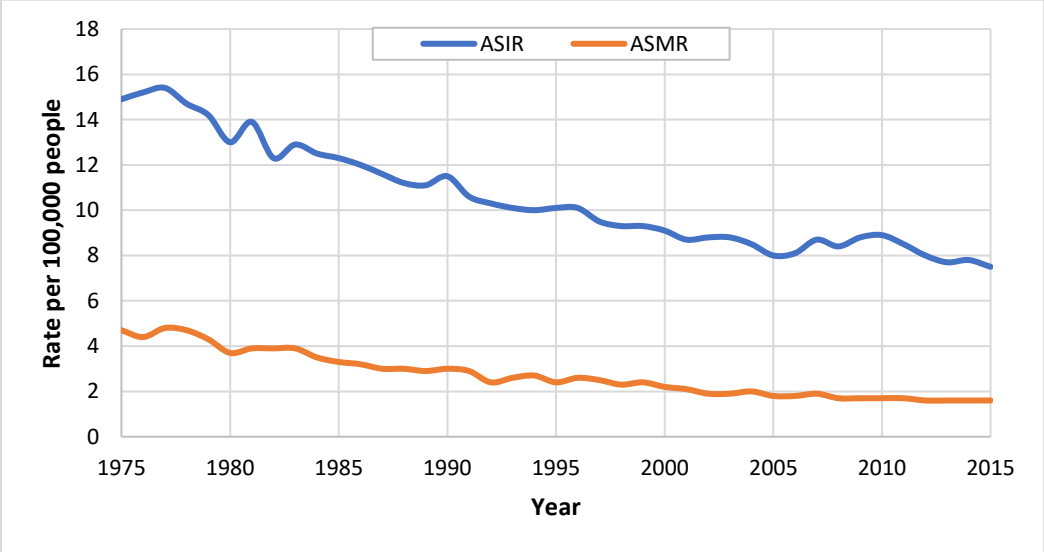
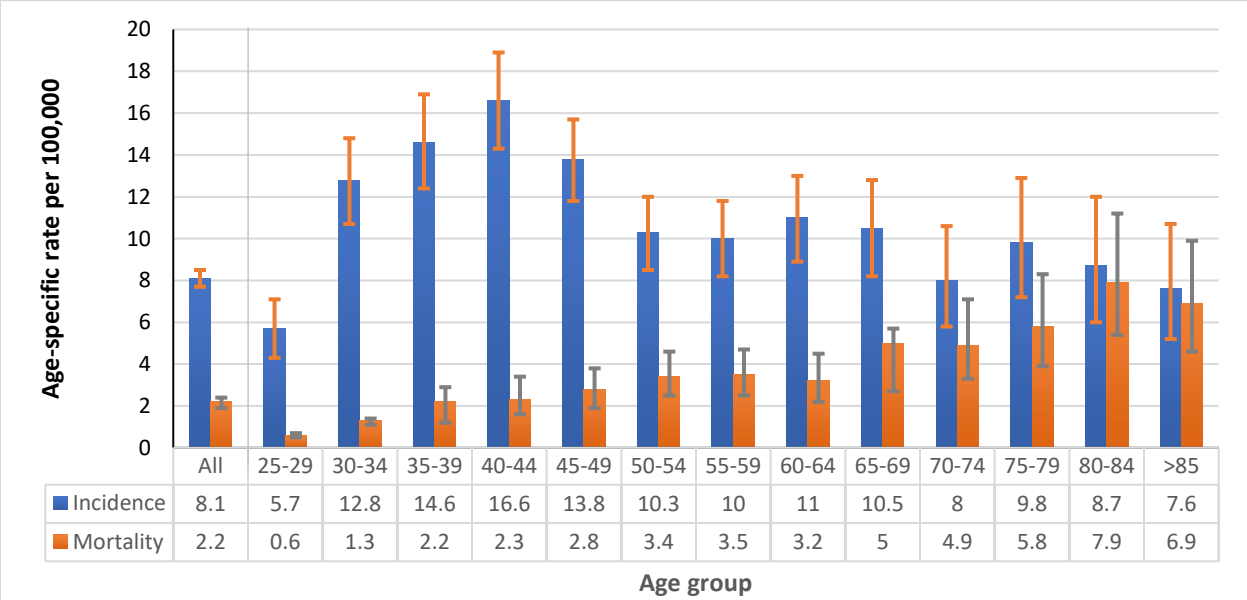


Figure 1 *Age standardized incidence and mortality rates per 100,000 people for invasive cervical cancer in Canadian women according to the Canadian Cancer Registry and Statistics Canada [18, 23].*

The dampening of incidence reduction over the past three decades may be attributed to an increased understanding of the cancer's cytopathology, and sequential improvements and availability of new diagnostic techniques such as liquid-based cytology (LBC), colposcopy, cervical biopsy, human papillomavirus (HPV) testing, and modern sectional imaging. Some of these techniques are presently used in tandem with, or in place of the Pap smear and are especially useful in the detection of the glandular variety of cervical cancers (adenocarcinomas) which are on the rise [48]. These make up about 10% of all diagnoses, and for them cytological screening is less effective [19, 20]. The apparent trend may thus originate in part due to previous false-negatives being correctly diagnosed. Some evidence also reveals that a possible resurgence of disease may be occurring due to trends in oncogenic viral infection [10, 17]. This is primarily based on studies showing that high-risk human papillomavirus (HPV) incidence and prevalence is highest in teenage girls and young women [52, 53]. These kinds of viral infections are responsible for causing intraepithelial lesions – forms of cervical abnormalities (dysplasia) known to lead to invasive cervical cancer – which have been found with highest prevalence in young women as well [55]. The literature on trends of precancerous lesion incidence in the West are scarce due to constantly evolving terminology, but some evidence suggests that rates were on the rise until the vaccine era which commenced around 2006 [54]. There is now some data from British Columbia showing that vaccination during a woman's teenage years reduces the incidence of moderate high-grade squamous intraepithelial lesions (HSILs) by 48-77% [56]. However, a US study suggests that rates of severe HSILs have doubled between 2007 and 2014 and are around 900 per 100,000 in women 25-29 [54]. The study did not decouple vaccination status from trend results, and it is possible that these increases occurred largely in unvaccinated females.

The trend in mortality further highlights the importance of proven screening strategy to prevent unfavourable disease severity at time of diagnosis. Data from numerous Canada Health Surveys comparing screening uptake among Canadian women reveals rapid decreases to the proportion and frequency of screening in women older than 49 [17]. This is a source of concern because the median age of cervical cancer diagnosis is 50 [16]. Moreover, disease severity at time of diagnosis increases with age – 78.6% of women 18 to 24 years old are diagnosed with early stage disease versus 26.6% of women over 70 [3]. Recurrence is also more common in older women [51]. Even with cutting edge treatment options, advanced and/or recurrent disease results in much lower odds of survival because of disease progression and treatment aggressiveness [2]. Accordingly, mortality rates are found to increase with age, and are highest for older women [49, 50]. The presence of terminal cases as a result of increasing late-stage diagnoses may explain the plateauing of mortality rate reductions in recent times. Figure 2 showcases the age-specific incidence and mortality rate data for Canadian women.



	All	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>85
Incidence	8.1	5.7	12.8	14.6	16.6	13.8	10.3	10	11	10.5	8	9.8	8.7	7.6
Mortality	2.2	0.6	1.3	2.2	2.3	2.8	3.4	3.5	3.2	5	4.9	5.8	7.9	6.9

Figure 2 *Age-specific incidence and mortality rates per 100,000 for invasive cervical cancer in Canadian women. Data from the Canadian Cancer Registry in 2010. Mortality rate data for women under 35 was unavailable and was taken from current U.S. mortality data; the values are corroborated by earlier Canadian reports [17, 49]. The incidence and mortality rates for women under 25 are 1.5 and 0.2 per 100,000, respectively [17]. Upper and lower 95% confidence intervals are denoted with error bars.*

1.2.1 Etiology

1.2.1.1 Cervix anatomy and physiology

The uterus is the larger portion of a woman's reproductive system. Along with the attached ovaries and vagina, it is situated posterior to the urinary bladder, and anterior to the rectum and sigmoid colon [25]. These organs are critical during treatment; their positioning relative to the uterus is outlined in Figure 3A. The uterine cervix is a cylindrical canal encompassing the lower 2.5 cm portion of the uterus, delimiting the uterus from the vagina [23]. The top third of the cervix is a narrowed section referred to as the uterine isthmus which attaches to the cervical canal, formally the endocervix, via an opening called the internal os (orifice). The inferior aperture of the endocervix is referred to as the external os [23]. The region surrounding the external os is known as the transformation zone, a region wherein more than 90% cervical squamous cell lesions occur [74]. This is also known as the ectocervix. Soft tissue known as the parametrium surrounds the ectocervix laterally and anchors to the pelvic side wall. Several parametrial lymph nodes are found within this region. These can act as passageways for disease spread, and the severity of disease progression is presently evaluated on tumour parametrial extension, pelvic side wall involvement, and lymph node invasion [90]. Figure 3B presents these anatomical structures.

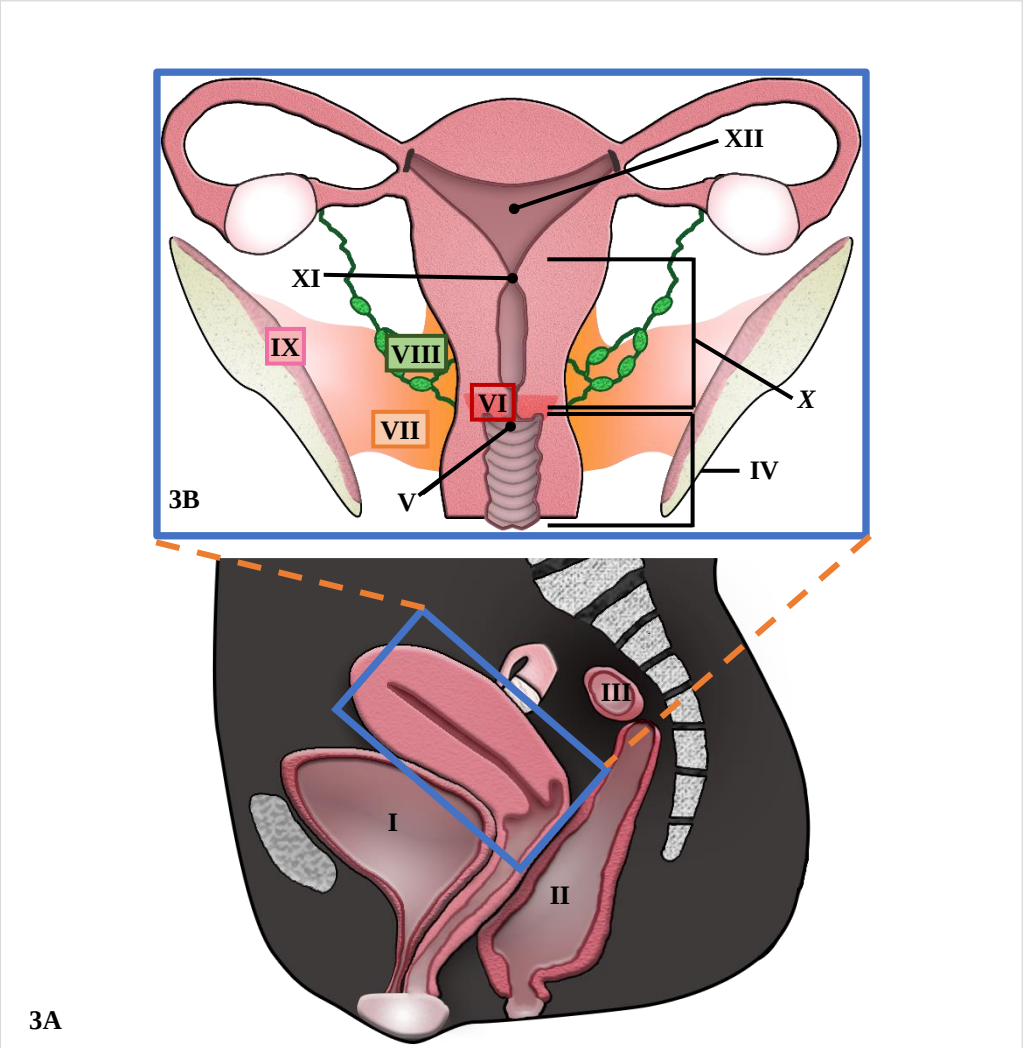


Figure 3 *Sagittal anatomical cross-section showcasing the critical organs in the vicinity of the uterus (blue bounding box). Urinary bladder (I), rectum (II), and sigmoid colon (III). (B) Coronal anatomical cross-section of the vagina, cervix, and uterus. The vaginal canal (IV) terminates at the external os (V) which is surrounded by the transformation zone (VI). The parametrium surrounds this zone (VII), and the parametrial lymph nodes are found therein (VIII). The parametrium anchors to the pelvic side wall (IX). The endocervix (X) follows thereafter, and terminates at the internal os (XI). The uterine cavity (XII) begins thereafter.*

The external os prevents herniation of the amniotic sac during pregnancy, and prevents microbial ascent into the cervix while allowing the transport of sperm during the fertile phase of the menstrual cycle [24, 25]. Ciliated epithelial cells in the endocervix actively promote the passage of sperm into the uterine cavity after it has mixed with the mucus produced locally [25, 26]. During pregnancy, endocervical mucus hardens to create a cervical plug that prevents fluid

leakage and bacterial infiltration. Additionally, the inferior portion of the uterine cavity called the isthmus thickens and the internal os narrows in order to inferiorly support the developing fetus [23, 25].

1.2.1.2 Persistent HPV infection – an oncogenic risk factor

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI); however, the majority of infections do not persist for longer than two years [26]. Persistent infection with one of sixteen high-risk variants (hrHPV) is a major risk factor for cervical cancer. The prevalence of infection with one or more of these subtypes is correlated with the degree of cytological atypia, which in turn is an indicator of invasive cervical cancer risk [7, 27, 28]. Close to 100% of all invasive cervical cancer cases test positive for infection with single or multiple hrHPV variants, and of those, HPV16 and HPV18 are found in more than 70% of cases [29, 30]. Due to the rarity of hrHPV-negative invasive cervical cancer cases, it is accepted that the relationship between hrHPV infection and invasive cervical cancer is causal [26, 29, 30]. Despite this, most infections are acute and clear within 12 months – hence the predictive value of HPV testing remained unclear until recently [28]. Emerging evidence from the completed first round of the HPV for Cervical Cancer (HPV FOCAL) trial showed that HPV-positive women across all age groups had a significantly higher proportion of HSILs, with women over 35 having nearly double the prevalence [59]. These pre-cancerous lesions appear within 24 months, and greatly increase the risk of invasive cervical cancer [28, 60]. Moreover, a recent analysis found cleared HPV16 infection to reappear on average 6 years later in nearly 20% of women [61]. These findings highlight that HPV vaccination and screening should not be understated. As a result, all provinces and territories in Canada now have HPV immunization for school boys and girls [46].

1.2.1.3 Lifestyle risk factors

Lifestyle factors that contribute to, or are the source of a direct carcinogenic effect – along with those that suppress the recovery process from directly carcinogenic factors – are strong candidates for increasing invasive cervical cancer risk. The risk is highest for persistent infection with hrHPV during sexual intercourse. Women with an HPV-positive partner have been found to be at a 5-fold increased risk of cervical cancer [57]. The risk is further exacerbated by an increasing number of lifetime sexual partners, and a younger age of sexual debut [29, 31, 43]. Past oral contraceptive use was also found to be associated with a 1.6-fold risk of invasive cervical cancer, with use of 5 or more years increasing the risk to 1.9 to 2-fold [45,58]. Current users have been found to be at a 2.2-fold risk [58].

Smoking is another serious lifestyle risk factor for developing invasive cervical cancer [32]. A study found that HPV16 negative smokers had a 1.7-fold increase in risk compared to HPV16 negative non-smokers, while HPV16 positive smokers had a 2.57-fold increase in risk compared to HPV16 positive non-smokers. Risks were highest in long-term smokers, and those with high viral load [33]. The addition of smoking resulted in a synergistic effect, suggesting both a direct and indirect carcinogenic component to the associated risk. This is in line with the present understanding that smoking is both independently carcinogenic and immunosuppressive [34].

Diet is a frequently overlooked factor that may strongly modulate invasive cervical cancer risk. Observational, interventional, and mechanistic data suggests that dietary reduction of animal products is protective against cancer. In particular, a multivariate analysis of the Adventist Health Study-2 data found a 29% reduction in breast and gynecological cancer risk among women consuming a vegan diet [35]. This may be due to a reduction in serum Insulin

Growth Factor 1 (IGF-1) which is a known potent promoter of invasive cervical cancer proliferation and invasiveness [36]. One of the main causal factors was identified to be the animal derived protein. When controlled for protein amount and energy intake, plant-derived protein was associated with decreases in serum IGF-1 levels compared to animal-derived protein with which increases were observed [37]. A number of post-intervention ex vivo bioassay experiments on tumour cell growth and proliferation across a number of cancers and cancer cell lines support these findings. Reductions up to 55% in serum IGF-1 levels, 20-30% increases in cell apoptosis, and notable increases in serum IGF binding protein-1 (IGFBP-1) levels were observed when exercise was coupled to vegetarian and vegan diets [38-40]. More specific to invasive cervical cancer, a high intake of vegetables was found to significantly increase HPV clearance ability resulting in a 54% lower infection persistence [41]. Vegetarian diets were also found to be independently protective against HPV infection in a study on Eastern women, with a 23% reduced risk compared with non-vegetarians [42].

Finally, some observational studies report an association between obesity and increased invasive cervical cancer risk. One possible explanation for this may be the detrimental impact of weight gain on cancer-promoting hormonal profiles in women [43]. However, a 2009 meta-analysis of literature up to the data of publication found that the increased incidence and mortality from invasive cervical cancer in obese women is likely the result of lower screening uptake [44].

1.2.2 Screening and diagnosis

Organized national screening for cervical cancer has been instituted throughout most of Canada by the mid-2000s, with the exception of Northern Canada wherein screening takes place but without official involvement or recruitment by the provincial government [46]. The goal of

screening in general is to test for the presence of preinvasive disease, or to catch invasive disease early on in its course. The Canadian Task Force on Preventative Health Care (CTFPHC) routinely publishes screening recommendations and protocols for Canadian clinicians and policy-makers. The recommendations are age-group specific, and are accompanied by a rating (either weak or strong) depending on the quality of the available evidence. A summary of the latest cervical cancer screening recommendations can be found in Table 1 below:

Group	*Recommendation*	*Rating and Evidence Quality*
<20	*No routine screening is recommended.*	*Strong; high quality evidence*
20-24	*No routine screening is recommended.*	*Weak; moderate quality evidence*
25-29	*Screening every 3 years.*	*Weak; moderate quality evidence*
30-69	*Screening every 3 years.*	*Strong; high quality evidence*
>70	*Screening until 3 negative tests within 10 years.*	*Weak; low quality evidence*

Table 1 *The 2013 cervical cancer screening recommendations by the Canadian Task Force on Preventative Health Care [47]*

Provinces typically exercise their own discretion regarding adherence to the CTFPHC guidelines. To date, only British Columbia, Alberta, and Nova Scotia have implemented the change to increase the onset of screening from 21 to 25, while other provinces are considering making the change. Other differences in screening exist as well, such as screening frequency and screening onset upon sexual debut. Recruitment methodology throughout Canada is uniform, with an initial letter of invitation to a cytology exam sent to eligible women. The only exception is Nunavut wherein a phone call is made [47].

1.2.2.1 Cytology

The first step of the screening process involves directly measuring the degree of cellular abnormality at the ectocervix (and frequently endocervix). This is accomplished with the Pap smear test via physical removal of a small number of cervical cells using a specialized medical

brush. Cytology refers to the microscopic examination of this sample either by direct transfer onto a microscopy slide (conventional cytology) or by submerging the sample into a liquid medium and processing it further (liquid-based cytology, LBC) [62]. LBC approaches typically have a 10-20% higher sensitivity for detecting carcinomas and HSILs [63,64]. This manifests in a highly significant reduction in the number of ambiguous cases referred to as atypical squamous cells of undetermined significance (ASCUS) [64,65]. The end result is as much as double the number of low and high-grade diagnoses [66]. LBC has also been shown to be as effective in decreasing the rate of false-negative adenocarcinomas as much as squamous cell carcinoma cases [62, 67]. Finally, the technology provides the ability to homogenize cells through the removal of blood and mucous which allows modern implementations to also test for the presence of hrHPV infection with the same sample, frequently referred to as reflex testing [68]. For these reasons, Canada has largely phased out conventional cytology in favour of LBC, with a national target of 14 days for sample turnaround [60].

The Bethesda System (TBS) is the current gold standard for reporting cervical cytology findings [69]. It provides a unified set of clinical terminology and an atlas of real cases that fosters clarity and reproducibility across disciplines and geographical regions [70]. The system is two-tiered, mainly categorizing Pap smear samples as belonging to either low-grade or high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively). The system also contains categorization for glandular atypia. In 2014, the most recent release of TBS maintained that the two-tiered approach was superior to introducing medium-grade nomenclature. The already existent categorizations of atypical squamous cells of undetermined significance (ASC-US) or of those wherein high-grade presence cannot be ruled out (ASC-H) were found to adequately address cases that do not overtly fall into the two tiers [60]. Table 2 outlines the current abnormal

cytology follow-up guidelines for various types of cervical atypia, and provides an overview of the prevalence in each age-group of Canadian women [60, 71]:

Abnormal cytology category	LSIL	ASC-US	AGC	ASC-H	HSIL+
Recommended next step	Repeat cytology within 6 months		Colposcopy +/- biopsy within 6 weeks		
Age group	**% of test results**				
21-29	4.7	4.4	0.1	0.6	1.0
30-39	1.8	2.3	0.1	0.3	0.7
40-49	1.1	2.0	0.2	0.2	0.3
50-59	0.6	1.5	0.2	0.1	0.2
60-69	0.3	1.0	0.2	0.1	0.1

Table 2 *Current abnormal cytology follow-up recommendations, with % breakdown of cytological result in various Canadian women's age groups in 2012-2013 [60, 71]*

1.2.2.2 HPV DNA testing

Persistent hrHPV infection has been established as an unequivocal cause of invasive cervical cancer, but the value of HPV DNA testing as an adjuvant to or a replacement of Pap testing is still being evaluated. A Canadian expert panel reviewed the major randomized control studies on the subject up to 2013 and concluded that caution must be exercised when phasing in hrHPV testing, especially in younger populations, due to a large disparity between the negative and positive predictive values of the test [72]. Even though women with or without cervical atypia that are hrHPV negative are not at risk of cervical cancer, the test especially in women younger than 30 has a considerably high false-positive rate due to the much higher prevalence of hrHPV infection, which is likely to clear [74]. The panel concluded that HPV DNA testing should be evaluated provincially/territorially. Since the publication of these recommendations, the main use of HPV DNA testing across Canada was in the triage of women older than 30 with ASC-US, or as a follow-up strategy after treatment [46, 60]. The use of the test as a modality for routine primary screening is presently under consideration across Canada [46].

1.2.2.3 Colposcopy and biopsy

The method by which the transformation zone of the cervix is examined is known as colposcopy. Its procedure is generally well tolerated with low rates of complications [74]. The procedure involves widening the vaginal canal using a speculum and the positioning of an illuminated magnification setup near the cervix. A variety of staining methods that capitalize on the disparate responses between normal and neoplastic cells help identify abnormal regions which can be treated directly or biopsied for histological study [74]. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that any visible lesion be biopsied, and that in general, taking two biopsies from different sites confers a sensitivity benefit [75]. Lesions that are pre-cancerous are treated with a variety of techniques, the best of which are with ablative (laser, usually) technologies which result in far less adverse effects compared to excisional methods [76]. If biopsy at time of colposcopy is uncertain, endocervical curettage and cone biopsy are used to remove larger amounts of tissue from the endocervix and ectocervix. In the event that histology indicates the presence of invasive cervical cancer, sectional imaging is used to evaluate the extent of tumour growth for the purposes of cancer staging [77]. Data from provinces reporting statistics on cytology-histology agreement rates indicates that the Canadian average is below the 65% target. This has been suggested to be the result of the low (20-30%) 6-month follow-up rate of colposcopy in women with AGC, ASC-H, and HSIL, as opposed to issues with biopsy efficacy [60].

1.2.3 Clinical definition and diagnosis of invasive cervical cancer

Nearly a century of research on the etiology and evolution of cervical cancer reveals that the disease develops in stages. In light of continually emerging evidence, the International Federation of Gynecology and Obstetrics (FIGO) has been delineating universal staging criteria

crucial for the selection of appropriate therapeutic management [78]. This is done by classifying types of disease presentation and distinguishing prognostic factors strongly correlating with differences in outcome [89, 90]. As data regarding the subtler differences within these classifications becomes available, further modifications to the system are made to allow for the improvement of treatment specificity [87]. In particular, the 2018 revision of the FIGO system includes a number of changes to the way cervical cancer is clinically defined in light of a better understanding of disease progression [90]. Despite such revisions, the review process for a universal system is extensive and is associated with a low update frequency. This necessitates clinical organizations to implement supplemental recommendations in line with impactful research that may or may not be incorporated in future FIGO updates [91]. Differences in protocol are therefore expected between individual centers.

1.2.3.1 Disease progression

Historically, tumour size and geometry have always been at the foundation of staging guidelines. It has been long understood that tumour volume and depth of stromal invasion were the chief measures of progression; they have been subject to modification under various iterations of the FIGO guidelines [91, 109, 111]. One important advancement has been the understanding that pelvic lymph node metastases (PLNM) decisively dictate whether an escalation in treatment complexity is warranted as patients with this criterion have substantially lower odds of survival [92, 93]. This was addressed in the current FIGO system wherein nodal status was fully incorporated into Stage IIIC locally advanced disease criteria for the first time [89, 90]. There is, however, ongoing discussion regarding the nature of the transformation of disease from early to locally advanced disease in the context of lymphatic propagation [91]. Lymphovascular space invasion (LVSI) is often broadly reported for patients presenting with any stage early and locally

advanced disease because the absence of LVSI was thought to safely rule out PLNM according to a number of early studies [95, 96]. Some research found that LVSI was a strong predictor of PLNM [99]. However, these studies often include more advanced versus early disease in the analysis, do not stratify the results by stage, find stronger predictors such as parametrial invasion (PI), and use an outdated version of the FIGO guidelines. In contrast, a recent analysis of an aggregate of applicable literature has found that lymph node metastases and recurrence in stage IA1 disease are extremely rare, even though up to 40% of these cancers present with LVSI [91]. Due to the questionable status of LVSI as a predictor for PLNM in low-risk early disease, radical surgery in these patients has likely led to substantial overtreatment, and thus avoidable morbidity and mortality [91, 109]. There is lack of complete certainty regarding stage IA2 disease primarily because recent retrospective research has found these patients to benefit from radical surgery – however, the study group included stage IB1 patients, most of which would be classified as stage IB2 under the current FIGO guidelines [120]. Despite this, the status of LVSI in stage IB to IIB is considerably clearer, with a linear relationship between stage and PLNM – specifically sentinel nodes [97, 99]. This is an important point provided that positive sentinel nodes in early disease predict PI in 100% of cases [109]. Accordingly, it is understood that PI is a critical factor differentiating early and locally advanced disease [96, 99, 100]. At the point of PI, the cancer may grow laterally until it reaches the pelvic wall. This can result in bladder and/or rectal invasion, and/or pressure on the urinary system thus leading to hydronephrosis or complete kidney failure [101]. Moreover, further lymphatic propagation can result in metastasis to the para-aortic lymph nodes which often results in distant organ (ex. pulmonary) invasion [102, 178]. The definition criteria of the most recent FIGO system are summarized in Table 3, supplemented by Figure 4 to demonstrate progression graphically.

1.2.3.2 Diagnostic process

The diagnostic workflow of the FIGO system has been largely based on clinical examination in the form of inspection and palpation of the rectogenital region for markers of disease progression [79]. Although standard practice, these techniques come with a variety of challenges. The associated steep learning curve and a large interobserver variability result in a diagnostic accuracy of approximately 50% [80]. Moreover, the locally limited nature of the technique prevents proper assessment of tumour parametrial involvement, and lymphovascular space invasion (LVSI) extent which are major prognostic factors for early-stage disease [81]. For these reasons, surgical methods have supplemented clinical examination for a more comprehensive diagnosis.

Laparoscopy has emerged two decades ago as a minimally invasive surgical (MIS) method allowing for pelvic lymph node biopsy (lymphadenectomy) and the delineation of true tumour extent [82]. MIS is done interchangeably with open surgery (laparotomy) however recent analyses of the data to date reveal disappointing results [120, 142]. Sentinel lymph node biopsy is performed by examining the first drainage node near the tumour in an effort to spare unnecessary full lymphadenectomies, and has resulted in specificity over 90% [83, 84]. However, the technique is associated with a steep learning curve and does not offer global information, such as micrometastases in surrounding or distant organs [85]. As a result, the current practice recommendation is pelvic lymphadenectomy [144].

Sectional imaging has become a major component of contemporary diagnostic strategy as it is minimally/non-invasive and can stage local and advanced disease. In particular, magnetic resonance imaging (MRI) is most used in this application because it provides the best soft tissue contrast of all imaging modalities available today [86]. MRI was demonstrated to be appropriate

for delineating tumour extent with a 95% negative predictive value of PI and a 94% staging accuracy in early-stage disease [77]. It is also capable of evaluating pelvic node involvement in advanced disease, with an overall sensitivity of 79% [79]. MRI is reliable in ruling out bladder and rectal metastases, reducing the need for clinical examination often done under local anaesthesia [88]. Finally, using MRI to delineate tumour extent greatly streamlines the transition between diagnostic, treatment, and follow-up workflows that already utilize MRI.

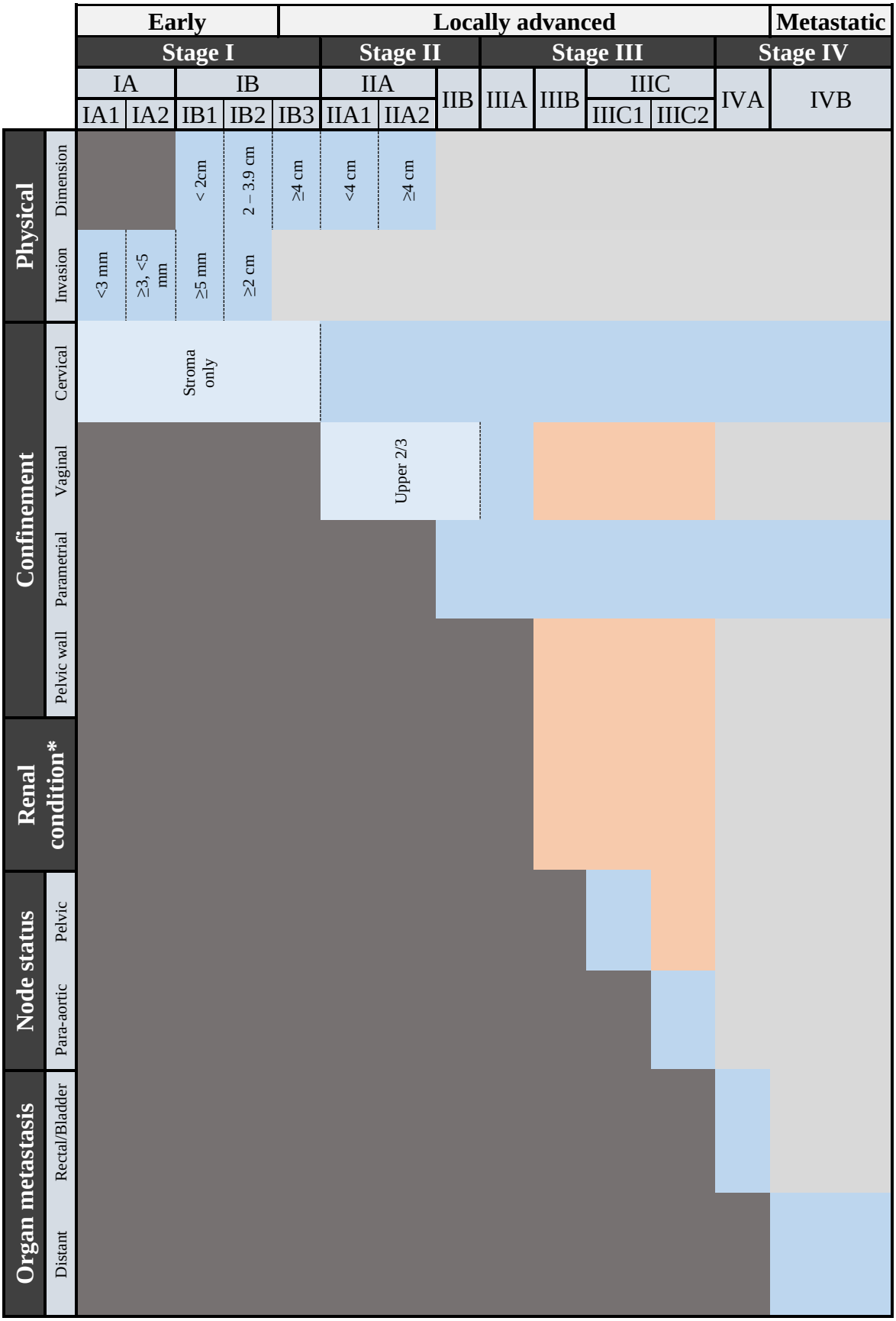


Table 3 The 2018 FIGO cervical squamous cell carcinoma staging system [89, 90]. Box colours indicate the level at which a stage meets the staging criterion: No specification needed (redundant), staging criterion not met, staging criterion met (partial), staging criterion met (full), and/or

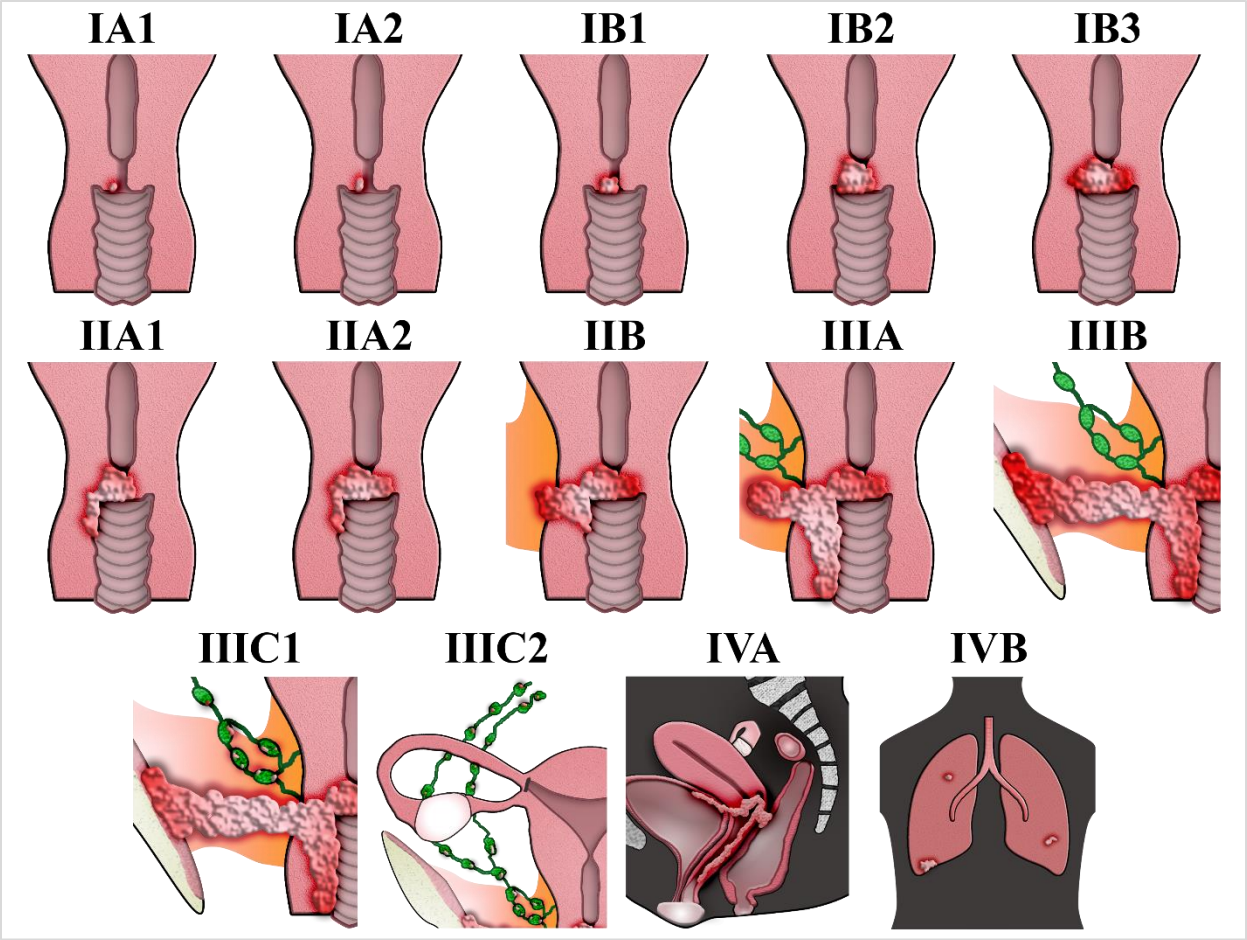


Figure 4 Graphical representation of cervical squamous cell carcinoma progression according to the 2018 FIGO cervical staging system [89, 90].

1.3 Cervical Cancer Treatment

Modern cervical cancer management is a multi-faceted field incorporating the effective treatment of disease and its symptoms while carefully mitigating treatment associated pain, discomfort, and side-effects. An increased understanding of the disease and the availability of cutting-edge imaging and therapeutic technologies allows for individualized treatment that best conforms to patient needs. Various histopathologic evaluation systems incorporating FIGO recommendations are used to characterize a cancer's subtype and to select the most appropriate treatment protocol [94]. A typical, comprehensive system is summarized in Table 4.

While early disease affords the use of modest surgical procedures that can be modulated by patient age and fertility preference, locally advanced and metastatic disease has progressed significantly and is classified as high-risk due to a much higher failure and recurrence rate [103, 104]. Such patients require protocols that leverage a combination of customizable surgery, radiotherapy, and chemotherapy [94]. In particular, contemporary radiation therapy techniques have notable fine-tuning potential for the delivery of individually tailored plants for complex advanced disease [87, 94, 106, 113]. Novel radiation delivery approaches are actively being researched due to potentially unprecedented levels of customization, further addressing the need for treatment that conforms to patient anatomy [95].

Histopathologic evaluation criteria
Dimensions of the tumour
Stromal invasion/depth of the wall involved
Tumour differentiation
LVSI
Status of resection margins
Status of parametria and vaginal cuff
Number and status of lymph nodes

Table 4 *Typical histopathologic system*

1.3.1 Prognosis of new, recurrent, and palliative patients

Stage at diagnosis is the most important prognostic factor in the progression of cervical cancer [115]. Disease at early, locally advanced, and metastatic stages presents with varying types and quantities of tissues affected, progression rates, and invasiveness. Cases are mostly of new

disease, but recurrence being not uncommon and the existence of palliative cases creates a further demand for extensively differing treatment protocols.

New cases of early disease (stages I-IIA) are presently treated with surgery, and pre/post-operative chemoradiation if needed. Patients in stages IA to IB1 are treated with conservative surgery, are ideal for fertility conserving treatment (if low risk), and have excellent prognoses with 5-years disease-free survival rates (5-yr DFS) between 95-100% (115, 117, 118). Stage IB2 to IIA patients are treated with surgery and preoperative radiotherapy have lower 5-yr DFS in the range of 83-94% [115, 116].

Those with locally-advanced disease in stages IIB-IIIC are treated more extensively with definitive chemoradiation and adjuvant chemotherapy [119]. Patients between stage IIB and IIIA have 5-yr OS in the range of 52-85%, and those with stage IIIB and IIIC are at a significantly lower 19-52% [115, 92, 93].

Patients with metastatic disease have poor prognosis due to nearly double the hazard ratio of Stage III – they are mostly palliative as they are prone to treatment failure and recurrence [115, 93]. The 5-year post-relapse survival in recurrent disease regardless of stage is around 25% with a median recurrence-free interval (RFI) of 15 months; the number of relapse sites remains the greatest prognostic factor in these patients [114, 121].

1.3.2 Surgery

Surgical intervention is the oldest, most frequently utilized therapeutic option found within the majority of cervical cancer treatment protocols. The goal of surgery is to remove the primary tumour plus a margin of tissue likely to contain microscopic disease to reduce the likelihood of recurrence [135]. As such, it is suitable as a primary option only if tumour

extension is minimal [146]. In such cases, surgical procedures ranging in invasiveness are selected based on stage. In early disease with low-risk characteristics, surgery is curatively sufficient as a standalone treatment and can be modified if, for example, a patient desires fertility conservation [160]. High-risk early disease or locally advanced disease disqualify a patient from undergoing surgery alone because of high-risk characteristics such as large tumour size, deep invasion, extensive LVSI, parametrial invasion, and often positive lymph nodes. Such cases require radical surgery and post-operative radiotherapy [154, 155]. If during staging cancer cells are detected beyond the maximal excisional boundaries, surgery is an unsuitable treatment option. These cases are treated with external beam radiotherapy, brachytherapy, chemotherapy, and most frequently a combination thereof [156]. Ultra radical surgery for pelvic organ removal (pelvic exenteration) is rare but possible in moderate to high-risk locally advanced disease [163]. Novel surgical reconstruction techniques have recently been utilized to significantly improve the quality of life of these patients [179].

1.3.2.1 In early stage disease

Early stage cervical cancer represents 60-65% of total diagnoses in Canada today and traditionally encompassed stages IA1 through IB1 [3]. With the recent changes to stage IB in the FIGO staging system, it is possible that stage IB3 (formerly IB2) will be classified as locally advanced disease, while stage IB2 relegated to early. The past two decades have seen an increase in data suggesting that de-escalation in the surgical management of a portion of these diagnoses is possible, and perhaps even necessary in order to prevent avoidable treatment morbidity. Conization is a form of less invasive surgery for stage IA1 wherein a cone of tissue containing the tumour is excised. Even in the case of positive exocervical margins, the curative rate of the technique is near 100% and the recurrence rate 0%; in the rare case of positive endocervical

margins, patients are recommended repeat conization or escalated surgery [124, 125]. Conization has been shown to be an effective prediction tool for the need of hysterectomy in stage IA2-IB1 disease [126].

Stage IA2-IB1 disease presents with an incremental increase to tumour volume and depth of invasion, accompanied by higher rates of LVSI. These factors are understood to put patients at a greater risk of parametrial invasion and lymph node involvement [145, 146]. Despite this, researchers of early studies have hypothesized the existence of a low-risk subgroup of patients that have better outcomes. These patients consistently presented with a maximal tumour size of 2 cm, a maximum depth of invasion of 10 mm, and negative pelvic lymph nodes [117]. Covens et al. demonstrated that this subgroup can account for more than 65% of stage IA1-IB1 diagnoses, and in them the prevalence of parametrial invasion (PI) was nearly 0% despite LVSI rates of 45%. They were treated with radical surgery, the standard of care in the West for all early disease at the time, and had 5-year recurrence-free survivals of 96% and 98% in another study [133, 127]. Much literature has since confirmed that PI is seldom found in these patients, and that they definitively require treatment de-escalation whether fertility conservation is desired or not [117, 121, 122, 123, 128-130]. MRI has been proposed to be the chief imaging modality capable of identifying these patients non-surgically, and there are now proposed criteria for doing so [131, 132].

Presently, the North American standard of care for patients with high-risk stage IA2-IB1 or stage IB2-IIA disease is radical hysterectomy wherein the uterus, cervix, and parametria are removed [152]. Low-risk patients up to and including stage IB1 are treated with a simple hysterectomy wherein only the uterus and cervix are removed. Compared to the radical approach, this intervention has lower rates of surgery-associated morbidity, better patient

recovery times, and a higher quality of life [144, 150]. This is primarily due to the absence of substantial parametrial resection which often damages surrounding innervation leading to urinary and rectal dysfunction [109, 149]. Despite its adoption clinically, the technique has only been evaluated in low to moderate-powered studies [133]. The SHAPE trial is a presently ongoing evaluation of the technique with over 500 participants across 130 centers; data from this study and the smaller ongoing ConCerv study are highly anticipated and will likely shape forthcoming treatment guidelines [144, 134, 137].

The practice recommendation for patients that wish to conserve their fertility is the removal of the ectocervix and a portion of the parametrium called radical trachelectomy [141]. This technique results in excellent curative outcome, and some research suggests this is the case even for patients with tumour sizes over 2 cm and favourable histology [138-140]. A very recent study by Alvarez et al. reveals that the size of the residual cervix (the endocervix) as assessed on MRI is an important predictor of pregnancy outcomes in these patients. A size under 10 mm was found to be associated with premature delivery and rapture of membranes [143]. This may be incorporated in future surveillance strategy to offer patients better counselling and improved pregnancy management.

The need for lymph node biopsy in all cases staged IA2 and beyond is well established. Pelvic lymphadenectomy (PLND) is a comprehensive technique that resects a significant portion of the lymph nodes around the pelvic organs – however, it is often associated with further surgical morbidity, and its omission has been proposed in low-risk cases [147]. Sentinel lymph node dissection (SLND) has subsequently emerged as a proposed technique to reduce the number of resected nodes by detecting macrometastases in the immediate vicinity of the primary tumour [109, 135]. Despite the impressive results in many of the studies, a recent review

concluded that the oncological safety of the technique must be further investigated for patients diagnosed with stage IB1 and beyond due to the inherent difficulty of detecting micrometastasis with SLND [136].

There is ongoing debate regarding the status of minimally invasive surgery (MIS) performed through small laparoscopic incisions since its clinical adoption in 2006. Subsequently, a number of studies with moderate statistical power have shown MIS to be an adequate alternative compared to open surgery, bolstering lower intraoperative and postoperative morbidity [148]. In spite of this, an interrupted time-series evaluation of the technique by Melamed et al. revealed a steady decline in the 4-year relative survival rate of early disease cases between 2006-2010. In their study of nearly 2500 patients, MIS was associated with a 72% increase in the 4-year mortality compared to open surgery [120]. Data from the LACC trial comparing laparoscopic, robot-assisted, and open surgery has recently been published showing a 10% drop in the 4.5-year disease free survival and higher recurrence in patients treated with the technique [142]. At the moment, the mechanism responsible for the lacking results has been hypothesized to be a combination of the inferior visibility and maneuverability associated with the smaller laparoscopic incisions as well as inadvertent dissemination of malignant cells by the surgical tools used in MIS [120].

1.3.2.2 In locally advanced stage disease

Locally advanced disease is incrementally extensive compared with early disease and has traditionally encompassed a broad range of patients staged IB2 to IVA. It generally presents with a significant risk of nodal metastases, making surgery inapplicable in many cases [156]. While the North American standard of care for these patients is chemoradiation, there is evidence that surgical techniques utilized in early disease can be implemented adequately in locally advanced

cases of lesser severity (traditional stage IB2 to IIB) [157-159, 161]. In particular, Ma et al. reported that the 3-year overall and disease-free survival of stage IB2 and IIA patients treated with radical surgery after neoadjuvant brachytherapy and one cycle of chemotherapy were equal to those treated by standard external beam radiotherapy plus brachytherapy (both 90%), but had fewer side effects [154]. Another recent study by Mori et al. investigated the role of radical hysterectomy in treatment of stage IB2 to IIB patients. Surgery was performed after neoadjuvant and during adjuvant chemotherapy, and a 79% 5-year relapse-free-survival rate was achieved. Interestingly, all patients had bulky disease (tumour size greater than 4 cm), and the main reason for treatment cessation was post-operative discovery of lymph node involvement in 22% of patients [153]. This is congruent with other researchers' findings, and those of Trattner et al. which suggest that tumour size in stage IB-IIB locally advanced disease treated with radical hysterectomy seems to serve limited prognostic value if the status of lymph nodes is known [D, BW]. On the other hand, a study by Gupta et al. with much higher statistical power found that a neoadjuvant chemotherapy plus surgery arm had a 7% reduction in 5-year disease-free survival, but the same 5-year overall survival as the concomitant chemoradiation group (75%). It is important to note that unlike Mori et al., surgery was not followed by another round of chemotherapy [155].

1.3.2.3 In late locally advanced and metastatic disease

Disease beyond the bounds of the cervix, vagina, and parametrium has the potential to spread in numerous ways, manifesting in a heterogeneity of cases. This makes it difficult for clinicians to provide broad recommendations for stage III and especially stage IV patients who account for 8% of all diagnoses [168]. Despite this, it is clear that traditional surgical approaches are inadequate for treating extensive disease spread characteristic of these stages. The only

curatively sufficient surgical option for patients with persistent, recurrent, or advanced disease is pelvic exenteration (PE) also referred to as salvage surgery [164, 170]. PE involves the removal of most or all organs in the pelvic cavity (bladder, rectum, and genital tract) followed by urinary, rectal, and vaginal reconstructive procedures [163, 179]. Considering the extent of disease progression in these patients, the 5-year overall survival rate is a modest 36-61% [163, 165, 166-168, 179]. However, this understandably comes at the expense of up to 14% operative mortality, 50-78% post-operative morbidity, and recurrence rates in the range of 6-42% [166, 169, 171, 174, 175, 176, 177]. The most important factors for favourable survival are curative intent (nearly six times higher than palliative), negative resection margins, and primary treatment (nearly two times higher than recurrent). For recurrent cases, a longer time interval between primary treatment and recurrence is much more favourable [166, 172, 173].

1.3.3 Chemotherapy

The value of systemic control is immense in a cancer documented to progress through both regional and distant microscopic infiltration. Chemotherapy is utilized for the purpose of arresting invasive cells' division biochemically, and with great effectiveness in the treatment workflow of cervical cancer. While conferring great benefit alone in the form of neoadjuvant chemotherapy, one of the most important past developments in cervical cancer treatment was the recognition that chemotherapy is highly synergistic and well tolerated with radiation therapy [210]. Following this, concurrent chemoradiation definitively became the gold standard of treatment for a large proportion of cervical cancer diagnoses [215]. Such a protocol typically involves administering a weekly dose of a platinum-based chemotherapy agent for the duration of radiotherapy [216].

1.3.3.1 Concurrent chemoradiation

A literature review on the role of chemotherapeutic agents for the management of locally advanced cervical cancer revealed that across 30 clinical trials, platinum-based agents such as cisplatin, carboplatin and/or nedaplatin led to superior tumour size reduction, micrometastasis elimination, operability improvement, and downstaging of surgery [211]. GOG 120 and RTOG 90-01 were seminal trials setting the standard for cisplatin-based concurrent chemoradiation (CCRT) protocols. When added to traditional EBRT, a 51% reduction in the risk of recurrence and upwards to a 40% improvement in the 4-year overall survival of patients was observed [213]. However, the role of chemotherapy agent combination was not possible to establish due to conflicting results in the examined literature [214]. Despite this lack of certainty, it is understood that individual variability in chemotherapeutic response exists and that combination chemotherapy may be an appropriate solution to this challenge [215]. Presently, the gold standard is weekly cisplatin at 40mg/m^2 per week which was shown to have the lowest toxicity of all CCRT regimens in a recent multi-analysis [216, 222, 232].

1.3.3.2 Neoadjuvant chemotherapy

Additional courses of chemotherapy are being investigated at various points in surgical and radiotherapeutic treatment workflows – however, results are mixed. For instance, independent studies find benefit to NAC, such as a recent study illustrating that neoadjuvant chemotherapy (NAC) in operable cervical cancer increases the 5-yr OS of patients by 23% over surgery alone [217]. Further investigation also revealed that a protocol of surgery plus NAC confers a 10% benefit over radiotherapy alone [218]. However, Fu et al. noted that their meta-analysis confirms a suspected heterogeneity of reported results reported by other analyses [216]. In their investigation, NAC conferred no benefit over surgery alone [219]. Moreover, even in the event

that NAC improves clinical outcomes after surgery, studies routinely show that CCRT is superior in locally advanced cervical cancer [220, 221]. Based on the results of similar studies, the National Comprehensive Cancer Network (NCCN) recommends that chemotherapy be limited strictly to those patients that are not eligible for radiotherapy [141].

1.3.4 Radiation therapy

The efficacy of ionizing radiation in treating disease was posited as early as 1896 when Emil H. Grubbe was reported to utilize ionizing radiation to treat cancer, even before formalized principles of x-ray generation [180]. 20 years later, Marie Curie introduced radon therapy in France after her experience with wound sterilization during World War I [181]. Since then, the physics of ionizing radiation and the biochemical mechanisms of radiation-induced DNA damage have become understood, solidifying radiation therapy as an indispensable part of the treatment of cancerous lesions [182]. In particular, external beam radiation therapy (EBRT) utilizes highly focused beams to irradiate deep lesions from outside the body while brachytherapy (BT) places the source of radiation inside the patient and as close as possible to the tumour. Both of these modalities provide a far less invasive alternative to surgery in treatment of locally advanced cervical cancer, with excellent clinical outcomes [141].

The core challenge in radiation therapy is the maximizing of dose delivery to the tumour (planning target volume, PTV) while sparing healthy tissues (organs at risk, OARs) [191]. From a radiobiological perspective, there are two solutions to this problem. The first is to leverage the differential radiosensitivity of normal and cancerous cells by employing a hyperfractionation regimen wherein the therapeutic ratio is low [193, 194]. This is the case in EBRT wherein radiation damage occurs along the entire beam path, limiting the maximum dose that can be delivered at one given time to spare healthy tissues [192]. The second solution is to capitalize on

the higher biologically equivalent dose (BED) of large dosages by utilizing a hypofractionation regimen, thus increasing the therapeutic ratio [194]. This occurs mainly in brachytherapy and in select permutations of EBRT wherein considerably less irradiation of normal tissues occurs compared to traditional EBRT as a result of source placement next to or inside the tumour [189].

There is also the necessity of accurately visualizing internal patient anatomy with respect to the radiation source and determining the spatial distribution of radiation dose throughout the irradiated volume [282]. Presently, this is accomplished through 3D sectional imaging of patients visualized through software referred to as the treatment planning system (TPS). TPSs provide an immediate, accurate representation of the actual dose that a particular treatment plan will deliver to the target and surrounding tissues along with important dose statistics [289]. The main statistics used for the determination of target coverage are the dose received by some percentage of the total volume (typically 90%, D90) and the volume irradiated to at least some percentage of the prescribed dose (typically 100%, V100). Additional statistics are generated for each of the surrounding OARs, such as the mean dose to given OAR volume (Dmean) and the minimum dose to 1 cm^3 of the most irradiated OAR volume (d1cc) in order to prevent overdosing and to predict toxicity [186, 205].

1.3.4.1 External beam radiation therapy

EBRT has been at the foundation of cervical cancer management since the early 1990s. Using standard medical linear accelerators enables the irradiation of virtually any desired point within the patient, making EBRT especially valuable for its ability to deliver concentrated dose to disease that has advanced beyond the uterus such as the pelvic and paraaortic nodes [202].

1.3.4.1.1 3D Conformal radiotherapy

In the past, cervical tumours and their periphery were irradiated by the use of four large beam fields positioned laterally, posteriorly, and anteriorly in reference to patients' pelvic bony anatomy [184]. With the advent of 3D imaging, 3D conformal radiotherapy (3D-CRT) enabled planners to position custom-weighted beams of various sizes with respect to patients' internal anatomy. Forward-planning algorithms were then used to calculate the dose based on the selections, and the procedure was repeated until the dose distribution was satisfactory [195]. Despite having great utility as an early adaptation of EBRT for cervical cancer, this procedure was crude and provided only modest ability for optimization. 3D-CRT was often found to inadequately maintain target coverage and routinely yielded substantial toxicity [183]. In particular, acute and chronic gastrointestinal (GO) toxicity occurs in upwards to 80% and 34% of post-operative patients due in part by to the technique's inability to account for the movement of the bowel into the space previously occupied by the uterus [187].

1.3.4.1.2 Intensity modulated radiotherapy

Intensity modulated radiotherapy (IMRT) helped enhance target coverage and the sparing of organs at risk (OARs) by leveraging the benefits of inverse treatment planning along with beam modifying devices [196]. Most notably, multi-leaf collimators (MLCs) dramatically increased the ability to manipulate fields into irregular shapes, matching tumour geometry as it appeared on patients' imaging datasets at given beam angles [197]. Inverse-planning provided the capability to select optimal PTV metrics and dose constraints to OARs first, followed by iterative optimization of a plan most suited in meeting these clinical targets [196].

While the time required to create and control IMRT plans is considerably higher than for 3D-CRT, the consensus in the literature is that this is outweighed by the benefits conferred by

the technique. In particular, early investigations suggested that the volumes of bowel, bladder, and rectum receiving 95% of given prescription dose can be reduced considerably – up to 46%, 33%, and 17% in IMRT plans of locally advanced cases compared with 3D-CRT [184, 198]. After a decade of observational research showing superior clinical outcomes after IMRT plans, a large study with long patient follow-up reported significantly reduced rates of high-grade toxicity – in particular proctitis, enteritis, and cystitis – and more than a 20% improvement to the 5-year progression-free survival (PFS) and a 10% improvement to the 5-year OS compared with 3D-CRT. In the same study, the PTV dose achieved with IMRT was more then 20% higher, and the median exposure to the bladder and rectum was reduced by more than 28% of the prescription dose [184].

Because IMRT treatment plans are delivered through fixed beam angles, limiting the number of planned fields in order to reduce treatment time is imperative. However, decreases to the number of irradiating fields compromises the tight margins of IMRT dose. Therefore, despite the overt advantages of IMRT, it still suffers from the same issue as its predecessor.

1.3.4.1.3 Volumetric-modulated arc therapy and stereotactic body radiotherapy

Volumetric-modulated arc therapy (VMAT) is an extension of IMRT enabling treatments with continuous irradiation by virtue of dynamically sliding MLCs, variable dose rates, and variable gantry speeds [199]. In practice, this allows the equivalent of an infinite number of beam angles and fields in IMRT. The degree of optimization in VMAT plans can therefore be superior, and the technique was shown to save significant treatment time while achieving superior clinical metrics [200, 201, 204]. Of note, while peripheral doses are still existent with VMAT, those 10-15 cm away from primary cervical tumours treated with VMAT were found to be 31-54% lower than IMRT. This entails a mean reduction of 12% in the dose to healthy tissues [203]. Similarly,

a recent comparison of the two techniques in postoperative cervical cancer patients found that while both are capable of attaining mean target coverage of more than 99%, the conformity index with VMAT was consistently 6% better than IMRT [204].

Modern linear accelerator suites possess the ability to deliver both IMRT and VMAT plans; additionally, most are able to deliver stereotactic body radiotherapy (SBRT). Compared with hyperfractionated regimens, SBRT delivers larger doses with higher BED at a time thus reducing the number of patient visits for a course of treatment. However, these procedures are more resource intensive compared to traditional IMRT and VMAT due to the need for higher accuracy during radiation delivery [207]. Being a relatively new technique in cervical cancer radiation therapy, it has yet to be evaluated in the literature to the extent of other alternatives [208]. That said, a pioneering work by Pedicini et al. in 2012 revealed that SBRT delivered in VMAT fashion accomplished an 11% lower rectal d1cc, and a 10% lower bladder d1cc compared to high dose-rate brachytherapy (HDR BT), while requiring nearly 60% less treatment time [206]. Despite this, the mean PTV doses with this technique were up to 55% lower than HDR BT which significantly diminished their tumour control probability. Moreover, bowel doses were more than double since the technique is limited much like other types of EBRT.

Given the recency of the technique and sparsity of research with long follow-up evaluating it, the use of SBRT in cervical cancer is largely predicated in the treatment of patients that do not qualify for HDR BT [209].

1.3.4.2 Brachytherapy

The challenge of treating deep disease without impacting surrounding healthy tissues is the ameliorated by the use of brachytherapy (BT) [223]. BT utilizes various devices to position strongly ionizing radioactive seeds in the immediate vicinity of the primary tumour, which

allows for the considerable sparing of OARs [224]. Anchorage of these devices to the patient also greatly reduces concerns of organ displacement which is a major concern for EBRT [225-227]. The radiation of BT seeds possesses an intrinsic sharp dose falloff and so optimization of seeds' dwell positions and times leads to highly conformal dose distributions in treatment plans [228]. These distributions provide more leeway in escalating the dose to the target, hence why BT is generally referred to as a "boost" on top of EBRT. These approaches confer great benefit to locally advanced cervical cancer primarily because disease presentation is in the immediate vicinity and/or proximal to the vaginal cavity, and typically within 15-40 mm of the topmost dwell position [234]. Moreover, high-dose-rate (HDR) approaches allow for significant reduction in the number and duration of fractions, decreasing the amount of time a patient spends in the clinic.

1.3.4.2.1 Foundational concepts

The chief advancement of modern BT was the shift towards a 3D image-guided adaptive protocols (IGABT) [216, 230]. This necessitated a paradigm shift in dose prescription methodology based on new target definitions. In particular, the high-risk clinical target volume (HR CTV) was defined as the extent of macroscopic disease, while the intermediate-risk clinical target volume (IR CTV) was a designated 5-15 mm region surrounding the HR CTV representing microscopic disease spread [233]. Based on data of clinical outcomes, margins of tumour remission as assessed on imaging were defined along with the appropriate EBRT + BT dosing schema to attain them. Namely, the current standard is to maintain an equieffective dose (EQD2) of 90-95 Gy to 90% of the HR CTV (D90) typically accomplished with 25 fractions of 1.8 Gy delivered by IMRT plus 4 fractions of 7 Gy by HDR BT. Additionally, limitations are place on the minimum dose to the maximally irradiated 2 cm^3 of normal tissue (D2cc) for the

bladder, rectum and the sigmoid. The recommended values for these constraints are 90, 75, and 75 Gy EQD2, and their surpassing sharply raises the risk of severe radiation toxicity [235, 240].

Most frequently, the BT fractions are carried out by intracavitary approaches, employing the use of specialized applicators that contain a channel for exocervical/vaginal irradiation called a tandem, and another for endocervical irradiation (typically a ring). Patients that are ineligible for intracavitary BT due to bulky disease, deep extension or anatomical limitations are treated with interstitial approaches. These utilize a transperineal template mounted to an obturator cylinder or an intracavitary cylinder to guide a series of needles with central channels directly into the target [237]. Novel additive manufacturing techniques are also being investigated for the ability to rapidly prototype BT implants based on patient anatomy. This has the potential to achieve incrementally conformal dose distributions, enhancing implant anchorage, and reducing patient discomfort [232].

1.3.4.2.2 HDR IGABT workflows for cervical cancer

The current clinical workflow for HDR IGABT patients commences after diagnostic MR-based staging confirms patient eligibility for a particular procedure. Namely, tumour volume and extent of progression are evaluated to select the most appropriate applicator for the patient, as well as to assess the need for interstitial needles. If an interstitial implant is required, a pre-implant MR dataset with the obturator/intracavitary cylinder in place is acquired in order to determine the most appropriate number, position, and depth of needles. Once complete, the implant is inserted, typically under transrectal ultrasound guidance (TRUS), and affixed to the patient [236]. Another planning MR dataset is then acquired and imported into the treatment planning system – this is the first dataset acquired in the case of an intracavitary approach. Target and OAR volumes are then delineated alongside applicator and/or needle reconstruction. Once these are verified,

dosimetric constraints are selected within an inverse planning environment. Iterative algorithms calculate the optimal dwell positions and times of the radioactive seed to fulfill these criteria. Dose-volume parameters of the target and OARs are then evaluated, manually optimized (as needed), and approved. A pre-treatment MR dataset is acquired immediately prior to treatment delivery to confirm a match between the position of the applicator and OAR contours. Adjustments are made as needed, validated, and the treatment is delivered. In following fractions, are pre-fraction MR is acquired to make any needed adjustments prior to irradiation [237, 238].

1.3.4.2.3 Clinical outcomes

IGABT for locally advanced cervical cancer is routinely reported with favourable outcomes in local control, pelvic control, overall survival and severe morbidity [241, 242]. In particular, the results of the largest multicenter study RetroEMBRACE showed that the overall 5-yr local and pelvic controls after HDR BT procedures are 89% and 84%, and an overall cancer specific survival of 73% at 5 years. While initial late toxicity was high (86.2%), the value reduced to a gastrointestinal and bladder toxicity of 11% at 5 years. Death as a result of treatment occurred in 0.3% of patients [231]. The follow-up EMBRACE II prospectively appraised that the greatest current challenges related to this treatment is achieving loco-regional control in advanced tumours, preventing distant metastasis, and reducing late term morbidity of treatment [11].

1.3.5 Medical imaging in HDR BT

Medical imaging represents an immense step in the evolution of cervical cancer management. Compared with clinical examination which often yields unsatisfactory results, modern imaging techniques for the staging of cervical cancer are minimally invasive and bolster sensitivity and accuracy levels of 85-100% even for advanced stage disease [243-245]. As a result, imaging has

distinguished utility in the monitoring and follow-up of patients across all treatment groups, substantially aiding in the identification of recurrent patients requiring repeat treatment [246]. Most notably, these techniques have set the foundation for computerized treatment planning which significantly increase the level of sophistication in dose prescription and reporting, leading to notable improvements in clinical outcomes [247].

The purpose of sectional imaging in HDR BT is to provide an environment in which internal patient anatomy can be visualized. First, this enables for the computerized delineation of the target and surrounding healthy organs referred to as contouring. Secondly, this allows for applicator and/or needle reconstruction which is seminal for dose-volume calculations to take place. Traditionally, this involved using computed tomography (CT) techniques combined with magnetic resonance (MR) imaging [247]. Adjuvants to these alternatives, such as positron emission tomography plus CT or MRI (PET/CT or PET/MRI) and transrectal ultrasound (TRUS) have also been proposed [248, 249]. However, due to its particular advantages, MR has become the gold standard modality of all patients in the HDR BT workflow [250, 251].

1.3.5.1 Target-volume definition

Due to the heterogeneity of cases and the potential of advanced disease, target-volume definition is a task incrementally more difficult compared to organ delineation. However, aside from correctly representing the true volume and geometry of the primary tumour, an imaging modality must be evaluated on its ability to assess for markers of disease progression such as parametrial invasion (PI) and lymph node metastases (LNM). Despite reported preference among some clinicians, CT significantly underperforms compared to MR on most of these metrics [252]. In particular, CT is not able to adequately discern the depth of stromal invasion, and consistently overestimates tumour width resulting in poor accuracy of volume estimation [253-255]. Even

with the addition of PET to CT, thereby greatly improving visualization of micrometastatic infiltration, MR performs better in detection of parametrial infiltration – however, it has substantially lower sensitivity for lymph-node metastasis [256]. Diffusion-weighted imaging, a novel development in MR imaging, was proposed as an alternative to PET/CT as it was hypothesized to significantly improve the sensitivity of MR to lymph nodes and distant metastasis. However, the technique is still in its infancy and a recent comparative evaluation revealed that PET/CT is still better [261]. On the other hand, MR coupled with PET confers greater benefit to staging and target-volume definition compared to PET/CT – but is far less available [262]. For these reasons, MRI is strongly recommended for locoregional target-volume definition, while whole body PET/CT is preferred for assessing lymph node and distant metastases [141].

1.3.5.2 Contouring of organs at risk

Adequate soft-tissue contrast is the most important requirement for accurate representation of the volumes and geometry of organs at risk. MR sequence parameters are typically varied to greatly enhance or reduce sensitivity to various tissue types, resulting in high and adjustable soft-tissue contrast [257]. In particular, T2-weighted MR images provide an essential level of soft-tissue contrast manifesting as high signal from both fat and water. This is especially useful in contouring because the edema frequently surrounding cancerous lesions can be visualized at the same time as the surrounding normal tissues [258]. In a preliminary study comparing contouring of OARs on MRI versus CT, Viswanathan et al. reported greater ease in visualizing the boundaries of OARs on MR, and difficulty distinguishing normal cervical tissue from the target on CT. While the final results have shown minimal differences between contoured OAR volumes, qualitative evaluation of contour geometry revealed differences between MR and CT

contours [FO]. Most of the contouring studies comparing CT to MRI to date confirm the agreement between OAR volumes – however, additional recent studies by Krishnatry et al. and Eskander et al. report finding the same geometrical disparity between contours [259, 260]. For all of the above reasons, MRI is understood to be the preferable modality for OAR and target contouring in HDR BT [250]. Contouring is performed on acquired axial slices, with sagittal and coronal slices serving as guidance.

1.3.5.3 Applicator and needle reconstruction

The process of identifying source positions relative to the defined target and delineated OARs begins with applicator and/or needle reconstruction. While differences exist in their appearance on MR and CT, the procedure of reconstructing them is similar.

The library reconstruction method (LIB) for rigid applicators superimposes a three-dimensional model onto the imaging dataset. Applicator reference points, physical landmarks along the applicator, are utilized to precisely orient the model to match its appearance on the patient dataset. The benefit of this method is that source dwell positions within the applicator are known from previous applicator commissioning and verification, and are thus readily available after affixing the applicator model to the dataset. Direct reconstruction (DR), also called digitization, is used when irregular delivery devices such as flexible needles are utilized, such as in interstitial brachytherapy. Digital tracks of points are placed along needles' deflected trajectories in order to define their orientation but also to identify the source length. Dummy sources are often placed inside of these needles in order to make identifying the dwell positions easier. If these are not used, it is crucial that the needle tips are identified precisely. Once this is done, dwell positions can be generated along the tracks based on measurements from the manufacturer [247].

Applicator and needle reconstruction are considerably more difficult on MRI compared with CT. In CT, the lumen (outer shell) of applicators and needles is visible with strong signal. However, due to MR's susceptibility to artefacts, only applicators and needles made of specific MR-compatible materials can be used. These produce little to no signal, and appear as black on T2W images. To rectify this, catheters containing a contrast enhancer are inserted into the channels of applicators and needles when the patient is imaged for treatment planning [263].

The main drawback to utilizing MR for applicator/needle reconstruction is the fact that CT utilizes thinner slices, thus reducing the likelihood that applicator reference points, needle tips, and thus first dwell positions are positioned between slices. However, if this occurs, interpolation techniques are used to resolve this point with sufficient accuracy. However, the main benefit of reconstructing on MR is the ability to utilize the same image dataset for contouring. This removes the need to acquire a separate CT dataset which introduces a source of uncertainty associated with patient transport and transfer, as well as image registration. Due to reduction of uncertainty and imaging resources, MR reconstruction is now a standardized practice [264].

1.3.5.4 MR datasets in HDR Brachytherapy

To best visualize internal patient anatomy for the purposes of staging, MR datasets require information in three principle planes – axial, sagittal, and coronal [250]. However, treatment MR datasets are acquired with the applicator and/or needles in place which results in oblique angles between the planes and the needle trajectories and/or intra-uterine channel of the applicator (the tandem). In order to provide a circumferential view of the cervix thereby simplifying the visualization and contouring of the target, the planes are rotated such that the axial plane aligns with the longitudinal axis of the tandem [265]. A series of snapshots at predefined planes (slices) are taken within the anatomical volume spanning the superior aspect of the uterine fundus to the

inferior edge of the pubic symphysis longitudinally, and transversely spanning the maximal breadth of the patient's pelvis [266]. For the purposes of target and OAR delineation, the image in-plane resolution of these datasets must be high and match the level found in diagnostic MR [297, 298]. The recommended range for the in-plane resolution of T2W images for HDR BT is approximately 0.4 – 0.7 mm [250]. For this reason, MR datasets are time consuming, especially if a large number of slices is desired. Long acquisitions are particularly susceptible to motion artifacts from the movement of internal organs either due to voluntary patient movement or breathing [267]. Therefore, the number of slices is decreased and the slice thickness increased in order to capture the entire imaging volume. The volumes and geometries of structures on these images are then approximated via the contouring process, which introduces a level of volumetric and geometrical uncertainty. **Figure 5** provides a visual representation of this process.

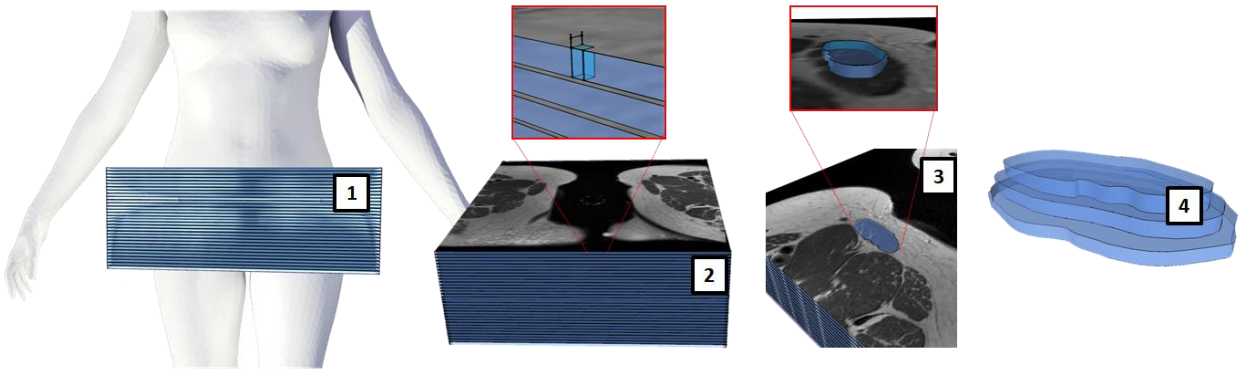


Figure 5 *An illustration of the slicing and contouring process (1-3), and its impact on the potential accuracy of the resultant datasets (4).*

Notably, increasing the slice thickness further introduces partial volume effects when the boundary of imaged structures changes considerably within the volume of the slice. This can reduce the quality of the acquired datasets considerably, making contouring the true boundary of structures difficult. Therefore, considerable optimization of these trade-offs takes place [268, 269]. For MR-guided HDR BT, the para-axial, para-sagittal, and para-coronal datasets (**Figure**

6) are acquired at slice thicknesses between 3-5 mm as per the recommendations of the Gynaecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GYN GEC-ESTRO) as well as the American Brachytherapy Society (ABS) [270, 271].

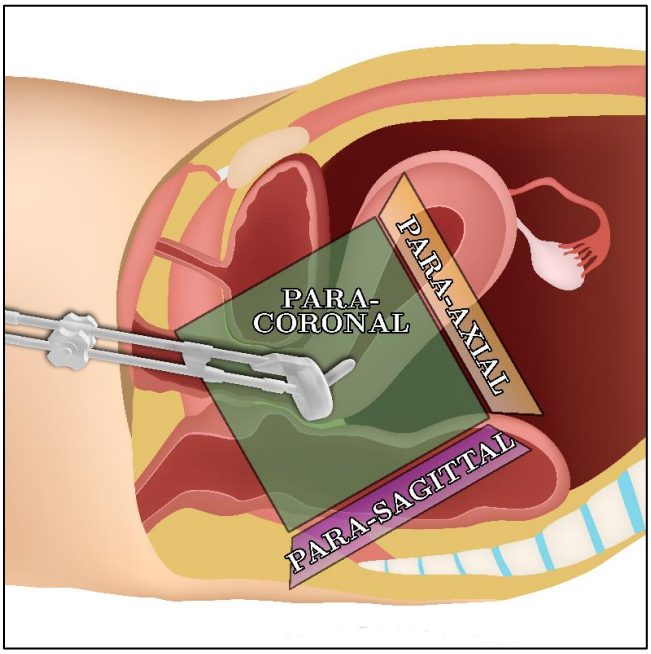


Figure 6 Graphical representation of the planes of acquisition in MR for HDR BT with the applicator (ring and tandem) in place.

1.4 Definition of the problem

1.4.1 Challenges in MR imaging for HDR BT

Treatment uncertainty is a collection of factors that can significantly skew the true dose delivered to the patient away from the planned dose. This can manifest as clinically significant underdosing of the target volume leading to incomplete treatment response, but it can also cause substantial overdosing of healthy tissue resulting in toxicity. Therefore, quantifying where these errors occur throughout the HDR BT workflow can ensure these uncertainties are alleviated, leading to potentially notable improvements in clinical outcomes.

An uncertainty budget analysis by Tanderup et al. reveals that combined uncertainties in HDR BT propagate up to a 12% uncertainty of the dose to 90% of the HR CTV (D90) [240]. The analysis did not investigate the level of uncertainty associated with slice thickness selection, which is imperative given that the AAPM has recommended a threshold of 15% to the dosimetric uncertainty in HDR BT [296]. Despite this, to reduce the current level of uncertainty, Tanderup et al. suggest that the implementation of "state of the art reconstruction using appropriate imaging" may significantly reduce the uncertainties associated with HDR BT [240].

1.4.2 State of the art reconstruction using appropriate imaging

Although MR in gynaecological HDR BT is an active area of research, there have been no main-organizational recommendations published in the past 7 years. Notably, to the author's knowledge, there have not been inquiries into the optimum slice thickness for gynaecological HDR BT in the literature. While GYN GEC ESTRO and ABS have cited ranges of appropriate slice thicknesses, investigation as to the origin of these recommendations reveals that they are largely pragmatic and were born out of the need to carefully balance the risk of patient movement in acquisitions with thin slices, and the partial volume effects associated with thick slices. Moreover, the acquisition of three registered datasets makes MR in gynaecological HDR BT a prime candidate for super-resolved image reconstruction.

1.4.3 Hypothesis

Traditional slice thickness in high-dose-rate magnetic resonance-guided brachytherapy introduces volumetric and geometric uncertainties that will exceed the AAPM guideline of 15%. Trilinear interpolation of traditionally acquired datasets can reduce this uncertainty to a level that does not exceed the AAPM's guideline of 15%.

1.4.4 Specific objective

The objective of this work is to (1) characterize the relationship between slice thickness and datasets' ability in reproducing the true volumes and geometry of patient anatomy (2) quantify the benefit conferred by trilinearly interpolated datasets.

1.5 Thesis overview

Chapter 2 of this thesis describes the methods and results of the characterization of the impact of slice thickness on datasets' ability to reproduce the true volumes and geometry of patient anatomy. In addition, Chapter 2 describes the methods and results of generating and evaluating trilinearly interpolated datasets from traditional datasets in HDR MR-guided BT. A complete overview of the thesis, discussion of overall findings, and future work are included in Chapter 3.

CHAPTER 2: AN EVALUATION OF THE IMPACT OF MR IMAGE SLICE THICKNESS ON THE ACCURACY OF HIGH-DOSE-RATE BRACHYTHERAPY FOR GYNAECOLOGICAL CANCERS

2.1 INTRODUCTION

Cervical cancer is the fourth leading cancer in women with over 560,000 new cases in the world in 2018, 310,000 of which are fatal [2]. Concurrent chemoradiation (CCRT) is foundational in the therapeutic strategy of up to 63% of Canadian patients [3]. High-dose-rate (HDR) magnetic resonance (MR) guided brachytherapy (BT) plays a major role in this management strategy, offering localized, adaptable dose escalation with a high therapeutic ratio to the primary tumour while sparing healthy tissues [11, 231, 272]. Proper delivery of HDR BT relies on the precise visualization of internal patient anatomy with respect to the BT applicator and catheter needles due to steep heterogeneous dose gradients. MR is the imaging standard for these procedures because it offers excellent soft-tissue contrast required for adequate delineation of the tumour and normal tissues [79, 254]. In addition, recent studies reveal that the BT applicator and needles can be successfully reconstructed on MR, paving the way to workflows based entirely on MRI [250, 273, 274]. This would improve the efficiency of the treatment and also reduce the amount of time a patient has to be in discomfort with the applicator in place. Typically, T2-weighted fast-spin-echo para-axial, para-sagittal, and para-coronal sequences are acquired as they require no contrast enhancement and accurately estimate tumour extension [275, 276]. However, they are prone to motion artifacts that often reduce image quality [277]. Scanning time may be reduced by increasing the slice thickness to reduce the total number of acquired slices, but this introduces partial volume effects [268, 269]. CT has been proposed as it allows for rapid, high-resolution imaging; however, the requirement to fuse CT with MRI introduces a separate source of error and difficulties associated with variations in patient anatomy as a result of transport and transfer [278]. ABS and GYN GEC-ESTRO recommend that 2D T2W datasets for cervical HDR BT be limited to slice thicknesses of 3-5 mm – however, the relationship between slice thickness

and the uncertainty in the reproduced volumes and geometry of patient anatomy has not been characterized in the literature [235, 264, 279]. Moreover, previous uncertainty budget analyses have not investigated how slicing influences dosimetric uncertainty in HDR BT, which according to the AAPM should be limited to a threshold of 15% [288, 289, 296]. This study serves to characterize this relationship and to demonstrate that a super-resolved dataset combining data from coarse para-axial, para-sagittal, and para-coronal datasets has the potential to retain the benefits of thicker imaging slices which offer a higher signal to noise ratio (SNR), and result in shorter imaging time.

2.2 MATERIALS AND METHODS

2.2.1 Digital evaluation phantom

Adult Reference Computational Phantom 'Laura' (ICRP, International Committee for Radiation Protection) from ICRP report 110 was imported into the MATLAB (Mathworks, Natwick, MA, USA) environment for analysis [280]. The original voxel dimensions of the phantom were 1.78 mm x 1.78 mm x 4.84 mm. Five structures relevant to gynaecological HDR IGBT (ovaries, bladder, sigmoid + rectum, uterus, and cervix) were isolated as binary matrices. A cervix structure was created from a region in the inferior uterus sized 3.2 cm x 2.5 cm x 4 cm. The structures were converted into 3D models and imported into BLENDER (Blender Foundation, Amsterdam, Netherlands). Each structure's mesh was smoothed to create a finer structure. These structures were imported into MATLAB, and processed into a 3D grayscale matrix with an isotropic voxel size of 0.25 mm. Voxels within the structures were assigned a grayscale value of 255; all other voxels were assigned a grayscale value of 0. These matrices were denoted as reference datasets (REF). **Figure 7** showcases the most critical steps in the creation of these structures.

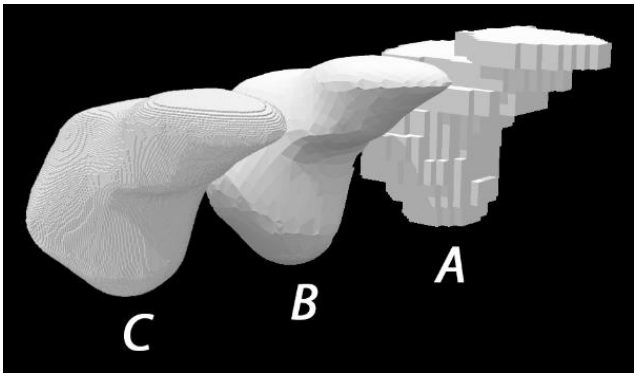


Figure 7 *A structure (bladder) as isolated from the full ICRP 119 phantom and represented as a 3D matrix (A), the structure after smoothing in BLENDER (B), and the structure after importing back into MATLAB and being represented as a 3D matrix called REF (C). Voxel volumes at (A) and (C) were 15.33 mm^3 and 15.62 x 10^{-3} mm^3.*

2.2.2 Imaging workflow

Figure 8 outlines the process by which reference objects with an isotropic voxel size of 0.25 mm were re-sliced to produce reference datasets with slices whose thickness was varied from 0.25 mm to 10 mm, at increments of 0.25 mm, and with a slice gap between each slice equivalent to 10% of the slice thickness. These datasets had voxels sized 0.25 mm x 0.25 mm x [slice thickness] mm.

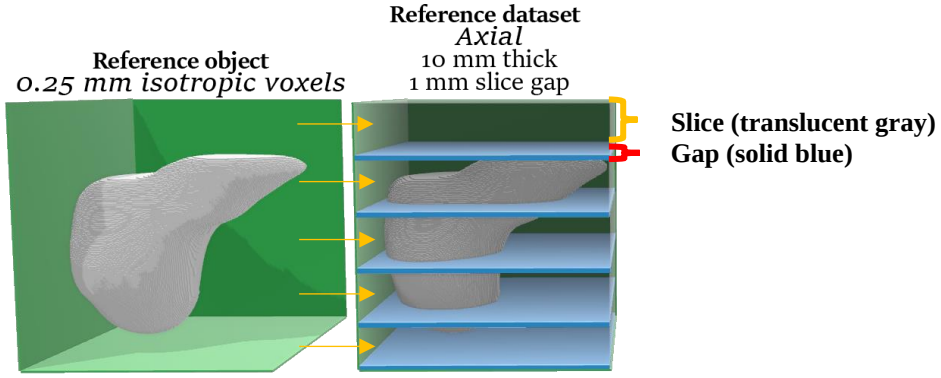


Figure 8 *The process of re-slicing reference objects. The translucent gray portion represents the slice, while the solid blue portion represents the slice gap*

Figure 9 illustrates the subsequent process by which axial (AX), sagittal (SA), and coronal (CO) test datasets were generated, with an example of axial test datasets. First, the signal within each slice of the reference dataset was aggregated and weighted to produce a 2-dimensional image with pixel size equivalent to the length and width of the voxels of the reference slice (0.25 mm x 0.25 mm). The pixel intensities of these images were then assigned to voxels in the test dataset,

corresponding to the region occupied by the voxels of the reference dataset slice. The process was repeated for all slices, until the entire space of the test dataset was filled with slices of dimensions

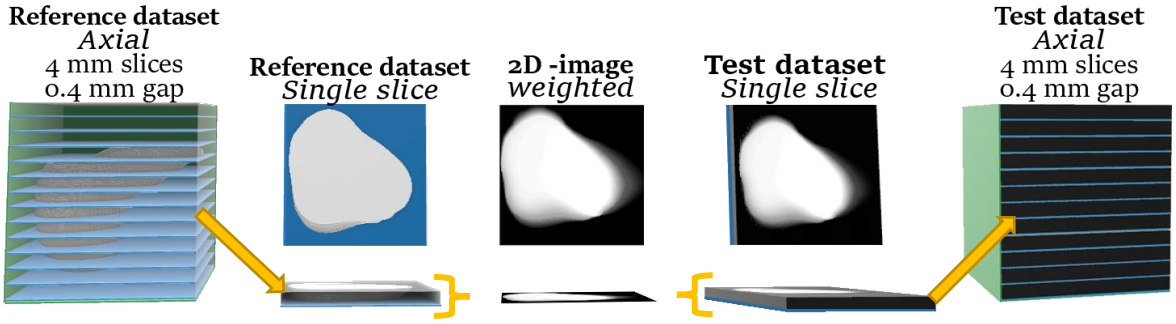


Figure 9 . *Physical representation of the slice generation workflow – an example of the axial dataset.*

and locations identical to the reference dataset. The same method was used for SA and CO datasets. In order to reduce the possibility of statistical artifacts in the data, additional positional shifts equal to $\pm$ 0 to 90% (at 10% increments) of the slice thickness were applied to reference objects in the X, Y, and Z (total 60 shifts per dataset), relative to where the arranged slices will be. For instance, if 2 mm were to be used, reference bladders were shifted […-0.4, -0.2, 0, 0.2, 0.4…] millimeters in the X, Y, and Z direction relative to where the slices would be arranged. These objects then underwent the same dataset generation process outlined above. Finally, zero-mean white noise profiles (σ = $\pm$ 0, 5, 10, 15 and 20%) were added to each reference dataset prior to test dataset generation in order to reflect typical and extreme cases of clinical MR data. In total, 240,000 datasets were generated (**Table 5**).

Property	Permutations	Total number
Organ structures	Bladder, Sigmoid + Rectum, Ovaries, Uterus, and Cervix	5
Types of dataset	Axial (AX), Sagittal (SA), Coronal (CO), and Trilinearly interpolated (TRI)	4
Noise profiles	σ = $\pm$ 0, 5, 10, 15 and 20%	5
Slice thicknesses	0.25 mm to 10 mm, 0.25 mm increments	40
Structure shifts	$\pm$ 0-90% (10% increments) of slice thickness in X, Y, and Z	60
Total number of datasets		240,000

Table 5 *Summary of the acquired dataset types*

2.2.3 Trilinear interpolation

AX, SA, and CO datasets of each structure were spatially registered. Voxels within the volume were filled by trilinear interpolation which weights the intensity of the 6 orthogonal pixels around a voxel of interest by their distance to it. **Equation 1** demonstrates this process mathematically:

Equation 1 *Trilinear interpolation to resolve voxels in 3D. Note that in the case of datasets with isotropic resolution, d_s is constant and can be factored out of the main summation.*

$$I_V = \sum_{n=1}^{6} I_P(n) \cdot \left(1 - \frac{\mathrm{d}_{VP}(n)}{d_s(n)}\right)$$

where I_V is the grayscale intensity of the voxel of interest, I_P is the grayscale intensity of the pixel perpendicular to the voxel, d_{VP} is the distance between the voxel V and the pixel (A, B, C, D, E or F), d_S is the distance between two successive images in the current imaging direction (e.g. sagittal), and n is the nth pixel, of 6 total, that bounds the voxel. **Figure 10** illustrates this process visually.

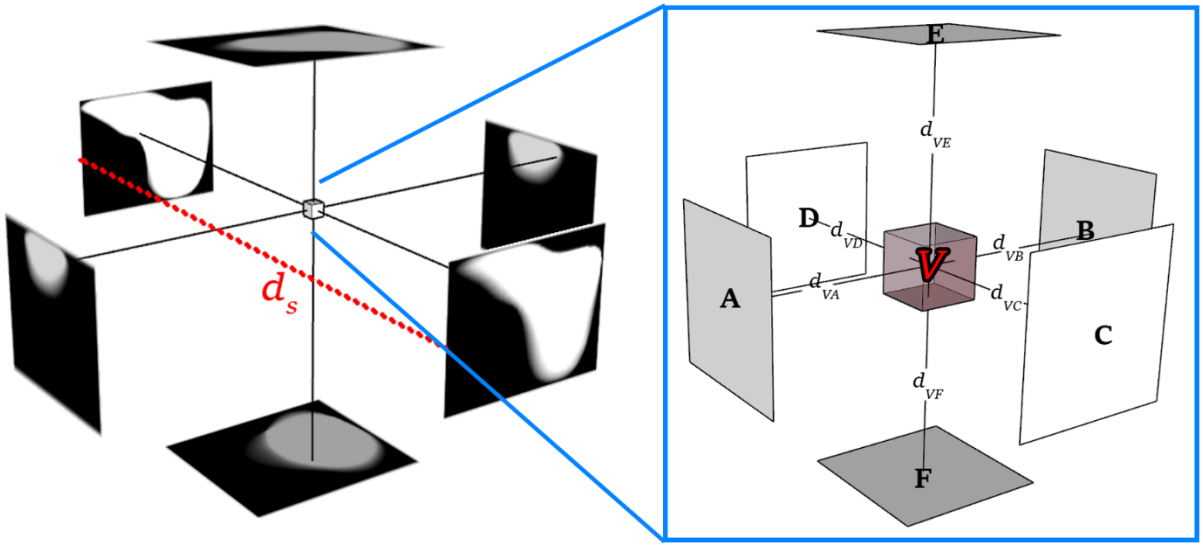


Figure 10 Visual representation of the trilinear interpolation process. (I) showcases that each voxel within the empty starting TRI dataset is surrounded by 6 images, 2 in each imaging plane orientation. The distance between two successive images is denoted by d_s. The perpendicular solid black lines represent the distance between the center of the voxel, V, and the pixels within the images that are to be weighted in the voxel's intensity calculation (II) is a zoomed in portion of the prior image, showing the 6 perpendicular pixels to be weighted.

2.2.4 Dataset analysis

In total 240,000 datasets were created. Geometric measurements were obtained through direct comparison to reference (REF) structures, and the results were pooled by slice thickness. In order to gain an understanding of the overall physical dimensions of the reconstructed structure, the total signal within each slice within the dataset was measured and compared to the total signal in corresponding slices in REF. This yielded a normal distribution of percentages across all slices, whose mean we denoted as the percent relative volume, RV. The spread of data around this mean can be utilized as a range for evaluating the volumetric uncertainty of a dataset – we thus denoted the standard deviation of this data as σ_{RV}. **Equation 2** and **Equation 3** demonstrate the calculation of RV and σ_{RV}.

Equation 2 *Calculation of the percent relative volume (RV) and its standard deviation*

$$RV_{DS} = \frac{1}{S} \times \sum_{s=1}^{S} \left[\frac{\sum_{n=1}^{N} I_{V_{DS}}(n,s)}{\sum_{n=1}^{N} I_{V_{REF}}(n,s)} \right] \times 100\%$$

Equation 3 *Calculation of the standard deviation of the percent relative volume (RV).*

$$\sigma_{RV_{DS}} = \sqrt{\sum_{s=1}^{S} (RV(s) - RV_{DS})^2}$$

where DS is the dataset of interest (i.e. AX, SA, CO, or TRI), RV_{DS} and $\sigma_{RV_{DS}}$ are the mean percent slice volume and standard deviation of the dataset, *s* is the slice number and *S* is the total number of slices, *RV(s)* is the individual percent slice volume of slice *s*, $I_{VDS}(n,s)$ is the grayscale intensity of voxel *n* in slice *s* of *DS*, $I_{VREF}(n,s)$ is the intensity of corresponding voxel *n* in slice *s* of REF, and *N* is the total number of voxels.

However, the volume within a slice is not indicative of its geometrical integrity. The Sørenson-Dice Coefficient (DSC) and the Hausdorff Distance (HD) enable quantitative evaluation of the geometry of the structure boundary within the slice. DSC is a measure of the degree of contour overlap and is calculated by the ratio between the area shared between a test and reference images, and their individual areas combined. HD is a measure of contour distance and is calculated by identifying the maximal distance of any point in the test image's boundary to the reference's boundary. These were calculated with MATLAB by first thresholding the data using MATLAB's built-in image thresholding function based on the method published by Otsu [298]. The resultant contours were then processed with MATLAB functions based on the publications by Sørenson, Dice, and Dubuisson et al. to yield DSC and HD data [281-283]. Finally, the SNR of each dataset was calculated to characterize how the dataset would appear to a clinician. Geometrical data were juxtaposed with estimated scan times typically observed in recommended GYN GEC-ESTRO T2 FSE acquisitions to allow for a cost-benefit analysis. All data were processed using MATLAB's included statistical library; normality testing was performed with the one sample Kolmogorov-Smirnov (KS) test, which compares how well a test distribution is represented by a normal distribution.

2.2.5 Estimating imaging acquisition time

GYN GEC-ESTRO recommends fast spin echo (FSE) T2-weighted MR datasets to be acquired with the following parameters: a repetition time (TR) of 2000-5000 ms, 256 phase encoding steps (M_p), 2 excitations (N_{ex}), an echo train length (ECL) of 4-20, and a slice thickness of 3-5 mm [250]. Given that the required depth-wise coverage in gynaecological HDR BT is approximately 20 cm, the number of 4 mm (typica slice thickness used in clinical sequences) slices required to fully image the volume, provided a 10% slice gap, is 45. Using a mid-range TR and 2 excitations, the approximate scan per imaging direction is approximately 5 minutes based on **Equation 4**. The ability of FSE sequences to acquire an entire MR image within one repetition depends on the selected ECL; however, this value is limited by tissue relaxation values and is tuned for specific applications [284, 285]. Therefore, if thinner slices are desired, the only way to increase the number of slices without jeopardizing image quality is by increasing the number of repetitions – the number of slices – which linearly increases imaging time [286].

Equation 4 *The relationship of sequence parameters and acquisition time in MR imaging [286].*

$$T_{scan} = TR \times N_{ex} \times N_{slice}$$

where T_{scan} is the total scan time, N_{ex} is the number of excitations per slice, and N_{slice} is the number of slices to be acquired.

Noise added to medical images has the potential to obscure anatomical features that are necessary for their delineation. We thus quantified the mean signal to noise ratio (SNR) of the images in accordance to **Equation 5** to assess the performance of each dataset when noise is added.

Equation 5 *SNR calculation in medical imaging.*

$$SNR = \frac{\mu_{signal}}{\sigma_{noise}} = \frac{\frac{S}{N_{lines}}}{\sqrt{\frac{Var_{noise}}{N_{lines}}}}$$

where μ_{signal} and S are the average and total signal values within a selected region of signal, σ_{noise} and Var_{noise} are the standard deviation and variance of the noise values in a selected region of noise, and N_{lines} is the number of lines in the image.

In trilinear interpolation, a voxel's value is assigned by averaging the values of three images. Provided datasets are independent, the signal and variance of the noise will be additive. For the general case of N averaged images, the resultant image's SNR increases by a factor of $\sqrt{N}$:

$$SNR(N \times S, N \times Var_{noise}) = \frac{\frac{N \times S}{N_{lines}}}{\sqrt{\frac{N \times Var_{noise}}{N_{lines}}}} = \frac{N}{\sqrt{N}} \times SNR(S, Var_{noise}) = \sqrt{N} \times SNR$$

With trilinear interpolation, the theoretical improvement in the SNR is a factor of 1.73.

2.3 RESULTS

Data from a total of 240,000 datasets with 41,760,000 slices were pooled by slice thickness and evaluated. **Figure 11** provides a visual comparison between the datasets.

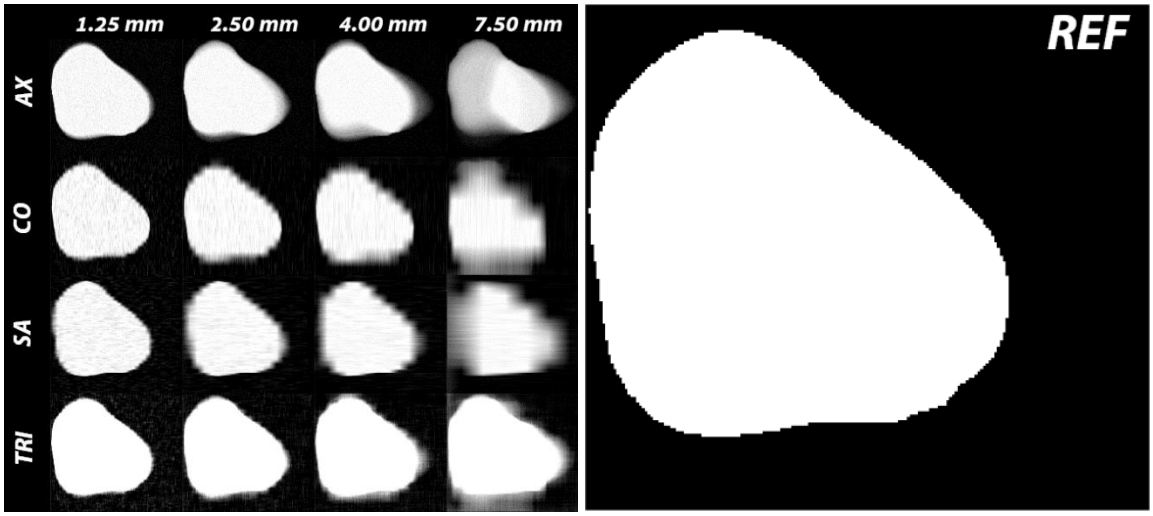


Figure 11 *Axial slice of the bladder REF structure reconstructed on various datasets at 10% noise. All images are individually normalized, however SNR in TRI was 1.75 [1.69, 1.80 95% CI] times that of AX, SA, and CO.*

KS tests of normality confirmed all metrics to be normally distributed at $\alpha = 0.001$.

2.3.1 Relative volume

Figure 12 summarizes the pooled relative volume data. All pooled data were inversely correlated with increasing slice thickness. The effect was more pronounced as structure volume decreased, particularly for the ovaries and the cervix structures**.** Noise had a minimal but statistically significant influence on RV (+1.3% [0.2-2.4 95% CI] for every 10% of noise added).

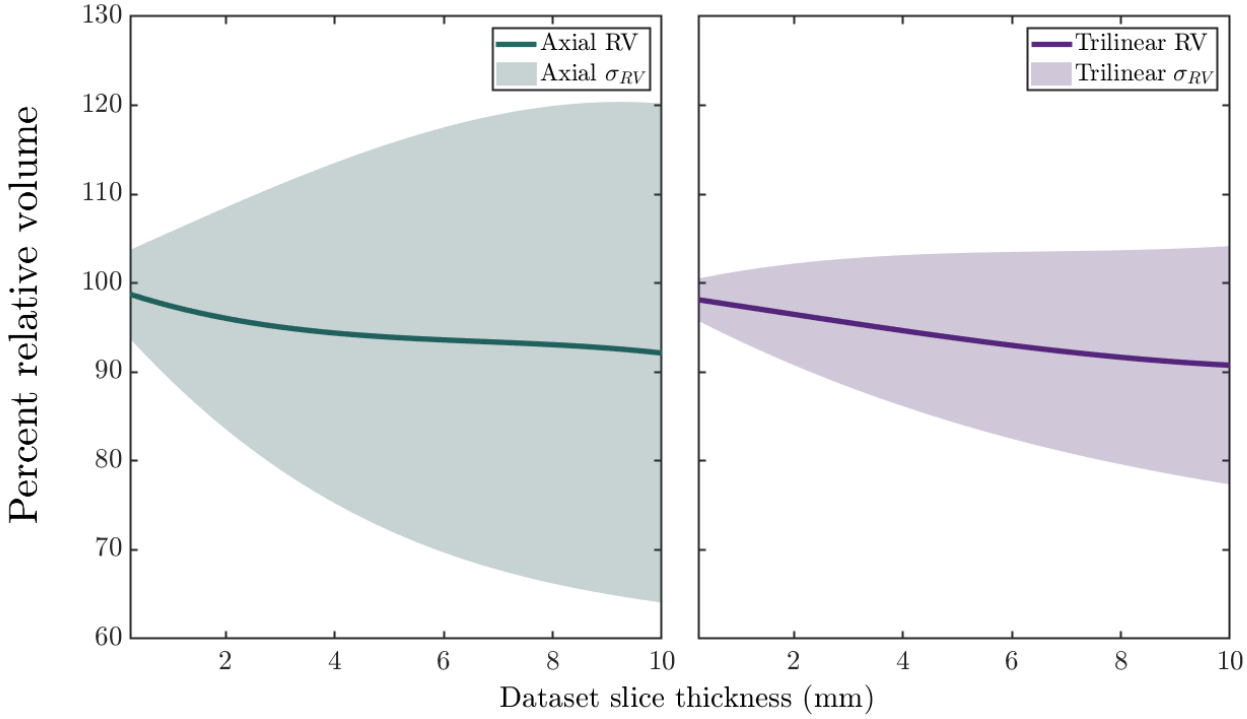


Figure 12 *Pooled noiseless data of RV versus slice thickness for AX (n = 12,000) and TRI (n = 12,000) datasets at 0% noise. The means of the data are represented by the solid lines, while the standard deviation, σ_{RV}, is represented by the shaded region. The x-axis begins at 0.25 mm as this was the lowest utilized slice thickness.*

The standard deviation data in **Figure 12** was isolated, and is shown separately in **Figure 13.**

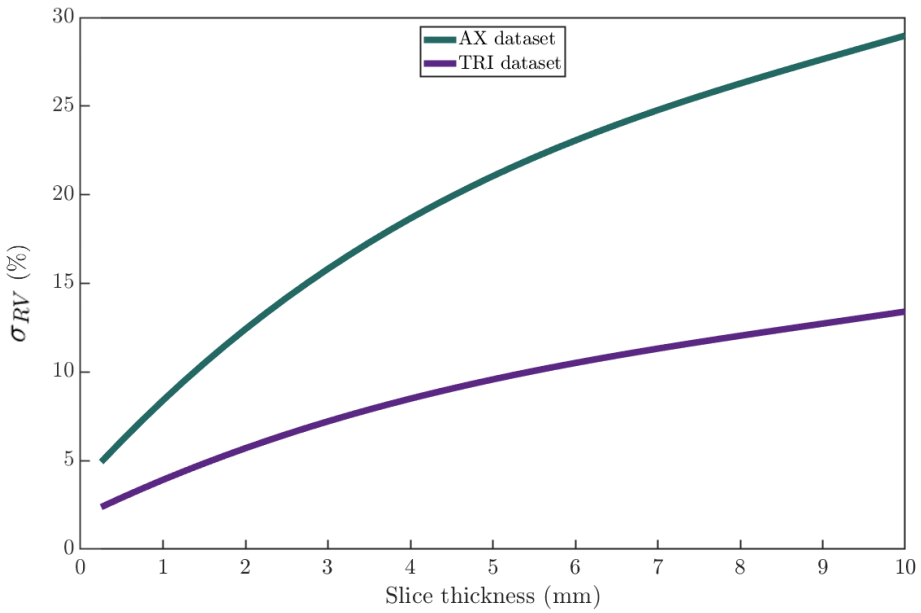


Figure 13 The standard deviation of RV, σ_{RV}, plotted against slice thickness.

2.3.2 Sørenson-Dice coefficient and Hausdorff Distance

DSC and HD data were normally distributed (α = 0.001) and inversely correlated in AX (R^2 = 0.91 [0.87-0.95, 95% CI] and 0.89 [0.83-0.94, 95% CI]) and TRI (R^2 = 0.88 [0.80-0.98, 95% CI] and 0.85 [0.79-0.89, 95% CI]) datasets with 0-10% noise. The model response declined with increasing noise levels (30% noise: R^2 = 0.74 and 0.81, 40% noise: R^2 = 0.54 and 0.69) primarily for DSC at lower slice thicknesses. TRI datasets were 5% less sensitive to noise on reconstructions with thin slices (< 2 mm) and up to 22% with thick slices (> 6 mm). The rate of DSC degradation with TRI was 67.23% [65.75-68.71 95% CI] lower than AX. DSC at 4 mm differed by 7% between AX and TRI (**Figure 14 and 15**).

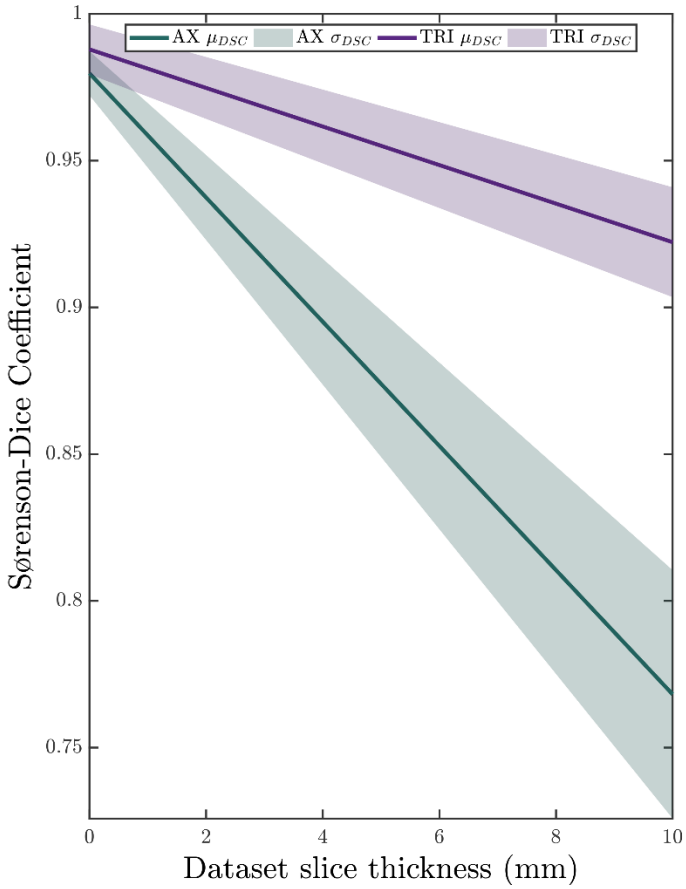


Figure 14 *Pooled and fitted DSC data (n = 24,000) at 0% noise. The solid line and shaded region represent the mean and standard deviation of the data, respectively.*

	Axial – "Traditional"		Trilinearly-interpolated	
	AX μ	AX σ	TRI μ	TRI σ
9% reached:	4.1 mm	3.4 – 5.7 mm	6.8 mm	5.6 – 8.0 mm

Trilinearly interpolate

5% reached:	4.1 mm	3.4 – 5.7 mm

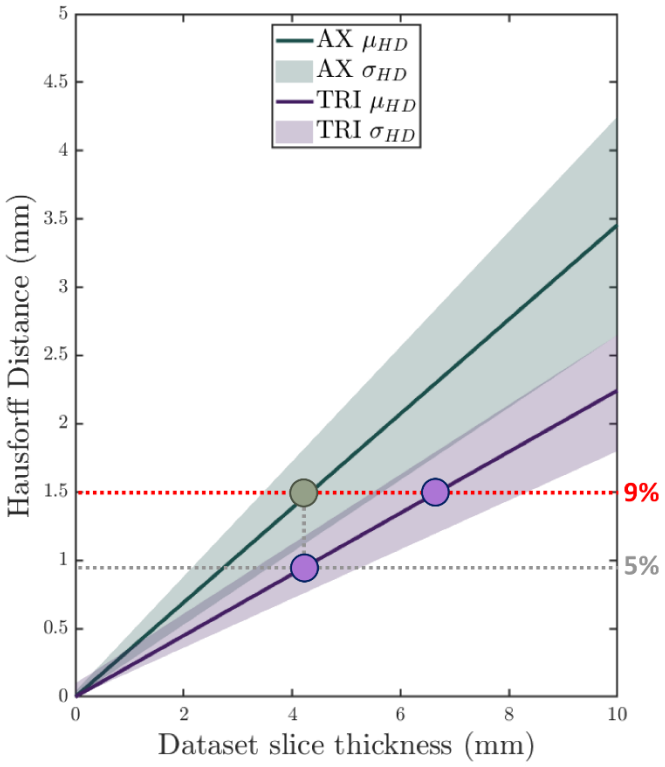


Figure 15 *Pooled and fitted HD data (n = 24,000) with 0% noise sorted by structure volume. The solid line and shaded region represent the mean and standard deviation of the data, respectively.*

HD data further revealed that at 4.1 mm (range 3.4-5.7 mm) slice thickness, HD of AX and TRI were 1.5 mm and 0.869 mm. Based on a 6% per mm shift in dosimetry, AX datasets resulted in 9% which corresponds to the level at which the AAPM guideline of 15% is exceeded – however, TRI datasets reduce in 5.2% at this slice thickness. TRI datasets accomplish the same 9% result at a slice thickness of 6.8 mm (range 5.6-8.0 mm).

2.3.3 Signal to noise ratio

The signal component in SNR increased linearly with increased slice thickness with $R^2 = 0.98$ [0.95-1.00, 95% CI], while noise statistics were unaffected by slice thickness. **Figure 16** compares the SNR data of AX and TRI datasets with noise to the baselined of AX with 5% noise. Relative to AX, the SNRs of TRI were higher by a factor of 1.75 [1.61-1.88, 95% CI] at equivalent slice thicknesses.

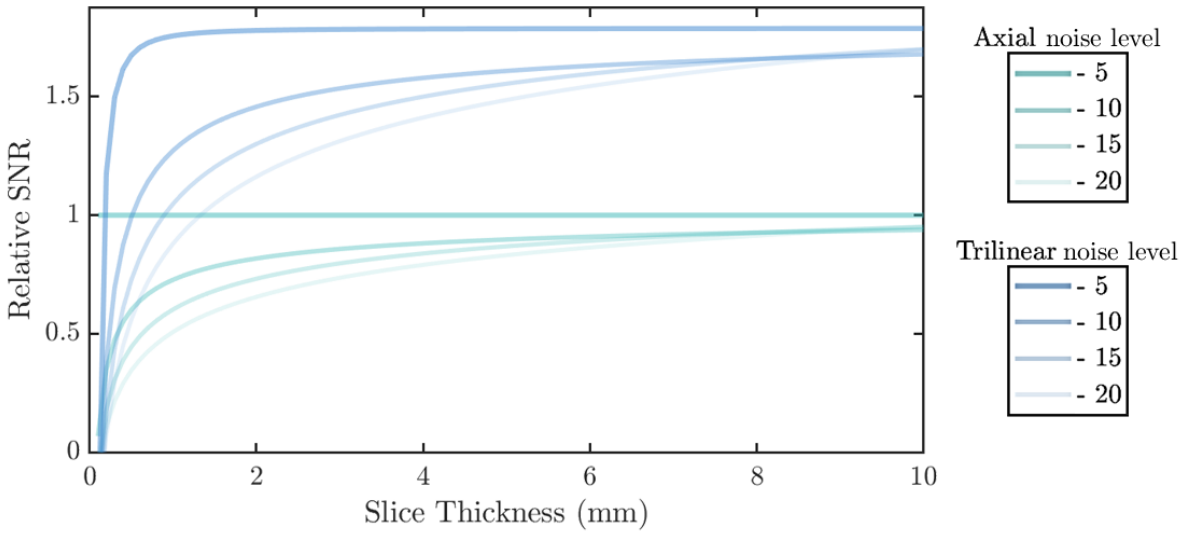


Figure 16 *Pooled and fitted SNR data at 5%, 10%, 15%, and 20% (σ = 0.05, 0.10, 0.15 and 0.20) noise. Absolute SNRs were normalized to AX data at 5 percent noise (horizontal line at 1) to yield relative SNRs.*

2.4 DISCUSSION

2.4.1 Volume and geometry

The results reveal that para-axial T2W datasets for gynaecological brachytherapy with 3-5 mm slice thickness may poorly represent the true volumes and geometries of imaged organs. This introduces a source of uncertainty to the contouring process which is intimately dependent on the ability to accurately delineate organ boundaries [266]. However, this has yet to be investigated and quantified, and is absent in uncertainty budget evaluations and recommendations for image-guided gynaecological brachytherapy [288, 289].

Clinical research reveals that the implications of a few millimeters in reconstruction uncertainty, applicator mispositioning, interobserver variability, and organ movement can be severe. Boundaries like the anterior rectal wall, inferior-anterior sigmoidal wall, and the superior-posterior wall of the bladder are extraordinarily sensitive as they are most heavily irradiated in intracavitary BT [234]. For this reason, the American Association of Physicists in Medicine (AAPM) recommend a maximal uncertainty of 15% in the delivery of prescribed dose in brachytherapy [296]. Authors have noted that typical levels of uncertainty in the positioning of the radiation source can compromise treatment constraints, specifically of the bladder and rectum, up to 6.3% per mm [264, 290]. GYN GEC-ESTRO reports that a 2 mm uncertainty during applicator reconstruction can impact target and OAR dose-volume parameters up to 12% [291]. This is disconcerting given applicator reconstruction take place in the para-axial plane, and interobserver variations up to 0.7 mm have been noted [265, 292]. Moreover, Hellebust et al. report that interobserver variability during target and OAR delineation is already responsible for 10% deviations in dosimetric parameters on average; this is described by other authors as well [293, 294]. While the aforementioned errors are largely a consequence of the human factor in the highly complex process of treatment planning and delivery, characterizing the errors that are inherent to the tools utilized during the workflow can prevent further additive error. Heerden et. al have revealed that on average distortions of 0.3 mm are already present during applicator imaging with MRI [295]. In total, most of the uncertainties in the HDR BT workflow account for upwards to 12% in the D90 of the HR CTV [240]. However, the impact of slicing uncertainty, and whether it exceeds the remaining 9% (as calculated by quadrature) allowable by the AAPM is to our knowledge not known.

In our study, we demonstrate that the standard deviation of RV, $|\sigma_{RV}|$, was highly sensitive to variation in slice thickness (absolute increase of 9% and 22% from 0.25 mm to 10 mm slice thickness for trilinear and axial datasets). This metric provided a direct estimate of the volumetric inaccuracy that can be expected when a particular dataset type and slice thickness are selected. For example, even though 10 mm axial datasets maintain a RV of 92%, the gamut of this data indicates that up to 27% of the volume in the images was either missing or superfluous. Moreover, **Figure 11** highlights that AX datasets return ambiguous results for locations of structure boundaries starting at approximately 4 mm slices. This called for geometrical analysis with DSC and HD to quantify the overlap and distance between the contours of REF structures and generated datasets. **Figures 14 and 15** present quantitative data to corroborate the pattern observed visually, showing that the boundary integrity of AX datasets as assessed with DSC declined at triple the rate of TRI. Our data reveals that the relationship between maximal HD and slice thickness is also linear and for AX can be generalized as one one-third of the slice thickness (for example, at 4.1 mm slice thickness, maximal HD is approximately 1.5 mm).

In order to remain safely below the uncertainty threshold, traditional datasets may be acquired at a slice thickness of 3.4 mm, or at a slice thickness of 5.6 mm and trilinearly interpolated. However, if imaging at the middle of the range that may exceed the threshold (4.1 mm for AX, 6.8 mm for TRI), trilinearly interpolated datasets will confer a time savings benefit of approximately 6 minutes. This is illustrated in **Figure 17.**

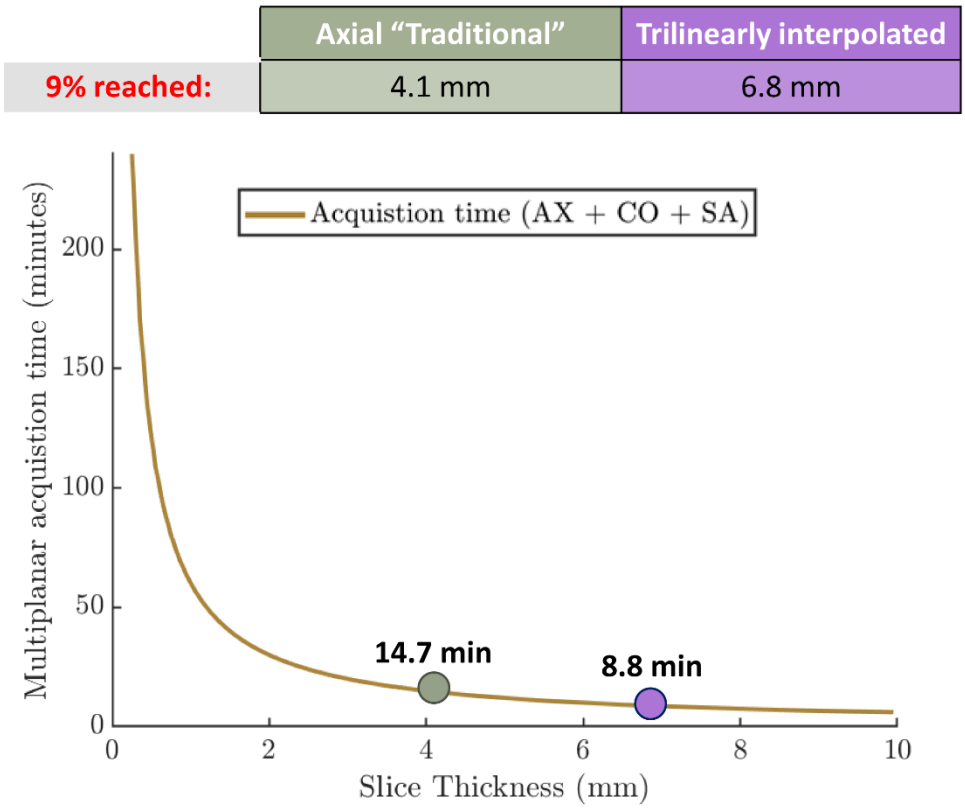


Figure 17 *Approximate scanning acquisition time of axial, coronal, and sagittal datasets required for either traditional or trilinearly interpolated approaches. Trilinearly interpolated datasets exceed the 9% dosimetric uncertainty threshold later than the traditional approach, allowing approximately 6 minutes of imaging time savings for the same quality.*

2.4.2 Signal to Noise Ratio (SNR) data

Our evaluation included characterization of the SNR trends in the generated datasets in **Figure 16**. These results can be used to indicate how a particular dataset may appear to the human eye. The theoretical SNR improvement in trilinear interpolation is a factor of $\sqrt{3}$ or 1.73. Our data corroborates this, finding an average SNR improvement in TRI over AX by a factor of 1.75 ± 0.14.

CHAPTER 3: CONCLUSION

3.1 Thesis overview

The primary focus of this thesis was to characterize the relationship between datasets' slice thickness and their ability to accurately reproduce the true volumes and geometry of patient anatomy. Furthermore, this work sought to evaluate trilinearly interpolated datasets in reducing the uncertainty associated with datasets with thicker slices.

The combined impact of the major uncertainties identified within high-dose-rate magnetic resonance-guided brachytherapy (HDR BT) amount up to a 12% uncertainty in the percentage of the dose received by 90% of the target volume (D90), [240]. The AAPM has recommended that dosimetric uncertainty in HDR BT be limited to 15% [296] This is concerning, because the slicing uncertainty associated with the presently utilized 3-5 mm range as recommended by GYN GEC-ESTRO and ABS has not been characterized. Knowing that partial volume effects can significantly diminish image quality, the evaluation of slice thickness as a source of additional uncertainty was imperative - especially provided that the propagation of positional uncertainties in HDR BT are known to result in upwards to 6% changes in the target and/or OAR dose per millimetre [264, 269, 290, 291, 293, 294].

Chapter 2 describes the methodology by which traditional datasets ranging in thickness from 0.25 mm to 10 mm were evaluated volumetrically and geometrically. The purpose of this investigation was to characterize the slice thickness versus structure volume/geometry relationship and to assess if significant uncertainty was being introduced. Moreover, this analysis enabled the direct comparison of trilinearly interpolated datasets to the traditional imaging approach to characterize their feasibility and utility.

One of the primary findings in the study was that the recommended range of slice thicknesses between 3-5 mm confer a volumetric uncertainty on the order of 27% to the reconstructed structure volume. Additionally, the structure contours as appearing on these slices were found to be a distance of up to one third of the slice thickness away from where they were supposed to be (e.g. 1.5 mm for 4.1 mm slices). This resulted in a level of positional uncertainty that contributes a dosimetric uncertainty of 9% and more, which exceeds the AAPM's threshold. The secondary finding was that trilinearly interpolated datasets reduce these uncertainties significantly at the same slice thickness. These datasets allow the use of coarser slices to achieve the same uncertainty levels, meaning a considerable time savings advantage can be had if they are utilized. This may further improve the image quality due to a reduced susceptibility to patient movement. Moreover, by virtue of the $\sqrt{N}$ enhancement in the signal to noise ratio that occurs after the signal within N images is added and weighted, these datasets yielded SNRs that were 1.76 times higher than the traditional approach. Therefore, the use of trilinearly interpolated datasets can significantly reduce the cost to benefit ratio of the current imaging workflow of MR-guided HDR BT.

3.2 Discussion and future work

One of the drawbacks of the findings is the fact that they pertain to synthetically imaged/re-sliced organs from a reference anthropomorphic phantom. In this study, structures were isolated, and the signal intensities within their boundaries were homogenous. This was done deliberately in order to increase the precision of the evaluation. However, the reality is that images of a patient contain multiple structures, all with heterogeneous signal intensities. Furthermore, while the imaging of structures in this study mimicked conventional MR imaging techniques, the true scale of complexity associated with this type of imaging cannot be simulated. Due to these

differences, how the findings carry over to a clinical context is therefore an important question to answer. Future research should aim to carry out a similar investigation to the one presented herein but on a physical, multi-structured phantom imaged with a real MR machine.

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