Local Therapeutic Approaches for the Management of Recurrent Gynaecological Cancer

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Declaration

I confirm that the data presented in this thesis arise from my own work, done at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research between September 2017 and September 2020. Where others have contributed work, or information has been derived from other sources, this has been indicated. The work is original and has not been submitted for any other degree.

The work reported in relation to patients with recurrent gynaecological tumours in Chapter 4 was granted Institutional Research and Development ethical approval under references CCR4360 (REC number: 15/WM/0470).

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Abstract

Surgery, radiotherapy and chemotherapy combinations are used to treat recurrent gynaecological malignancy. Stereotactic body radiotherapy (SBRT) delivered to the involved surgical margin could improve clinical outcomes after pelvic exenteration (PE). In radiation-naïve recurrent gynaecological malignancy, SBRT and proton-beam therapy (PBT) allow tumour dose escalation while potentially offering reduced toxicity. Magnetic resonance guided high intensity focussed ultrasound (MRgHIFU) has not been trialled in recurrent gynaecological malignancy. This work investigates the feasibility of SBRT, PBT and MRgHIFU to achieve local and symptom control in these patients.

Chapter 2 describes patterns of relapse and determines histological prognostic factors affecting overall and disease-free survival and loco-regional control in patients after PE. Five-year loco-regional control was 66.7% for those with negative surgical margins compared to 35.0% for those with involved/close margins. It further demonstrates feasibility of post-operative SBRT to the involved/close margin regardless of exenteration type; doses to organs-at-risk were equivalent when planned to a narrow or high-risk target.

Chapter 3 compares tumour dose escalation and dose to organs-at-risk using simultaneous integrated boost (SIB) intensity modulated radiotherapy, SBRT and PBT in radiation-naïve central and pelvic side-wall recurrent gynaecological malignancy. SIB boosts of 55 Gy only were feasible for central disease compared to 65 Gy for side-wall disease. SBRT and PBT were dosimetrically deliverable for recurrences at both locations.

Chapter 4 investigates HIFU for symptom palliation in recurrent gynaecological malignancy. It highlights the challenges when treating these patients and shows that pain and emotional functioning improve. Changes in imaging metrics were seen in extra-pelvic but not intra-pelvic lesions. Finally, health economic evaluation indicated high costs for a single visit on the day of the procedure but with low costs for subsequent follow-up.

Thus, this work demonstrates the feasibility and potential role of state-of-the-art local therapeutic approaches in curative and palliative management of recurrent gynaecological malignancy.

List of Abbreviations

AcoRD	Attributing the cost of Research and Development
AEs	Adverse Events
AUC	Area Under the Curve
BED	Biological Equivalent Dose
BMI	Body Mass Index
BNF	British National Formulary
BPI-(SF)	Brief Pain Inventory (short form)
BRCA	BReast CAncer gene
BSO	Bilateral Salpingo-Oophorectomy
CE	Conformité Européenne
CI	Conformity Index
CORT	Combined Operative and Radiotherapeutic Approach
CRD	Centrally Recurrent Disease
CRUK	Cancer Research United Kingdom
CtE	Commissioning through Evaluation
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DFS	Disease Free Survival
DICOM	Digital Imaging and Communications in Medicine
DNA	DeoxyriboNucleic Acid
DWI	Diffusion Weighted Imaging
EBRT	External Beam Radiotherapy
ECG	Electro-CardioGram
EM	Equivalent Minute
EORTC	European Organisation for Research and Treatment of Cancer
EPI	Echo Planar Imaging
EPR	Electronic Patient Record
ER	Eostrogen Receptor
FA	Flip Angle
FDA	Food and Drug Administration
FDG	Fluoro Deoxy Glucose
FFF	Flattening Filter-Free

FIGO	Federation Internationale Obstetrique Gynaecologie
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GA	General Anaesthetic
Gd	Gadolinium
GEC-ESTRO	Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology
GI	GastroIntestinal
GRASE	GRadient and Spin Echo
GTV	Gross Tumour Volume
GU	GenitoUrinary
Gy	Gray
HCA	Health Care Assistant
HDR	High Dose Rate
HI	Homogeneity Index
HIFU	High intensity Focused ultrasound
HR	Hazard Ratio
ICR	Institute of Cancer Research
IGRT	Image Guided Radiotherapy
IMPT	Intensity Modulated Proton-Beam Therapy
IMRT	Intensity Modulated Radiotherapy
IORT	Intra-Operative Radiotherapy
IRB	Institutional Review Board
LDL	Lower Dose Limit
LITT	Laser Interstitial Thermal Therapy
LVSI	Lymphovascular Space Invasion
MDT	Multi Disciplinary Team
MLC	Multi Leaf Collimators
MR	Magnetic Resonance
MRg	Magnetic Resonance guided
MRgHIFU	Magnetic resonance guided High Intensity Focused Ultrasound
MRI	Magnetic Resonance Imaging
MWA	MicroWave Ablation
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
NSA	Number of Signal Averages

NTO	Normal Tissue Objectives
OAR	Organ At Risk
OS	Overall Survival
PA	Para-Aortic
PACS	Picture Archiving and Communications System
PBT	Proton Beam Therapy
PE	Pelvic Exenteration
PET	Positron Emission Tomography
PLDH	Pegylated Liposomal Doxorubicin Hydrochloride
PNI	Peri Neural Invasion
PR	Partial Response
PRFS	Proton Resonance Frequency Shift
PRV	Planning Risk Volume
PSSRU	Personal Social Services Research Unit
PSWD	Pelvic Side-Wall Disease
PTV	Planning Target Volume
PV	Per Vaginal
QA	Quality Assurance
QoL	Quality of Life
QLQ-C15 PAL	Quality of Life Questionnaire Core 15 PALliative Care
QLQ-BM 22	Quality of Life Questionnaire Bone Metastases 22
RTPS	Radiotherapy Planning System
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RF	RadioFrequency
RFA	RadioFrequency Ablation
RMH	Royal Marsden Hospital
ROI	Region of interest
ROC	Receiver under the operating curve
RTOG	Radiation Therapy Oncology Group
RT-pCT	Radiation Therapy planning Computerised Tomography
SAEs	Serious Adverse Events
SABR	Stereotactic Ablative Body Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SBS	Shared Business Services
SD	Standard Deviation
SE	Spin Echo

SIB	Simultaneous Integrated Boost
SPAIR	Spectrally Attenuated Inversion Recovery
SPIR	Spectral Pre-saturation with Inversion Recovery
SSGR	Slice Selective Gradient Reversal
T1W	T1 weighted
T2W	T2 weighted
T	Tesla
TE	Echo time
TD	Thermal Dose
TFE	Turbo Field (gradient) Echo
THRIVE	T1W High Resolution Isotropic Volume Examination
TI	Inversion time
TR	Repetition time
TSE	Turbo Spin-Echo
TV	Tumour Volume
UDL	Upper Dose Limit
USg	Ultrasound guidance
UTI	Urinary Tract Infection
VMAT	Volumetric Arc Therapy
VVB	Vaginal Vault Brachytherapy
WHO-CHOICE	World Health Organisation-CHOosing Interventions that are Cost-Effective
2D	Two dimensional
3D	Three dimensional

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Chapter 1 – Introduction

1.1 Gynaecological cancer – Overview

Cancers of the female reproductive organs arise primarily in the ovaries, endometrium and cervix. Of these, endometrial cancer is commonest, followed by ovarian cervical and then rarer cancers arising from the vagina and vulva. Unlike other cancer types which follow a TNM classification system for staging, gynaecological malignancies have largely been staged using the Federation Internationale Gynaecologie Obstetric (FIGO) system that describes disease by its local invasiveness, loco-regional and distant spread by assigning a Stage of I-IV, with various substages (**appendix 1.1**). As expected, management strategies for each cancer type vary with stage at presentation and disease stage is strongly associated with prognosis and outcome.

Endometrial cancer is the commonest gynaecological malignancy (35/100,000 women [1]. It is an adenocarcinoma arising in the endometrium, usually of endometroid type (85%), but is of serous histology in 15% of cases. It occurs mainly in post-menopausal women on a background of endometrial hyperplasia. A high body mass index with increased circulating oestrogen is a risk factor as the tumour is hormonally driven. Endometrial cancer presents with post-menopausal bleeding, and the diagnosis is made on histology of a pipelle cytology sample or following curettage at hysteroscopy. Early stage endometrial cancer is treated with hysterectomy, with node dissection if there is myometrial invasion and adjuvant radiotherapy. Unfortunately, despite potentially curative measures, recurrence rates are between 3 and 17% [2] and are more frequent in higher stage tumours and those with adverse histological subtypes e.g. papillary serous and clear cell subtypes.

Ovarian cancer occurs in 28/100,000 women [1]. It is often asymptomatic in the early stages, only becoming manifest once there has been peritoneal dissemination of disease causing non-specific symptoms such as bloating and abdominal distension. Thus, patients present with advanced disease and despite developments in treatment, 5-year survival rate for stage III/IV disease is still poor at less than 50%. High grade serous ovarian cancer which accounts for 70% of all ovarian cancers is highly mutated with a number of genes associated with its development including p53 and BRCA1/2. The cornerstone of curative treatment is achieved by complete debulking surgery followed by adjuvant chemotherapy.

Cervical cancer has become a rare tumour in the Western world (12/ 100,000 women [1] because of the success of screening programmes. The disease is strongly linked to infection with the Human Papilloma Virus (HPV; predominantly types 16 and 18) and develops from a preinvasive phase of cervical dysplasia. It is this phase that the screening programmes seek to identify and treat. In countries that lack screening, cervical cancer remains a common cancer. It presents with pain and bleeding. Where the tumour is confined to the cervix, surgical options are first-line; where disease has spread into the parametrial tissues, down the vagina or to the pelvic side-wall, a regimen of chemoradiotherapy at the outset provides better long-term outcomes. Nevertheless, recurrence rates have been reported between 9 and 42% in FIGO stages IIB–IVA [3].

Vaginal and vulvar cancers are rare. Here too the principles of primary surgery for early stages of disease where there is lack of neighbouring organ involvement (urethra, anal sphincter) or chemoradiotherapy for more advanced disease apply. Chemoradiotherapy is used in more advanced disease and chemotherapy is used in an adjuvant or palliative setting. Recurrence rates in these rarer cancers are similar to those for cervical cancer [1].

1.2 Available treatment modalities for managing locally recurrent gynaecological malignancy

Surgery, various forms of radiation therapy, including external beam radiotherapy (EBRT) and brachytherapy and chemotherapy, alone or in various combinations may be used for treatment of recurrent gynaecological malignancy. More recently, ablative techniques such as High Intensity Focused Ultrasound (HIFU) have been advocated in highly selected patients.

1.2.1 Exenterative surgery

A large proportion of patients who experience an isolated pelvic recurrence have received radiotherapy for treatment of their primary disease. Re-irradiation with traditional radiotherapy techniques is associated with significant morbidity, and chemotherapy has been shown to be ineffective at controlling disease in the previously irradiated field due to reduced vascularisation [4]. Pelvic Exenteration (PE) is therefore the only curative option for a select cohort of previously irradiated patients with centrally recurring or persistent gynaecological malignancy [5].

Retrospective studies have identified several factors that affect the disease-free survival of patients undergoing pelvic exenteration. These include the size of tumour recurrence, time to recurrence, lymph node involvement at presentation, lymphovascular space invasion (LVSI) and surgical resection margins [5-9].

Pelvic exenteration (PE) was first described in 1948 by Alexander Brunschwig as a palliative operation aimed at relieving symptoms caused by locally advanced and recurrent gynaecological cancer. It refers to the radical en-bloc resection of pelvic organs including the genital tract, bladder (anterior PE), rectum (posterior PE) or both (total PE) (**Figure 1.1**). Early methods were associated with significant post-operative mortality however enhancements in surgical techniques has reduced this to 3 -5%. Rigorous patient selection using clinical factors as identified by Shingleton

including time to recurrence, size of recurrence and likelihood of PSWD, combined with detailed imaging to exclude extrapelvic disease mean that patients undergoing PE could expect a chance of cure with 5-year survival rates between 40% and 60% [4, 10-13].

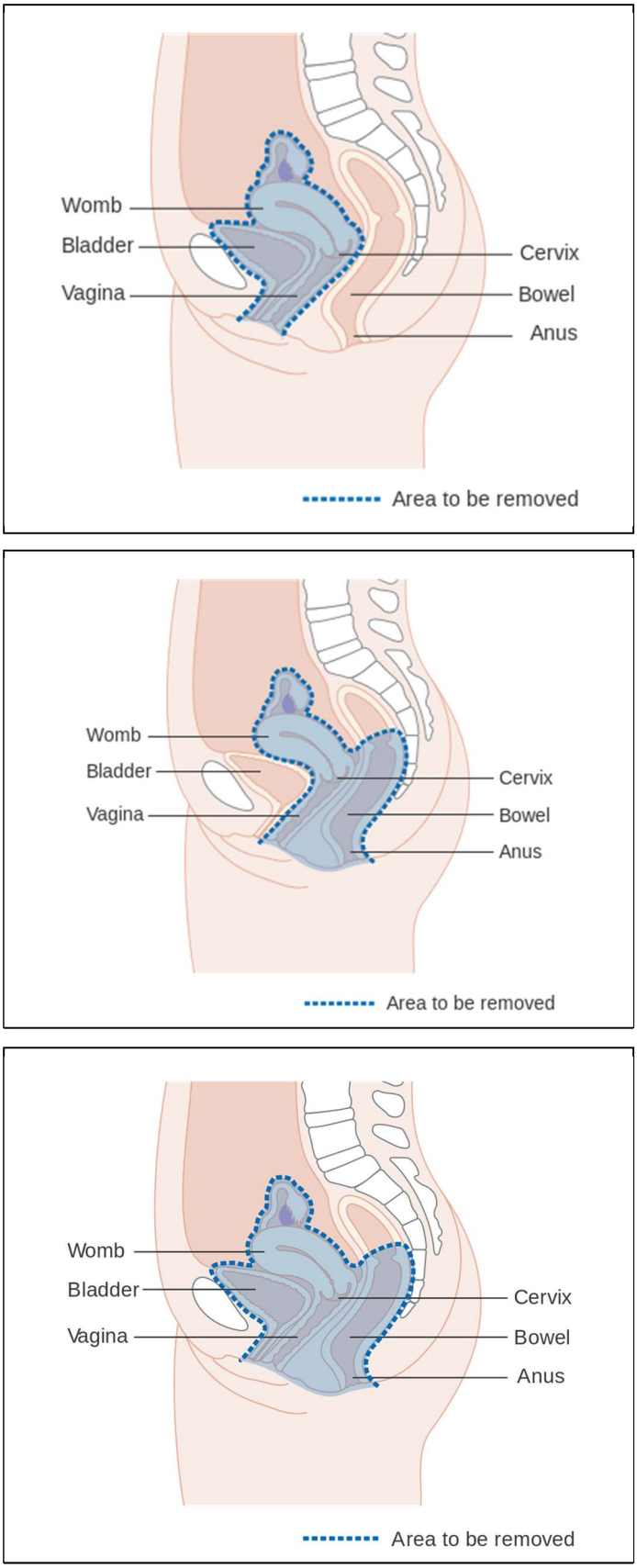


Figure 1.1 Area to be removed in an anterior exenteration (top), posterior exenteration (middle) and total exenteration (bottom).

By Cancer Research UK - Original email from CRUK, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=34334056

1.2.2 Radiotherapy

Radiotherapy needs to be delivered cautiously in the previously irradiated pelvis because of high potential morbidity.

1.2.2.1 Delivery of photon radiotherapy

Radiotherapy is delivered by generation of x-rays. Photons have no mass and no charge and are highly penetrating so damaging the DNA of cells within tissues through which they pass either by direct damage by ionisation of cell structures, particularly DNA, or from indirect damage through free radical generation. However, depending on their initial energy, most of the radiation is deposited 0.5 to 3 cm from the patient's skin, with progressive reduction in energy as photons travels towards a tumour target at depth within the body. It is therefore necessary to deliver multiple beams from different angles that intersect at the target to achieve a therapeutic dose at the target while sparing surrounding organs [14].

Photon based radiotherapy is delivered using linear accelerators (Linac) that accelerate electrons to produce x-rays. Radiation beams are precisely shaped using multi-leaf collimators (MLCs).

Intensity modulated radiotherapy (IMRT) allows for modulation of the beam intensity in addition to beam shaping by varying the delivered dose and hence allowing for dose painting to avoid organs at risk (OARs).

Rotational IMRT or Volumetric Arc Therapy (VMAT) is delivered by rotation of the Linac gantry around the patient allowing lower total monitor units and lower doses to OARs. However it increases the low dose "radiation bath" to organs that may not have otherwise received a dose. Tomotherapy is a form of rotational IMRT that does not use MLCs.

Image Guided Radiotherapy (IGRT) utilises imaging to enhance radiation target accuracy and reduce planning volumes. This is usually performed "off-line" using

cone beam CT scans which are compared to the planning CT or “on-line” with real-time tracking such as with Cyberknife™. Fiducial markers inserted prior to SBRT can further improve delivery certainty and allow for real-time tumour tracking.

Brachytherapy plays a pivotal role in the treatment of primary gynaecological cancer. It utilises the concept of rapid dose drop off to escalate the dose delivered to the tumour while reducing dose to OARs. Adjuvant vaginal vault brachytherapy reduces the risk of vaginal vault recurrences and is mostly delivered using channel cylinders loaded with an Iridium-192 radioactive source. Intrauterine brachytherapy allows significant dose escalation to the primary hence improving local control and cure rates (**Figure 1.2,** *adapted from [15]*). High dose rate (HDR) brachytherapy uses Cesium-137 or Iridium-192- delivered using modern applicators including tube and ovoids or a ring combined with an after-loading device that allows remote therapy.

Stereotactic body radiation therapy (SBRT) administers ablative doses of radiation to target the tumour. Higher radiation dose can be achieved at the tumour, with a sharper fall-off of dose away from the target resulting in greater normal tissue sparing. SBRT was initially developed for use in the brain, where sparing of adjacent normal brain was critical for functional outcome [16]. It has since been widely adopted for body applications in lung cancer, abdominal cancers and pelvic cancers [17]. One SBRT platform, the Cyberknife™ system [Accuray, USA)] achieves submillimetre targeting accuracy by utilising a linear accelerator mounted to an industrial robotic arm to direct radiation dose, precisely aiming at cancer targets while tracking target motion during the treatment [18].

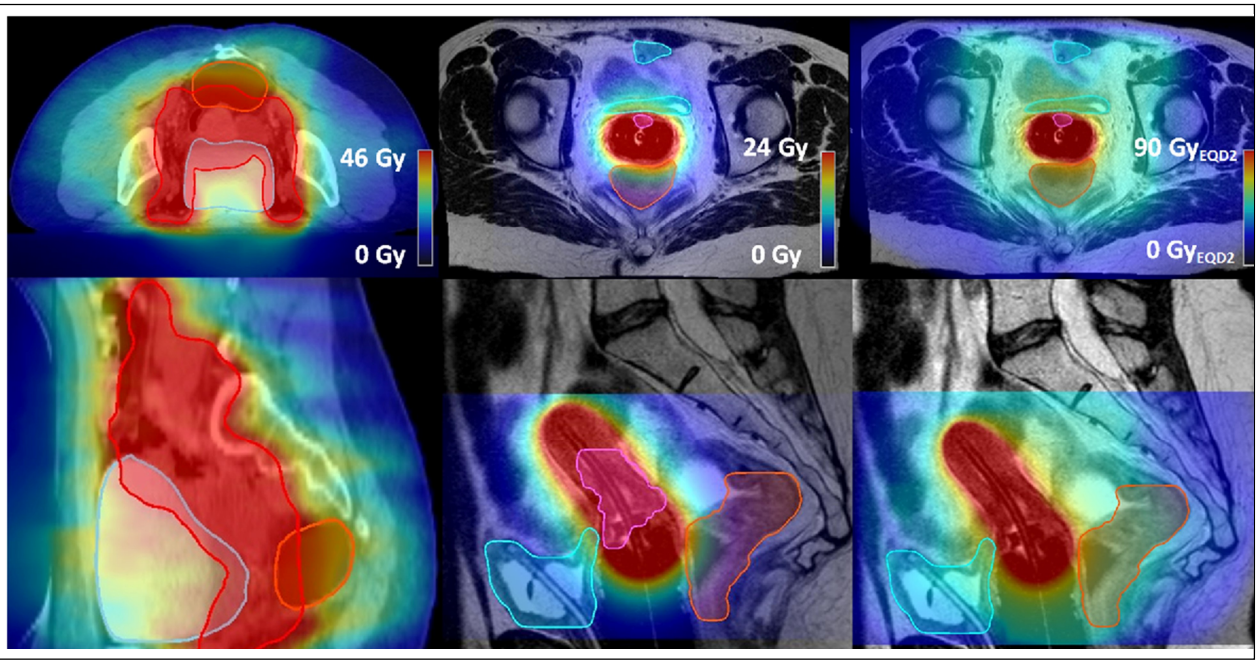


Figure 1.2 Dose accumulation of external beam radiotherapy and brachytherapy in cervical cancer. Axial (top row) and sagittal (bottom row) on CT (left column) and MRI (middle and right columns). A colour wash of the planned VMAT/BT dose (middle column) and the accumulated dose (right column) from EBRT and BT is overlaid. The EBRT dose is not uniform at the bladder/rectal walls (blue/orange) closest to the target.

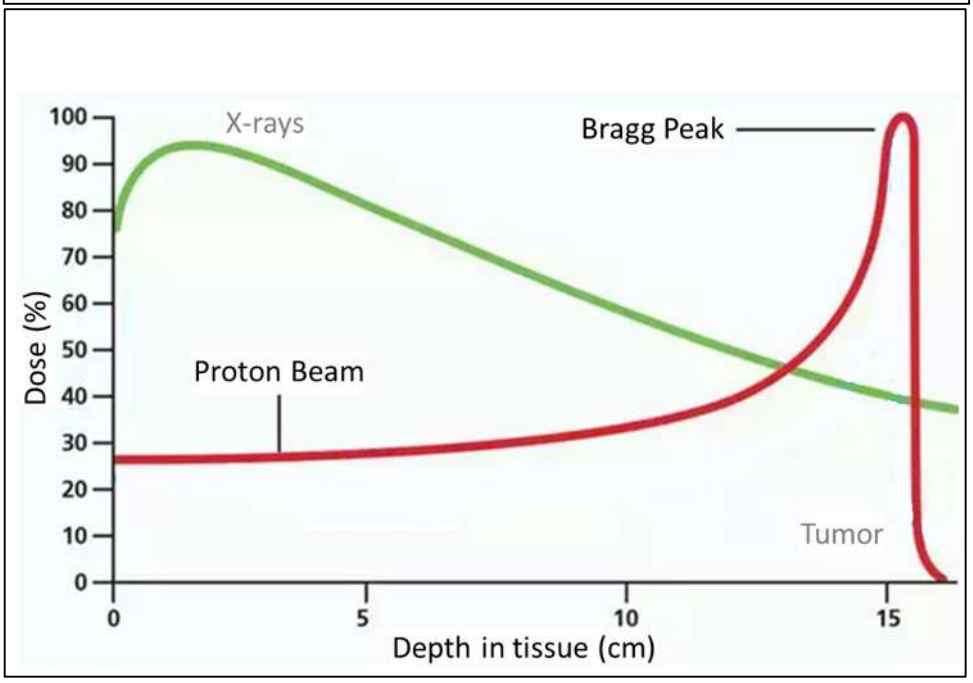
Figure adapted from Heerden, L.E et al [15]

1.2.3 Newer local therapeutic options

1.2.3.1 Proton therapy

Protons are heavy charged particles generated by a cyclotron and like photons are attenuated as they pass through the tissue. At the entry point, protons travel quickly depositing only a small dose on their way [14]. The absorbed dose increases gradually with greater depth and lower speed, suddenly rising to a sharp energy peak (Bragg peak – **Figure 1.3**) which spreads out to cover the target volume before the proton is ultimately stopped. This results in decreased dose proximal to the tumour with minimal exit dose distal to it [19] unlike the exit dose experienced when delivering photon radiation. Clinically, This translates to lower dose to surrounding normal tissue with substantial reduction in the areas of tissue that would normally receive an intermediate or low dose (< 40 Gy), so late toxicity is less common and the risk of a second malignancy due to radiation is low [20]. In lung [21], gynaecological [22] and oesophageal [23] cancers, several studies have documented the reduction in toxicity of proton compared to photon therapy as a result of better avoidance of organs-at-risk.

Figure 1.3: Dose depth curve comparing energy deposition in tissue of proton compared to photon external beam radiotherapy



1.2.3.2 Ablative techniques -HIFU

Therapeutic ultrasound is a thermal ablative technique gaining popularity in treating a variety of cancers.

When ultrasound (a pressure wave in the 20 kHz to 20 MHz frequency range) passes through tissues, compressions and rarefactions occur so that molecules oscillate in the direction of its propagation [24, 25]. Friction between oscillating molecules results in thermal energy, a process known as acoustic absorption [26]. This property is exploited to produce thermal ablation by generating enough energy and focussing the beam to a focal point, a technique known as High Intensity Focused Ultrasound (HIFU). It can be used to cause permanent ablation to a tissue target of interest, leaving other penetrated tissues unaffected by significant heating (**Figure 1.4**).

The likelihood of thermal damage to tissues depends on both the amplitude and duration of the temperature increase and is estimated using a measure known as Thermal Dose (TD) [27]. The unit of thermal dose is the Equivalent Minute (EM) at 43°C. This relates the temperature and time combination to a reference standard, which assumes that irreversible tissue damage will occur if tissue is exposed to a temperature of 43°C for 240 minutes (240 EM). Some tissue types are more susceptible to irreversible thermal damage than others, and therefore the potential for lethal ablation is estimated to occur from 25 to 240 EM [28].

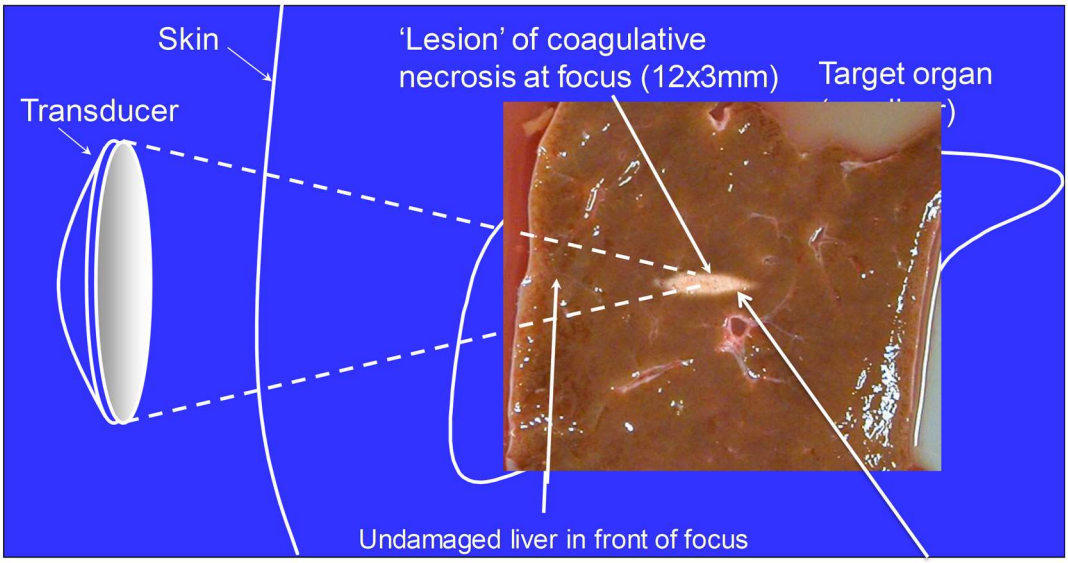


Figure 1.4 Diagram of focused ultrasound delivery to ex vivo liver. A white scar of coagulative necrosis (arrows) is seen at the focus, while tissue in the re-*focal region is unaffected. Image courtesy of Prof Gail ter Haar*

Focusing is achieved using specially designed ultrasound transducers [29]. For high intensity applications, transducers are usually of a phased array design. These are composed of multiple single elements, each of which has an independent electrical supply. This means that the ultrasound beam can be manipulated, or 'steered' electronically, as well as moved mechanically [30]. In addition, the activation of only selected transducer elements offers the possibility of 'shaping' the beam [31]. As the acoustic energy propagates through the tissues that lie between source and target [32] there is energy loss depending on the tissue type and on the ultrasound

frequency [33], which determines absorption and scatter. In soft tissues, absorption is the dominant process accounting for 70 – 90% of energy loss [34]. At tissue interfaces where acoustic impedances are similar most ultrasound energy is transmitted effectively. Where there is a differential acoustic interface, more energy is reflected, e.g. approximately half is reflected between soft tissue and bone and almost all of it is reflected between soft tissue and gas [35]. Extra-corporeal ultrasound transducers require a coupling medium of water or gels to provide an acoustic path between the transducer and the skin.

Although HIFU may be delivered under ultrasound guidance, the use of magnetic resonance imaging (MRI) has unique advantages. Not only does MRI offer superior image contrast and resolution [30] but vitally it provides temperature measurement (MR Thermometry) in the range between body and ablative temperatures. Temperature is indicated on MRI by measuring a parameter known as the Proton Resonance Frequency Shift (PRFS). PRFS is the change in phase of the resonant frequency of a water proton that occurs as a result of heating. A dynamic series of images is acquired before, during and after heating and subtractions of the pre- from post- heating data allow temperature maps to be generated, because the phase difference images are proportional to the temperature dependent PRFS change. The temperature maps derived from the phase data are superimposed on the magnitude (imaging) data acquired from the same sequence[36]. One of the limitations of PRFS thermometry is its dependence on the presence of hydrogen bonds; as these are absent in fat, it cannot be used to measure temperature changes in fatty tissues. It may also be inaccurate in tissues containing a mixture of water and fat [31].[31][31][31][31][30] Additionally, since the PRFS method is a subtraction technique using reference data, it is highly degraded by motion, which is mitigated when performing the procedure under heavy sedation or general anaesthesia.

In clinical practice, MRgHIFU has largely been developed to treat uterine fibroids because it is non-invasive [37] and can take place in an out-patient setting [38].

Ultrasound guided HIFU treatments of fibroids (and other benign gynaecological conditions) have been found to be feasible and safe. A retrospective review of 10,018 patients (approximately 75% fibroids, 25% adenomyosis) treated at 10 centres in China between 2006 and 2013 [39] showed that the rate of AEs was 10.6% (of which 95.7% were classified as minor). Nevertheless, efficacy is driven by carful patient selection to treat targetable lesions; some studies report that fewer than 25% of symptomatic patients referred for consideration of HIFU were subsequently recommended for treatment [40, 41].

The use of extracorporeal MRgHIFU for the treatment of malignant disease is limited. A major application has been in palliation of pain from bone metastases (cf. 1.5.4) where a multicentre international randomized-controlled phase III trial showed statistically significant differences in reduction of pain scores between the treatment and placebo groups 1-3 days after treatment, that were maintained at every time-point at which patients were assessed [42]. Other applications are emerging [43] for treatment of the primary site in prostate, renal [44], hepatic [45] and pancreatic cancers [46].

1.2.3.3 Other ablative techniques with cancer applications

Other thermal ablative techniques used in oncology include radiofrequency (RFA) and microwave ablations (MWA), laser interstitial thermal therapy (LITT) and cryotherapy. RFA and MWA make use of electromagnetic energy, causing the rotation of water molecules. RFA ranges from 300 MHz to 300 GHz, whereas MWA generators currently allow only two frequency spectrums, namely 915 MHz and

2.45 GHz. MWA devices function within the RF spectrum and can technically be defined as a subset of RFA. RFA, LITT and cryotherapy require insertion of probes and are invasive, while microwave ablation like HIFU is delivered extracorporeally. RFA, MWA have been trialled primarily in abdominal neoplasms mainly liver[47], but also renal and pancreas while LITT has been used in neuro-oncology [48] and cryotherapy in cervical intraepithelial neoplasia [49]. None of these techniques are used in invasive gynaecological cancers and their further discussion is outside the scope of this work.

1.2.4 Chemotherapy

To provide context to the local therapeutic approaches, the use of chemotherapy in these patients is also discussed briefly.

Chemotherapy is used frequently as a neoadjuvant, concurrent, adjuvant or palliative treatment in gynaecological malignancy. The combination of drugs, dose and number of cycles differ by tumour type, but the goal of these treatments is ultimately to cause necrosis of cancer cells through a cytotoxic or cytostatic effect on cell proliferation. Highly proliferative tissues such as tumours are highly sensitive to these cytotoxic effects, but unfortunately highly proliferative normal tissues are also affected causing treatment toxicity. The bone marrow therefore is particularly susceptible to the toxic effects of chemotherapy, where anaemia and neutropenia can often occur. Myelosuppression leads to infection due to neutropenia and bleeding disorders due to platelet dysfunction, both are extremely common side-effects of cancer chemotherapy. Other highly proliferative tissues such as the gastrointestinal mucosa and hair follicles also lead to poorly tolerated gastrointestinal side-effects and hair loss.

The commonly used classes of drugs used are the alkaloids, alkylating agents, antimetabolites and antitumour antibiotics. The alkaloids (paclitaxel, etoposide,

(antimicrotubule agents) to halt cell division at specific points in the cell cycle. Alkylating agents such as carboplatin and cyclophosphamide are cell cycle non-specific and damage DNA at any point in the cell cycle. Methotrexate, an antimetabolite, competes with folic acid during cell division. Vincristine and vinblastine exert their effects on microtubules within the cell. Antitumour antibiotics such as bleomycin and doxorubicin halt DNA replication by altering enzyme activity required for this process. Topotecan blocks topoisomerase 1 and inhibits repair of DNA during cell replication. Chemotherapeutic regimes used in primary and metastatic or recurrent gynaecological malignancy are given in **Table 1.1.**

Cancer Type	Chemotherapy regimen +/- RT or surgery for Primary Disease	Chemotherapy regimen +/- RT or surgery for Metastatic or Recurrent disease
Ovarian	• Paclitaxel 175mg/m^2 in combination with a platinum-based compound or platinum based therapy alone (cisplatin or carboplatin) are offered as first line chemotherapy (usually following surgery). 4 – 6 cycles are usually administered with surgery. • Beyond first recurrence: paclitaxel, carboplatin, gemcitabine, PLDH and PARP inhibitors may be considered.	• Paclitaxel in combination with platinum or as monotherapy • Pegylated liposomal doxorubicin hydrochloride (PLDH). • Beyond first recurrence: paclitaxel, carboplatin, gemcitabine, caelyx and PARP inhibitors may be considered.
Endometrial	• Total abdominal hysterectomy and bilateral salpingo-oopherectomy • Adjuvant chemotherapy in stage III high risk disease – 4 cycles of: q3w paclitaxel 175mg/m^2 + carboplatin AUC5 • Adjuvant VVB in G1/2 Stage I disease • Adjuvant radiotherapy in Stage II+ or Stage I G3 disease followed by VVB 8 Gy in 2 Fractions	• Multiagent Chemotherapy e.g. q3w Paclitaxel 175mg/m^2 + Carboplatin AUC5 +/- Bevacizumab 15mg/m^2 • Hormone therapy in ER+ disease e.g. Aromatase inhibitors Letrozole 2.5mg OD • Radiotherapy if not previously irradiated – and VVB for isolated vaginal recurrences • Surgery including pelvic exenteration
Cervical	• Surgery in early invasive disease • Radical chemoradiotherapy for Locally Advanced (>IIB) disease with weekly concurrent cisplatin (40mg/m^2) • Intrauterine brachytherapy to dose-escalate dose to primary +/- boost to para-aortic nodes If involved	• Chemotherapy for metastatic disease with platinum and taxol containing regimes +/- Bevacizumab. • Surgery including pelvic exenteration • Radiotherapy if not previously irradiated and VVB for isolated vaginal recurrences

Table 1.1 Chemotherapy protocols used in conjunction with radiotherapy or surgery for treating primary and metastatic or recurrent gynaecological malignancy
EBRT=External beam radiotherapy, ER=Estrogen receptor, VVB=Vaginal vault brachytherapy, PLDH=Pegylated liposomal doxorubicin hydrochloride

1.3 Treatment of recurrent gynaecological cancer with curative intent

1.3.1 Surgery

Although PE offers a curative option in locally advanced pelvic cancers [50], its use remains highly selective in patients with recurrent gynaecological malignancy because it has a high risk of morbidity (40-80%), with almost 50% of patients experiencing post-operative complications such as fistulae formation [51] and achieving only 20-48% 5-year survival [12, 52]. Nevertheless, it has been practised for more than 30 years in this context [53]. A large series of 167 cases treated with PE, where 63% were for recurrent disease showed an overall 5-year survival of 38% [54]. A more recent series of 38 cases of recurrent cervical cancer operated with curative intent showed a median overall survival (OS) and disease-free survival (DFS) of 28.5 months (range 9-96 months) and 23 months (range 4-96 months), respectively, and 5-year OS and DFS of 48% and 40%, respectively [55]. Other smaller series yield very similar results [56]. A systematic review of the literature over the last 25 years has indicated that clear margins are required for curative PE but were poorly predictable by pre-operative assessment and were achieved in only half of PE procedures [12].

Although central pelvic recurrences can be treated surgically, many patients are inoperable particularly those with nodal recurrences. In a study of isolated pelvic recurrences in 67 patients, 42% of whom received salvage surgery, 25% received chemotherapy alone, and 33% received neither surgery nor chemotherapy, the median time to distant failure after isolated pelvic failure was 20 months, with no significant difference between patients treated surgically vs. non-surgically. Median OS for patients treated with surgery, chemotherapy alone, and neither surgery nor chemotherapy was 29 months, 12 months, and 3 months, respectively. ^{18}FDG-

avid pelvic and para-aortic nodes at initial presentation were associated with worse distant control after isolated pelvic failure [57].

1.3.2 Radiotherapy

Regional failures of endometrial, cervical, and ovarian cancer frequently include areas of prior radiation therapy used in the initial treatment of the pelvic sidewall and para-aortic lymph node regions. Potential morbidity does not permit re-irradiation at effective doses with conventional techniques. Particularly for pelvic side-wall failures, SBRT is now becoming a viable treatment option for attempted cure of recurrent disease [58].

Recurrences of gynaecological cancer that have been treated with SBRT described in the literature are in small or heterogeneous patient populations. Some studies combine the results of primary and recurrent tumours [59], others include non-gynaecologic primaries [60-62], and some have less than 10 patients [63-65]. In a study of 30 patients with gynaecological recurrences alone (11 central, 11 pelvic side-wall, 13 para-aortic), Hasan et al showed that five-year survival for all patients was 42% with a median survival of 43.4 months. Multivariate analysis revealed better performance status, and smaller clinical tumour volume was significant for improved survival [66]. The largest series of safety of SBRT for recurrent or oligometastatic cervical cancer comes from a multicentre Korean study of 100 lesions treated in 85 patients. Most lesions (89%) were lymph node recurrences. SBRT sites were within the previous RT field in 59 and partially overlapped in nine. Re-irradiation appeared to be related to inferior local control ($p<0.001$), but the SBRT biological effective dose in this group was much lower than in those without previous irradiation (median 79 Gy vs. 90 Gy). Chronic toxicities of grade 3 or more were only seen in five cases (5.8%) [67].

Every SBRT study for recurrent pelvic malignancy reports at least one grade 3 or higher toxicity. In one series of 50 patients with metastatic gynaecological malignancy treated with SBRT, the incidence of grade 3 or grade 4 possible SBRT-related non-haematological toxicities was 6%; these events included non-infectious diarrhoea and enterovaginal fistula formation [61]. Enterovaginal fistulae were described in 7 patients from four other series comprising a total of 81 patients [66, 68-70]. Three of these were in the pelvic side-wall recurrence study by Seo et al., who determined that a $D_{5cc} < 30$ Gy, $V40 < 50$ cm^3, or a $GTV < 50$ cm^3 drastically decreased the risk of developing a fistula [70]. Despite these difficulties, in Hasan's series, only 26% of lesions failed locally, resulting in local control rates of 80% and 73% at 1 and 2 years respectively, and 73 and 67%, respectively at 3-year and 5-years [66]. This favours the consideration of re-irradiation with SBRT as a curative treatment option in pelvic recurrences of gynaecological tumours.

Brachytherapy also has been used for re-irradiation of a previously irradiated pelvis where the recurrence is isolated to the vagina with increasing evidence in this setting as summarised by Armstrong et al [71]. Several studies have reported excellent survival of up to 68% at 3 years and Grade 3 – 4 toxicity as low as 7%. The largest of those, a retrospective study of 52 patients treated with high dose-rate interstitial brachytherapy had a local control rate of 76.9% (40/52), with a median post-recurrence survival period of 32 months. Grade 3 or 4 late toxicities were observed in 25%. Tumour size and the treatment-free interval were significant poor prognostic factors of post-recurrence survival on multivariate analysis [72].

1.3.3 Chemotherapy

A variety of chemotherapeutic agents may be used for the treatment of recurrent gynaecological cancer. Platinum based chemotherapy may be used in combination with radiotherapy in particularly when there has been no prior pelvic irradiation. In a

study of 47 cases where all but one patient received cisplatin-based concomitant chemotherapy during radiotherapy (median dose of 64.8 Gy) to a previously non-irradiated pelvis (primary management was surgical), 33 (70%) showed a complete response and 9 (19%) a partial response with 5-year overall and DFS rates of 44% and 41%, respectively. Grade 3-4 acute hematologic toxicity was the most frequent toxicity and was observed in 29 (62%) women [73].

A retrospective data set of 75 patients from my centre, recorded second line chemotherapy for recurrent/metastatic cervical cancer as being Carboplatin-based (24.5%), targeted agent monotherapy within clinical trials (22.6%), docetaxel-based (13.2%), topotecan (9.4%) and gemcitabine (1.9%). Only 22 patients (41.5%) achieved stable disease at 4 months. The median progression-free survival was 3.2 months and median overall survival was 9.3 months [74]. Early studies of oral agents alone were disappointing. More recently, large randomised Phase 3 trials have investigated platinum-based [75-77] and non-platinum based [78] combinations; however, it is the inclusion of multiple agents, for instance bevacizumab that improve overall survival (**Table 1.2**).

In ovarian cancer, chemotherapy remains the standard of care in recurrent disease as confirmed by the recent randomised Phase III trial (GOG-0213) where platinum-sensitive patients treated with surgery in addition to paclitaxel–carboplatin or gemcitabine–carboplatin did not have improved survival compared to those treated with chemotherapy alone. The hazard ratio for death (surgery vs. no surgery) was 1.29; *P*=0.08), which corresponded to a median overall survival of 50.6 months and 64.7 months. Adjustment for platinum-free interval and chemotherapy choice did not alter the effect [79]. Within the same trial, patients were also randomised to carboplatin and paclitaxel, with or without bevacizumab. The addition of bevacizumab to standard chemotherapy, followed by maintenance therapy until

progression, improved the median overall survival in patients with platinum-sensitive recurrent ovarian cancer (42.2 months versus 37.3 months (HR=0·829; *P*=0·056) [80].

Treatment of recurrent gynaecological malignancy with curative intent				
Modality	**Study**	**Treatment details**	**Toxicity**	**Outomes**
Pelvic exenteration	n=167[54]	63% recurrent disease		5-yr OS 38% whole cohort
Pelvic exenteration	N=282 [52]	Anterior 5%, posterior 2%, Total 93% of patients	One major complication in 26%, two complications in 15% and >3 complications in 10% of patients.	5-yr OS 41%, 10 yr. survival 38%
Pelvic exenteration	N=38 [55]	Anterior 29%, Posterior18% Total 53% of patients.	Early complications 55%, late complications 40%	5-yr OS 48% (DFS 40%)
Salvage hysterectomy	N=58 [81]		Intestinal grades 3-4 toxicities in 10.4% and urinary grade 3-4 toxicity in 8.6%	4-yr OS 50% (DFS 51%) in patients with residual macroscopic disease
Cyberknife SBRT	N=50 [61]	24 Gy in 3 daily doses	Acute fatigue (16%), nausea (8%), and diarrhoea (4%)	Median OS 20.2 months, median DFS 7.8 months
Cyberknife SBRT	N=38 gynaecological cases [62]	15-60 Gy in 2-5 fractions	Grade 3-4 acute toxicities in 7% late toxicities in 15%	Median OS 20 months for whole cohort
SBRT	N=30 [66]	15-40 Gy in 3-5 fractions	Grade 2 radiation proctitis in 1, grade 2 cystitis in 1, enterovaginal fistulas in 1	5-year OS 42% (median DFS 47 months)
SBRT	N=100 [67]	39 Gy in 3 fractions	Chronic toxicities grade 3 or more in five cases	5-year OS 33%
SBRT	N=19 [69]	50 Gy conventionally fractionated	late toxicity>grade II was 25% at 3years	3-year OS 34%
SBRT	N=23 [70]	27-45 Gy in 3 fractions	Rectovaginal fistula in 13%	2-year OS 43% (DFS 52%)
High dose rate interstitial brachytherapy	N=52 [72]		Grade 3 or 4 late toxicities in 25%	Median survival 32 months
Chemotherapy (ovarian cancer)	N=485, GOG-0213, phase 3 RCT [79]	Carboplatin and paclitaxel ± secondary cytoreduction	Surgical morbidity at 30 days 9%	median OS 50.6 months without surgery, 64.7 months with surgery,HR1.29
Chemotherapy (ovarian cancer)	N=674 GOG-0213, phase 3 RCT [80])	Carboplatin and Paclitaxel ± Bevicizumab	96% in the chemotherapy plus bevacizumab group had at least one grade 3 or worse adverse event compared with 86% in the	median OS in the chemotherapy +bevacizumab group 42.2 months vs. 37 months in the chemotherapy group

			chemotherapy group	
Chemotherapy (cervix cancer)	N=53 retrospective study [74]	Carboplatin-based (24.5%), targeted agent monotherapy (22.6%), docetaxel-based (13.2%), topotecan (9.4%), gemcitabine (1.9%)		Median OS 9.3 months (DFS 3.2months)
Chemotherapy (ovarian cancer)	N=976, Phase 3 RCT [75]	Carboplatin-pegylated liposomal doxorubicin vs. carboplatin-paclitaxel		Median OS 30.7 months for carboplatin+doxorubicin and 33 months for carboplatin+paclitaxel
Chemotherapy (endometrial cancer)	N=273, Phase 3 RCT [78]	Doxorubicin and cisplatin ± paclitaxel	Neurotoxicity higher in those receiving paclitaxel (12% grade 3, and 27% grade 2 peripheral neuropathy, compared with 1% and 4%, respectively in those without paclitaxel)	OS and PFS improved in group receiving paclitaxel (median OS 15.3 v 12.3 months; P =.037, median PFS 8.3 v 5.3 months; P <.01)
Chemotherapy (cervix cancer)	N=452, Phase 3 RCT [76]	Cisplatin +paclitaxel vs. topotecan + paclitaxel, each group ± bevacizumab	Fistula (any grade) in 15% in the chemotherapy plus bevacizumab groups vs. 1% in the chemotherapy-alone groups Grade 3 fistula in 6% of those receiving chemotherapy plus bevacizumab versus <1% in chemotherapy alone group.	OS better in chemotherapy plus bevacizumab groups compared with the chemotherapy-alone groups: (16.8 months vs. 13.3 months, hazard ratio 0·77; *P*=0·007).
Chemotherapy (ovarian cancer)	N=356, Phase RCT [77]	Gemcitabine + carboplatin vs. carboplatin alone	No statistically significant differences in quality of life scores between arms	Median PFS 8.6 months for gemcitabine plus carboplatin, 5.8 months for carboplatin; HR for OS 0.96 (P = .7349)
Chemoradiotherapy	N=47, retrospective [73]	Cisplatin-based concomitant chemotherapy during salvage radiotherapy median dose 64.8 Gy (range, 36-100.2), including brachytherapy boost in 10patients	5-year actuarial cumulative GI toxicity 13%, GU toxicity 7%	5-year OS 44% and DFS 41%

Table 1.2 Studies treating recurrent gynaecological cancer with curative intent with more than 10 reported cases in the series. Surgical studies are shown in blue, radiotherapy studies in orange and chemotherapy studies in green.
DFS=disease-free survival, GI= gastrointestinal, GU=genitourinary, HR=Hazard ratio, OS=overall survival, RCT=randomised controlled trial, SBRT=stereotactic body radiotherapy

1.4 Palliation of recurrent gynaecological cancer

1.4.1 Surgical options

Palliative PE is a technically complex operation with high morbidity and mortality rates and is rarely considered in patients with limited life expectancy. A small series of 18 patients at a single institution reported major surgical morbidity in 50%, but with good symptom control and patient satisfaction [82]. Earlier this year, the PelvEx Collaborative [83] reported on 23 historical cohorts and case series were included, comprising 509 patients. Common indications for palliative PE in colorectal, gynaecological and urological cancers were pain, symptomatic fistula, bleeding, malodour, obstruction and pelvic sepsis. The pooled median postoperative morbidity rate was 53.6% (13-100%), the median in-hospital mortality was 6.3% (0-66.7%), and median OS was 14 months (4-40 months). Some symptom relief was reported in a median of 79% (50-100%) of the patients, although the magnitude of effect was poorly measured. Data for QoL measures were inconclusive. Five studies discouraged performing palliative PE in any patient, while 18 studies concluded that the procedure can be considered in highly selected patients.

1.4.2 Palliative radiotherapy

Palliative radiotherapy, usually delivered as a hypofractionated course of 8 – 30 Gy in 1 – 10 fractions, is delivered for symptom control and has been shown to be well-tolerated and effective (overall response rates of 93.8% and 66.7% for control of vaginal bleeding and pelvic pain, respectively) [84]. A recent study in 64 patients with recurrent ovarian cancer who received radiotherapy for pain (44%), bleeding (32%), obstruction (15%), and other symptoms (9%) showed significantly higher response rates for pain (87%) and bleeding (93%) than for obstruction (62%) and other symptoms (60%; $P < 0.01$) [85]. Palliative radiotherapy has also been shown

to be effective when delivered as a hypofractionated short course (median dose 25 Gy in 5 Gy daily fractions).

1.4.3 Palliative Systemic Therapy

Where re-irradiation is not feasible, or where there are multiple metastases at distant sites, palliative chemotherapy is the only option as previously described. However, it has a very low response rate within previously irradiated fields (< 20%) [86]. Platinum based chemotherapy is the most effective: carboplatin-paclitaxel is an active combination and has been shown to be deliverable and well-tolerated in previously irradiated patients where the most observed toxicity was anaemia [87].

Immunotherapies are finding a role in the management of recurrent gynaecological malignancies. Pembrolizumab recently was granted FDA accelerated approval for tissue or site agnostic use in the treatment of patients with unresectable or metastatic solid tumours associated with microsatellite instability or mismatch repair-deficient disease. Approximately 26% of recurrent endometrial cancers harbour mismatch repair deficiency in the recurrent disease setting and may be excellent candidates for Programmed cell death-1 (PD-1) targeting immunotherapies as there is expression of PD-1 and its ligand PD-L1 in metastatic endometrial cancers [88].

1.4.4 High Intensity Focussed Ultrasound

HIFU has been used extensively to palliate pain from bone metastases. A multicentre randomised Phase 3 trial showed its effectiveness in comparison to placebo (“sham” treatments) [42], which led to CE marking of the equipment for this purpose. Experience in 20 cases with painful bone metastases indicated a substantial positive effect on physical functioning, and improving other symptomatic quality of life measures [89].

Studies utilising HIFU in a palliative setting for soft-tissue lesions are limited. The biggest experience comes from China. Two separate studies of MRgHIFU in

pancreatic cancer have shown symptom relief in ~80% [90, 91]. No severe complications or adverse events were seen in the first study, while in the second where chemotherapy was given concurrently major complications were reported in 3 patients (1 case of severe pancreatitis with bleeding, 2 cases of grade 3 skin burns, requiring plastic surgery). Another safety evaluation in 224 pancreatic patients treated with HIFU found no severe complications (skin burns, bleeding or perforation) in any of the patients. In 10 patients (4.5%), abdominal distension and anorexia with slight nausea was observed after HIFU treatment [92].

There are only 2 single case reports of HIFU being used to treat recurrent gynaecological tumours. In 2008, a group in Israel [93] used the Ex-Ablate™ system to treat a 27-year-old women with a highly symptomatic and aggressive recurrent cervical tumour. Treatment was done on compassionate grounds in a 27-year old female and was not expected to be curative. After treatment, the patient reported significant improvements in pain and bleeding without adverse events, which enabled her to resume normal activities. The improvement lasted for 4 months, before the patient succumbed to her disease. Another report 7 years later [94], used a trans-rectal Sonablate™ Ultrasound-guided (USg) HIFU device to treat a 38-year-old woman with recurrent cervical cancer and profuse vaginal discharge. Treatment was delivered under general anaesthetic (GA). Only the inferior portion of the cervical mass could be targeted. Symptom relief was temporary: vaginal bleeding and discharge stopped completely immediately after treatment, re-started less profusely after 7 days, but resumed to pre-treatment levels by 30 days after treatment.

1.4.5 Analgesia and Supportive Care

Supportive palliative care teams play a pivotal role in the palliation of cancer patients using analgesics, adjuvant therapies and psychosocial support that is outside the scope of this thesis.

1.4.6 Psychosocial aspects

Assessment of psycho-social stress is particularly important in recurrent gynaecological malignancy. Information about the available options for psychosocial support, counselling and access to these services are vital factors in managing recurrent disease successfully. Options vary according to individual patient needs. The indications for psycho-social interventions must be ascertained on an individual basis and the individual patient's setting, therapy being administered and life expectancy; wishes of the patient must be considered. The issues around sexuality must be actively addressed and appropriate support provided. Self-help groups are a valuable resource and can be utilised as needed.

Managing recurrent gynaecological cancer effectively in a curative or palliative care setting thus requires multiple complex interventions. A balance needs to be struck between treatment efficacy and morbidity that may substantially impact quality of life, which is particularly critical if life expectancy is limited. Utilising newer approaches that potentially maximise efficacy and minimise toxicity in treating recurrent gynaecological malignancy are therefore a priority.

1.5 Hypothesis

In recurrent gynaecological cancer it is feasible to use new targeted therapeutic approaches including SBRT, PBT or HIFU under imaging guidance to achieve local and symptom control.

1.6 Aims

- To describe patterns of relapse and determine histological prognostic factors affecting OS, DFS and loco-regional control in patients who have undergone exenterative surgery at the Royal Marsden Hospital (RMH).

- To determine whether SBRT can be feasibly planned in patients who have undergone pelvic exenteration and have a positive or close surgical margin.

- To dosimetrically compare simultaneous integrated boost versus sequential external beam radiotherapy techniques to escalate dose to central and pelvic side wall recurrent gynaecological cancer not suitable for brachytherapy.

- To document the safety of MRgHIFU in a pilot group of patients with recurrent gynaecological malignancy, monitor changes in symptoms on patient reported outcome measures and make a preliminary assessment of the health economics of this treatment modality.

Chapter 2 – Determining patterns of relapse following pelvic exenteration and the feasibility of post-operative stereotactic radiotherapy

2.1 Introduction

Pelvic exenteration (PE) may be performed with curative intent in patients with a single-site isolated recurrence of a gynaecological tumour in the pelvis [95]. As previously described in 1.4.1, it involves radical en block resection of pelvic organs in the anterior (anterior PE) or posterior compartments (posterior PE) or both (total PE). Nevertheless, despite modern imaging techniques and intraoperative histopathological margin evaluation, exenterative procedures performed with curative intent result in involved margins in 7 – 35% of cases [12]. Because complete tumour resection is associated with higher overall survival (OS) and DFS and micro- or macro tumour residuals have been shown to reduce survival to as low as 0% at 5 years[4, 10], there is a clear clinical need to try and case select those in whom a complete resection can be achieved and to try and manage those in whom this has not been achieved to address this strong prognostic factor post-operatively.

To improve rates of local control, one approach has been to add intraoperative radiotherapy (IORT) to aim for complete disease ablation. Results have been variable but there is suggestion that IORT can improve local control with one series has shown it to increase 5-year survival from 11 to 42% following complete macroscopic resection. However, it was associated with fistulae formation and significant gastrointestinal (25%) and sciatic nerve (30%) toxicity [96-98].

There currently is a paucity of data on post-operative therapeutic approaches to improve clinical outcomes. Chemotherapy is feasible but patients often have a long post-operative recovery, its efficacy is still uncertain in the adjuvant setting for cervical cancer and it is unlikely to improve local control rates [4, 12]. There are no

studies describing the role of traditional EBRT in patients with positive or close margins after PE where re-irradiation has been traditionally associated with unacceptable toxicity. Post operatively, SBRT offers an attractive option for complete non-surgical ablation following thorough histopathological assessment of surgical margins. It allows the delivery of highly conformal ablative doses of radiation and has been shown to result in little toxicity in the previously irradiated field and can be delivered with OAR sparing with minimal compromise to target coverage [61, 99, 100] (cf. 1.6.1).

The dose constraints for re-irradiation are not yet established, as it may depend on previous treatment dose and volume, time from previous treatment and variable recovery of the organs at risk tolerances (Sturdza et al paper summarises all this). The cumulative dose is the dose received by the OAR from previous treatment added to the dose from the second treatment. There is emerging clinical data to support this approach, and for the purpose of the dosimetric study we have defined cumulative tolerances for the bowel, bladder, rectum and nerves.

The main challenge with delivering SBRT following surgery is defining the target volume particularly as the tumour has been removed and the soft-tissue anatomy has changed following removal of the pelvic organs. Since patients will have previously had radical radiotherapy, there is the need to minimise the extent of irradiated normal tissue as re-irradiation does increase the risk of late toxicity. Therefore, there is the need to develop a robust method for defining the target volume following pelvic exenteration.

2.2 Hypothesis

It is dosimetrically feasible to deliver SBRT to the previously irradiated pelvis with an involved/close surgical margin after PE for recurrent gynaecological malignancy.

2.3 Aims

- To describe patterns of relapse and determine histological prognostic factors affecting OS, DFS and loco-regional control in patients who have undergone exenterative surgery at the Royal Marsden Hospital (RMH).
- To determine whether SBRT can be feasibly planned in patients who have undergone PE and have a positive or close surgical margin.

2.4 Methods

2.4.1 Patterns of relapse following PE

This study evaluated the pattern of relapse following pelvic exenteration, and then applied the results to develop a dosimetric study. A service evaluation for assessing outcomes following exenteration was approved by the RMH ethics board.

2.4.1.1 Patient Selection – generating a database from a 25-year experience at the RMH

Prior to determining the feasibility of delivering radiotherapy post-PE, it is essential to study the patterns of relapse in order to determine the relationship between the surgical margin and the site and nature of recurrence. I therefore carried out a retrospective analysis of patients who underwent exenterative surgery for a gynaecological malignancy at RMH by interrogating a surgical database, the surgical lists and the electronic patient recording (EPR) system between 1982 and 2018. I excluded patients between 1982 and 1993 in whom both electronic and paper records were missing (n = 105), and patients who had a PE for a palliative indication (n= 5) and those in whom the procedure had been abandoned predominantly due to pre-operative understaging (n = 34). The final cohort comprised 104 evaluable patients. Patient characteristics including age at time of PE, primary malignancy, histology, stage at diagnosis, previous treatment, indication for PE, type of surgery, node status, LVSI, perineural invasion (PNI), post-surgical

treatment, surgical margin size, time to recurrence following PE and time of last follow up or death were recorded.

2.4.1.2 Classifying relapse

I classified the relapse into local-regional, distant or both. This provided a descriptive pattern of the relapses but did not provide any detail on the exact location of loco-regional relapses or their relationship to the surgical margin status.

2.4.1.3 Three-Dimensional Tumour Mapping

To study the patterns of loco-regional relapse in more detail, I created three-dimensional tumour volumes (3DTVs) using DICOM (Digital Imaging and Communications in Medicine) data, either CT or MRI scan at the point of relapse, for all patients who had a loco-regional relapse from 2006 onwards – the picture archiving and communication system (PACS) was introduced to the RMH that year. I exported the DICOM data from PACS and imported them onto a reference female pelvic CT scan within the Eclipse radiotherapy treatment planning system (RTPS - v13.6, Varian Medical Systems). I outlined the relapsed volumes for each of the patients and created a cumulative anatomical map. I was then able to use the RTPS to classify each of the cumulative volumes according to the type of PE carried out.

In patients with loco-regional recurrence, the pre-operative DICOM data were also imported into Eclipse and the images were co-registered using a bone-match fusion. I chose bone-matching as the bony anatomical land marks were little changed pre- and post-PE in comparison to soft tissues. For each co-registered image, I outlined pre- and post-exenterative tumour volumes at relapse, pre_3DTV and rel_3DTV respectively. I added a 5 mm isometric expansion to the pre-operative tumour volume to allow for outline uncertainties and any subclinical microscopic disease. Using a Boolean operation, I subtracted the rel_3DTV from the pre-3DTV and calculated the volume of overlap to assess the relationship between the pre- and post-exenterative margins (**Figure 2.1**).

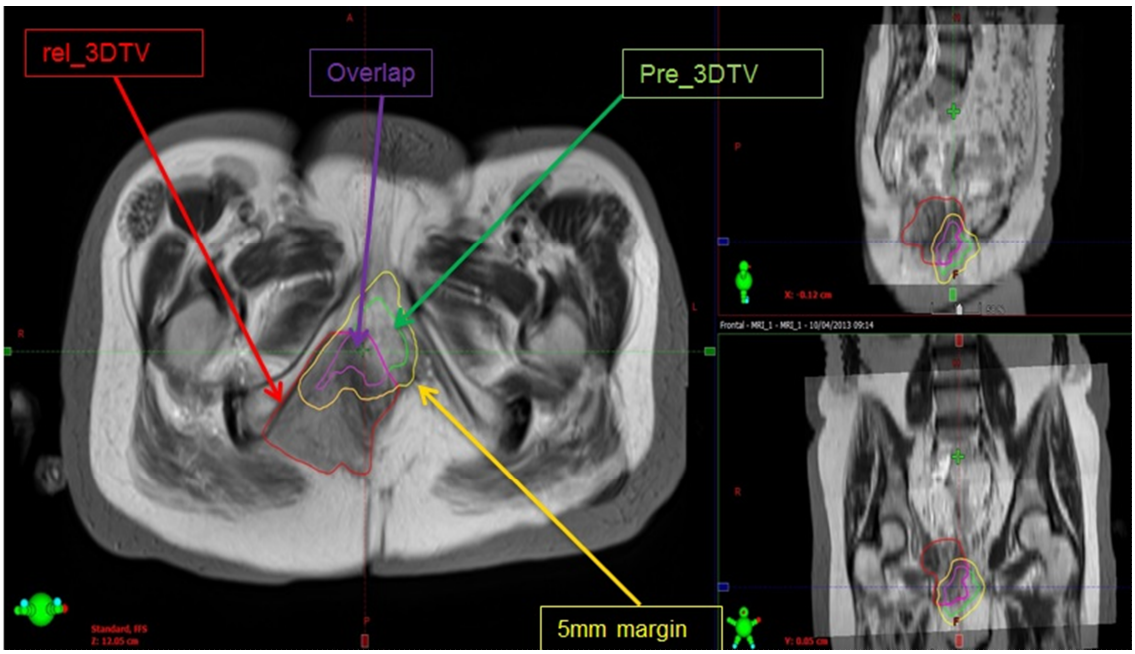


Figure 2.1 3DTV= pre-operative tumour volume, rel_3DTV= post-operative relapsed tumour volume.

The case of one patient who underwent a translevator total PE for recurrent squamous cell carcinoma of the cervix at the vaginal vault is illustrated in **Figure 2.2**. At PE, there were surgically involved margins laterally, medially and posteriorly including the lateral margin of the levator specimen. The pre-operative GTV and the post-operative GTV have been copied onto the pre-operative image set (**Figure 2.2a and b**). Using a Boolean subtraction, the volume of overlap of disease was 3.9 cm^3. This corresponded to the right anterolateral levator margin (**Figure 2.2 c**).

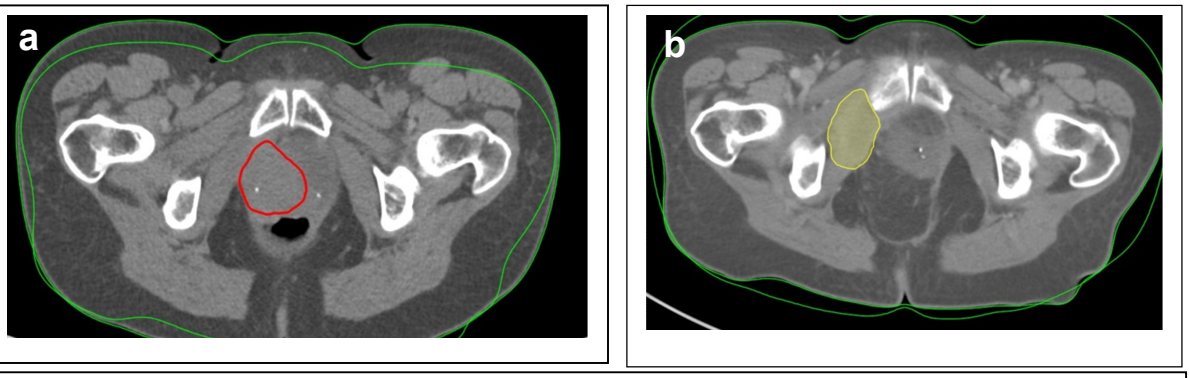


Figure 2.2. CT scans at 2 different levels through the femoral heads (a, superior section, b, inferior section). Pre-operative tumour contour (red) and post-exenterative relapsed tumour volume GTV (yellow) as outlined on Eclipse radiotherapy planning system.

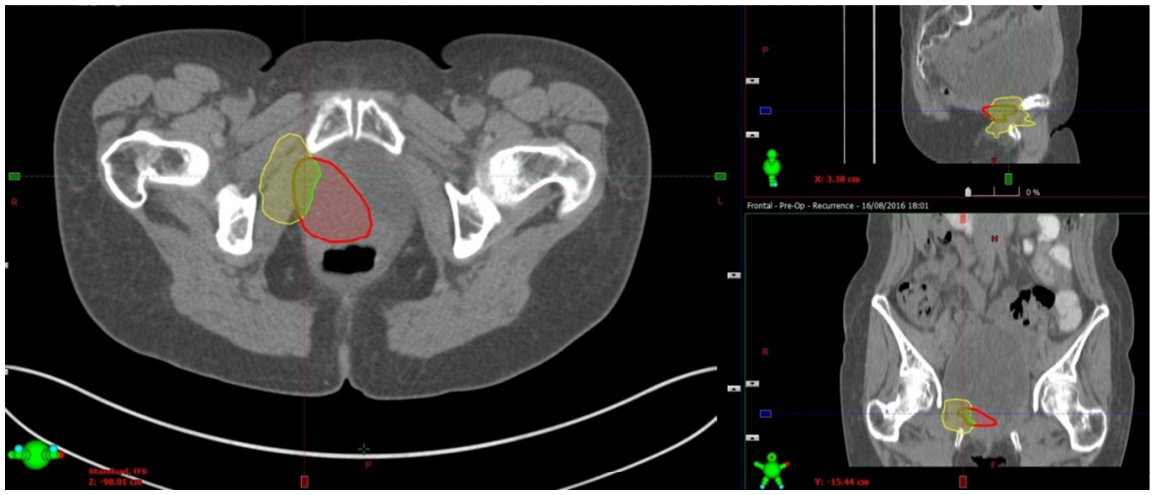


Figure 2.2c Overlay of pre-operative (red) and relapsed (yellow) tumour volumes with the overlap shown in green, which coincided with site of positive margin. Volume of overlap =3.9cm^3

2.4.2 A dosimetric study planning SBRT in post-PE patients

2.4.2.1 Patient selection

I conducted a planning dosimetric study to assess feasibility and compare three different clinical target volumes (CTVs) to deliver SBRT. This was done to i) compare two methods of targeted SBRT to the positive/close margin, *CTV_margin* and *CTV_highrisk*, and ii) determine feasibility of a much larger radiotherapy volume encompassing the pre-operative GTV, *CTV_total*.

Ten patients who had undergone PE for recurrent gynaecological cancer and had a positive or close surgical margin were included in this dosimetric study. Patients analysed had a CT scan post operatively that was imported onto the Eclipse planning system. All participants had completed written informed consent giving permission for their scans to be used for research purposes.

2.4.2.2 Contouring

Contouring was carried out in the Eclipse radiotherapy treatment planning system (RTPS - v13.6, Varian Medical Systems) using CT imaging with the aid of fused MRI if available together with the reports from surgical histopathology.

2.4.2.3 Clinical and planning target volumes

CTV_margin, *CTV_highrisk* and *CTV_total* were outlined with the aid of Mr Des Barton, gynaecologic oncologist who performed the PEs, and Dr Alexandra Taylor, consultant clinical oncologist.

CTV_margin was defined as the area of positive or close margin as described by the histopathological report and in correlation to imaging. The margin was firstly identified on imaging and an area equivalent to the length of the margin was contoured. The contour was then expanded to follow the affected site of the margin e.g. if this was the left lateral vaginal wall then this area was covered beyond the length described to allow for post-operative anatomical changes (**Figure 2.4**). In two

cases there were fiducial markers inserted by Mr Barton at the time of surgery which aided the contouring.

CTV_highrisk was a larger target volume incorporating *CTV_margin* as well as the high risk area bordering the positive/close margin (determined by Mr Barton and Dr Taylor) e.g. the entire muscle bordering the margin but not the lymphatic pathways.

As central recurrences remain the predominant pattern of relapse, subclinical microscopic spread needed to be accounted for. *CTV_total* volume therefore incorporated *CTV_highrisk* with the addition of the pre-PE GTV contoured by fusing the pre- and post-operative imaging within Eclipse as described in section 2.4.1.3.

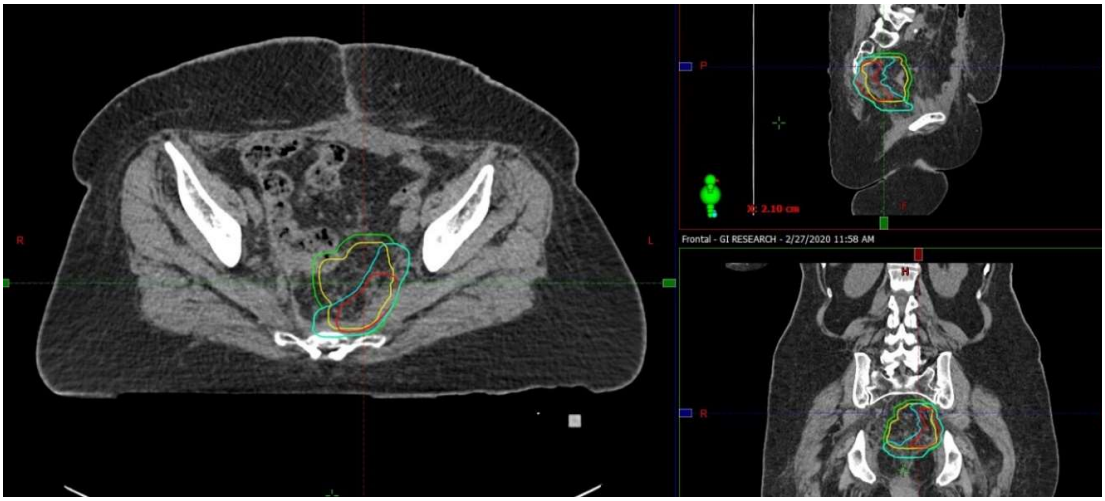


Figure 2.3 Planning target volumes demonstrating CTV_margin (red), CTV_highrisk (blue), CTV_total (green) and pre-operative GTV (yellow).

Planning target volumes, *PTV_margin*, *PTV_highrisk* and *PTV_total,* were created using a 5 mm isotropic expansion. This is the standard CTV to PTV expansion at the RMH but is also in line with other published literature on image guided linear accelerator (Linac) based SBRT.

2.4.2.4 Organs at risk

Depending on the type of PE, OARs were contoured following the Radiation Therapy Oncology Group (RTOG) contouring guidelines including bilateral femoral heads, the bowel, sciatic nerves, bladder (posterior PE) and rectum (anterior PE). The rectum was contoured from the level of the sigmoid flexure to the anus. The individual loops of small bowel, sigmoid and colon were contoured from 2 cm above the planning target volume (PTV) to the lower part of the pelvis. The sciatic nerve was contoured according to Yi et al sacral plexus contouring guidelines and a 5 mm isotropic expansion was used to create the nerve planning risk volume (*PRV_SacralPlexus*).

2.4.2.5 SBRT Planning

All SBRT plans were generated using Eclipse™ (Version 13.6, Varian Medical Systems). The flattening filter-free (FFF) Acuros XB™ dose calculation algorithm was used with a single 6 MV arc. All cases were planned to receive 30 Gy in 5 Fractions as per local RMH SBRT policy based on the Commissioning through Evaluation (CtE) standards. Plans were normalized for 95% coverage by the prescription isodose (100% isodose covering 95% of PTV) and a Dmax of 125-140% while maximally sparing the OARs. PTV planning tolerances are given in **Table 2.1.**

	R50%: V_{15GY}/PTV $V_{100\%}$		***CI: V_{30GY} / PTV $V_{100\%}$***	
PTV (cm^3)	Target	Tolerance	Target	Tolerance
<20	5.5	7.5	1.2 (1.25-1.40)	<1.25
20-40	4.5	6	1.1 (1.20-1.30)	<1.20
>40	4.5	5.5	1.1 (1.15-1.20)	<1.15

Table 2.1. SBRT PTV planning tolerances

The OAR dose constraints were pre-defined and based on the SABR consortium guidelines. As all patients had received prior irradiation, a prior radical pelvic radiotherapy dose of 50 Gy (EQD2) was assumed with a 6 month period of recovery and the final cumulative dose constraints were based on work previously undertaken by Drs Megan Llewelyn and Dr Taylor as described by Murray et al (**Table 2.2**) [101]. A successful plan was one where the PTV dose coverage and OAR dose constraints were all met.

OAR	*Constraint*	*Target (Gy)*	*Optimal (Gy)*
Bowel	***0.1cc (Dmax)***	31	-
	2cc	-	27.1
	5cc	25	18.1
	15cc	18.1	13.9
Rectum	***Dmax***	32	-
	2cc	-	30
	5cc	25	
	15cc	-	20.9
Sacral PRV	***0.1cc (Dmax)***	32	-
	3cc	-	29
	5cc	30	16.9

Table 2.2. Planning dose constraints to the OARs used for SBRT plans

2.4.2.6 SBRT Plan evaluation

Comparative analysis was carried out between each of the plans comparing tumour median dose, dose conformity, dose drop off, dose homogeneity, dose to OARs and number of successful plans.

2.4.2.6.1 PTV

The conformity of prescription dose was measured for each plan, V_{pres}, as the volume receiving prescription dose (cm^3) and V_{PTV} is the PTV volume (cm^3) receiving prescription dose.

$$Conformity\ Index\ (CI)\ = \frac{Vpres}{VPTV}$$

Dose drop-off (*R50%*) was also measured for each plan where V15 Gy is volume of body receiving 50% prescription dose divided by VPTV (x).

$$R50\%\ = \frac{V15\ Gy}{VPTV}$$

The homogeneity index (HI) was also determined for each plan as follows where the D2% is the maximum dose received by 2% of the PTV, D98% is the minimum dose received by the 98% of the PTV, and D50% is the dose received by the 50% of the PTV.

$$HI = \frac{D2\% - D98\%}{D50\%}$$

2.4.2.6.2 Organs at risk

Dose-volume histograms (DVH) for all OARs within the radiation field were plotted and analysed. This included the femoral heads, the bladder in the case of posterior PE, the rectum in anterior PE, the sciatic nerve and small bowel, if any, within 2 cm superior to the PTV.

2.4.2.7 Statistical analysis

For each case, matched pairs of treatment plans were compared using a paired non-parametric t-test to compare means. Wilcoxon signed rank tests at the 5% significance level were used for statistical comparisons. The biological equivalent dose (BED) in 2 Gy fractions (EQD2) were calculated for maximum dose points for

the OARs where D, is the total physical dose, d is the dose per fraction and a/b was dependent on the OAR being compared.

$$EQD2 = D \times \left[\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right]$$

2.5 Results

2.5.1 Whole cohort patient characteristics

Median age at time of PE was 56 years (range 24 – 83 years). Cervical cancer was the commonest presentation (47 cases, 45.2%) and the majority of the patients (57 patients, 54.8%) had a squamous histology. The median time interval between initial diagnosis or end of treatment of primary or previous recurrence and PE was 9.4 months (0.2 – 280.8). 83.7% of patients had previously received radiotherapy to the pelvis as part of treatment for their primary or recurrent disease. PE was carried out for recurrence in 66 patients (63.5%), for persistent disease in 35 patients (33.7%) and for primary treatment in 3 patients (2.9%). The type of surgery was anterior PE in 40 (38.5%) patients, posterior PE in 18 (17.3%) and total PE in 46 (44.2%) patients. 19 patients received post-PE treatment, of which 9 had radiotherapy and 7 had systemic therapy. **Table 2.3** summarises the patient and tumour characteristics in more detail.

2.5.2 Comparing histological features in patients without and with post-exenteration relapse

2.5.2.1 Lymphovascular and perineural invasion of tumour

The majority of patients (37, 71.2%) with LVSI experienced a relapse compared to 16 patients (44.4%) who did not have LVSI. The majority of patients with PNI also experienced a relapse compared to those with no PNI; 23 patients (65.7%) vs 11 (45.8%) respectively. However, LVSI was far more common in the relapsed population (58.7%) than in those without relapse (37.5%), whereas PNI was

equivalent between the relapsed (36.5%) and no relapse groups (30%) although PNI was not recorded for a large number of patients (43.2%) (**Table 2.4**).

Characteristic	n = 104	Range / %	Median
Age at exenteration		**24 – 83**	**56**
Time from last treatment to exenteration		**0.2 - 280.8**	**9.4 months**
Primary Tumour			
Cervix	**47**	**45.2%**	
Endometrial	**18**	**17.3%**	
Vaginal	**18**	**18.2%**	
Vulvar	**18**	**17.3%**	
Bartholin Gland	**1**	**1.0%**	
Ovarian	**1**	**1.0%**	
Tumour Histology			
Squamous Cell	**57**	**54.8%**	
Adenocarcinoma	**24**	**23.1%**	
Other	**22**	**21.2%**	
Tumour Diff /Grade			
Well / 1	**6**	**5.8%**	
Mod / 2	**34**	**32.7%**	
Poor /3	**56**	**53.8%**	
Prior Treatment			
Surgery Only	**17**	**16.3%**	
Previous Radiation	**87**	**83.7%**	
Tumour Status			
Primary	**3**	**2.9%**	
Persistent	**35**	**33.7%**	
Recurrent	**66**	**63.5%**	
Type of Surgery			
Anterior PE	**40**	**38.5%**	
Posterior PE	**18**	**17.3%**	
Total PE	**46**	**44.2%**	
Margin Status			
Negative	**38**	**36.5%**	
Involved	**26**	**25.0%**	
Close	**38**	**36.5%**	
LVSI			
+	**52**	**50.0%**	
-	**36**	**34.6%**	
PNI			
+	**35**	**33.7**	
-	**24**	**23.1**	

Table 2.3 Summary of all patient and tumour characteristics.
LVSI: lymphovascular space invasion, PNI: perineural invasion. +positive, -negative. Percentages may not add up to 100% due to missing data.

	LVSI - n=36 (%)	LVSI + n=52 (%)	LVSI NR n=16 (%)
Relapse	16 (44.4%)	37 (71.2%)	10 (62.5%)
Local	12 (33.3.%)	25 (48.1%)	5 (31.2%)
No Relapse	19 (52.8%)	15 (28.8%)	6 (37.5%)
Unknown	1 (2.8%)	0 (0%)	0 (0%)
	PNI - n=24 (%)	**PNI + n=35 (%)**	**PNI NR n=45 (%)**
Relapse	11 (45.8%)	23 (65.7%)	29 (64.4%)
Local	9 (37.5%)	16 (45.7%)	17 (37.7%)
No Relapse	12 (50.0%)	12 (34.3%)	16 (35.6%)
Unknown	1 (4.2%)	0 (0%)	0 (0%)
	Margin - n=38 (%)	**Margin Involved n=26 (%)**	**>0 mm ≤ 5 mm, n=38 (%)**
Relapse	20 (52.6%)	20 (76.9%)	22 (57.9%)
Local	11 (28.9%)	15 (57.7%)	16 (42.1%)
No Relapse	18 (47.4%)	6 (23.1%)	15 (21.4%)
Unknown	0 (0%)	0 (0%)	1 (2.6%)

Table 2.4 Relapse in relation to histological characteristics and margin status.
LVSI = lymphovascular space invasion, PNI = perineural invasion, + = positive, - = negative, NR = not recorded.

2.5.2.2 Surgical Margin Status

38 patients (36.5%) had a negative margin, 38 (36.5%) patients had a close margin defined as > 0 mm and ≤ 5 mm and 26 (25%) had an involved margin. 20 patients (52.6%) with negative margin relapsed and 11 of those were loco-regional. In contrast, 20 patients (76.9%) and 22 patients (57.9%) experienced a relapse in the involved and close margin group respectively. A positive margin status was twice as common in the relapsed group compared to those without relapse (31.7% vs 15.0%). Of the 42 relapsed patients with positive or close margin, 31 patients (73.8%) experienced a loco-regional relapse. **Table 2.4** summarises relapses in comparison to margin status.

2.5.3 Patient Outcomes

I used Kaplan Meier curves constructed on GraphPad Prism (version 7.04) for illustrating post-PE relapse and survival.

Median follow up was 102.9 months (2.04 – 276.49). Sixty-three patients (60.6%) experienced a relapse. Median DFS was 14.7 months and median OS was 26.1 months (**Figure 2.4**) with 52.2% and 32.1% of patients alive at 2 years and 5 years respectively. Of the relapses, 42 (40.4% of total, 66.7% of relapses) were local only – one patient had no information on relapse and was therefore censored.

There was a trend for worse DFS in involved (0 mm) or close (> 0 margin ≤ 5mm) versus those with negative (> 5mm) margin, but this was not statistically significant. There was no difference in overall survival between the two groups. The median DFS and OS for positive/close versus negative margins were 19.8 versus 13.6 months (*P*=0.09), and 24.80 versus 24.05 months (*P*=0.60) respectively.

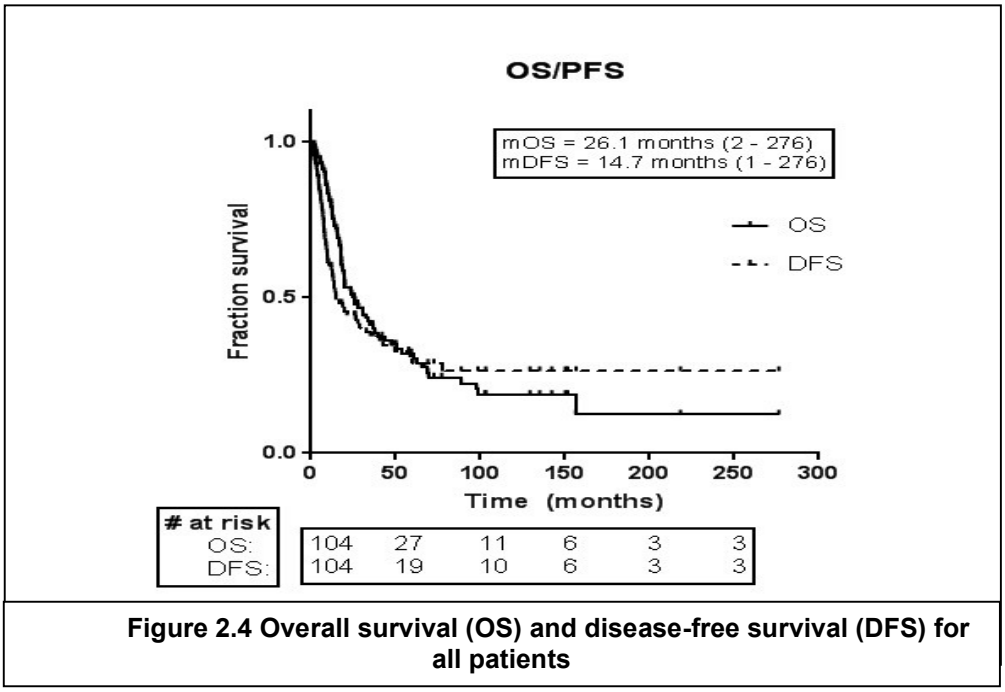


Figure 2.4 Overall survival (OS) and disease-free survival (DFS) for all patients

Loco-regional relapse was defined as post-PE recurrence within the pelvis. The Kaplan Meier 5-year loco-regional control was 66.7% for the negative margin group compared to 35.0% for the involved/close margin group with a statistically significant difference in loco-regional control between the two groups in favour of those with a negative margin (*P*=0.04; HR=0.54, 95%CI 0.30 – 0.97) - **Figure 2.5**. This provides an argument for the need of a post-operative therapeutic approach for patients with involved and close margins.

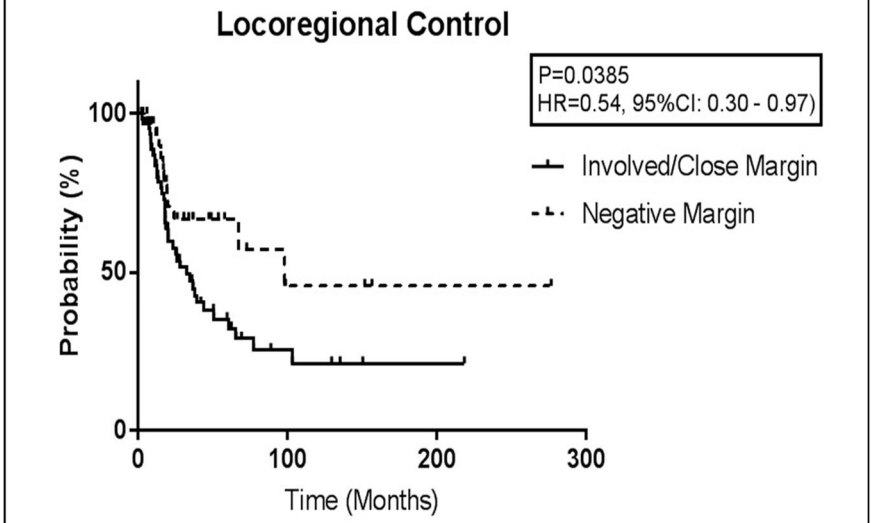


Figure 2.6 Locoregional control in relation to surgical margin status. HR = hazard ratio, 95%CI = 95% confidence interval.

Figure 2.5 Loco-regional control in relation to surgical margin status.

HR= hazard ratio, 95%CI = 95% confidence interval.

2.5.4 Patterns of loco-regional relapse

Of 63 recurrences, 21 patients (33.3%) had distant metastases (pulmonary n=10, liver n=8, bone n=2). Loco-regional relapses by anatomic site are described in **Table 2.5** and illustrated in **Figures 2.6** and **2.7**. Of the 63 recurrences, there were 26 evaluable patients and 21 patients with post-operative DICOM data to create rel_3DTVs. At median follow up of 59.4 months, irrespective of type of PE carried out, the most common site of loco-regional recurrence was central at 42% followed by 27% at pelvic side-wall, 23% anterior, 8% posterior and 19% inguinal. After anterior PE, loco-regional recurrence is predominantly central (50%), after posterior PE is predominantly PSW (50%) and after total PE is mainly anterior (40%). Rel_3DTVs were outlined for 21 patients, 15 with close or positive margins (defined above). Mean pre_3DTV was 61.2cm^3 (1.4 - 474.8cm^3) and mean rel_3DTV was 70.4cm^3 (1.3 - 436.6cm^3). With a 5mm isotropic expansion of pre_3DTV, there was overlap in 65% cases with a mean overlap volume of 14.3cm^3 (0-138.5cm^3).

Anatomic site	Number of cases (% of relapses)
Vaginal Vault/wall only	16 (25.4%)
Pelvic side wall	14 (22.2%)
Pre/Sacral	5 (7.9%)
Involving bladder (post PEs	4 (6.3%)
Involving rectum (ant PEs	4 (6.3%)
Lymph nodes only	4 (6.3%)
Perineum	1 (1.5%)
Abdominal wall	2 (3.1%)
Distant metastases only	13 (20.6%)

Table 2.5 Anatomical sites of relapse following PE.

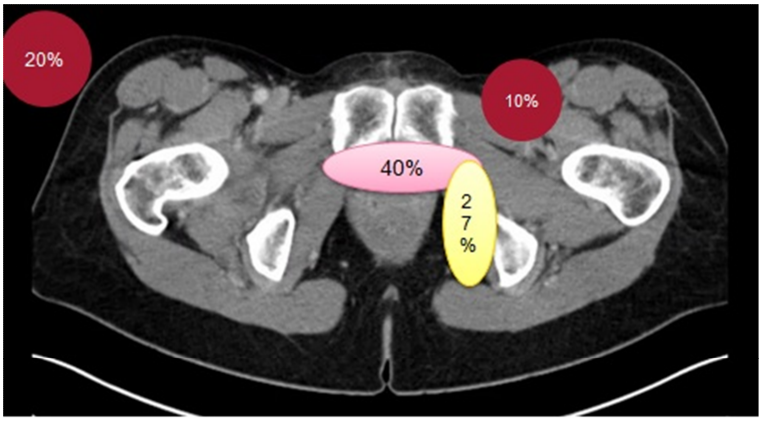


Figure 2.6 Patterns of relapse following PE for recurrent gynaecological malignancy regardless of exenteration type.

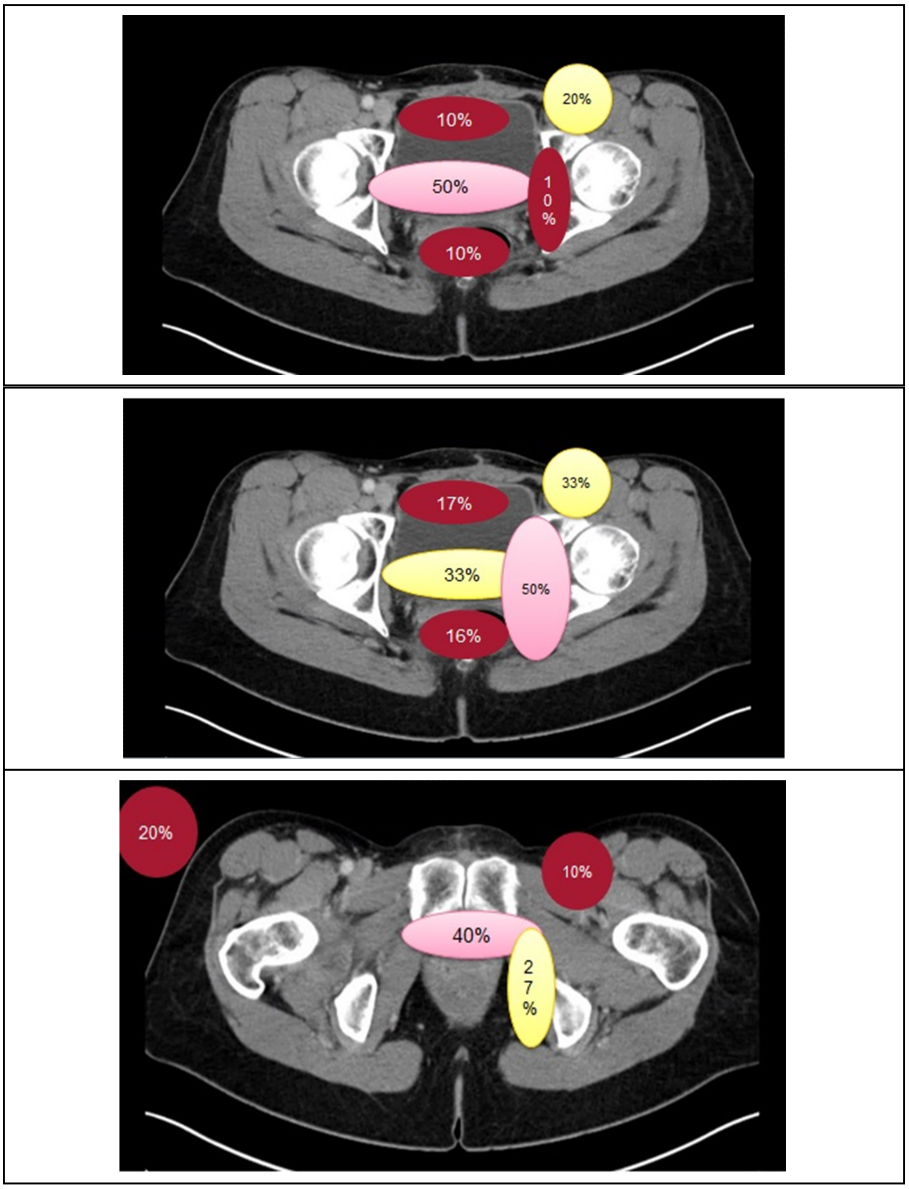


Figure 2.7 Patterns of relapse following anterior (top), posterior (middle) and total (bottom) PE.

2.5.4 Feasibility of SBRT planning

2.5.4.1 Patient characteristics

10 consecutive patients were selected with equivalent representation of the type of exenteration as per table 2.3. 6 had cancer of the cervix, 3 had cancer of the endometrium and 1 had cancer of the Bartholin gland. Six patients had total PE and 4 had an anterior PE. However, as posterior PE became less favoured over the last decade, there were no patients in this category with post-operative CT imaging available for planning.

2.5.4.2 Target volume and SBRT plan characteristics

29 plans were developed with one patient having only two plans as the pre-PE GTV was too large to define *CTV_total* for SBRT planning. Six cases had a PTV close to the sciatic nerve where the PRV_*SacralPlexus* was used for plan optimisation. The rectum was an OAR and was used for optimisation in 4 cases where an anterior PE was undertaken.

Mean PTV volumes were 70.8 cm^3 for *PTV_margin*, 155.76 cm^3 for *PTV_highrisk* and 214.89 cm^3 for *PTV_total*. Minimum dose to PTV decreased as the PTV size increased with *Dmin* for *PTV_margin*, *PTV_highrisk* and *PTV_total* at 26.2 Gy, 25.22 Gy and 24.69Gy respectively. Maximum dose to *PTV_margin*, *PTV_highrisk* and *PTV_total* was 37.47 Gy, 38.36 Gy and 38.55 Gy respectively. The mean conformity index was comparable between plans. The mean dose drop-off was lower as the PTV increased in size with the R50% for *PTV_margin*, *PTV_highrisk*, and *PTV_total* of 4.37, 4.11 and 3.78 respectively (**Table 2.6**).

	Margin	High Risk	Total
Mean PTV Vol (cm^3)	70.80	155.76	214.89
Mean Dmin (Gy)	26.27 ± 2.74	25.22 ±2.58	24.69 ±3.2
Mean Dmax (Gy)	37.47 ±1.97	38.36 ±1.84	38.55 ±2.65
Mean CI100% (<1.15)	1.08 ±0.10	1.02 ±0.07	1.02 ±0.07
Mean R50% (<4.5)	4.37 ±1.07	4.11 ±0.70	3.78 ±0.48

Table 2.6 Target volume and SBRT plan characteristics

2.5.4.3 Comparing mean OAR doses between plans

Dose to OARs increased with the larger CTV_*highrisk* and CTV_*total* volumes. **Table 2.7** summarises the mean OAR dose in relation the target OAR dose constraints.

	Margin	High Risk	Total
OAR (target Gy)		Mean dose	
Bowel			
15.0cm^3 (18.1)	11.09 ±7.00	17.27 ±8.68	20.29 ±10.37
5.0 cm^3 (25)	16.77 ±8.68	24.48 ±7.26	26.13 ±8.05
0.5 cm^3 (31)	26.45 ±7.79	31.53 ±2.58	32.37 ±2.62
Nerve			
5.0 cm^3 (30)	16.79 ±9.14	23.95 ±7.81	22.52 ±6.47
0.5 cm^3 (32)	22.74 ±8.88	28.25 ±5.25	27.38 ±5.68
Rectum			
5.0 cm^3 (25)	21.35 ±9.00	28.43 ±3.91	30.83 ±2.57
0.5 cm^3 (32)	26.45 ±10.81	31.53 ±1.01	32.37 ±1.05

Table 2.7 Mean OAR doses in relation to target dose constraints

Table 2.8 shows a summary of plans that met the planning target and optimal OAR dose constraints. **Figure 2.8** shows two SBRT plans for the same patient where all target and optimal OAR dose constraints were met for PTV_margin and not met for PTV_total due to proximity of rectum and sciatic nerve.

	Margin	High Risk	Total
Meeting "target" OAR			
All OARs (n)	5	0	0
Bowel (10)	5	3	2
Nerve (6)	5	4	1
Rectum (4)	2	0	0
Meeting "optimal" OAR			
All OARs (n)	4	2	0
Bowel (10)	5	2	1
Nerve (6)	3	1	0
Rectum (4)	2	1	0

Table 2.8 Number of plans meeting the planning target and optimal OAR dose constraints

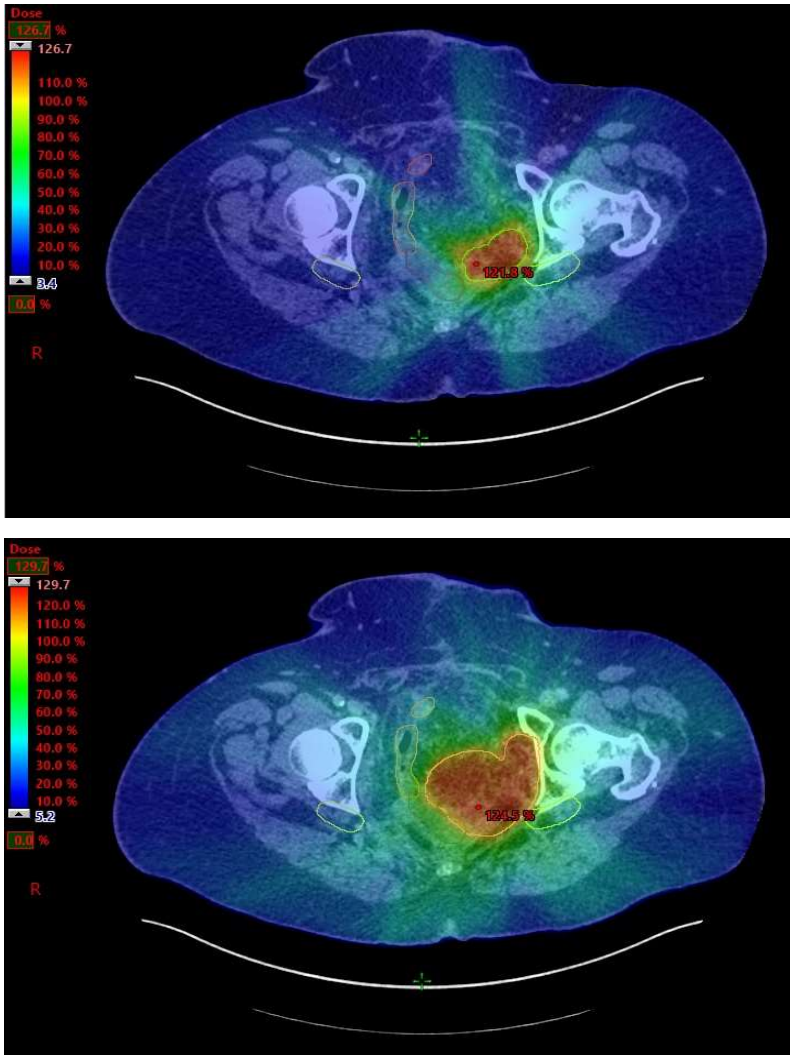


Figure 2.8 Two SBRT plans for the same patient with anterior PE where all target and optimal OAR dose constraints (table 2.2) were met for PTV_margin (top) and not met for PTV_total due to proximity of rectum and sciatic nerve (bottom).

2.5.4.4 Comparing target OAR doses

All target OAR dose constraints were met in 5 cases (50%) for PTV_*margin* with no plans achieving this for PTV_*highrisk* or PTV_*total*. For PTV_*margin*, the bowel was the dose limiting OAR in 5 cases (50%), the sciatic nerve in 1 case (16.7%) and the rectum in 2 cases (50%). For PTV_*highrisk*, the bowel was the dose limiting OAR in 7 cases (70%), the sciatic nerve in 2 cases (33.3%) and no plans met the target dose constraint for the rectum. For PTV_*total*, the bowel was the dose limiting OAR in 8 cases (80%), the sciatic nerve in 5 cases (83.3%) and the rectum in all cases. **Figure 2.9** demonstrates the D0.5cc for each of the plans.

2.5.4.5 Comparing optimal OAR doses

All optimal OAR dose constraints were met in 4 cases for PTV_margin with only 2 cases achieving this for PTV_*highrisk* and no cases achieving it for PTV_*total*. It is worth noting that a higher proportion of plans met the optimal but not the target dose constraint because the optimal 2cc dose constraint was met in 2 cases that did not meet the target Dmax i.e. they were still clinically unacceptable plans. For PTV_*margin*, the bowel was the dose limiting OAR in 6 cases (60%), with the sciatic nerve the limiting OAR in 3 cases (50%) and the rectum in 2 (50%). For PTV_*highrisk*, the bowel was the dose limiting OAR in 8 cases (80%), the nerve in 5 cases (83.3%) and the rectum in 3 cases (75%). For PTV_*total*, the bowel was the dose limiting OAR in 8 of 9 cases (88.8%) with no plans meeting the optimal OAR dose constraints for the nerve or the rectum (c.f. 2.7).

2.5.4.6 Feasibility of SBRT post-PE

The results of the dosimetric study demonstrate that defining the CTV is key for determining the feasibility of delivering SBRT post-PE. Using the smaller of the targeted volumes, CTV_*margin*, allows for better plan characteristics including CI and R50% and allows SBRT delivery with a higher likelihood of respecting the OAR dose constraints. SBRT can also be delivered in a large proportion of plans but only for target OAR dose constraints as only a small proportion of plans were successful with CTV_*highrisk*. With no plans meeting all target or optimal dose constraints and only two plans meeting the bowel OAR, using a target volume with the pre-PE GTV i.e. CTV_*total* is not feasible.

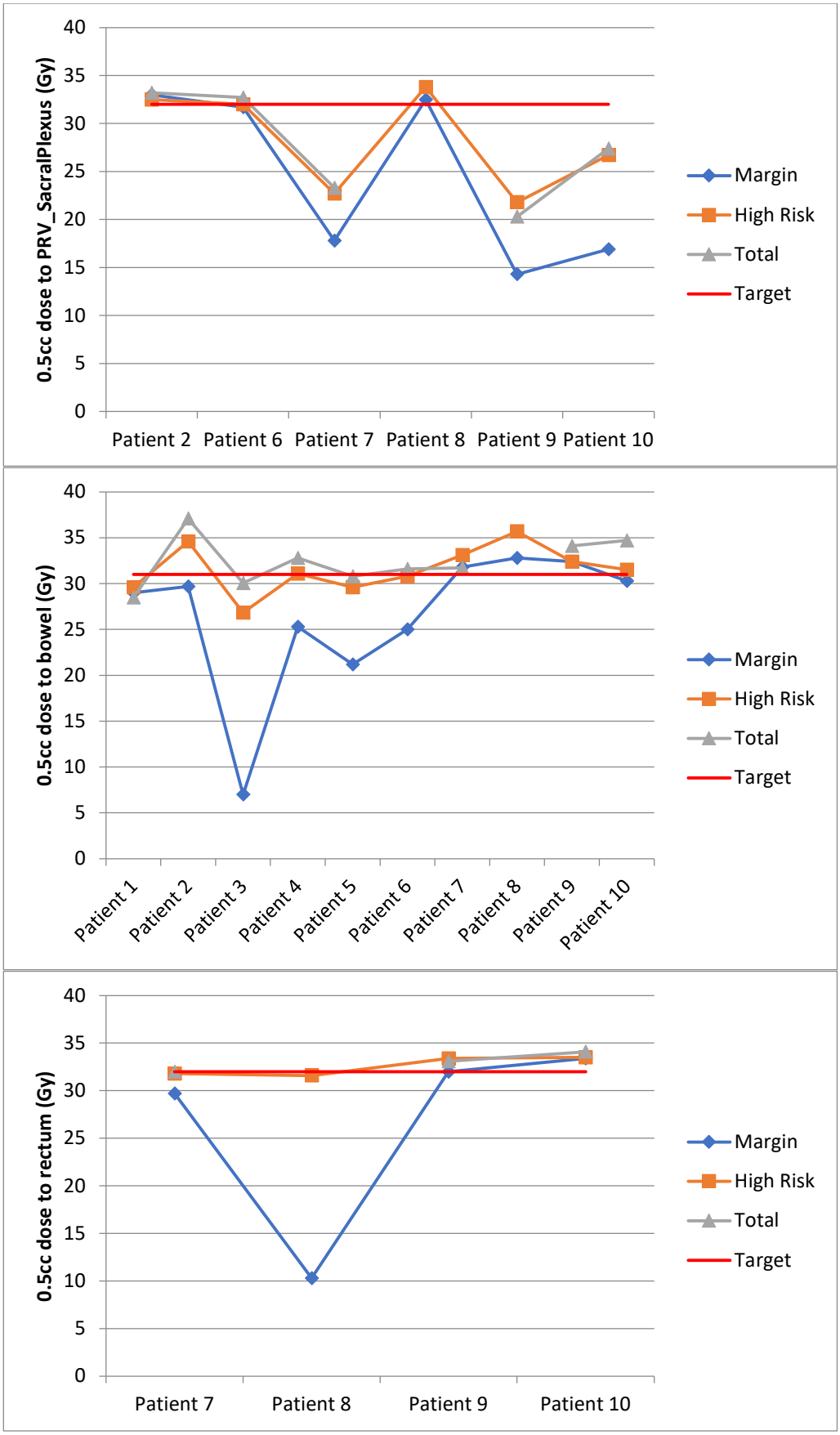


Figure 2.9 0.5cc dose to each of the OARs and the target dose constraints in red.

2.6 Discussion

2.6.1 Location of pelvic recurrences and their management

It is well documented that following primary treatment of gynaecological malignancies, recurrences are either local or distant. Although it is the distant metastases that are the primary determinant of overall survival (53% of patients with endometrial cancer who died of disease had metastases beyond the pelvis at the time of death), it is the local recurrence that causes the greatest morbidity and determines the evolution to distant metastasis. In a Danish national cohort study of nearly 5000 patients with endometrial cancer, 623 of whom were high-risk and did not receive adjuvant treatment, there were significantly more isolated vaginal recurrences in non-irradiated high-risk patients [102]. Control of local recurrence is therefore crucial.

Genetic and molecular targets have been identified as predictive models of recurrence. Lee et al [103] constructed a prognostic scoring model from a 12-gene selection to predict recurrence in cervical cancer. In endometrial cancer, the Cancer Genome Atlas Collaborative (TCGA) and the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) have identified molecularly distinctive subgroups for prognostication including MMR, p53 and POLE mutation status [104]. Several studies have also examined factors that affect survival after gynaecological cancer recurrence. In isolated pelvic recurrence, tumour volume appears to the be the strongest correlate with patients with poorer performance status, older age and previous irradiation likely to have worse survival [66].

Pelvic recurrences occur either centrally or on the pelvic side-wall. Initial attempts at curative treatments for these recurrences involve exenterative surgery for centrally relapsed disease and re-irradiation for pelvic side-wall disease, where combined operative and radiotherapeutic approach (CORT) have been attempted [105]. With the improvement in surgical techniques, the ability to include pelvic side-wall disease in surgical exenterative procedures has gained more traction. However,

these procedures are technically challenging because of adherence to neighbouring nerves, vessels and muscle, so that margins may be close and the risk of further recurrence remains high.

2.6.2 Management of post-PE relapse

My data indicates a relapse rate of 60.6% after a median follow-up of 102 months, with a median DFS of 14.7 months and an OS of 26.1 months. This is a large 25-year experience. In 2005, Roswell Park published their 20-year experience of 48 women treated with PE for recurrent gynaecological malignancy between January 1980 and December 1999 [8]. The majority of patients had received prior radiation therapy. They also demonstrated a post-PE recurrence rate of 60%. However, the median OS of their patient cohort was 35 months, and the DFS was 32 months. It is likely that in this cohort, who preceded our cohort by 20 years, advancements in surgical techniques, and increasing patient expectation of curative procedures, resulted in greater inclusion of patients with inherently poorer tumour biology into this study. This is further borne out by the Roswell Park data where 8 patients received intra-operative radiation, but despite this did worse (median survival 11.3 vs. 35 months, P=0.003), indicating that those at high enough risk to warrant radiotherapy had outcomes similar to ours. In a univariate analysis of their data, there was no association between the type of PE and recurrence. Another series of 100 cases, where 45 were for relapsed disease, mainly gynaecological, 18 (40%) relapsed by 18 months [106]. There are other small early series describing relapse post-PE. In one such study, in cervical cancer, where the central recurrence was treated with PE (n=14) and the side-wall recurrences with radiation therapy (n=18) after a median observation of 24 months (range, 5-48 months) 7 patients with central recurrences and 11 patients with pelvic wall recurrences had progressive disease in the pelvis and/or distantly but interestingly, the site of recurrent tumour progression (local vs. distant) was similar in both groups. Only size of the recurrent

tumour significantly influenced survival in the multivariate Cox analysis [107]. Compared to these series, my data comprises a much larger cohort, in whom PE was performed at a tertiary oncology centre, by a specialist surgeon, and exploits the advancements in surgical techniques over the subsequent 2 decades. Despite this, the outcomes were very similar, which further reinforces the adverse biology of these tumours and the need for additional measures to avoid post-PE recurrence in these patients.

A study reporting the experience at The Memorial Sloan Kettering attempted to address post-PE recurrence with the use of adjuvant chemotherapy [108]. In their series, treated between January 2005 and February 2011, patients were referred for 4 to 6 cycles of platinum-based doublet chemotherapy based on surgeon's discretion and/or presence of high-risk features: positive margins, positive lymph nodes, and/or lymphovascular space invasion. Of 42 patients who underwent PE during the study period, 11 (26%) were referred for adjuvant chemotherapy, 8 actually received it and 7 completed the course. Median follow-up time was 25 months (range, 6-56 months). The 3-year DFS and OS of the 8 patients who received chemotherapy were 58% (CI 95% confidence interval, 18%-84%) and 54% (95% confidence interval, 13%- 83%), respectively. Although these numbers are small, they lend weight to the argument for additional treatment in high-risk patients post-PE in order to improve survival.

2.6.3 Feasibility of SBRT post-PE

SBRT has the capability of delivering a highly conformal dose of radiation to the target volume. Moreover, it can be adapted to deliver a small focused CTV covering the margin only and a larger CTV that includes areas at high-risk of relapse as well as the pre-PE tumour volume. I therefore explored this potential in a planning study for treating patients with locally recurrent gynaecological cancer who were deemed potentially curable and had therefore undergone major pelvic surgery. SBRT has

not previously been used in this context because of lack of evidence of efficacy, and reluctance to incur further morbidity in patients with a previously irradiated pelvis. A key challenge, therefore, was in carefully defining the area to be irradiated to avoid these risks while maximising radiation coverage of the area at highest risk of relapse.

Contouring the target in the post-surgical pelvis can be fraught with difficulty. Imaging appearances are variable with the time from surgery. Immediately following surgery, fluid collections and haematomas confound the appearances particularly on CT. Availability of MRI has hugely improved the assessment of the post-surgical pelvis [109]. I performed my contouring largely on CT scans but had MRI available in all cases for reference, and used these images alongside the CT. The images were done at 2 months (range 1 – 4 months) post-PE and so post-operative changes are unlikely to have affected the results of contouring.

Defining the post-operative high-risk bed was challenging due to lack of anatomical boundaries usually created by removed viscera. The challenge was greatest in anterior PEs where the predominant pattern of relapse was central. In the case of total PE where relapse was more likely in the PSW, delineating of the high risk area was facilitated by the PSW and anterior pubic bones which acted as a surrogate landmark to the area most at risk of relapse- the deep retropubic space.

Moreover, and with advances in intra-operative histological assessment and improved surgical experience, it is now possible to insert radio-opaque fiducial markers at the time of surgery that can help with target delineation on post-operative imaging. This is increasingly being adopted by the RMH and other specialist cancers centres in this setting and is well established in other tumour types were adjuvant radiotherapy is indicated such as in breast cancer.

2.6.4 Coverage required vs. toxicity for treating high-risk patients post-PE

There are no previous reports of how best to define the regions of high-risk post-PE. Although there is overwhelming evidence that a positive or close surgical margin causes a statistically significant reduction in loco-regional control [10, 96], the extent of the microscopic disease at a positive margin remains difficult to visualise with current imaging methods, and hence the CTV that is most likely to result in effective disease control remains to be established. Nevertheless, it was possible to construct plans that met the OAR planning criteria, despite the previous pelvic radiation. The lack of significant difference in dose to the OARs between plan_*margin* and plan_*high risk* indicates that a larger, but still targeted, CTV can be considered post-operatively to reduce the risk of recurrences at the edge of the field without incurring undue toxicity. This is particularly true following total PE where the lack of pelvic organs made planning and dose constraints easy to achieve. Where SBRT has been delivered to locally recurrent cervical or endometrial cancers out of context of PE, the rate of late toxicity > grade 2 has been shown to be 25% at 3 years (grade 4 intestino-vaginal fistula and grade 4 small bowel ileus) [69].

2.6.5 Addressing study limitations and future recommendations

This study is limited by its single-centre, retrospective design. However, PE is a highly specialised surgical procedure, only performed at a limited number of centres nationally. Selection of patients for this procedure is strongly led by surgical skill and experience, so pooling data from multiple centres is difficult. Even with pooled data, the number of cases of recurrent gynaecological malignancy suitable for PE is low. Lessons learned from this experience will enable selection of patients for appropriate adjuvant SBRT.

I undertook a limited planning study for determining feasibility of making SBRT plans in patients with anterior, posterior and total PE. Contouring the surgical bed was done by 2 experienced operators working at a tertiary oncology centre where the experience of treating recurrent disease and viewing planning scans in patients with multiple previous therapies is high. Establishing whether this technique is more widely applicable amongst radiation oncologists may be useful but difficult to justify as PE is only performed at specialist centres. A simple method to improve delineation of the surgical bed would be with the use of radio-opaque fiducials inserted at the time of surgery. Post lumpectomy in breast cancer patients where adjuvant therapy is planned [110], fiducials improve the consistency of CTV delineation and hence the delivery of radiotherapy to the surgical bed [111]. Significant clip migration or displacement is not problematic [112] but needs to be accounted for [113].

Multimodality imaging may also be used to visualise residual or recurrent tumour. In the future, techniques such as PET-MR may provide a combination of the anatomical definition needed together with functional data on the location of likely foci of residual or further recurrent disease [114, 115]. Imaging also adds information on the development of distant metastases. Where there is evidence of the appearance of distant metastases, the decision to deliver further loco-regional control may be revised. Imaging therefore should also be incorporated appropriately into the decision pathway particularly if there are significant time delays before initiating treatment.

2.7 Key Points

- Relapse following PE for recurrent gynaecological malignancy occurs mainly loco-regionally within the pelvis -anteriorly and centrally (40%) and on the PSW (27%); 20% of relapses are at distant sites.

- 5-year loco-regional control was 66.7% for the negative margin group compared to 35.0% for the involved/close margin group, which was statistically significant.
- There was a trend for worse DFS in involved (0 mm) or close (> 0 margin ≤ 5mm) versus those with negative (> 5mm) margin, but this was not statistically significant. There was no difference in overall survival between the two groups. The median DFS and OS for positive/close vs. negative margins were 19.8 vs. 13.6 months (*P*=0.09), and 24.80 versus 24.05 months (*P*=0.60) respectively.
- It was feasible to deliver SBRT after anterior and total PE. The dose to OARs was comparable when the CTV was planned to the positive margin, CTV*_margin*, compared to a larger targeted CTV*_highrisk* encompassing the high risk area bordering the margin.
- SBRT was not feasible when a target volume encompassing the pre-exenterative tumour volume, CTV*_total* was used.
- In post-exenterative SBRT, coverage of the high risk area is optimal but further prospective studies are needed to ascertain toxicity and determine efficacy.

Chapter 3 – A comparison of methods for escalating radiotherapy dose to recurrent gynaecological malignancy not suitable for brachytherapy

3.1 Introduction

In patients with cervical or endometrial cancer treated with surgery alone, 10-15% experience an isolated pelvic recurrence [57]. Treatment usually involves EBRT to the pelvis including pelvic nodes and then a boost to macroscopic disease. The boost is most commonly delivered with intracavitary or interstitial brachytherapy for central disease [116, 117]. Where brachytherapy is not feasible, for example because of anatomical location of the pelvic recurrence, EBRT is considered. The total deliverable dose with EBRT to macroscopic disease is usually limited to 60 – 65 Gy due to the proximity of OARs. However, survival rates of recurrent cervical and endometrial cancer treated with EBRT because the disease is bulky or lateral (0 – 30%) are lower compared to those with central disease in whom a brachytherapy boost is feasible (40 – 75%). The likely cause of these poorer outcomes is the lower delivered dose to macroscopic disease [118-120].

For bulky recurrences, further refinements that allow dose escalation (such as SBRT) or alternatives (such as PBT) are being explored. Outcomes for bulky recurrent tumours not suitable for brachytherapy could potentially be improved if it were feasible to deliver a higher dose with EBRT. Recent advances in radiotherapy techniques mean that there are several approaches that could be applied. IMRT (including VMAT) is the standard EBRT technique used for treating gynaecological cancer as it reduces toxicity because increased dose conformity avoids the OARs.

3.1.1 Simultaneous Integrated boost IMRT

IMRT provides the option of “dose painting” delivering an integrated boost to macroscopic disease while delivering a lower dose to sites at risk of microscopic spread. This approach is established for boosting involved lymph nodes with doses of 55 - 57.5 Gy for lymph node positive cervical cancer while 45 Gy in 25 fractions is delivered to the larger pelvic volume. SIB-IMRT allows the delivery of a single plan throughout the course of treatment and can accelerate treatment to achieve a shorter total treatment time than with a sequential approach. However, when designing a SIB-IMRT treatment it is important to consider the potential changes in size and position of tumour throughout treatment and to account for this with sufficient margins since tumour shrinkage, of up to 65%, may result in a high dose delivered to OARs while too small a margin can result in a geographical miss. This can be overcome by using an adaptive approach where a new plan can be depending on tumour regression during treatment which may be up to 65% in cervical cancer.

3.1.2 Sequential Boost

The conventional method for boosting disease with EBRT is to use a second phase of treatment where the target volume comprises the macroscopic disease (GTV phase 2) with a margin added that accounts for motion and set-up, (depending on the method of treatment verification), to create the planning target volume. This would typically involve a conformal or IMRT/VMAT plan delivering 15 - 20 Gy in addition to the 45 Gy from the phase one treatment [121]. SBRT allows conformal hypofractionated dose escalation in this way with OAR sparing in a similar fashion to brachytherapy [122-124]. The use of on-line / near on-line image guidance allows a smaller GTV-PTV margin to reduce the OAR dose, while the option of delivering a much higher central dose in a similar manner to brachytherapy can potentially

increase median tumour dose. SBRT typically uses a higher dose per fraction so radiobiologically the effective dose is escalated.

Previous dosimetric studies by Dr M Llewelyn and Dr A Taylor have demonstrated feasibility of isotoxic planning of an SBRT boost using the established intrauterine brachytherapy OAR dose tolerances [58]. They also demonstrated equivalence of Cyberknife™ and linear accelerator delivered SBRT for recurrent gynaecological cancer, and assessed impact of different GTV-PTV margins on the deliverable dose. Internationally, several retrospective case series have demonstrated excellent local control rates > 70% with low toxicity in both primary and recurrent gynaecological cancer not suitable for brachytherapy, albeit with wide variation in the dose and fractionation schedules [70, 125-127]. Even in the UK, the variation in radiation therapy practice of treating radiation-naïve recurrent gynaecological malignancy remains unknown and undocumented.

PBT is another treatment alternative whose utility and role in recurrent gynaecological malignancy needs to be established. PBT, with its characteristic Bragg peak, provides high tumour coverage while reducing dose to OARs compared to recommended MRI-guided brachytherapy [22, 128, 129]. In the UK, the use of PBT, has not currently been available to patients with recurrent gynaecological malignancy. However, with one UK NHS proton beam centre open and another due to open later this year [130], new opportunities will arise. Furthermore, intensity modulated PBT (IMPT) can be used to simultaneously modulate beam intensity while taking into account normal tissue tolerance and tumour coverage [131]. To date, there are no studies comparing the potential dose to the target and to OARs of SBRT techniques versus PBT when treating isolated pelvic recurrences of gynaecological tumours not suitable for brachytherapy.

3.1.3 OAR dose constraints

Intrauterine brachytherapy has established OAR dose tolerances for cervical cancer, which are used for isotoxic planning where the GEC-ESTRO group have developed international standards with 2cc doses for the sigmoid/bowel, rectum, bladder and related these to late toxicity. A similar approach is being proposed for use of brachytherapy following hysterectomy. In this scenario the OARs are closer to the target volume after the surgery so that tolerances are likely to be different.

In comparison, there are no established and validated normal tissue dose constraints for EBRT in recurrent gynaecological tumours in a post-PE context. It is possible to extrapolate evidence from EBRT doses used for other pelvic tumours. However, in recurrent gynaecological tumours, the combination of previous radiotherapy to pelvic nodes, the impact of prior surgery, the use of concurrent chemotherapy and patient co-morbidities have a profound effect on toxicity profiles and may be limiting. A literature review of the dose constraints used for pelvic tumours and any clinical outcome data was undertaken (**Appendix 3.1)** to inform the OAR dose tolerances for the dosimetric work described in this Chapter.

3.2 Aims

In radiation-naïve recurrent gynaecological cancer:

1. To establish current UK radiation therapy practice for treating patients with radical radiotherapy when brachytherapy is not feasible.
2. To compare a simultaneous integrated boost versus sequential boost approach for external beam radiotherapy for central and pelvic side wall recurrences
3. To compare the doses deliverable with VMAT, SBRT and PBT boost techniques.

3.3 Establishing current UK radiation therapy practice for treating radiotherapy-naïve recurrent gynaecological cancer not suitable for brachytherapy

3.3.1 Feasibility questionnaires

A feasibility questionnaire was sent to multiple oncology centres nationally who had expressed a potential interest in participating in a multicentre trial of SBRT for treating radiotherapy-naïve recurrent gynaecological cancer. This was done in order to ascertain current national practice in treating recurrent gynaecological cancer before setting up a prospective trial. The questionnaire aimed to determine:

- Current practice in treating this group of patients
- The extent and experience of using SBRT in treating recurrent gynaecological cancer
- The clinical need for a prospective trial
- Feasibility of recruitment into such a trial by identifying the number of eligible patients currently treated at each centre

3.3.2 Questionnaire Results

The questionnaire, (**Appendix 3.2**), was sent to 17 centres (including RMH) across the UK in late 2017. In England this was to those participating in the SABR commissioning through evaluation programme (CtE) [130]. There were 9 responses (52.9% response rate). One of these centres indicated that they would be interested in partaking in a prospective trial, but they did not complete the questionnaire. **Table 3.1** summarises responses from 8 centres that responded.

	Barts	UCLH	Guy's	Leeds	Christie	Beatson	Velindre	RMH
Current Treatment Standard – Phase 1								
Technique	VMAT	SIB-VMAT	VMAT	VMAT	VMAT	VMAT	EBRT	VMAT
Dose	45-50 Gy in 25 F	45-50.4 in 25-28 F to pelvis + SIB boost 60-66 Gy to GTV	50.4 Gy in 28 F	45 Gy in 25 F	45 Gy in 25 F	45 Gy in 25 F	45 Gy in 25 F	45 Gy in 25 F
Nodal Boost	Yes	Yes	Yes	No	No	NR	No	Yes
Current Treatment Standard – Phase 2								
Technique	VMAT	VMAT - If SIB unfeasible	VMAT	3D Conformal	3D Conformal	NR	EBRT	VMAT
Dose	15-20 Gy in 8-10 F	10 -18 Gy in 5-10 F	15 Gy in 8 F	18 Gy in 10 F	20 Gy in 10 F	-	18 Gy in 10 F	19.8 Gy in 11 F
Current SBRT Practice								
Use of fiducial markers	No	No	No	No	No	No	No	Yes
Established for gynae cancers	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes
CtE	NR	Yes	Yes	Yes	NR	NR	NR	Yes
SBRT Technique	CK	Linac	Linac	Linac	Linac	NR	Linac	CK
Current SBRT indications								
Re-irradiation: sidewall	✓	✓	✓	✓				✓
Re-irradiation: central pelvis	✓		✓					✓
Primary: sidewall								
Primary: central								
Nodal metastasis	✓		✓	✓	✓		✓	✓
Trial Feasibility								
Estimated number of eligible patients per annum	4	2 - 3	4	5	20	5 - 7	6	6 - 10
Enough data to randomise?	No	No	No	No	No	No	No	No
Competing studies?	No	No	No	No	No	NR	No	No

Table 3.1 Summarised responses to questionnaire indicating current UK practice for treating radiation-naïve pelvic recurrences of gynaecological malignancy.

The current standard across 5 of the 8 centres for treating isolated recurrent gynaecological tumours not suitable for brachytherapy is with two-phase EBRT. One centre used simultaneous integrated boost (SIB) to boost dose to tumour to 60-66 Gy (EQD2) but adopted a two-phase treatment if SIB was not feasible. Three centres included a nodal SIB as part of phase 1. For phase 2, centres boosted the tumour with 10 – 20 Gy in 5-10 fractions using either VMAT/IMRT or 3D conformal radiotherapy to a total dose of up to 64.4 Gy (EQD2). None of the centres used fiducial markers routinely for SBRT but most were willing to consider it as part of a trial. CyberKnife was used to deliver SBRT in two centres, while the remaining centres used linear accelerators. 6 of 8 centres used SBRT to treat recurrent nodal metastases, 5 for re-irradiation of pelvic sidewall disease and 3 for re-irradiation of central pelvic disease. Not unexpectedly, SBRT was not used by any of the centres to treat primary disease not suitable for brachytherapy as this would be outside the CtE criteria and NHS funding indications.

All centres indicated that there was an unmet clinical need for dose escalation with stereotactic radiotherapy with no current competing UK trials. There was consensus that there was currently paucity of data on outcomes and toxicity. A two-arm randomised trial design was favoured.

3.4 Dosimetric comparison of integrated-boost and sequential boost radiotherapy techniques for treating recurrent gynaecological cancer

Data from the questionnaires (**Table 3.1**) indicated that there is a wide variation in the radiotherapy technique used to achieve this. I therefore assessed potential dose and fractionation schedules to optimise tumour dose while aiming to meet OAR dose constraints.

3.4.1 Patient Characteristics

I included 20 patients for this planning study: 10 patients with centrally recurrent disease (CRD) and 10 patients with pelvic side wall disease (PSWD). These were selected consecutively from a cohort of patients with recurrent gynaecological cancer treated with radiotherapy at the RMH gynae-oncology department. All patients had prior surgery at the time of recurrence and were radiation naive. Patients previously had a baseline radiotherapy planning CT scan (RTp-CT) for planning the phase 1 pelvic radiotherapy and a repeat RTp-CT either towards the end of the phase 1 of treatment or within 4 weeks of completing radiotherapy. Only the primary RTp-CT was used for all the planning studies including for sequential plans. Baseline MRIs were also fused using rigid bone matching on the RTp-CT to aid tumour contouring as detailed in Chapter 2 (cf. 2.4.2.2). RTp-CT had been carried out in the supine position with contrast as per RMH radiotherapy treatment protocol.

3.4.2 Target volume and OAR delineation

The Radiation Therapy Oncology Group (RTOG) consensus guidelines and local RMH protocol for post-operative radiotherapy were followed for delineation of the clinical target volume (CTV) and OARs. The OARs contoured included individual bowel loops the rectum, bladder and femoral heads. In PSWD cases, the sciatic

nerve was also contoured as per established guidelines [132]. For the purpose of this study, boost volumes for any involved regional or para-aortic (PA) nodes were not created. All contours were reviewed and approved by Dr Alex Taylor. **Table 3.2** summarises the guidelines used for creation of the contours.

Target site	Definition
Common iliac lymph nodes	From 7 mm below L4–L5 interspace to level of bifurcation of common iliac arteries into external and internal iliac arteries
External iliac lymph nodes	From level of bifurcation of common iliac artery into external artery to level of superior aspect of femoral head where it becomes femoral artery
Internal iliac lymph nodes	From level of bifurcation of common iliac artery into internal artery, along its branches (obturator, hypogastric) terminating in paravaginal tissues at level of vaginal cuff
Upper vagina	Vaginal cuff and 3 cm of vagina inferior to cuff
Parametrial/paravaginal tissue	From vaginal cuff to medial edge of internal obturator muscle/ischial ramus on each side
Presacral lymph nodes	Lymph node region anterior to S1and S2 region

Table 3.2 Guidelines for outlining from RTOG Clinical Consensus document
Source: RMH radiotherapy treatment protocol for gynaecological cancer

3.4.2.1 Gross Tumour Volume (GTV)

The primary gross tumour volume (GTVp) was outlined on the RTp-CT with the aid of bone-matched fusion of MRI where available.

3.4.2.2 Clinical Target Volumes (CTV)

The nodal CTV (CTVn) was delineated using the blood vessels (common, internal and external and obturator) as a surrogate target with a 7 mm margin subtracting anatomical borders such as bone and muscle. The clinical target volume (CTV) included the CTVn, GTVp, vaginal cuff, parametria and upper portion of the vagina (**Table 3.2**).

3.4.2.3 The planning target volume (PTV)

I created three different tumour PTVs (PTV(p)): PTV_SIB, PTV_sVMAT and PTV_SBRT. For CRD, PTV_SIB and PTV_sVMAT were created using GTVp and a 12 mm isotropic expansion while for PSWD I used a 10 mm expansion as the

disease is anatomically less mobile. For SBRT plans, as image guidance and daily matching using fiducials would be implemented, a tighter margin of 5 mm isotropic expansion of the GTVp was used to create PTV_SBRT for both CRD and PSWD. The nodal PTV, PTVn, was created by expanding CTVn with a 7 mm isotropic margin. The PTV45 was used as the planning PTV for the 45/48Gy dose level for SIB and sVMAT plans and was created by combining PTVn with PTV(p).

3.4.2.4 Planning volumes to aid optimisation

To improve PTV dosimetry during IMRT optimisation, I created a dose-limiting structure for all nearby OARs, including the bladder (RA_bladder), bowel (RA_bowel) and rectum (RA_rectum). These were created by subtracting the PTV(p) from the OAR structure and cropping an additional 2 mm as per established IMRT regional optimisation methods (**Figure 3.1**). I also created dose limiting structures for SIB plans, RA_PTV_SIB to improve the dose gradient by subtracting the PTV_SIB from PTV45 and cropping an additional 2 mm margin.

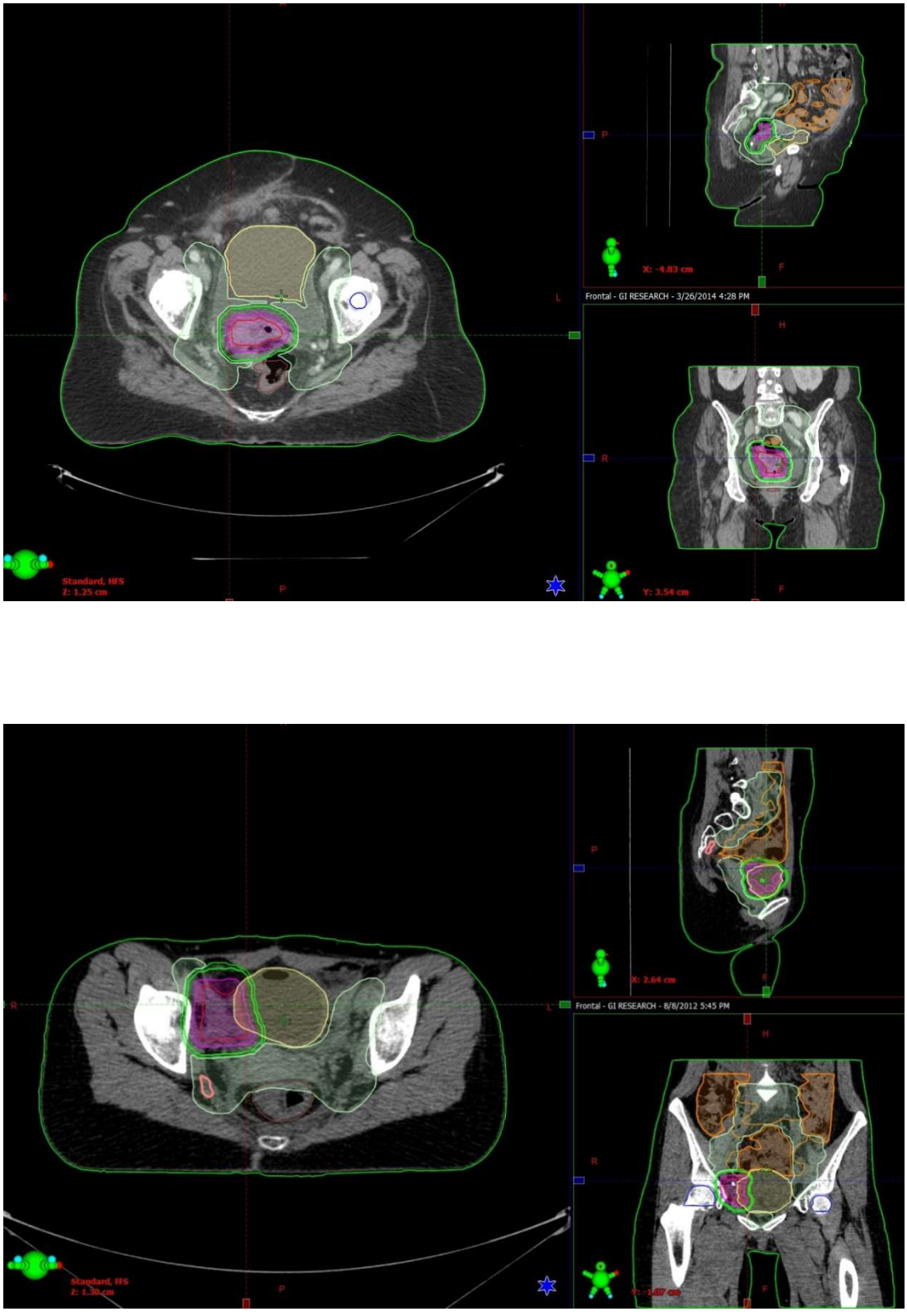


Figure 3.1 SBRT planning for central pelvic (top) and pelvic side-wall (bottom) disease.

The GTV outline is shown in red, the PTV_SBRT in magenta, PTV_SIB in green, CTVn in pastel green, the bladder in yellow, the rectum in brown and the sciatic nerve in pink.

3.5 Treatment planning techniques

Table 3.3 shows the 5 different dose levels and the EQD2 doses delivered to the tumour and the OARs when a dose and fractionation schedule is selected to match the current standard of sequential VMAT.

	CTV	SIB or Seq Boost	Tumour (EQD2 10)	OAR (EQD2 3)	OAR (EQD2 2)	Total time
seqVMAT65	45 Gy in 25 Fractions	45 Gy + 20 Gy in 10 F	64.3 Gy	63.2 Gy	57.8 Gy	7 weeks
SIB55	45 Gy in 25 Fractions	55 Gy in 25 Fractions	55.9 Gy	57.2 Gy	66.0 Gy	5 weeks
SIB60	45 Gy in 25 Fractions	60 Gy in 25 Fractions	62 Gy	64.8 Gy	72.8 Gy	5 weeks
SIB65	48 Gy in 30 Fractions	65 Gy in 25 Fractions	65.9 Gy	67.2 Gy	67.7 Gy	6 weeks
seqSBRT65	45 Gy in 25 Fractions	45 Gy + 20 Gy in 5 F	67.6 Gy	71.2 Gy	72.8 Gy (1.1 RBE)	6-7 weeks
seqPBT65	45 Gy in 25 Fractions	45 Gy + 20 Gy in 5 F	67.6 Gy (1.1 RBE)	71.2 Gy (1.1 RBE)	72.8 Gy (1.1 RBE)	6- 7 weeks

Table 3.3 Radiation dose and fractionation schedule for each dose escalation technique for both central and pelvic side wall disease.

3.5.1Planning techniques

3.5.1.1 SIB Treatment plans

Three dose levels of 55 Gy in 25 Fractions, 60 Gy in 25 Fractions and 65 Gy in 30 Fractions were chosen for planning with EQDs of 55.9 Gy, 62.0 and 65.9 Gy respectively. The PTV in all plans received 45 Gy in 25 fractions except for the 65 Gy dose level which received 48Gy in 30 fractions.

3.5.1.2 Sequential plans

All sequential plans assumed a prior delivery of 45 Gy in 25 fractions to the pelvis as is traditional for brachytherapy. They were designed to initially deliver a boost of 20 Gy; for stereotactic plans this was in 5 Fractions with stereotactic normalisation as described below while for other plans they were designed to be delivered in a traditional 2 Gy per fraction with median normalisation i.e. over 10 fractions.

3.5.1.3 VMAT plans

I generated all VMAT plans using Eclipse™ (Version 13.6, Varian Medical Systems) with the Acuros XB™ 13.5 dose calculation. In comparison to the two 6 MV full dual rotational arcs for SIB and pelvic plans, I implemented a single 6 MV full rotational arc for sequential VMAT plans. Dose rate was set to 800 monitor units (MU)/min. Plans were normalised for median coverage i.e. 100% dose covers 50% of the target PTV with the aim to deliver > 95 % of the dose to > 95% of the PTV volume. This applied to both the nodal PTV and the SIB/VMAT boost PTV.

3.5.1.4 Sequential SBRT plans

All SBRT plans were also generated on the Eclipse™ planning system with the Acuros XB™ 13.5 dose calculation algorithm and with the flattening filter-free (FFF) algorithm additionally applied. A single 6 MV full rotational arc was used with the dose rate set at 1400 MU/min and plans were normalized for 95% coverage by the prescription isodose i.e. 100% dose covers 95% of the PTV with a Dmax of 125-140%. **Table 3.3** details the SBRT PTV target aims.

3.5.1.5 PBT

I generated PBT treatment plans using the Raystation™ treatment planning system (v10A, RaySearch Laboratories). The Monte Carlo calculation algorithm was used with an optimisation of 10000 ions/spot. A PTV planning method rather than

robustness optimisation was used to ensure comparative results to photon plans. For CRD, a three-field arrangement was used after experiment with different field arrangement (**Figure 3.2**); anterior, right posterior oblique and left posterior oblique field. For PSWD, two parallel opposed pairs were used.

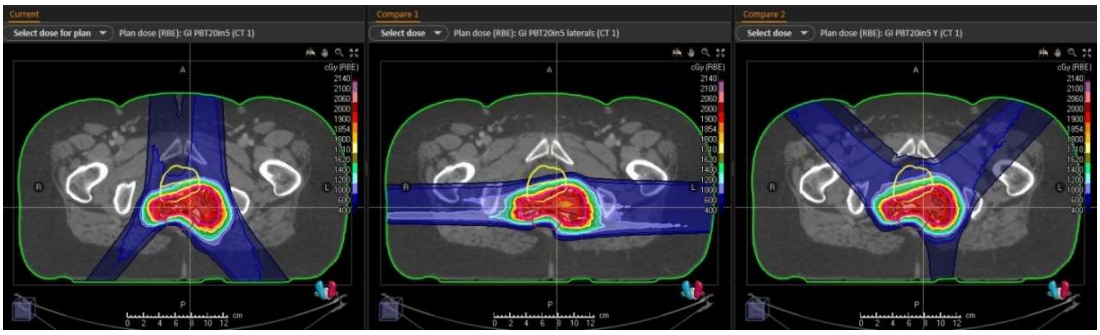


Figure 3.2. Three different beam arrangements for proton plans for CRD

3.5.2 Dose constraints and optimisation priorities

3.5.2.1 Dose constraints

Tables 3.4 and 3.5 detail the dose constraints used for planning as derived from **Appendix 3.1**.

3.5.2.2 Normal tissue and dose optimisation objectives

For photon plans, the planning normal tissues objective (NTO) was set to 150 and the PTV objective to 100 with a priority of 150 for all plans. The starting distance was set to 0.8 for SIB plans, 0.6 for sVMAT plans and 0.5 for SBRT plans. The start dose was set to 100% with an end dose of 30-50% for all plans. These were tightened during optimisation. The dose drop-off was set to 0.15 for non-SBRT plans and 0.2 for SBRT plans.

3.5.2.3 PTV and OAR optimisation priorities

For VMAT plans, the target PTV upper and lower optimisation dose levels (UDL and LDL) were set to the planning dose. In the case of SIB plans, these were the highest dose level i.e. the boost PTV dose. The PTV and OAR optimisation priorities were set to 100 and 50 respectively with the PTV45 set to 120 in SIB plans. The

optimisation was paused on the first iterative level and restarted as the optimiser reached a plateau at which point I interacted with the optimiser actively to push the OAR dose down while ensure the tail of the PTV dose remained within the required parameter.

Target	Constraint	Optimal/Soft	Mandatory/Hard
Rectum	V5	50%	60%
	V15	35%	50%
	V20	30%	30%
	V25	15%	15%
	V30	3%	5%
Bladder	V5	50%	-
	V15	50%	-
	V20	-	50%
	V25	5%	35%
	V30	3%	15%
Small Bowel	V5	110 cc	122 cc
	V10	28 cc	105 cc
	V15	6 cc	84 cc
	V20	0	26 cc
Femoral Heads	V5	50%	-

Table 3.4 Dose constraints to OARs in 2 Gy per fraction after 45 Gy in 25 Fractions

Once the initial iteration of a plan was complete, I created further optimisation structures for areas of the primary PTV that were “cold” i.e. receiving a dose lower than the minimum PTV target dose. This was created by converting the minimum PTV dose into an isodose level and subtracting it from the PTV receiving that dose and then adding a 1 mm for optimisation pick up.

3.5.2.4 Special considerations for SBRT and PBT boost

Although the SBRT and PBT dose constraints were adopted from the GEC-ESTRO brachytherapy guidelines, optimal dose constraints from the EMBRACE trial were also reported from these plans to compare to traditional planning techniques. As

such, it was important not to under report maximum OAR doses by avoiding dose "dilution" from larger OAR structures. To account for this, using a Boolean function, I created "nearby" OAR volumes from OAR contours within 1 cm of the PTV i.e. the nearby OAR region most likely to receive high doses.

Target	Constraint	Optimal/Soft	Mandatory/Hard
Rectum	Dmax		25.6 Gy (85)
	D2cc	17 Gy (65)	21.8 (75)
	D10%	-	19.5 Gy (70)
	D15%	19.5 Gy (70)	
	D30%	-	17 Gy (65)
	D50%	-	14.5 Gy (60)
Bladder	Dmax	-	30 Gy (100)
	D2cc	23.75 Gy (80)	27.5 Gy (90)
	D5%	21.8 Gy (75)	23.75 Gy (80)
	D20%		19.5 Gy (70)
	D50%		14.5 Gy (60)
Bowel	D2cc	19.5 (70)	21.8 Gy (75)
	D5cc	17.0 (65)	19.5 Gy (70)
	D10cc	14.5 Gy (60)	17.0 Gy (65)
	D30cc		14.5 (60)
Sciatic Nerve	Dmax	18.9 Gy (70)	-
	D1cc	16.7 Gy (65)	18.9 Gy (70)
	D3cc	14.3 Gy (60)	16.7 Gy (65)
Femoral Heads	D20%	18.8 (70)	-
	D50%	5 Gy (50)	-

Table 3.5 Dose constraints for 5 fraction SBRT after 45 Gy in 25 Fractions

3.5.3 Plan Evaluation Statistical Analysis

Comparative analysis between each of the SIB plans and separately between each of the sequential plans was carried out. Doses to PTV, GTV and OARs were compared using the same methods as described in chapter 2 (cf. 2.4.2.6 & 2.4.2.7).

3.6 Results

3.6.1 Patient and tumour characteristics

Table 3.6 details the patient and tumour characteristics.

	Central	Pelvic Side Wall
Characteristic	n = 10	n = 10
Median Age (range)	**56 (32 -74)**	**61 (37 – 76)**
Primary Tumour		
Cervix	**3**	**6**
Endometrial	**4**	**4**
Vaginal	**2**	**0**
Ovarian	**1**	**0**
Tumour Status		
Median GTV (range)	**72.9 (25 – 190) cm^3**	**31.2 (3.1 – 90) cm^3**

Table 3.6 Patient and tumour characteristics of the 20 cases with isolated recurrence of gynaecological malignancy selected for the dosimetric planning study.

In total 120 plans were created with 6 plans for each patient including three SIB plans at three different dose levels; SIB55, SIB60, SIB65; and three sequential plans using three different techniques; seqVMAT, seqSBRT and seqPBT. Examples of each of the planning techniques are shown in **Figure 3.3** for CRD and **Figure 3.4** for PSWD.

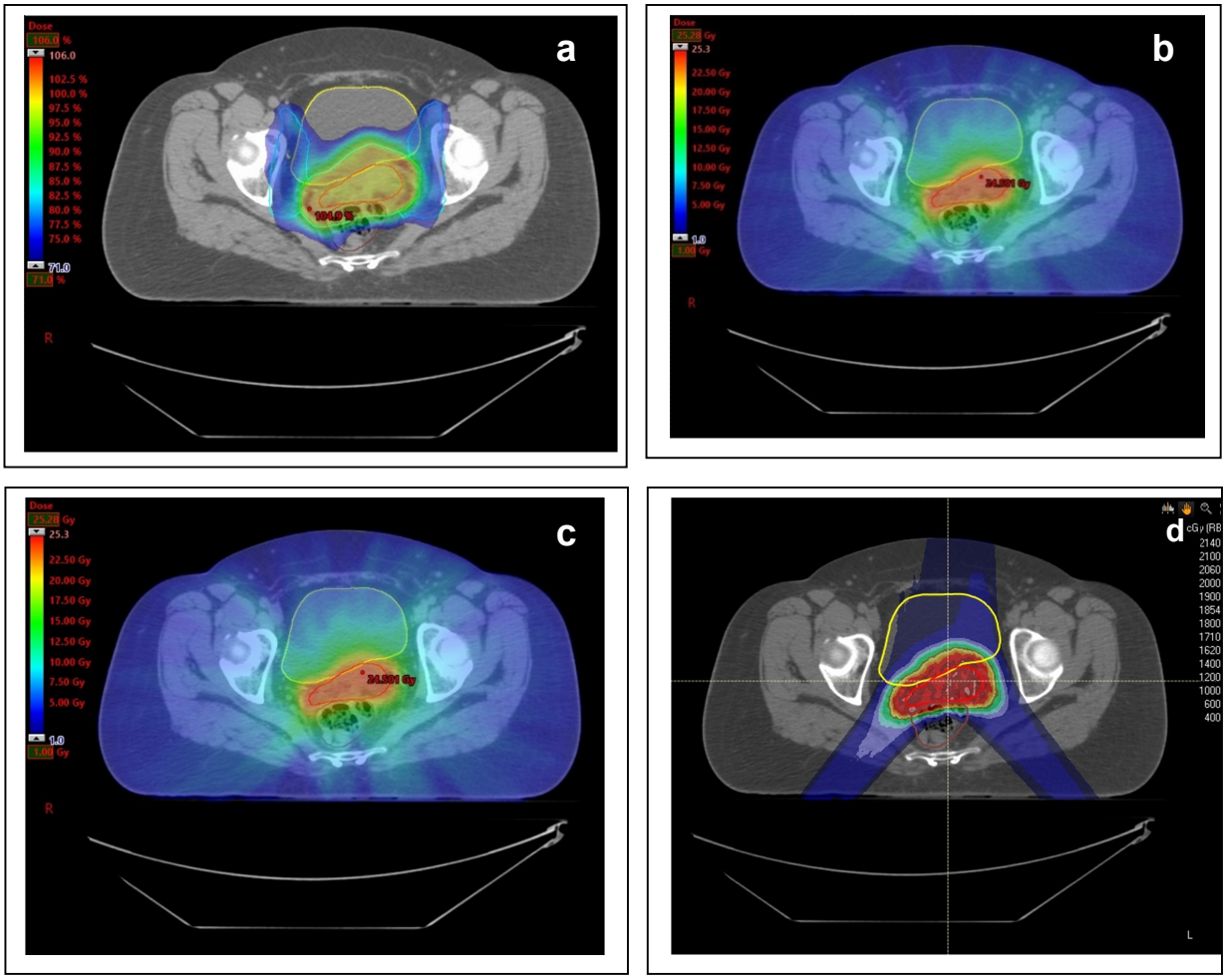


Figure 3.3 Treatment plans for central recurrences using a SIB60 technique (a) with relative dose colourwash where 70% is the 95% isodose for PTV45, seqVMAT (b), SBRT (c), and PBT (d) techniques with absolute dose colour washes.

GTV is shown in red, bladder in yellow and rectum in brown.

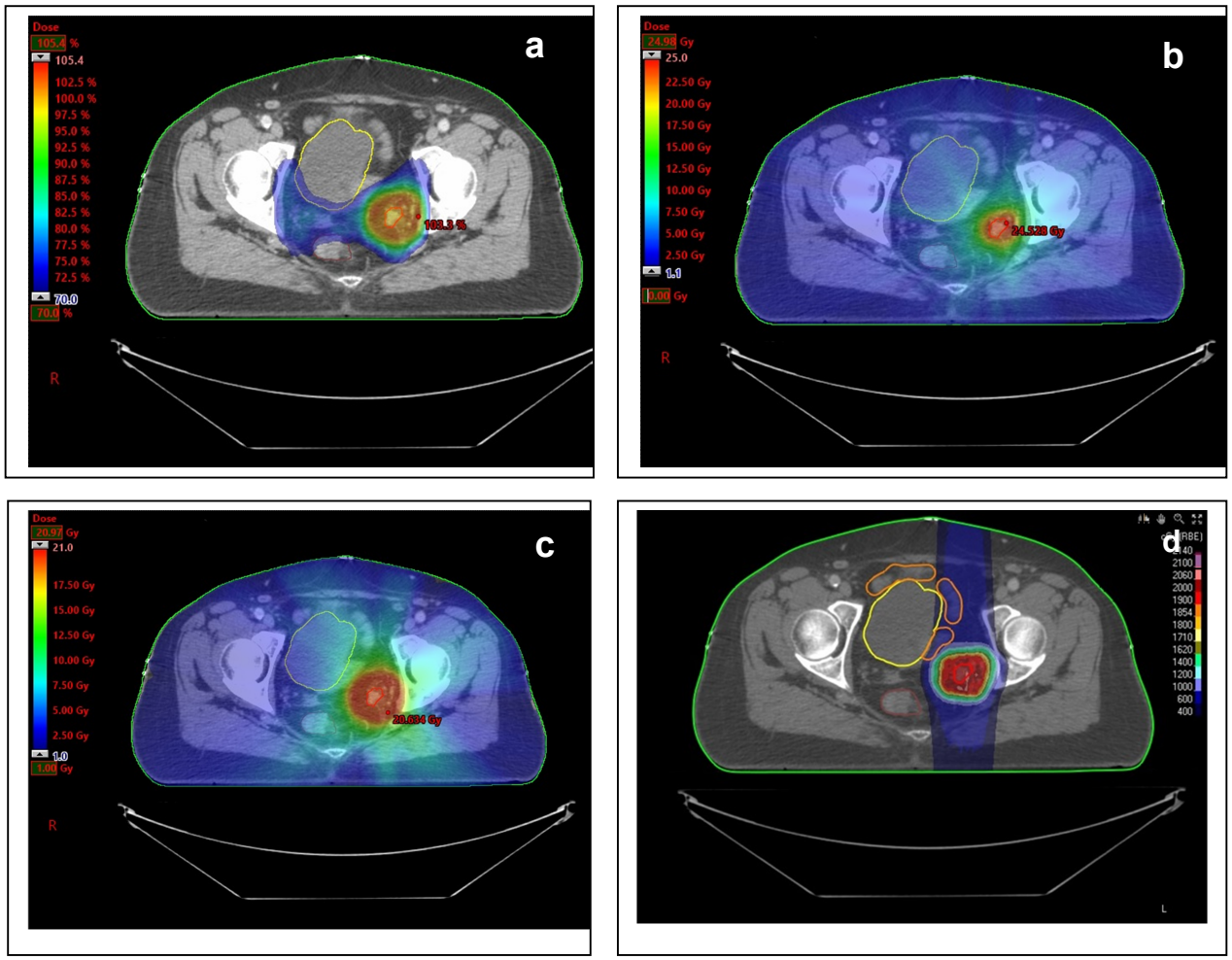


Figure 3.4 Treatment plans for pelvic side-wall recurrences using a SIB60 technique(a) with relative dose colourwash where 70% is the 95% isodose for PTV45, seqVMAT (b), SBRT (c), and PBT (d) techniques with absolute dose colour washes.

GTV is shown in red, bladder in yellow, rectum in brown and bowel in orange.

3.6.1 Comparing SIB plans

3.6.1.1 Dosimetric comparison of planning target volumes

A total of 60 SIB boosts plans were created; n=10 for CRD and n = 10 for PSWD each at 3 boost dose levels to the primary PTV of SIB55 Gy, SIB60 Gy and SIB65 Gy. **Table 3.7** summarises the target volume characteristics. The mean SIB PTV was 268.2 ± 140.2 cm^3 for CRD and 148.6 ± 98.6 cm^3 for PSWD. All plans met the target planning volume criteria of >95% of the PTV volume receiving 95% of the prescribed dose and 95% the pelvic PTV45/48 also receiving 95% of the prescribed pelvic PTV dose of 45 Gy and 48 Gy. The mean conformity index for all plans was 1. The mean dose to the PTV (± standard deviation) was 55 ± 0.1 Gy for SIB55,

59.8 ± 0.1Gy for SIB60 and 64.1 ± 1.9 Gy for SIB65. When accounting for the fractionation, the EQD2 doses to the PTV were 55.92Gy, 61.79Gy and 64.95Gy for SIB55, SIB60 and SIB65 plans respectively.

	CRD				PSWD			
	SIB55	SIB60	SIB65	VMAT	SIB55	SIB60	SIB65	VMAT
PTV SIB volume (cm^3)	68.2 (100 - 540)				148.6 (41 - 330)			
Conformity Index	1.2 ±0.5	0.99 ±0.1	0.98 ±0.1	1.08 ±0.4	0.9 ±0.3	0.94 ±0.3	0.98 ±0.2	1.10 ±0.1
PTV Dmean (Gy)	55.0 ±0.1	59.8 ±0.1	64.1 ±1.9	64.05 ±0.2	54.5 ±1	59.6 ±2	64.0 ±1.9	64.05 ±0.2
EQD2 PTV Dmean Total (Gy)	55.92	61.79	64.95	64.05	55.5	61.59	64.89	64.05

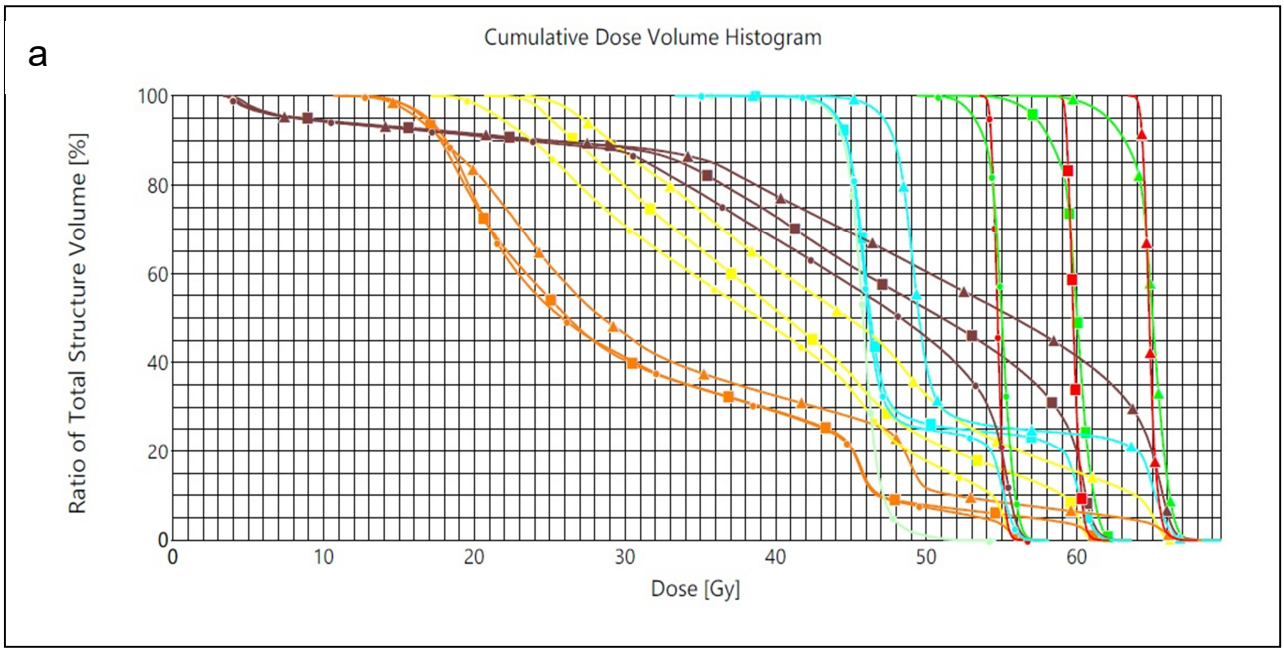
Table 3.7 Plan characteristics for SIB and sequential VMAT and PBT plans

3.6.1.2. DVH analysis and comparing OAR doses for SIB plans

Table 3.8 summarises DVH analyses (illustrated in **Figure 3.5**) and details the OAR doses for each of the target dose constraints. As expected the mean Dmax doses to the OARs increased with increase in the prescribed SIB boost PTV dose. However, there were higher OAR volumes exposed to the lower dose levels of V50/46 and V60/55 for SIB60 plans when compared to SIB65. Dose to the OARs, particularly the bladder and rectum was significantly lower in PSWD than in CRD because of the proximity of these OARs in CRD where the PTV usually jutted into them. The dose points to the bowel were higher in PSWD, likely due to the proximity of the bowel in PSWD compared to CRD where the recurrences were higher up in the pelvis.

	CRD			PSWD	
OAR DOSES	SIB55	SIB60	SIB65	SIB55	SIB60	SIB65
	RECTUM					
V50/46* < 60%	46.3±26	71.8±18.4	64.8±17.1	6.5±10.1	19.7±27.7	14.4±20.2
V60/55 < 50%	10.6±11.4	17.7±9	42.3±15.9	0±0	6.4±11.1	4.7±8
V65/60 < 30 %	0±0	0±0	18.4±9.4	0±0	0.9±2.3	1.5±3.3
D2cc	53.2±5.2	61±0.5	66.1±0.5	48.9±4.3	50.5±6.7	53.7±8.1
D0.1cc	54.3±5.1	62.1±0.7	67.3±0.7	48.8±4.4	50.6±8.5	53±9
	BLADDER					
V50/46*	13.8±3.6	28.8±7	25±6.5	5.5±7.5	14.5±15.3	10.1±11.6
V60/55	0±0	4.9±1.3	11.4±2.9	0±0	1±2.2	4.5±6.9
V65/60 < 50 %	0±0	0±0	4.7±1	0±0	0±0	1.2±1.9
D2cc	55.9±0.3	61±0.4	66.1±0.4	52.1±4.1	55.5±6.2	59.5±7.7
D0.1cc	56.1±0.4	61.7±0.6	67.1±0.7	53.3±4.8	58.2±8	61.1±9.7
	BOWEL					
V50/46 < 122cc	9.6±13.2	44.9±36.6	26.3±22.9	9.5±7.7	54.8±69.3	20.5±15.5
V55/50 < 105cc	3.9±6.2	14.5±15.6	13.4±15.2	2.2±2.1	30.6±53.3	10.6±8.4
V60/55 < 84cc	0±0	9.8±11.3	9.5±11.4	0±0	4.1±6.7	7±6
V65/50 < 26cc	0±0	4.6±5.9	4.9±6.2	0±0	0±0	2.3±2
D2cc	49.6±4.8	55.1±6.9	59.2±8.2	53.4±3.1	57.5±5.1	62.2±5.7
D0.1cc	51.5±4.9	54.3±7.1	57.8±9.1	55.9±0.6	61.6±1.3	66.3±0.8

Table 3.8 Summary of DVH analysis detailing OARs dose distributions for SIB plans.



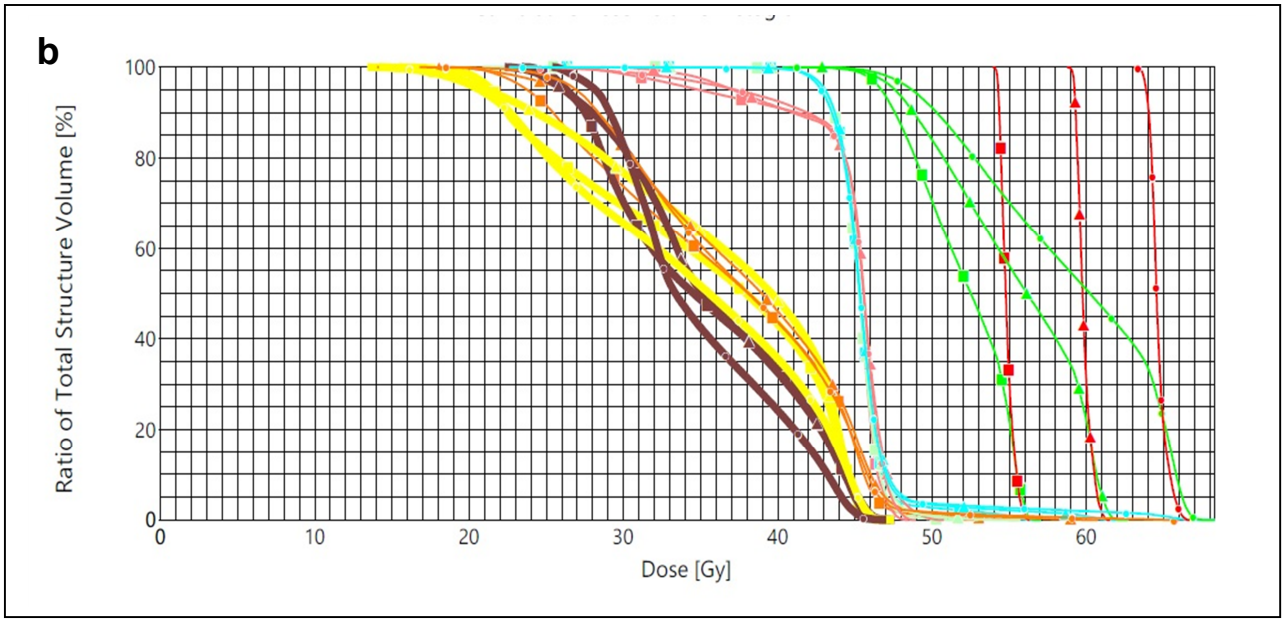


Figure 3.5 Example of comparative DVHs to OARs for SIB plans for (a) CRD (b) PSWD

Red: GTVp, Green: PTV SIB, Blue: PTV45, Brown: Rectum, Yellow: Bladder, Orange: Bowel. Circles: SIB55, Squares: SIB60. Triangles: SIB65. (NB doses are not EQD2 equivalent)

3.6.1.3 SIB plans meeting the OAR target constraints

In CRD, 8 of the 10 plans met all OAR dose constraints for SIB55Gy (**Table 3.9**). This was reduced to only 3 for each of SIB60 and SIB65 where the rectal dose constraint was not met in the majority of those cases. However, all plans for all levels met the bladder and bowel dose constraints.

For PSWD, all the 10 plans for SIB55Gy met the target OAR dose constraints, but only 9 and 8 met them for SIB60 and SIB65 respectively. This was due to the rectal dose in both cases; all bladder and bowel dose constraints were met. However, there was a larger low dose bath to rectum and bladder in PSWD. This only occurred at higher dose points for CRD. There also was a higher dose to the bowel both at the lower and higher doses for PSWD.

CENTRAL plans meeting OAR targets						
	SIB55	SIB60	SIB65	VMAT	SBRT	PBT
All OARs (n)	8	3	3	3	7	10
Bowel	10	10	10	10	8	10
Bladder	10	10	10	10	10	10
Rectum	8	3	3	3	7	10
PSW plans meeting OAR Targets						
	SIB55	SIB60	SIB65	VMAT	SBRT	PBT
All OARs (n)	10	9	8	7	9	10
Bowel	10	10	10	10	9	10
Bladder	10	10	10	10	10	10
Rectum	10	10	8	7	10	10

Table 3.9 Number of plans meeting OAR dose constraints for CRD and PSWD for SIB and sequential plans

3.6.2 Comparing sequential boost plans

3.6.2.1 Dosimetric comparison of planning target volumes

A total of 60 sequential plans were created; n=10 for CRD and n = 10 for PSWD each with a sequential VMAT, sequential SBRT and sequential PBT. All plans met their target constraints: 95% of the VMAT and PBT PTVs were covered by 95% of the prescription dose and SBRT plans met their distribution targets. For CRD, the mean PTV boost volume was 144.2 cm^3, for PSWD it was 70.9 cm^3 (**Table 3.10**). As expected the mean Dmax was highest for SBRT plans mean CRD GTV Dmax of 23.7 Gy and 23.9 Gy in PSWD. For both CRD and PSWD, the mean GTV Dmax for VMAT plans was 19.8 Gy; for PBT it was 20 Gy for both CRD and PSWD. For CRD, the EQD2 dose to the GTV, taking into account phase 1 of 45 Gy was 64.05 Gy, 73.36 Gy, and 67.58 Gy for VMAT, SBRT and PBT respectively; for PSWD it was 64.95 Gy, 73.69 Gy and 67.58 Gy respectively.

	CRD			PSWD		
	VMAT	SBRT	PBT	VMAT	SBRT	PBT
PTV Boost Vol (cm^3)	144.2±80.9			70.9±54.1		
Conformity Index	1.08±0.4	0.96±0.2	0.89±0.1	1.10±0.1	1.00±0.1	0.91±0.2
GTV Dmean (Gy)	19.8±0.2	23.7±0.2	20±0.1	19.8±0.2	23.9±0.9	20±0.1
EQD2 GTV Total (Gy)	64.05	73.36	67.58	64.95	73.69	67.58
GTV volume (cm^3)	72.9±51.9			31.2±29.4		
GTV Dmax (Gy)	20.6±0.3	25.8±0.4	21.4±0.7	20.6±0.1	25.3±0.5	21±0.5
GTV Total Dmax EQD2 (Gy)	64.9	76.8	69.7	64.9	76.0	69.5

Table 3.10 Plan characteristics for the sequential plans

3.6.2.2. Comparing OAR doses and DVH analysis

Table 3.11 summarises the OAR doses from the DVH analyses for both types of photon sequential plans illustrated in **Figure 3.6** and for PBT in **Figure 3.7**. In CRD, Dmax was highest for all OARs (rectum, bladder and bowel) with SBRT although differences were small. In PSWD, there appeared to be higher Dmax doses to all OARs (rectum, bladder and bowel) for the seqVMAT with better sparing using SBRT

and PBT. Doses to the rectum and bladder were significantly higher at the lower target volumes (V5 and V15) for the seqVMAT plans whereas for the bowel there was higher dose for the V5 and V15 level with the SBRT plans. Overall, there appeared to be good sparing of the OARs for the SBRT and PBT plan compared to seqVMAT plans. PBT offered much lower doses to the OARs (V5 and V15) in view of the beam arrangement and a reduction in the low dose bath.

			CRD			PSWD	
OAR DOSES		VMAT	SBRT	PBT	VMAT	SBRT	PBT
		RECTUM					
V5/6.15 60%	50	84.9±14	76.3±15.1	39.2±14.6	59.2±19.5	31.4±28.1	15.5±14.3
V15/14.6 < 50%	60	56.1±31.6	32.2±17	21.5±5.6	5.1±8.8	2.3±4.7	3.6±5.6
V20/17 < 30 %	65	11.8±9.4	23.6±15.4	15.8±6.2	1.2±2.3	1.1±2.4	1.8±3.3
V25/19.5 < 10%	70	0±0	15.2±13.7	3.2±1.6	0±0	0.4±0.9	0.4±0.7
D2cc < 21.8 Gy		20.2±0.3	21.6±1.6	20±0.7	14.5±4.1	10.1±5	10.7±6.4
D0.1cc	Dmax	20.8±0.1	23.1±1	21.4±0.7	14.9±4.9	13.4±6.7	14.2±6
		BLADDER					
V5/6.15 60%	50	45.8±15.5	45.8±15.5	36±9.1	51.1±28.3	26.6±28.3	22.6±18.8
V15/14.6 < 50%	60	11.1±9.2	11.1±9.2	17.1±3.5	7.1±8.8	3.3±5.5	8.8±11.1
V20/17 < 30 %	65	6.1±3.5	6.1±3.5	10.9±2	1.4±2.4	2.2±4.2	26.8±61.1
V25/19.5 < 10%	70	3.5±2.3	3.5±2.3	4.8±3	0±0	1.4±3.2	0.5±1.1
D2cc < 21.8 Gy		0.7±1.9	0.7±1.9	18.3±5.9	17.3±5.6	0.1±0.4	13.8±7.3
D0.1cc	Dmax	22.6±0.5	22.6±0.5	21±0.2	20.4±0.2	16.7±9.1	16±7.6
		BOWEL					
V5/6.15 < 122cc	50	5.2±5.9	15.6±18.7	15.5±15.7	10.6±10	45±47.8	35.6±27.2
V10/10.65 < 105cc	60	3.4±4.1	8.5±10.9	9.2±10.2	3.5±3.4	13.3±14.8	12±6
V15/14.6 < 84cc	65	2.2±2.7	4.9±6.5	5.1±6.4	1.5±1.4	5.3±5.6	6.7±3.7
V20/17 < 26cc	70	0.6±1	3.3±4.6	3±4	0.3±0.4	3.1±3.3	3.8±2.4
V25/19.5 < 5cc	75	0±0	2±2.9	1±1.6	0±0	1.6±1.9	1±0.8
D2cc		15.3±8.5	11.6±9.3	11.9±8.1	18±5.3	15.9±6.1	16.8±4.9
D0.1cc		14.1±10.8	15.1±10.4	14.8±7.6	20.6±0.1	20.1±6.7	20±6.2

Table 3.11 Summary of DVH analysis detailing OAR dose distributions for sequential VMAT, SBRT and PBT plans

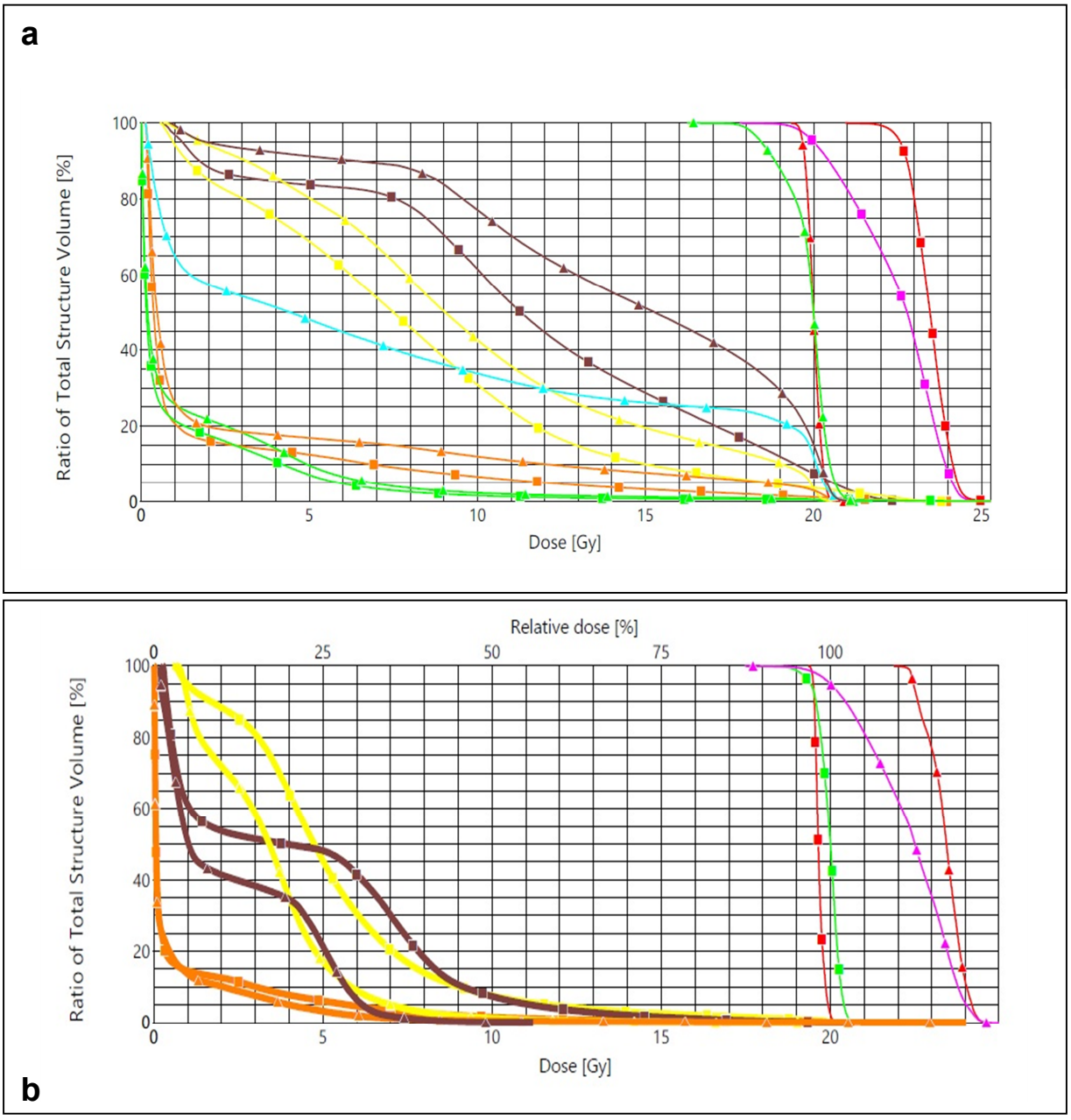


Figure 3.6 Example of comparative DVHs to OARs for sequential VMAT and SBRT plans in (a) CRD (b) PSWD.

Red: GTVp, Green: PTV SIB, Blue: PTV45, Brown: Rectum, Yellow: Bladder, Orange: Bowel. Squares: sequential SBRT 20 Gy in 5 F. Triangles: sequential VMAT 20 Gy in 10 F (NB SBRT doses are not in EQD2).

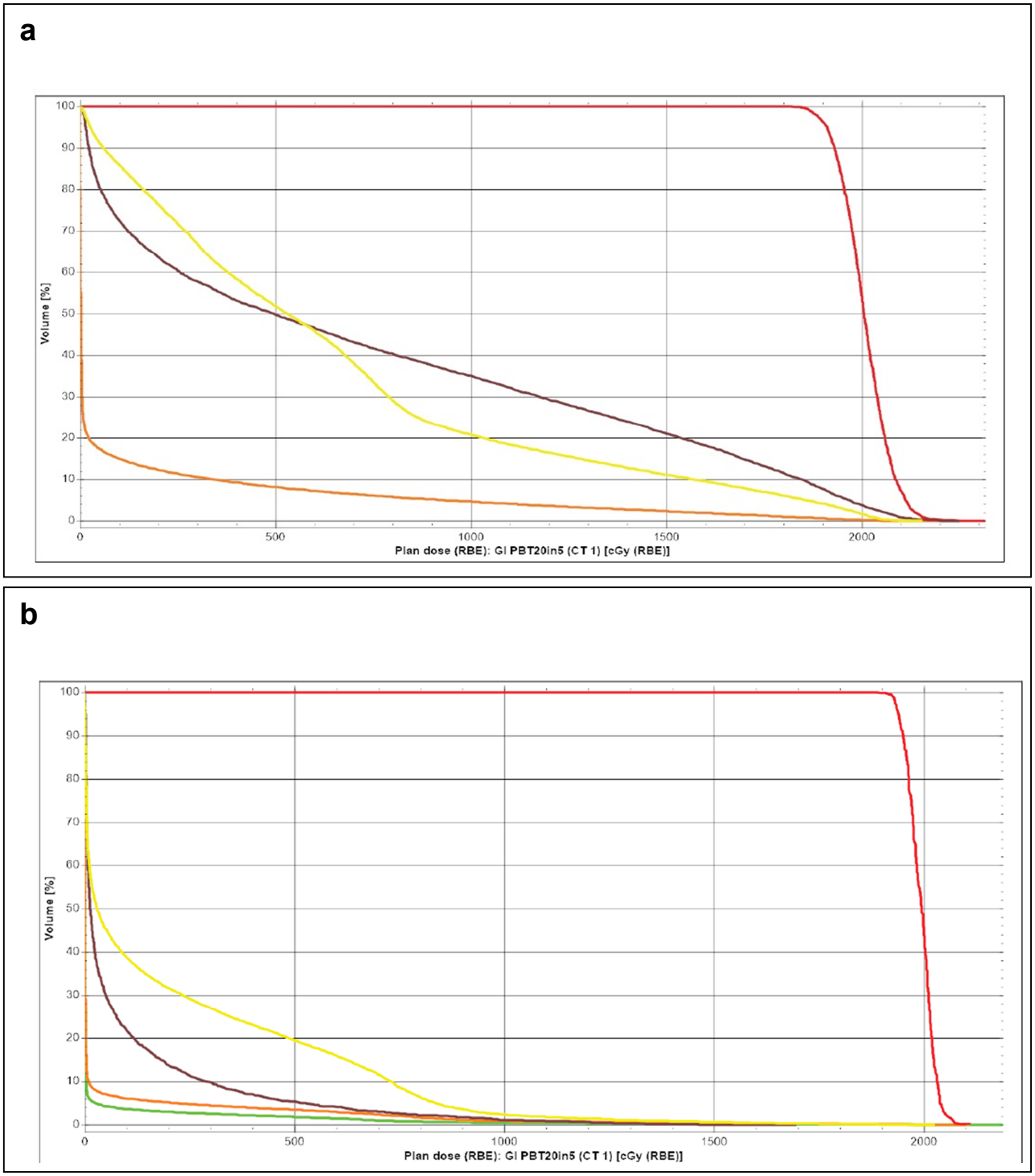


Figure 3.7 Examples of comparative DVH to OARs for sequential PBT plans (a) CRD and (b) PSWD.

Red: GTVp, Green: PTV SIB, Blue: PTV45, Brown: Rectum, Yellow: Bladder, Orange: Bowel. Circles: SIB55, Squares: SIB60. Triangles: SIB65. (NB doses are not EQD2 equivalent)

3.6.2.3 Plans meeting the OAR target constraints for CRD and PSWD

In CRD, 7 of 10 SBRT plans met the dose constraints where 3 failed due to rectal dose constraints (8 met the dose constraints for bowel and 10 for bladder) (**Table 3.9**). Only 3 of 10 plans met the dose constraints for seqVMAT, also mainly due to failures to meet the rectal dose constraints despite meeting all the ones for the bladder and bowel. All PBT plans were successful in CRD.

For PSWD, 9 of 10 of the SBRT plans were successful with 1 failing due to bowel dose. This was superior to seqVMAT where 7 of 10 plans met the OAR dose constraints with failures due to the rectal dose constraints despite successfully meeting bladder and bowel dose constraints. This, however, was higher than the number of successful seqVMAT in CRD, where the location of the recurrence meant that rectal dose constraints compromised seqVMAT plans. All PBT plans were successful meeting all the OAR dose constraints in PSWD.

3.6 Discussion

Although brachytherapy (either ring and tandem or interstitial) remains the gold standard for tumour boost in primary gynaecological cancer, it is not usually feasible in the recurrent gynaecological cancer setting either due to prior surgery or tumour topography. EBRT reduces the total deliverable dose to macroscopic recurrent disease to 60 – 65 Gy due to OAR proximity. This adversely affects outcomes. [66, 67, 69, 70].

Several dosimetric and prospective clinical studies, heterogenous in dose, fractionation and technique, have reported on dose escalation methods in primary gynaecological cancer where brachytherapy is not an option due either to patient anatomy or morbidity. These were summarised in a review by Mahmoud et al [122]. To my knowledge, this is the first study to compare 4 techniques simultaneously in a

purely recurrent gynaecological setting with a focus on comparing the feasibility of these treatments in isolated CRD vs. PSWD.

3.6.1 SBRT and PBT in recurrent gynaecological cancer

The results from my questionnaire to national centres indicated that although SBRT is well established in the treatment of gynaecological cancers, its use is limited to treating recurrent tumours in the previously irradiated pelvis. This is largely due to SBRT commissioning by the NHS and the stringent criteria for its use as set out by CtE[130]. As such, sequential VMAT boost remains the main treatment modality for radiation naïve gynaecological recurrences with some centres adopting SIB boosts. This contrasts with practice in other parts of the world where SBRT use is becoming more established including for the treatment of primary disease despite lack of prospective data on efficacy [133].

A number of studies have suggested SBRT offers superior target coverage with sparing of OARs compared to brachytherapy [134-136]. Although previous trials of SBRT boost in the primary setting were associated with little severe toxicity [123, 137], a recent prospective phase II trial of SBRT as a boost for locally advanced cervical cancer by Albuquerque et had to be halted due to concern regarding rectal toxicity. In a dosimetric study[5], SIB-PBT offered the best sparing of small bowel and rectum compared to photon based SIB.A remarkable five-year local control rate of 75% has been observed by Kagei at al [138] in long term follow up of patients treated with passively scattered PBT where the median tumour dose was 86 Gy and grade 4 genitourinary and gastrointestinal toxicity was as low as 4%.

3.6.2 Rationale for dose and fractionation schedules

SIB planning offers two advantages: firstly it allows for shorter overall treatment time by up to two weeks which radiobiologically translates into higher radiation dose to

the tumour but also negates the need for a re-scanning and re-planning which would normally take place after the five-week course of pelvic radiotherapy is complete. However, it does have its disadvantages: it uses a higher dose per fraction with a differential effect on the EQD2 to tumour compared to OARs in view of the high a/b ratio of gynaecological tumours and does not take into account the tumour regression during treatment. However, should a significant regression occur, it can usually be detected using daily imaging and a re-plan undertaken to improve dosimetry and reduce the dose to OARs that would likely fall into the treatment PTV as the tumour shrinks.

The reason for the slightly unusual fractionation of 1.6Gy per fraction was to facilitate calculations and ensure a fair comparison between the pelvic PTV doses compared to 25 fractions of 44.2 Gy vs. 44.3 Gy respectively. Although the 55 Gy dose level I used delivered a tumour dose of less than 60 Gy in EQD2 over 5 weeks, it was radiobiologically comparable to the sVMAT plan which is delivered over 7 weeks.

Sequential treatment, using IMRT, SBRT or IMPT, involves an extra 1 to 2 weeks of treatment and potentially allows for tumour cell repopulation. It also requires re-scanning and re-planning of the second phase of treatment which can be resource intensive. However, it allows for dose escalation that takes into account tumour regression after delivery of the initial radiotherapy dose and therefore better targeting of the tumour while sparing the OARs as the tumour shrinks.

3.6.3 Comparison of target and OAR radiation dose for CRD and PSWD

My studies have demonstrated that all four planning techniques were able to deliver a boost to the primary disease while respecting the OAR dose constraints in both CRD and PSWD. SIB plans were more successful in PSWD compared to CRD due

to tumour topography away from the bladder and the rectum. Of the SIB plans, it was not possible to escalate dose to the tumour beyond 55 Gy in the majority of cases for CRD which limits the utility of the SIB technique in this tumour group. In contrast, in PSWD, it was possible to escalate the dose to 65 Gy in 80% of the cases which suggests that SIB65 can offer a higher BED to the tumour compared to the seqVMAT plan in PSWD with the radiobiological advantage of a shorter overall treatment time of two weeks. This may be beneficial at overcoming tumour repopulation and offering a dose advantage of 0.5 Gy per day [139].

For sequential plans, VMAT was not feasible in CRD due to the rectal dose constraint. All other planning techniques were feasible in >70% of the cases with PBT offering the best tumour coverage while respecting OAR dose constraints for 100% of cases. SBRT also offered significant OAR dose sparing compared to VMAT and it is likely that further dose escalation using isotoxic planning will be possible.

Although not differentiating between CRD and PSWD, previously reported conformal RT boost techniques by Barraclough et al [140], Chan et al [141]and Park et al [67] have reported 79%, 83% and 60% 2-year local control rates, albeit with higher toxicity rates likely due to older radiation techniques and lack of image guidance. Mazzola et al [142] reported a local control rate of 80% using SIB-VMAT in the treatment of advanced cervical cancer in the elderly without severe toxicity. Newer IMRT techniques allow for reduction in toxicity by offering concave conformal radiation delivery, whilst also permitting dose painting by allocating two differential dose targets within a single treatment volume. SIB-IMRT offers a radiobiological advantage by shortening treatment times compared to sequential boost techniques by up to two weeks.

3.6.4 Limitations

One of the limitations of my dosimetric study is the heterogenous group of recurrent tumours studied which is due to the unique clinical situation as indicated by the questionnaire with low number of cases per centre. As such, there is radiobiological uncertainty on dose to tumour with lack of data on the α/β for non-squamous non-cervix histology. Moreover, two different radiotherapy planning systems were used as our institution does not currently have the appropriate licences for research proton planning on the Eclipse RTP so PBT plans had to be created within RayStation. However, contours were comprehensively checked when imported onto RayStation and peer reviewed by a pelvic radiophysicist. Another main limitation is that my sequential plans did not take into account the phase 2 scan carried out at the end of the pelvic radiotherapy where there is 50 – 70% tumour regression which might improve tumour and OAR dosimetry. Finally, the RMH is not a proton therapy centre with a lack of proton planning experience within the pelvis. Although they were peer reviewed by a physicist with experience in proton planning, his experience is mainly in breast cancer and therefore assessment of the plans is unlikely to be of the standard of other centres with dosimetric and clinical experience.

3.6.5 Future work

3.6.5.1 Sequential and Isotoxic planning

My dosimetric studies have demonstrated that in SIB planning, it was not possible to dose escalate in about 70% of the CRD cases. As highlighted in the discussion this is likely due to the proximity of the OARs, in particular the rectum to the treatment volume. With plan-of-the-day and adaptive planning now increasingly possible with improved scanning and planning technology, further studies are needed to account for tumour regression from the initial pelvic radiotherapy component.

In sequential planning, it was possible to escalate dose in 70 – 90 % of the selected cases using SBRT and PBT while respecting the OAR dose constraints. There remains a lot of uncertainty regarding radiobiology and PBT but it may be possible to use stereotactic normalisation in PBT plans to escalate dose as per SBRT. Further studies are also warranted using isotoxic planning like brachytherapy to escalate the dose even further until one of the OAR dose constraints is met which is why the REGENCY study was developed.

3.6.5.2 The REGENCY Trial

I contributed to the design and development of a proposed radiotherapy treatment protocol, patient information sheets and other trial documentation (REGENCY trial) for SBRT in isolated pelvic recurrence of gynaecological cancer. The trial schema (**Appendix 3.2**), details the proposed trial design. The primary end point is disease control at 1-year.

Unfortunately, applications to fund this trial have been unsuccessful (CRUK Early Phase and Feasibility Study Award in 2017, National Institute for Health Research, Research for Patient Benefit (NIHR RfPB) in 2018. The main feedback received on both occasions was the lack of randomisation. Based on the indicated numbers from each of the centres and the current lack of definitive evidence on control rates of SBRT, a randomised trial with the required patient numbers would only be feasible with multi-centre international collaboration.

To address the statistical considerations, with the help of the statistician Karen Thomas, I performed power calculations which demonstrated that a randomised trial at this stage would risk being underpowered. A smaller phase II trial to gain more information regarding the potential control rate and determine the toxicity of the intervention would be a more logical and practical step before proceeding to a randomised trial. Further funding applications are currently being undertaken.

3.7 Key Points

1. Re-irradiation practices for treatment of isolated pelvic recurrences vary widely in the UK.

2. A SIB boost allows for dose escalation of the primary tumour dose with a shorter overall treatment time than SBRT or VMAT. In CRD, it is not possible to escalate dose beyond 55 Gy while respecting OAR dose constraints unlike PSWD where dose can be escalated to 65 Gy.

3. In CRD, PBT offers the best sequential dose escalation technique while respecting OAR dose constraints followed by SBRT while VMAT was less feasible. For PSWD, all three options offer a feasible option for dose escalation with PBT being most successful at escalating dose while respecting the OAR dose constraints.
4. The main limiting OAR in the majority of the plans was the rectum due to its proximity to the recurrence and lower dose tolerance compared to the bladder.

Chapter 4 – Magnetic Resonance guided High Intensity Focused Ultrasound for symptom palliation in recurrent gynaecological cancer

4.1 Introduction

4.1.1 Use of HIFU for treating pelvic masses

HIFU is a highly precise thermally ablative technique. Within the HIFU focus or "thermolesion", localised areas of high temperature (50^0C – 80^0C) are generated causing protein denaturation and coagulative necrosis which in turn causes cell damage and death. Proximal to the focus, energy deposition is lower, so that pre-focal tissues are spared thermal or mechanical damage. Heating at the focus within a prescribed treatment "cell" occurs during the exposure, after which heat is dissipated to the surrounding tissues. This means that repeated exposures can be done over a relatively short period of time [143-145].

HIFU has been successfully utilised to ablate several malignant tumours [44, 45, 146-148]. When undertaken under MR guidance, it is possible to not only target the beam geometrically but to also provide real-time feedback on temperature changes within the treatment cell and the surrounding tissue using MR thermometry (**Figure 4.1**) [149, 150]. As a result, the therapeutic use of image guided HIFU has expanded over the last decade. Within the pelvis, MRgHIFU, is now an established ablative therapy for symptomatic benign uterine fibroid disease where it has been shown to be a cost effective and safe treatment modality compared to surgery (cf. 1.1.3.2) [149-152].

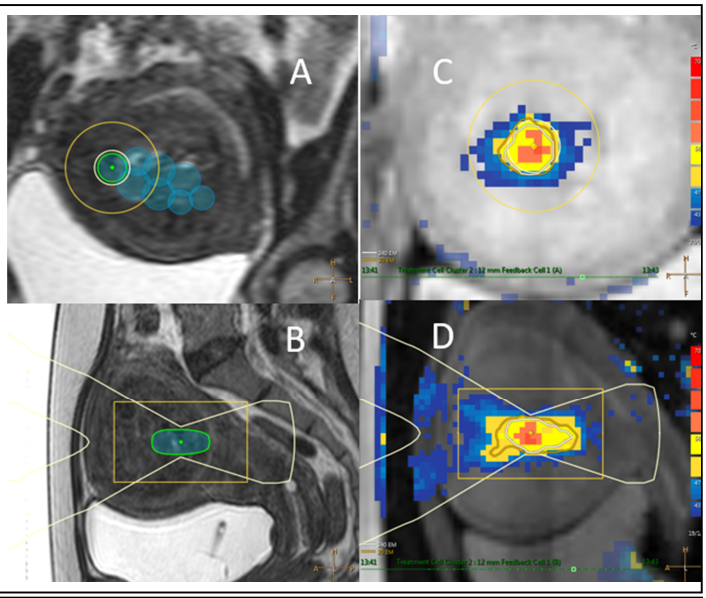


Figure 4.1 Placement of HIFU cells within a uterine fibroid seen in coronal (A) and sagittal (B) section and overlaid temperature maps based on MR thermometry in coronal (C) and sagittal (D) planes. Adapted from Philips Sonalleve user interface.

4.1.2 Need for additional treatment strategies in recurrent gynaecological cancer

Uncontrolled recurrent gynaecological cancer is associated with significant morbidity and causes progressive symptoms including pain and bleeding. Patients are usually not suitable for conventional therapies as they have previously received radiotherapy and do not meet the criteria for exenterative surgery. Moreover, response from systemic therapy within the irradiated pelvis is usually poor. As a result, treatment options are limited, and the progressive symptoms negatively impact the quality of life in these patients. The lack of ionizing radiation makes MRgHIFU ideal to use in the previously irradiated pelvis. Despite these advantages, it has not been exploited to treat recurrent gynaecological malignancy. This is the first trial examining its safety in this setting.

4.2 Hypothesis

In patients with symptomatic recurrent gynaecological cancer not suitable for other therapies, MRgHIFU can be delivered safely and improves patient reported symptom outcomes.

4.3 Aim and Objectives

Aim: To document the safety of MR guided HIFU in a pilot group of patients with recurrent gynaecological malignancy, monitor changes in symptoms on patient reported outcome measures and make a preliminary assessment of the health economics of this treatment modality.

Objectives:

1. Document adverse events related to treatment in a pilot cohort of 15 patients.
2. Document changes in pain scores at 30, 60 and 90 days from baseline, measured using a numerical rating scale (NRS) pain score and decrease in medication use.
3. Document changes in bleeding up to 90 days from baseline, measured by patient reported estimated blood loss and questionnaires.
4. Document changes in tumour size and enhancement pattern and correlate these with the thermal dose delivered.
5. Document the effect of MRgHIFU on patients' quality-of-life (measured by the changes in scores on EORTC-C15-PAL and EQ-5D-5L questionnaires).
6. Pilot a health economic assessment of MRgHIFU in this setting.

4.4 Methods

4.4.1 Trial Design

In a pilot single centre, non-randomised, non-blinded study, patients were recruited into two cohorts (clinical trial registration number NCT02714621). Cohort 1 predated the work in this thesis and was a non-investigational feasibility study in 20 patients with recurrent gynaecological pelvic malignancy where virtual treatment plans were constructed and an arbitrary threshold of targeting ≥ 50% of the lesion without damage to OARs in ≥ 20% was set as a success criterion to proceed to a treatment. As this criterion was met, patients were recruited to a treatment cohort (Cohort 2), which forms the work described in this chapter.

4.4.2 Patient selection and recruitment

Patients with recurrent gynaecological malignancy not suitable for other therapies or who declined standard treatment were recruited. Patients were symptomatic from their recurrent gynaecological target lesion with Numerical Rating Scale (NRS) pain score of ≥ 4 and/or bleeding, discharge or other pressure symptoms such as urinary or bowel symptoms. Inclusion and exclusion criteria for treating patients with MRgHIFU within the trial are summarised in **Table 4.1**.

Between December 2017 and September 2019, patients who met the inclusion and exclusion criteria were identified either through the weekly gynae-oncology multidisciplinary team (MDT) or from patients referred for consideration of trials to the gynae-oncology team at the RMH. They were provided with the patient information sheet at least 24 hours before obtaining written consent. Patients underwent an initial screening MRI scan in the treatment position with the HIFU device in place two weeks prior to treatment. The images were exported onto the Sonalleve™ treatment planning console and a theoretical treatment plan made to

ensure that the lesion was at least partly accessible to treatment whilst critical structures (bowel, bladder, bone, nerves and vessels) were outside the beam path.

INCLUSION CRITERIA	• Patients with recurrent pelvic gynaecological malignancy • Recurrent lesion is painful (NRS ≥ 4) or causing troublesome bleeding and not suitable for alternative treatments • Intended target volume accessible for MRgHIFU treatment • Intended target volume visible on non-contrast MR imaging • Distance between target and skin ≥1cm
EXCLUSION CRITERIA	• MRI contra-indicated (e.g. by incompatible metal implants, claustrophobia or body mass index precludes accommodation in the MR scanner) • Pregnancy • Sedation contra-indicated • MRI contrast agent contra-indicated • Critical anatomical structure, radiation fibrosis or scar cannot be avoided along the beam path or the at the target (assessed at screening) • Internal or external fixation device along the beam path or at the target

Table 4.1 Inclusion and Exclusion Criteria for the Treatment Arm of the MRgHIFU in recurrent pelvic malignancy study.

4.4.3 Patient preparation and Treatment procedures

Two patients had a previous pelvic exenteration and required no pre-HIFU preparation due to lack of bowel and bladder in the HIFU path. In 2 patients, inguinal nodes were treated, which also did not require bowel and bladder preparation. All patients were instructed to shave the area being treated to reduce any air trapping and create a uniform interface.

4.4.3.1 Bladder Preparation

Patients with pelvic target lesions and no prior exenteration had a catheter inserted under aseptic sterile conditions on the morning of the procedure. This was left on free drainage. Following anaesthesia, the bladder filled with 200 ml of sterile 0.9% normal saline solution and the catheter clamped. This not only improved visualisation of the tumour-bladder wall interface for centrally recurrent lesions but also served as a means of heat dissipation beyond the HIFU treatment focus.

4.4.3.2 Bowel Preparation

Rectal preparation was required for patients with pelvic lesions to reduce rectal air or faecal load and avoid the rectal wall being in the beam path.

I devised a rectal preparation protocol from the RMH bowel preparation guidelines for pelvic radiotherapy. Patients 2, 6 and 8 were commenced on a low residue diet a week prior to treatment (**Appendix 4.1**). I also provided patients with three days of micolette® enema for self-administration on the days prior to treatment; they also had an enema on the morning of the procedure if they had an afternoon treatment.

On the day of treatment for patients 2 and 9, I introduced a standard urinary catheter into the rectum after anaesthesia and prior to imaging to aspirate bowel gas. The catheter was removed in patient 9 after pre-treatment imaging as the rectum appeared completely empty and collapsed. In patient 2, the catheter remained in situ during treatment. I also introduced degassed gel (1:2 ultrasound gel to de-ionised gel constitution) via the catheter into the vagina to reduce the amount of air in the HIFU path. **Figure 4.2** demonstrates the bladder, vaginal and rectal preparation of patient 2 on the day of HIFU treatment compared to screening.

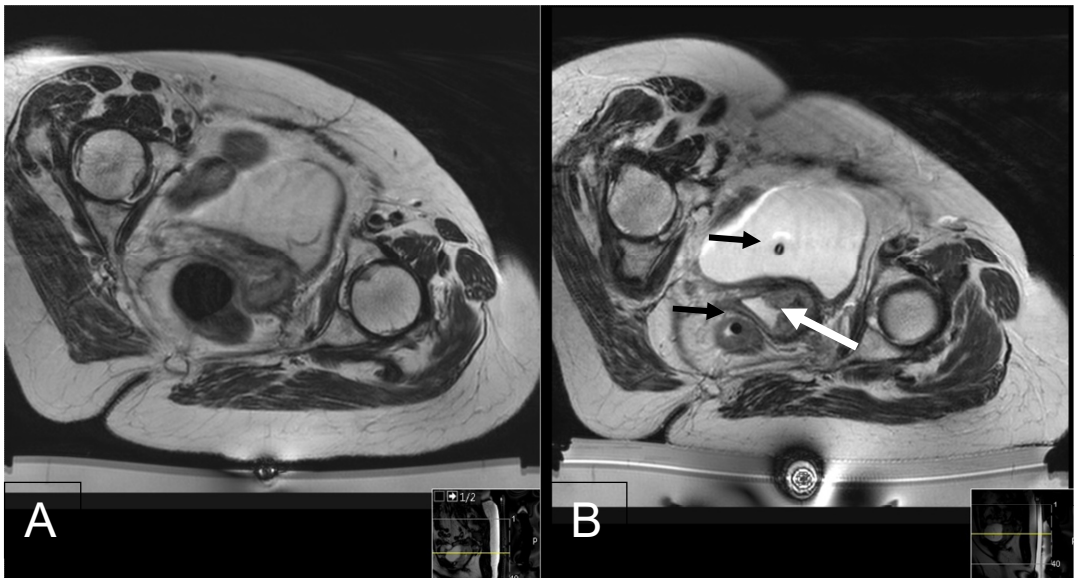


Figure 4.2 Patient with central recurrence in position within the MRI scanner with the HIFU device in place. T2-W image at planning study (A) and on day of treatment (B) after bowel and bladder preparation. In B, urinary and rectal catheters (black arrows) are noted in situ. The vagina is filled with degassed gel (white arrow).

4.4.3.3 Patient Positioning

Patient positioning on the day of treatment was guided by the planning study and aimed to place the target lesion as close as possible to the centre of the HIFU window. All patients with pelvic lesions and one with the perineal lesion were placed in the supine oblique position. The other three patients with extra-pelvic lesions were placed in the prone oblique position.

4.4.3.4 Ensuring Acoustic Coupling

All patients had direct skin contact with a dampened gel pad acoustically in contact with the HIFU window. Degassed gel was produced by trial physicist, Dr Ian Rivens, by combining ultrasound gel and de-ionised water in different proportions (1:1, 1:2 and 1:4) to achieve different consistencies. I used the gels to enhance the acoustic coupling between the MRgHIFU treatment window and the patient's skin in all cases. I also instilled it into the groin fold for patient 3 who had an overlying scar due to prior lymphadenectomy and a skin to skin interface due to large habitus. I

also instilled degassed gel into the vaginal vault of patient 2 (**Figure 4.2**), after sedation, where an exophytic tumour was associated with vaginal air. This displaced the air within the vaginal vault which would otherwise have interfered with the HIFU beam.

In two patients, due to the irregular nature of the skin overlying the buttock and the left knee, a custom made 40 mm gel pad was sculpted and used to achieve acoustic contact with the HIFU window. This allowed a larger volume of degassed water to be introduced between skin and gel pad. It improved acoustic coupling as the gel pad assumed the irregular contour of the skin overlying the target lesion.

4.4.3.5 Anaesthesia

This was overseen by the anaesthetic team lead by Dr Matthew Brown. For the first three treatments, patients underwent a combination of general anaesthesia and heavy conscious sedation. Two treatments were carried under spinal block with conscious sedation and one patient had only regional nerve block at her request. As the team became more experienced with the technicalities of remote anaesthesia and monitoring, the last four patients had general anaesthesia.

4.4.3.6 Imaging

4.4.3.6.1 Pre-treatment

In addition to conventional 2DT1W and T2W sequences, 3D T2W, Echo-Planar Imaging- Diffusion-Weighted Imaging (EPI-DWI), 16-echo T2W and 5-echo gradient and spin-echo (GRASE) T2W sequences were used with a field-of-view (FOV) that covered the entire region of interest. For centrally located tumour recurrences, this was the whole pelvis. The THRIVE (T1W high-resolution isotropic volume examination) sequence was acquired before and after administration of 0.2 mls/Kg gadolinium (Gd)-contrast agent because it provided a high quality T1W image with robust fat saturation. Sequence details are given in **Table 4.2.**

Parameter	3D TSE T2W	THRIVE	EPI-DWI	16 echo TSE	5 echo GRASE
TR (ms)	1500	5.4	9000	2000	2116
TE (ms)	165	2.6	65	9.8	20
Flip Angle (FA) (º)	90	12	90	90	90
Fat suppression	-	SPAIR	SPIR & SSGR		
Frequency offset (Hz)	-	220			
TSE/TFE factor	67	18	69	32	5
Voxel size (mm^3)	1.5 x 1.5 x 1.5	1.5 x 1.5 x 1.5	3.5 x 3.5 x 4.5	1 x 1 x 2	1 x 1 x 2
FOV (mm)	250 x 250 x 200	250 x 250 x 200	300 x 327 x 185	200 x 200	200 x 200
b values (s/mm^2)			0, 100, 700		
Echo spacing				13	20
Number of signal averages (NSA)	1	1	3	3	3
Number slices	133	133	41		
Scan duration min:sec	02:13	03:03	4:48	05:38	02:00

Table 4.2 Scan parameters used before, immediately post-treatment and at follow-up.

4.4.3.6.2 During treatment

Treatment planning utilised axial images with visualisation of the focus on three orthogonal slices. It was done in a research configuration of the Sonalleve system to allow variations from the planning utilised for fibroid treatments (e.g. plans done in the sagittal plane).

Proton Resonance Frequency Shift (PRFS) data were used to indicate temperature at and around the focus. They were first acquired without sonication to document the degree of noise or artefact present in the images, followed by their acquisition during low-powered test sonications to estimate the powers required to achieve ablative temperatures. Cells of 4 and 8 mm diameter were delivered with PRFS data before, during and after each exposure. This provided information on temperature increases and determined the required cooling time before the next exposure. Cells located at the greatest depth were delivered first, to avoid making exposures through already heated regions. The extent of treatment varied between patients and depended on the risk of exposure to surrounding structures. To reduce risk to

the skin and subcutaneous tissues, the time allowed for cooling between each exposure always exceeded the minimum cooling periods given by the software.

4.4.3.6.3 Post-treatment

The same MR imaging sequences were acquired at baseline and at the follow-up visits. Immediately post-treatment, the EPI-DWI, 12 echo fast field-echo (FFE) and Dixon sequences (for registration with post-contrast images) were re-acquired, followed by administration of 0.2 mls/Kg Gd-contrast agent and post-contrast Dixon imaging.

4.4.4 Patient Recovery

Patients were monitored briefly after ablation in recovery within the anaesthetic department before returning to the admitting ward. Two patients were discharged on the same day as their treatments and the remaining patients were discharged the following morning using the Trust's short stay <23 hours admissions policy after a period of overnight monitoring.

4.4.5 Data Collection

The schedule of visits and assessments at baseline and post-treatment is summarised in **Table 4.3**.

For each patient treated within the trial, I collected baseline demographic data and carried out an assessment of their symptoms at screening, treatment day and at days 1, 7, 30, 60 and 90 post-treatment using the NRS pain score. Patient symptomatology and quality of life data was collected by asking patients to keep a symptom diary (Day -7 to Day 30) and complete a Brief Pain Inventory (BPI), QLQ-C15-PAL and EQ-5D-5L (**Appendix 4.3 a, b, c**) at each visit.

The symptom diary (**Appendix 4.4**) detailed analgesic use as a surrogate of change in pain after treatment as well as blood loss, if any, by number of pads required per day. The BPI used a validated questionnaire to assess patients' pain levels and assess its impact on their daily life.

The QLQ-C15-PAL contains 7 symptom scales (dyspnoea, pain, insomnia, fatigue, appetite loss, nausea and vomiting, and constipation) and 3 functional scales (physical functioning, emotional functioning, and overall QoL), which were identified as being relevant to the palliative population. Items on the QLQ-C15-PAL were rated on a 4-point Likert scale from 1 (Not at All) to 4 (Very Much), with the exception of the overall QoL status item, which was rated from 1 (Very Poor) to 7 (Excellent). A higher score for the symptom scales represents a higher level of symptomatology, and therefore a decreased quality of life. In contrast, a higher score for the functional scales represents a higher level of functionality, and therefore an increased quality of life. Each scale was transformed to a score ranging from 0 to 100, according to their respective scoring manual. The EQ-5D-5L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems). The patient indicates the most appropriate statement in each of the five dimensions, which provides a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. Items are weighted and an algorithm applied that varies with cultural and societal influences (UK weightings used for this study) in order to derive an EQ-5D-5L index value. The EQ-5D-5L captured overall health status and the QLQ-C15-PAL assessed more specifically their QoL [153-155].

	Recruitment Stage	Baseline Tests	MRgHIFU (Day 0)	Day 1 ± 1	Day 7 ± 1	Day 30 ± 5	Day 60 ± 5	Day 90 ± 5
Hospital visit	✓	✓	✓		✓	✓	✓	✓
Telephone consultation				✓	**Available at any time**			
PIS and consent form provided	✓							
Consent signed		✓						
Demographic data recorded		✓						
Physical examination		✓	✓		✓	✓	✓	✓
Blood-work as per local requirement		✓						✓
Patient diaries				✓				
Pain medication recording		✓	✓		✓	✓	✓	✓
MRI		✓	✓		✓	✓	✓	✓
BPI		✓	✓		✓	✓	✓	✓
EORTC-C-15		✓	✓		✓	✓	✓	✓
EQ-5D-5L		✓	✓		✓	✓	✓	✓

Table 4.3 Schedule of patient visits and data collected at each time-point

Patients were categorised into responders and non-responders based on their baseline score compared to the average score of reported pain on the NRS score for days 28 – 30. They were considered a responder if they had: (i) an improvement of ≥ 2 points in their reported pain at time point ≥ day 30 provided they had < 20% increase in their analgesic use, (ii) ≥ 25% reduction in their analgesic use without change in their reported pain (iii) improvement in patient reported vaginal bleeding and/or discharge as indicated by number of required sanitary pads. Otherwise, if patients had no change in their pain scores or ≥ 20% increase in their analgesic use, they were deemed a non-responder.

4.4.6 Statistical Analysis

Analyses were descriptive in nature due to the low number of patients recruited. I summarised continuous variables using mean, standard deviation, median, quartiles, minima and maxima and categorical variables using counts and percentages. Safety data below is reported using the number and percentage of patients with adverse events by Common Terminology Criteria for Adverse Events (CTCAE) 4.1 grade as assessed by patient reported outcomes, and my review and clinical examination.

4.5 Results

In total, 13 patients were recruited and 11 treatments done in 10 patients (one patient had the same target pelvic lesions treated twice). Two patients failed screening. **Table 4.4** summarises the patients' demographic and tumour characteristics. Patients were divided into two groups based on the location of the target lesion: intra-pelvic versus extra-pelvic.

4.5.1 Adverse Events

There were no anaesthetic complications for any of the treatments. There were no serious adverse events (SAEs) observed during and immediately after any of the treatments. The most common treatment related adverse events (AEs) were skin erythema and pain.

Pt (Rx)	Age	Primary	Histology	Site recurrence	Time to recur (yrs)	Symptom	Base KPS	Prior surgery	Prior RT	Prior chemo
1	74	Bartholin gland	Adenoid cystic	Ischiorectal fossa	19	Pain	60	exenteration	Brachy, EBRT	
2	59	Endometrial	G2 endometroid AC	Left lateral vaginal vault	13	Pain, Bleeding	70	√	EBRT, VVB	√
3	69	Vulvar	G2 SCC	R inguinal node, perineal	1	Pain, lymphedema	60	√	EBRT	√
4	64	Cervical	G3 SCC	Rightischiorectal fossa	23	Pain	80	exenteration	EBRT, SBRT	√
2(5)	59	Endometrial	G2 endometroid AC	Left lateral vaginal vault	13	Pain, Bleeding	70	√	EBRT, VVB	√
6	42	Vulvar	G1 SCC	Left inguinal node	1	Pain	90	√	declined	√
7	54	Cervical	Mucinous AC	Left pelvic side wall	15	Pain	80	√	EBRT, VVB	√
8	49	Cervical	G3 SCC	Left popliteal fossa	1	Pain, lymphedema	70	√	EBRT	√
9	72	Endometrial	G1 endometroid AC	Left lateral vaginal vault	12	Pain, Bleeding	60	√	EBRT, VVB	√
10	54	Cervical	G3 SCC	Cervix	0.5	Pain	70	abandoned	EBRT	√
11	54	Vulvar	G3 SCC	Left inguinal node	0.16	Pain	70	√	EBRT	√

Table 4.4 Patient characteristics of those treated

AC= adenocarcinoma, SCC= squamous cell carcinoma, KPS= Karnofsky performance score, EBRT= external beam radiotherapy, SBRT= stereotactic body radiotherapy, VVB=vaginal vault brachytherapy. Blue filled rows indicate patients with extra-pelvic lesions.

4.5.1.1 Skin and subcutaneous changes

Patient 4 sustained a burn to the groin area within the treatment path. This was likely due to a combination of the skin to skin interface of the groin fold and the scar tissue where HIFU energy is deposited. Unfortunately, this developed into a grade 2 burn (**Figure 4.3**) which had not resolved by day 60 review; this is likely due to the poor vascular supply of the previously operated and irradiated overlying skin. This was managed conservatively in the community by the tissue viability team. This had not healed by Day 60 visit and was a significant contributor to the increasing pain scores for the patient.

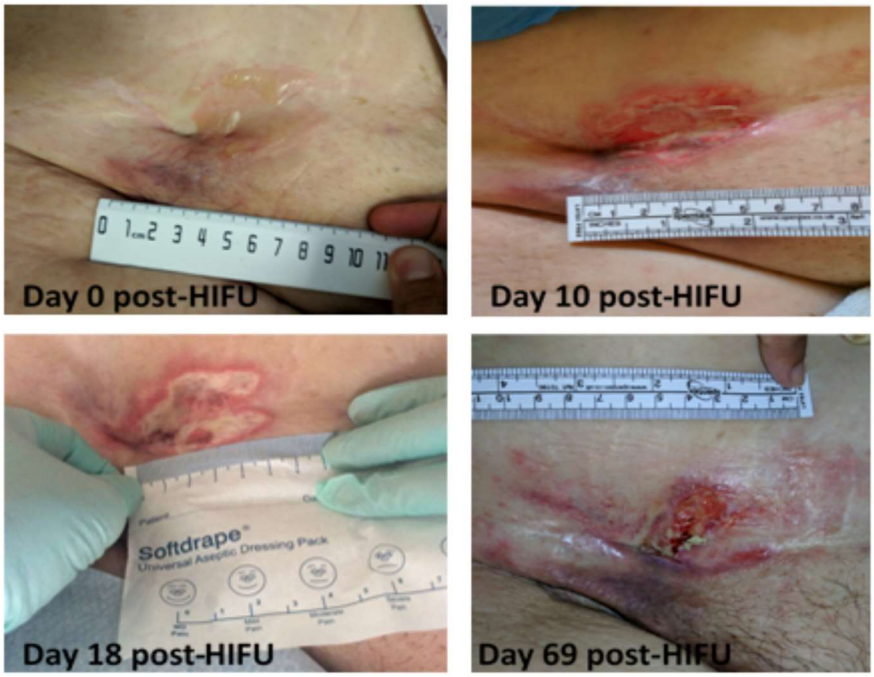


Figure 4.3 Photograph of skin burn appearance with blistering immediately after treatment (top left), and at 10 days (top right) when HIFU beam inadvertently traversed scar tissue. At 18 days post-treatment there was breakdown of overlying skin (bottom left), which healed slowly (bottom right).

In Patient 9, some erythema seen over the sacral area developed into 2 small blisters, that resolved within 30 days (**Figure 4.4**). In both these cases, the skin changes were indicated by the thermometry feedback during treatment.

Three other patients experienced mild G1 erythema that was managed with ice packing during recovery to good effect.

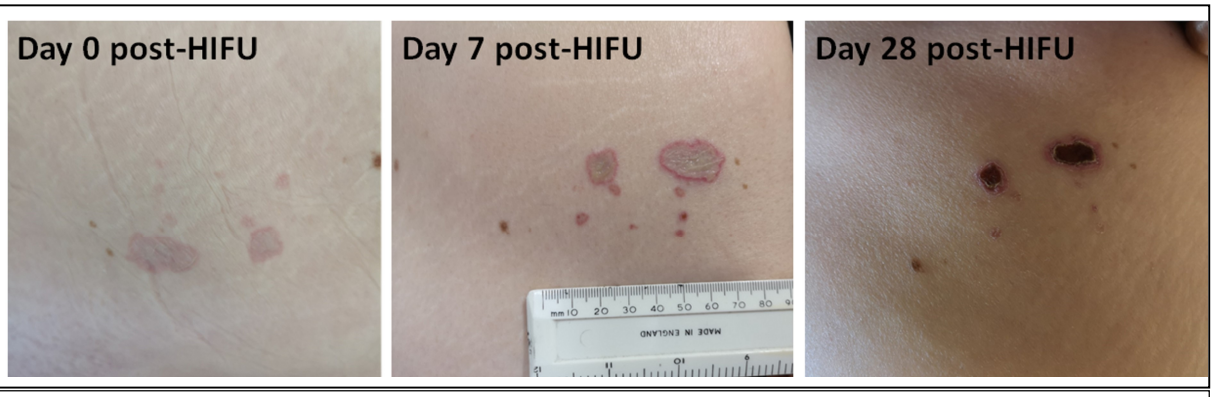


Figure 4.4 Photograph of reddening immediately after treatment (left), and at 7 days (centre) and 28 days (right) in overlying normal skin despite good acoustic contact and no demonstrable air trapping during treatment.

Pre-focal fat necrosis was evident post-treatment in 2 cases and was asymptomatic. It was not identifiable on the thermometry scans during treatment, as no thermometry information is obtained from fat.

4.5.1.2 Pain flare

Five patients, 2 with pelvic and 3 with extra-pelvic tumours, experienced pain within 24 hrs of treatment that was attributed to HIFU. This was recorded as acute increase in NRS pain score and subsided within 48 hours. In one patient, the pain flare had a delayed onset starting on Day 3 after treatment and subsiding by Day 7 follow up. In one patient, the pain was related to superficial skin burn.

Following her first treatment, patient 2 was admitted to hospital on day 18 with pelvic pain and was found to have a urinary tract infection (UTI). Although she was known to have recurrent infections and was discharged on three days of prophylactic antibiotics, this could have been related to HIFU treatment as she had a catheter inserted. Due to the nature of the pain, and to exclude HIFU-related damage to the adjacent rectum, she had a sigmoidoscopy. This confirmed no rectal

burn. Her pain resolved and she did not experience a similar episode following the second treatment where she had intravenous antibiotics prior and after catheterisation.

Patient 8 with a popliteal fossa lesion had immediate reduction in pain, which prompted a burst of activity and physiotherapy. This resulted in a pain flare at Day 7, which settled by Day 30.

4.5.2 Patient reported outcomes

4.5.2.1 Recording longitudinal changes in whole cohort

4.5.2.1.1 Pain

Pain was the commonest baseline symptom with two patients also experiencing vaginal bleeding and another experiencing significant leg lymphoedema as summarised in Table 4.4.

All patients completed their diaries which detailed pain, bleeding and analgesic use for the 7 days prior to treatment up to and including day 30. Baseline score was the average patient reported score for the eight days prior to treatment.

All patients also completed Day 30 follow-up with 4 patients completing all follow up end points as detailed in **Table 4.5**. The clinical status of the patient and their classification as a responder or non-responder is given in **Table 4.6**. **Figure 4.5** details average pain score for each patient at each of the completed time points and **Figure 4.6** compares median and quartile changes between those classified as responders vs. non-responders at Day 7 and Day 30 post treatment. Differences between responders and non-responders were greater at Day 7 than Day 30, although statistical evaluation was not possible given the small patient numbers.

Patient (Treatment)	Diaries D7- D30	MRI scans	BPI	QLQ-C15-PAL	EQ-5D-5L
1	√	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90
2	√	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90
3	√	B, D0, D7, D30, D60	B, D0, D7, D30, D60	B, D0, D7, D30, D60	B, D0, D7, D30, D60
4	√	B, D0, D7, D30, D60	B, D0, D7, D30, D60	B, D0, D7, D30, D60	B, D0, D7, D30, D60
2 (5)	√	B, D0, D7, D30, D90	B, D0, D7, D30, D90	B, D0, D7, D30	B, D0, D7, D30, D90
6	√	D0, D7, D30, D60	D0, D7, D30	D0, D7, D30	D0, D7, D30
7	√	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D60, D90	B, D0, D7, D30, D60, D90
8	√	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90	B, D0, D7, D30, D60, D90
9	√	B, D0, D7, D30	B, D0, D7, D30	B, D0, D7, D30	B, D0, D7, D30
10	√	B, D0, D7, D30	B, D0, D30	B, D0, D7, D30	B, D0, D30
11	√	B, D0, D7, D30	B, D0, D7, D30	B, D0, D7, D30	B, D0, D7, D30

Table 4.5 Details of completion of study procedures by each patient for the set time-points.

B=baseline, D0= day of treatment, D7= Day 7 post treatment, D30= Day 30 post treatment, D60= Day 60 post treatment, D90= Day 90 post treatment.

Patient (Treat)	Current Status/Completed	Treatment-related AE	Classification of response at D30
1	Alive, Completed trial	G1 erythema	Responder
2	Dead, completed trial	G2 Pain, UTI	Partial
3	Dead, completed day 60.	G2 HIFU burn G2 Pain	Non-responder
4	Dead. Completed day 60	Nil	Non-responder
2 (5)	Dead, completed day 30	asymptomatic fat necrosis	Non-responder
6	Lost to follow up, completed Day 90	G1 erythema	Responder
7	Alive, completed Day 90 - PD	Nil	Responder
8	Lost to follow up, completed Day 90 - SD	G2 pain flare	Responder
9	Dead, Completed day 30	Nil	Non-responder
10	Dead, completed D30, SD	Nil	Responder
11	Dead, completed D30, PD	Nil	Non-responder

Table 4.6 Clinical status of patients, adverse events (AE) and classification of response

SD: stable disease, PD: progressive disease.

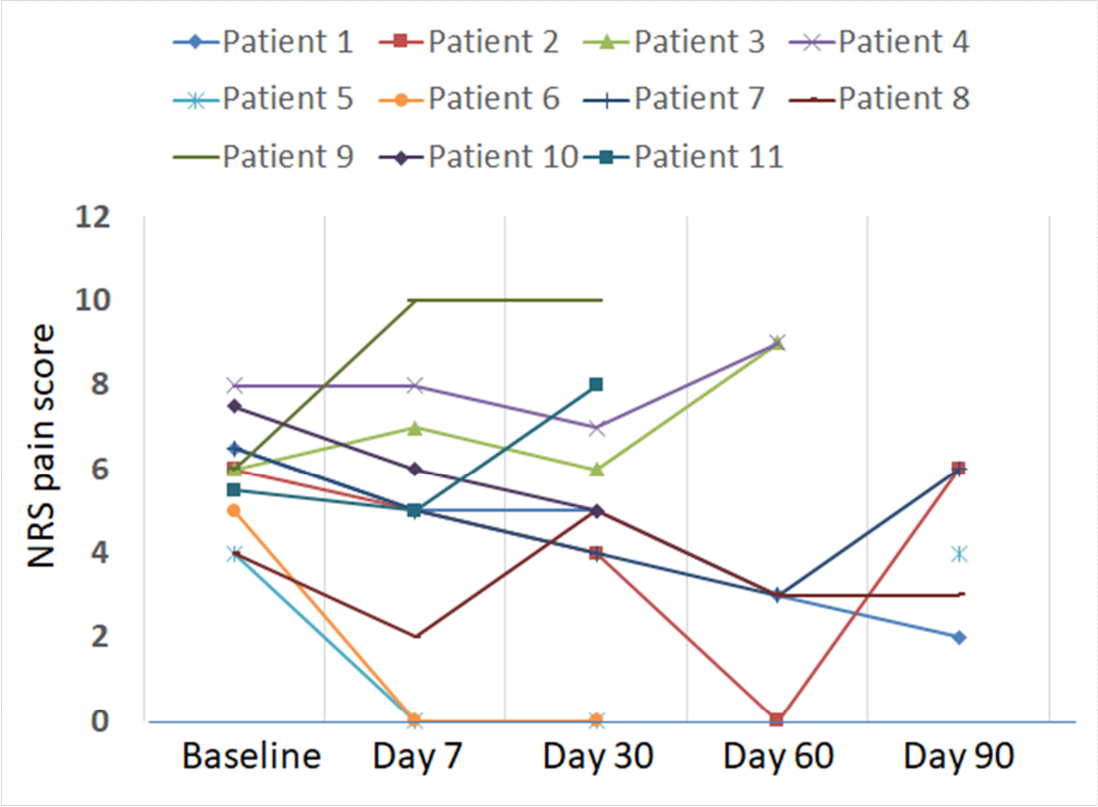


Figure 4.5 Longitudinal variation in NRS pain scores for each patient treatment over a 90-day period after HIFU. Baseline values are shown as the mean between screening and pre-treatment assessment.

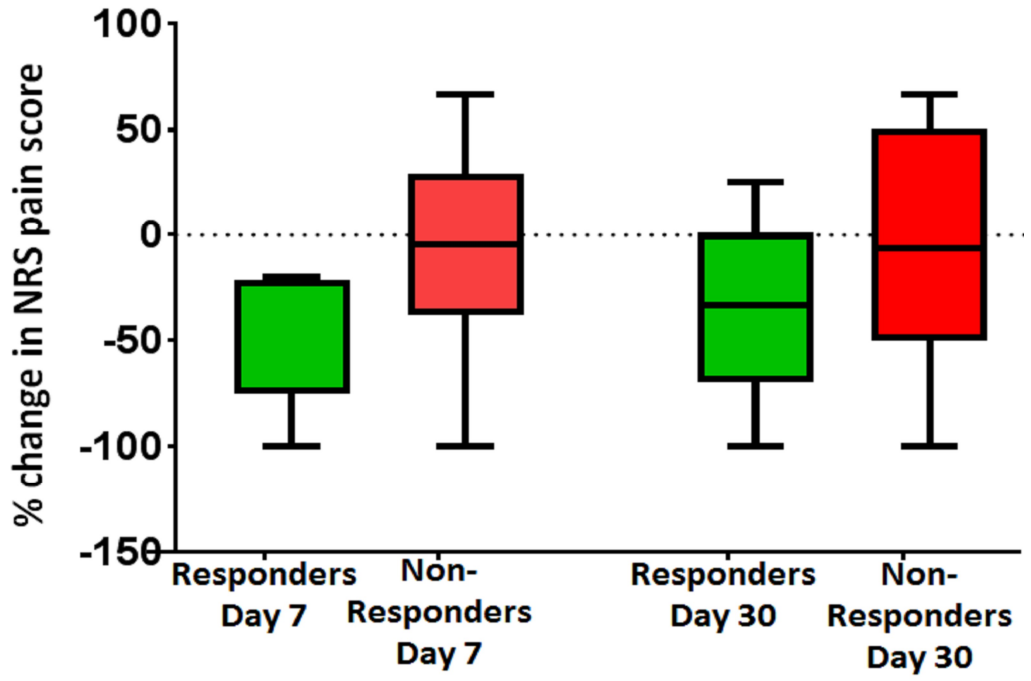


Figure 4.6 Box and whisker plot summarising percentage change in NRS pain scores for 5 responders (green) and 6 non-responders (red). Median (central line) and upper and lower quartiles are indicated by the upper and lower boundaries of the box. The whiskers denote maximum and minimum values.

4.5.2.1.2. Bleeding

Per vaginal (PV) bleeding was present at baseline in two patients. Patient 2, who was treated twice, had subjective and objective improvement in PV bleeding following her first treatment as reported by the patient and ascertained by speculum examination at each clinical visit. However, this was not reflected in her diary record as the severity score remained unchanged (mean score of 3) as did the number of reported pads used per day (3 per day, 7 days a week). This was because of a continuing colourless discharge which still required pads. Moreover, her bleeding resumed prior to her second treatment (severity score 3 at baseline, requiring 3 pads per day, 7 days a week), and it did not improve following MRgHIFU ablation. The second patient to experience PV bleeding had no change in bleeding reported (mean severity score 3, requiring three pads per day).

4.5.2.2 Patient diaries

Diaries documented pain on a score of 1-10 from Day -7 to Day 30. Average scores for Days -7 to immediately pre-treatment (n=8 observations) and from Day 23 to Day 30 inclusive (n=8 observations) are given in **Table 4.7**. Patients 1, 5, 6, 7, 8 and 10 showed a reduction in pain score post treatment, patients 3, 4 and 9 were unchanged and patients 2 and 11 recorded worsening pain by 30 days post-treatment.

Patient	Average diary score Day -7 to treatment	Average diary score Day 23-30
1	5.5	4.4
2	7.8	10
3	6.1	6.5
4	7.9	7.6
2 (5)	3.1	0.8
6	6.1	5.0
7	5.4	3.8
8	6.5	4.9
9	9.8	10.0
10	9.3	7.0
11	6.3	7.625

Table 4.7 Average pain diary score in the 8 days preceding treatment and in the eight days up to Day 30. Those classified as responders are colour coded green and those classified as non-responders in red.

4.5.2.3 Comparison of Symptom Control in Patients with Pelvic vs. extra-pelvic lesions

In the intra-pelvic lesion group, 1 of 5 patients responded. Partial response was seen in Patient 2 after her first treatment where she had subjective and objective improvement in vaginal bleeding, however this was not reflected on the number of pads used as there was on-going discharge. Two patients (40%) experienced pain progression at day 30 and one patient's pain and analgesic use remained unchanged (patient 4, 20%).

Three patients with extra pelvic lesions were classified as responders. All three patients had successful partial ablation of their target tumour. Patient 1 had sustained response throughout her trial participation with corresponding image changes at Day 90. Patient 8 was classified as a non-responder at Day 30, but by Day 60 clearly achieved good pain control. Change in pain score between those with pelvic and extra-pelvic lesions for each time point is given in **Figure 4.7**.

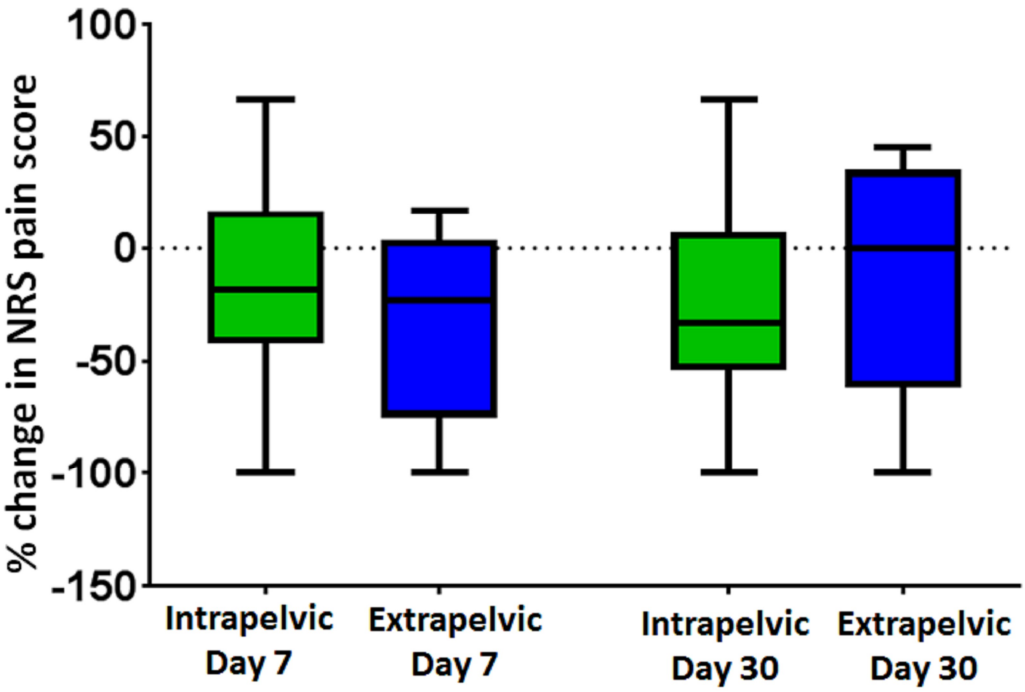


Figure 4.7 Box and whisker plots of percentage change in NRS pain scores of treated patients with intra-pelvic (green, n=5) vs. extra-pelvic (blue, n=6) lesions at Day 7 and Day 30 showing no differences between groups. Median (central line) and upper and lower quartiles are indicated by the upper and lower boundaries of the box. The whiskers denote maximum and minimum values. Only 3 data points at Day 60 and 2 at Day 90 for each group limited meaningful evaluation at these time-points.

4.5.2.4 Relating pain scores to thermal dose delivered

Table 4.8 summarises the delivered treatment parameters in relation to tumour location and estimated deposited thermal dose to tumour as obtained from the Sonalleve™ system with the aid of Dr Sharon Giles. Although thermal deposition was achieved in all patients, only three patients (all extra-pelvic) had 240EM dose contours at the tumour focus and one patient had 240EM contour at the scar tissue pre-focally. Lack of 240EM in all but one of the patients with pelvic tumours meant that mean focal temperatures were < 55°C. In patient 6 where there was pre-focal heating, treatment had to be terminated prematurely as high heating was seen in the region of the skin fold at site of her prior surgical scar.

Patient (Treatment)	Total thermal dose kJ	V_{240EM} ml	% change in pain score from baseline at D7	% change in pain score from baseline at D30	% change in pain score from baseline at D60	% change in pain score from baseline at D90
1	36.4	0.1	-23.1	-23.1	-53.8	-69.2
2	38.9	0	-16.7	-33.3	-100	0
3	80.3	0	16.7	0	50	-
4	61.7	0.1	0	-12.5	12.5	-
2 (5)	23.3	4.5	-100	-100	-	0
6	95.6	0	-100	-100	-	-
7	52.8	0	-23.1	-38.5	-53.8	-7.7
8	24.5	19.0	-50	25	-25	-25
9	97.1	0.6	66.7	66.7	-	-
10	86.4	0	-20	-33.3	-	-
11	31.2	0	-9.1	45.5	-	-

Table 4.8 Relationship of thermal energy delivered and dose to change in NRS pain score at each time-point.

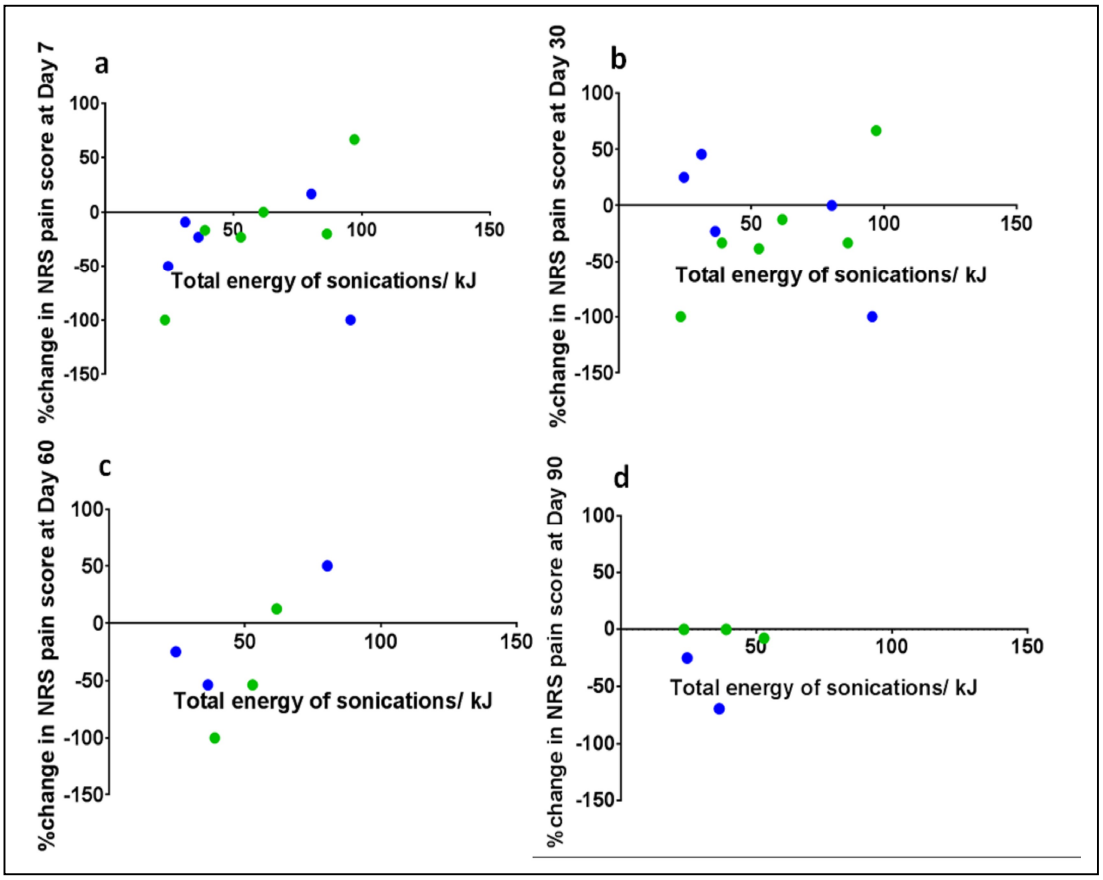


Figure 4.8 Scatter plots of association between thermal dose delivered and change in NRS pain score for all patients at Days 7, 30, 60 and 90 (a, b, c and d respectively). Patients with intrapelvic lesions are shown as green circles; patients with extra-pelvic lesions are represented as blue circles.

In this small patient cohort, there was no observable relationship between thermal dose delivered and percentage change in pain score (**Figure 4.8**). Also, where a V240EM was recordable, there was no relationship with change in pain score (**Figure 4.9**), but the small numbers of patients treated in this pilot study makes the interpretation of these data unreliable.

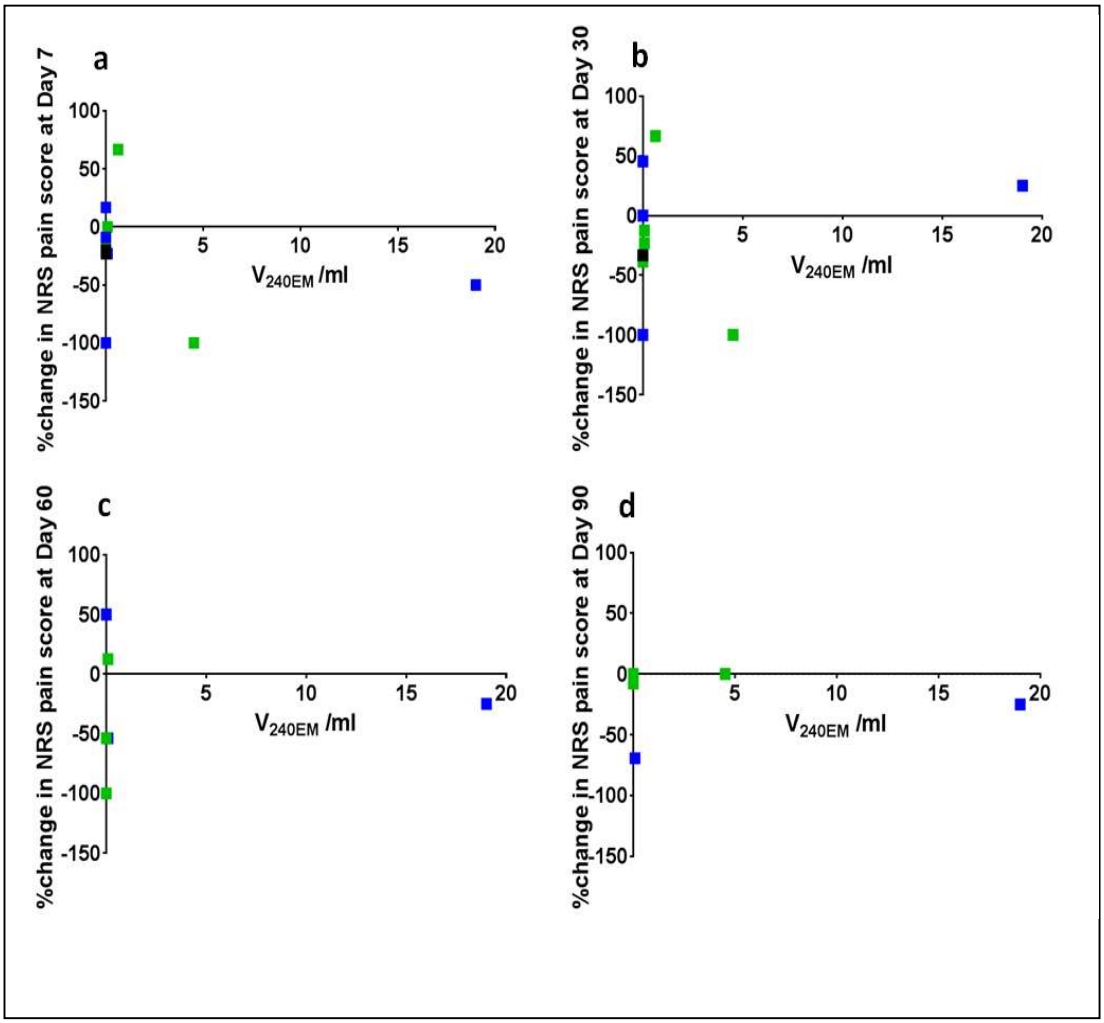


Figure 4.9 Scatter plots of association between V_{240EM} delivered and change in NRS pain score for all patients at Days 7, 30, 60 and 90 (a, b, c and d respectively). Patients with intrapelvic lesions are shown as green squares; patients with extra-pelvic lesions are represented as blue squares.

4.5.2.5 Quality-of-Life Measures

QoL scores were extracted from the QLQ-C15-PAL and EQ -5D-5L questionnaires.

4.5.2.5.1 EORTC C-15

All scales were normally distributed, with the exception of the dyspnoea and nausea and vomiting scales. Only nausea and vomiting was different between responders' and non-responders' baseline scores (**Table 4.9**).

Mean±standard deviation (SD) scores for each symptom and functional scale over time are presented in **Table 4.10**. Considering the whole cohort, although physical functioning did not improve with time, emotional functioning did. Other symptoms remained stable. Scores at 60 and 90 days are biased towards patients who completed these time points.

QLQ-C15-PAL	Baseline responders N=5	Baseline non-responders N=6
Physical Functioning	47.3±25.0	41.1±17.8
Emotional Functioning	67.5±22.2	66.7±14.8
Dyspnoea	15.0±18.8	5.6±13.6
Pain	65.0±13.8	63.9±27.7
Insomnia	60.8±38.3	44.4±32.1
Fatigue	53.6±18.5	51.9±19.2
Appetite Loss	30.8±30.1	27.8±25.1
Nausea and Vomiting	30.5±35.1	2.8±6.8
Constipation	33.3±31.9	33.3±32.0
Overall QoL	42.5±9.4	50.0±15.7

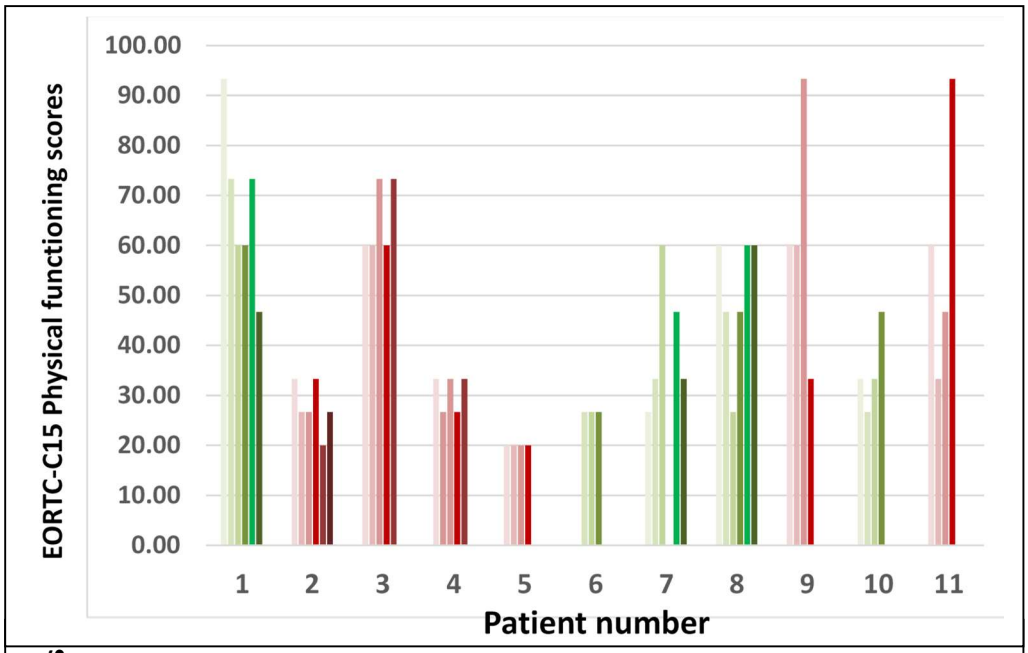
Table 4.9 Baseline scores in responders and non-responders for each QoL feature.

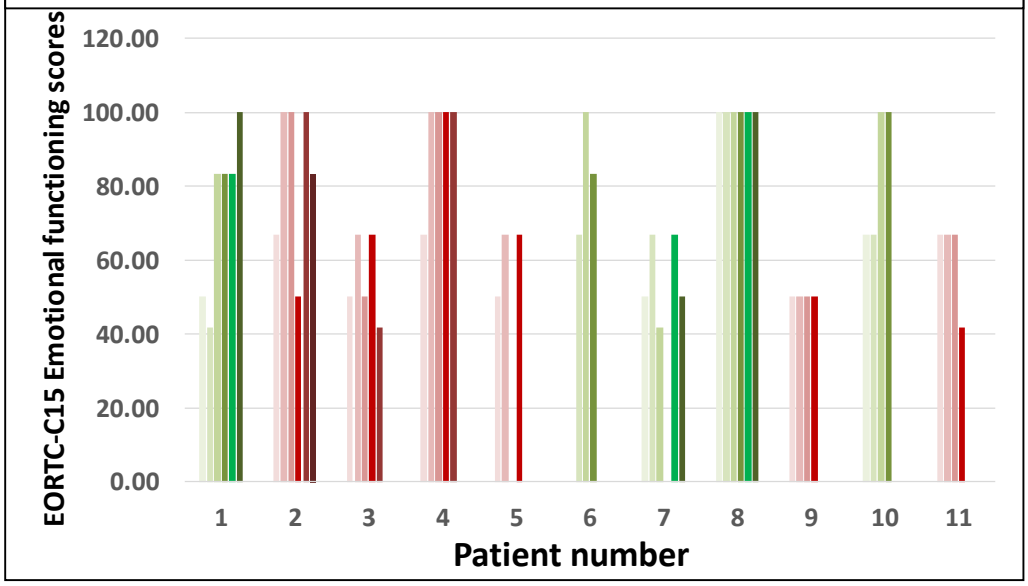
QLQ-C15-PAL	Baseline N=11	Day 7 N=11	Day 30 N=11	Day 60 N=6	Day 90 N=4
Physical Functioning ł	43.7 ±20.1	45.5 ±23.4	44.7 ±22.0	51.1 ±21.8	41.7 ±14.8
Emotional Functioning ł	66.8 ±17.8	72.0 ±33.4	74.2 ±22.4	82.0 ±23.8	83.3 ±23.6
Dyspnoea *	9.6 ±15.8	9.1 ±15.6	10.0 ±16.1	16.7 ±27.9	0.0 ±0.0
Pain *	64.3 ±21.8	60.6 ±29.1	60.0 ±33.5	58.3 ±20.4	50.0 ±36.0
Insomnia *	51.4 ±34.6	42.4 ±36.8	46.7 ±32.2	38.9 ±44.3	33.3 ±38.5
Fatigue *	52.6 ±18.0	45.5 ±24.6	46.7 ±21.5	51.9 ±19.5	44.5 ±20.3
Appetite Loss *	28.8 ±26.5	15.2 ±22.9	2.3 ±22.5	33.3 ±29.8	16.7 ±19.3
Nausea and Vomiting *	8.2 ±19.0	6.7 ±16.1	3.7 ±7.4	11.1 ±20.2	4.2 ±8.4

Table 4.10. Percentage change in mean scores for each QoL feature.

ł Increasing scores represent improving QoL.
**Increasing scores represent worsening QoL.*

The baselines scores, and the changes in physical functioning, emotional functioning and overall QoL over time for individual patients, are presented in **Figure 4.10 a, b and c** respectively.





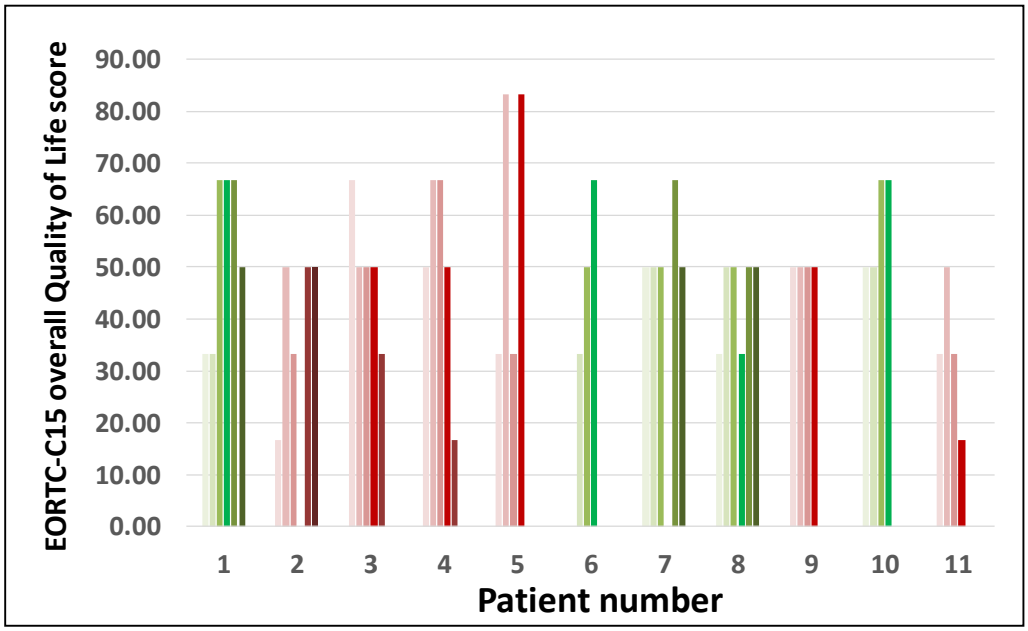


Figure 4.10 Individual patients change in physical functioning (top), emotional functioning (middle) and overall QoL (bottom) from baseline (light shades) to Days 7, 30, 60 and 90 (increasingly darker shades). Responders are denoted in green and non-responders in red.

Responders 1, 6 and 10 showed an improvement in their physical functioning, emotional functioning and overall QoL with increasing time after treatment. Non-responders 3, 4 and 11 showed a decline in their physical functioning, emotional functioning and overall QoL with increasing time after treatment, despite an early improvement in patient 4. Patients 2 at both treatments (5), 7 and 9 did not experience much change in their QoL.

4.3.2.4.2 EORTC EQ-5D-5L

	EORTC EQ-5D-5L index					
Patient	Screening	Treatment	Day 7	Day 30	Day 60	Day 90
1	0.155	0.097	0.378	0.516	0.448	0.555
2	0.698	0.443	0.171	0.647	1.000	0.770
3	0.546	0.410	-0.160	0.573	0.206	
4	0.479	0.527	0.527	0.739	0.456	
5	0.768	0.768	0.809	0.768		0.768
6		0.671	0.795	0.837		
7	0.647	0.708	0.570	0.691	0.567	0.553
8	0.642	0.698	0.723	0.555	0.604	
9	0.263	0.206	-0.035	-0.035		0.604
10	0.704	0.647		0.567		
11	0.548	0.238	0.406	-0.283		

Table 4.11a EQ-5D-5L index scores over time for individual patients summarising 22 QoL items and weighted for social and cultural differences (UK weightings used). Responders coded in green, non-responders coded in red.

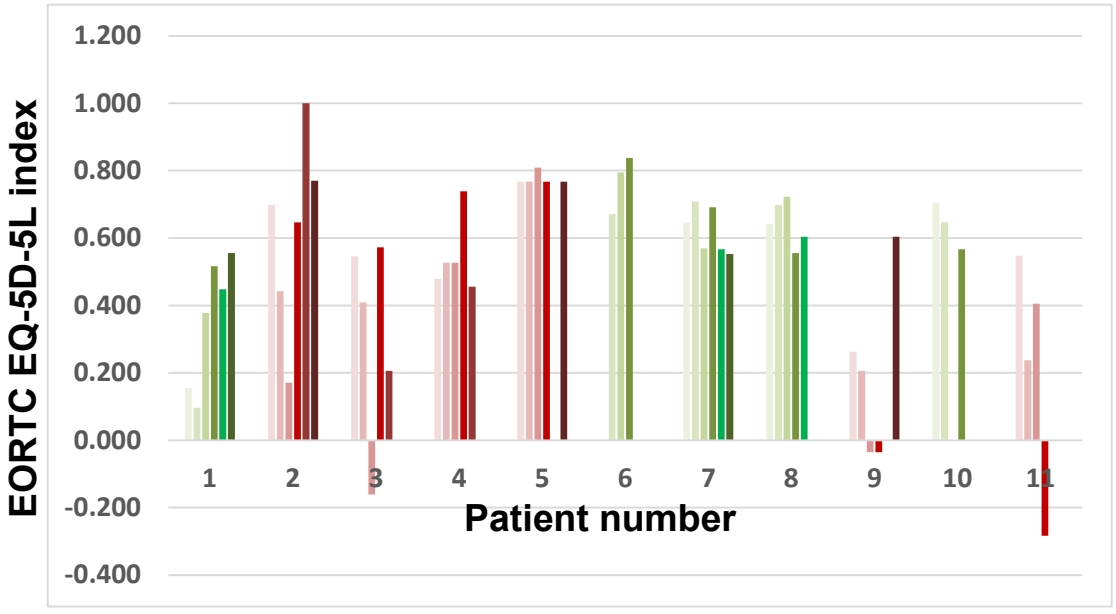


Figure 4.11a Individual patients change in EQ-5D-5L index value from baseline (light shades) to Days 7, 30, 60 and 90 (increasing darker shades). Responders are denoted in green and non-responders in red.

The EQ-5D-5L showed clear improvement in the index value and in the visual analogue pain score for patient 1 with time from treatment, and clear decline in patient 11, but data from all other patients was extremely variable, making it less useful than the C-15 in this context (**Tables 4.11a and b, Figures 4.11 a and b**).

	EORTC EQ-5D-5L visual analogue score					
Patient	Screening	Treatment	Day 7	Day 30	Day 60	Day 90
1	55	45	75	65	70	70
2	65	75	50	40	90	65
3	60	50	40	53	50	
4	90	70	80	90	30	
5	90	95	95	95		93
6		50	75	80		
7	75	75	78	80	83	60
8	70	60	80	50	65	60
9	50	50		60		
10	40	40		63		
11	70	57	50	20		

Table 4.11b EQ-5D-5L visual analogue QoL scores over time for individual patients. Responders coded in green, non-responders coded in red.

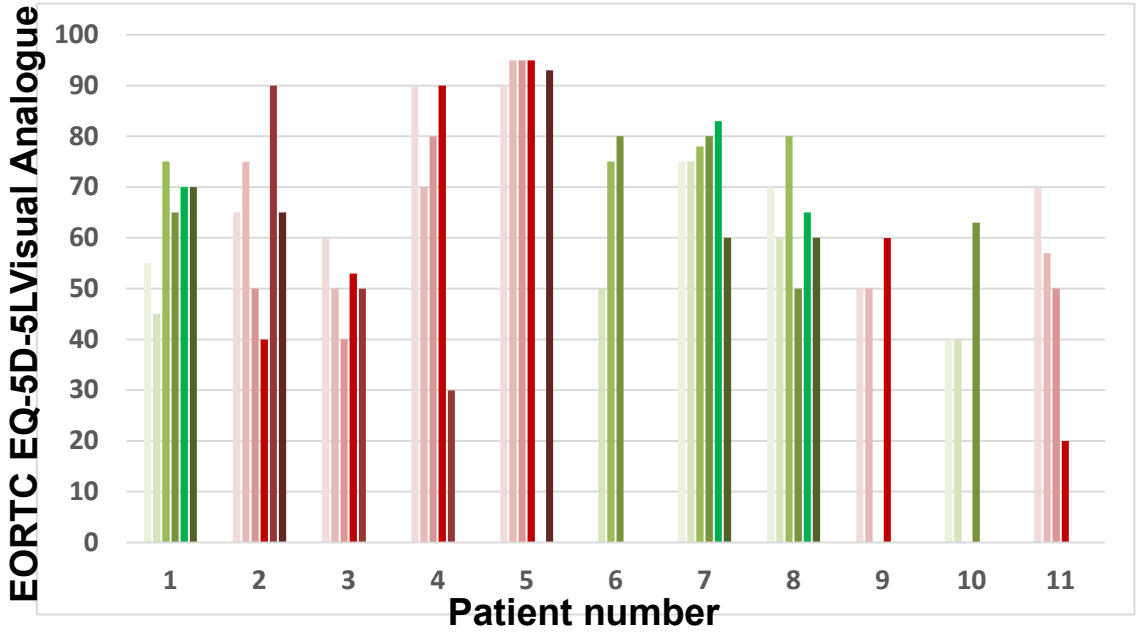


Figure 4.11b Individual patients change in EQ-5D-5L visual analogue pain score from baseline (light shades) to Days 7, 30, 60 and 90 (increasing darker shades). Responders are denoted in green and non-responders in red.

4.5.2.5 Imaging Changes

An analysis of imaging changes in lesion size and extent of enhancement at each time-point derived from the imaging reports are given in **Table 4.12**. More detailed quantitative analysis is beyond the scope of this work.

Pt (Tx)	Appearance	Baseline	% Change immediate post treatment	% Change at D7	% Change at D30
		INTRA-PELVIC TUMOURS			
2	Whole lesion volume (cm^3)	47.4	-13.9	26.2	40.9
	Ratio enhanced/ whole lesion volume	0.86	-3.5	-4.7	0
4	Whole lesion volume (cm^3)	38.2	6.4	6.8	16.0
	Ratio enhanced/ whole lesion volume	0.62	-4.8	-1.6	0
2 (5)	Whole lesion volume (cm^3)	52.7	17.0	36.8	70.6
	Ratio enhanced/ whole lesion volume	0.73	2.7	6.8	5.5
7	Whole lesion volume (cm^3)	34.7	-6.8	1.4	7.2
	Ratio enhanced/ whole lesion volume	1.0	0	0	-
9	Whole lesion volume (cm^3)	64.6	-3.4	3.6	16.6
	Ratio enhanced/ whole lesion volume	0.49	-12.2	-6.1	-4.1
10	Whole lesion volume (cm^3)	444	0.6	7.0	4.8
	Ratio enhanced/ whole lesion volume	1.0	0	0	0
		EXTRA-PELVIC TUMOURS			
1	Whole lesion volume (cm^3)	1.7	Total ablation	Total ablation	Total ablation
	Ratio enhanced/ whole lesion volume	1.0	-100	-100	-100
3	Whole lesion volume (cm^3)	128.7	13.9	19.9	27.7
	Ratio enhanced/ whole lesion volume	0.47	46.8	36.2	53.2
6	Whole lesion volume (cm^3)	54.5	13.2	68.1	41.7
	Ratio enhanced/ whole lesion volume	0.62	-16.1	-22.6	-25.8
8	Whole lesion volume (cm^3)	41.0	23.2	-1.0	13.9
	Ratio enhanced/ whole lesion volume	0.49	-2.0	-14.3	-18.4
11	Whole lesion volume (cm^3)	192.3	22.7	40.6	73.7
	Ratio enhanced/ whole lesion volume	0.61	-19.7	-16.4	-26.2

Table 4.12 Baseline imaging appearances and their change with time for intra- and extra-pelvic lesions

One extra-pelvic tumour was ablated entirely (no longer visible following contrast administration, **Figure 4.12**); the other 4 all showed an immediate increase in total tumour volume (18.3±5.4%). Intra-pelvic tumours did not show significant increase in volume immediately post-treatment (0±10.8%). At Day 7 and 30 both extra-pelvic and intra-pelvic tumours demonstrated tumour growth (**Table 4.12**).

Ratios of enhancing to whole tumour volumes at baseline ranged from 0.47-1.0. Immediately post-treatment there was a decrease in this ratio for extra-pelvic tumours, but no change in the intra-pelvic ones (**Figure 4.13**). However, variability in the extra-pelvic tumours was high (**Table 4.13**).

	Baseline values	% change-immediate	% change Day 7	% change Day 30
	INTRAPELVIC TUMOURS			
Whole lesion volume cm^3	113.6±162.2	0.0±10.8	13.6±14.4	26.0±25.3
Ratio perfused to non-perfused volume	0.78±0.21	-3.0±5.3	-0.9±4.6	0.3±3.4
	EXTRA-PELVIC TUMOURS			
Whole lesion volume cm^3	83.6±76.2	18.3±5.4	31.9±29.5	27.8±13.9
Ratio perfused to whole lesion volume	0.64±0.08	-18.2±52.9	-23.4±48.9	-22.7±62.6

Table 4.13 Whole tumour and enhancing tumour volumes at baseline and longitudinal changes over 30 days.

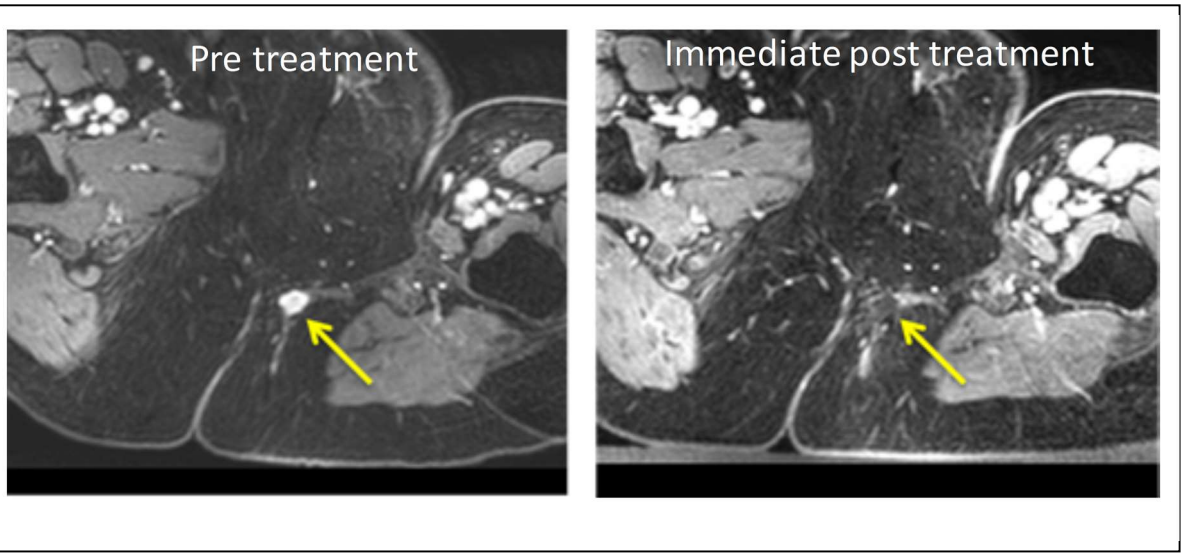


Figure 4.12 Axial T1W image with fat suppression pulse and after contrast enhancement with gadolinium chelate before and after treatment of an extra-pelvic tumour. The pre treatment image shows the enhancing nodule of recurrent tumour in the left ischio-rectal fat (yellow arrow). Immediately post-treatment there is complete ablation of this enhancing lesion (yellow arrow).

Figure 4.13 Axial T1W images with fat suppression pulse and after contrast enhancement with gadolinium chelate before and after treatment of an intra-pelvic tumour. The pre-treatment image shows the non-enhancing tumour mass at the vaginal vault on the left (red arrow). There is no substantial change in tumour volume post treatment, either at Day 7 or Day 30, and no change in the relative enhancing and non-enhancing components (red arrows).

4.6 The MRgHIFU Care Pathway: A Partial Cost Evaluation Study

This part of my thesis was carried out in consultation and with guidance from Dr Elisabeth Adams, managing director and health economist at Aquarius Population Health Limited. The main objectives were to process map the care pathway of MRgHIFU in this setting and then carry out a cost analysis of implementing this technology. As this was a feasibility study, this analysis was done to obtain a preliminary estimate of the costs of implementing MRgHIFU in the treatment of recurrent gynaecological cancers and guide the design and implementation of a Phase II/III trial.

This entailed process mapping the MRgHIFU pathway to establish all of the resources used pre-, intra- and post-MRgHIFU including staff time, equipment used, consumables, drugs, diagnostic and monitoring tests, and any other resources related to the procedure. I then carried out a micro-costing analysis by determining the cost of each step within the pathway using a combination of the RMH costing templates and the NHS attributing the cost of health and social care research and development (AcoRD) tool[156]. This cost evaluation, a first to my knowledge in this setting, should also be applicable to implementing MRgHIFU in the treatment of other malignant tumours.

4.6.1 Methods

4.6.1.1 Pathway mapping

Pathway mapping is a well-established method of identifying the steps in a healthcare pathway to map the patient journey. It allows for a detailed step by step visualisation of how clinical care is being delivered [157].This trial involved a recruitment and screening phase, a treatment phase and a follow-up phase. The steps involved at each phase are given in **Figure 4.14**.

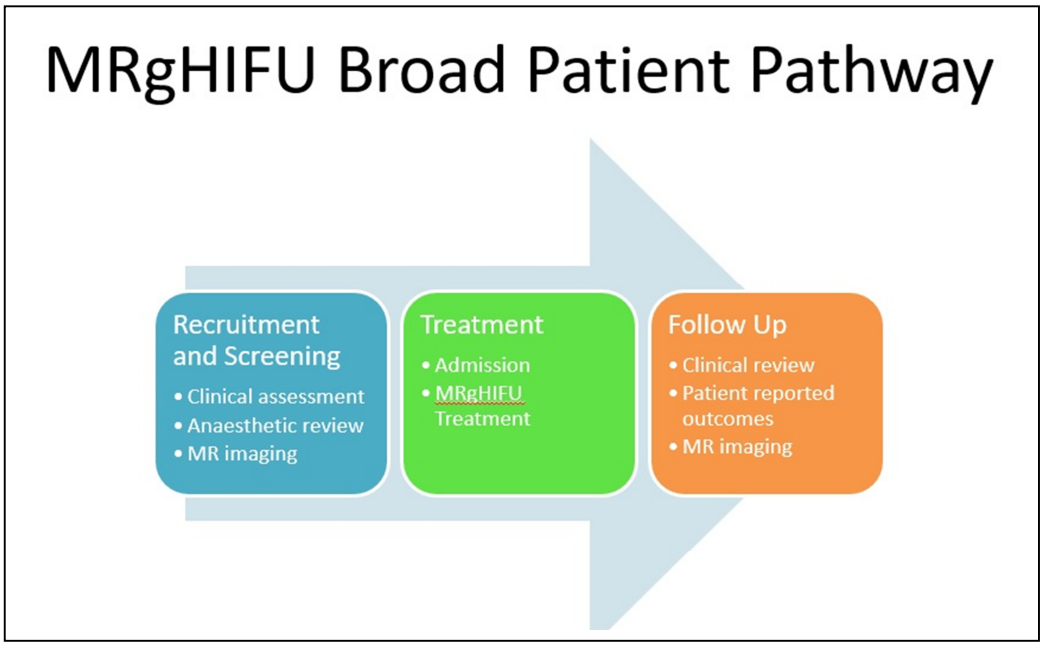


Figure 4.14 Patient pathway for MRgHIFU. Each coloured box represents a separate phase of pathway mapping, with bullet points detailing steps

As this was a research trial, it was important to identify which of the resources used in the pathway were trial-specific (i.e. incurred due to the research study itself) rather than MRgHIFU-specific (necessary for the clinical care); this is to differentiate between any research costs that will be incurred by the NHS in the design of an efficacy trial and identify steps that will not be required for wider implementation and adoption of MRgHIFU within the NHS.

I carried out pathway mapping as illustrated in **Figures 4.15 a, b, c** by:

(i) identifying the steps in the MRgHIFU pathway

I classified the pathway phases as either patient-centric or MRgHIFU-centric. Patient-centric steps involved the patient. Here I was able to follow each patient at the majority of their visits from their arrival at hospital to their departure. MRgHIFU-centric steps were those that did not involve the patient such as treatment planning and machine quality assurance (QA).

(ii) identifying the staff involved in each step

Within each step of each phase, I identified the staff members that were involved and categorised the steps as either clinically required or solely for research. For example, as this was a novel treatment technique one or two trial physicists were present on the day of treatment which would not be required for established techniques within trials or clinical treatments as noted from other MRgHIFU therapies in non-malignant disease.

(iii) estimating the staff time for each step

I then estimated the time taken by each staff member for each of the steps within each stream. For the majority of patient-centric steps, I noted the time taken for each step and rounded up to the closest 5 minutes to facilitate documentation. On treatment day, for any steps for which I was not present, I asked the nursing staff to note the steps, procedures, consumables and time they spent with the patient. For MRgHIFU-centric steps, I asked the chief investigator and research radiographer to estimate the time spent. It is worth noting that some steps had significant variation between patients not attributable to MRgHIFU specifically. I noted such discrepancy and estimated the true time the step would have taken to allow for better analysis **Appendix 4.4**.

(iv) identifying the consumables for each step

All non-staff consumables were noted for each of the steps. Administrative consumables such as patient letters were not included as these are unlikely to play a role when designing an efficacy trial or implementing the technology.

(v) specifying how many patients had each step

The number of patients that had each of the steps in the pathway were noted and converted to an average percentage. The main difference in steps was between patients who required pelvic preparation for pelvic treatments compared to extra-pelvic treatments e.g. catheterisation and bladder filling.

Moreover, for recruitment and follow up, the trial research radiographer documented the patient pathway for some of the visits, and I used these to ensure there were no omissions, over- or under-estimates. I also interviewed one of the patients who completed all follow-up end points and retrospectively analysed the pathways from recruitment stage to trial discharge in order to gain the patient perspective on the pathway.

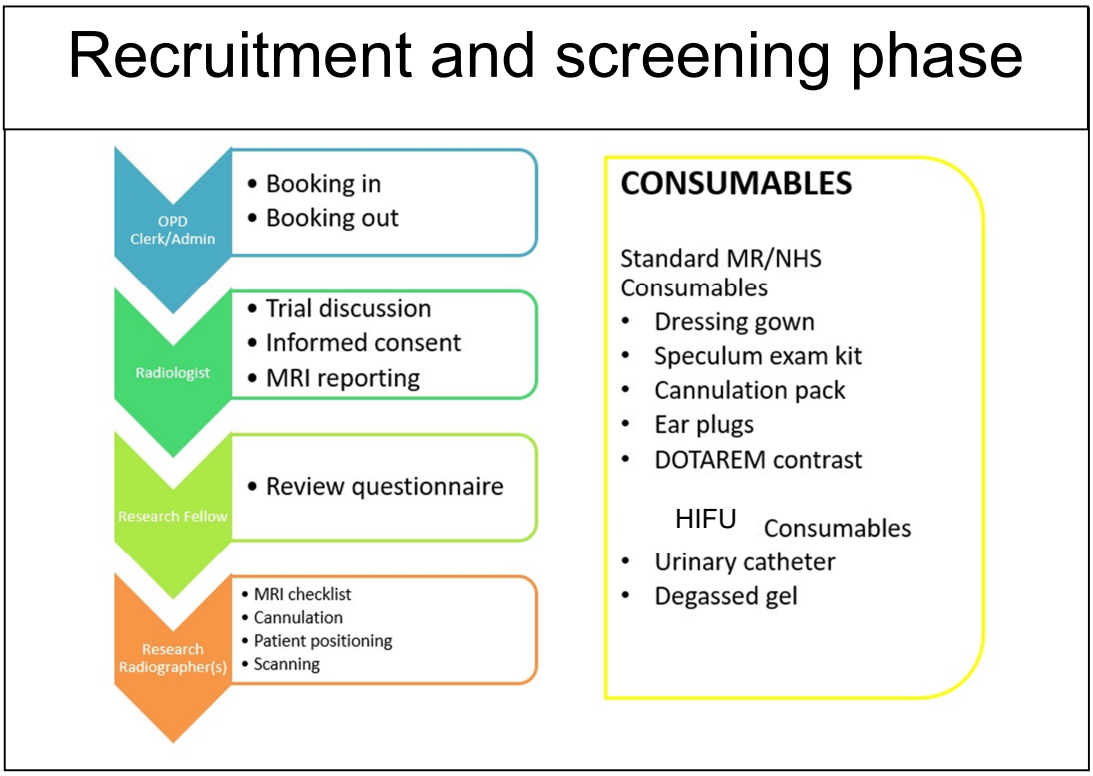


Figure 4.15a Steps required in chronological order at the screening visit to establish eligibility for MRgHIFU. If implementing for clinical care, the trial discussion in Step 2 and the review questionnaire in step 3 would not be needed.

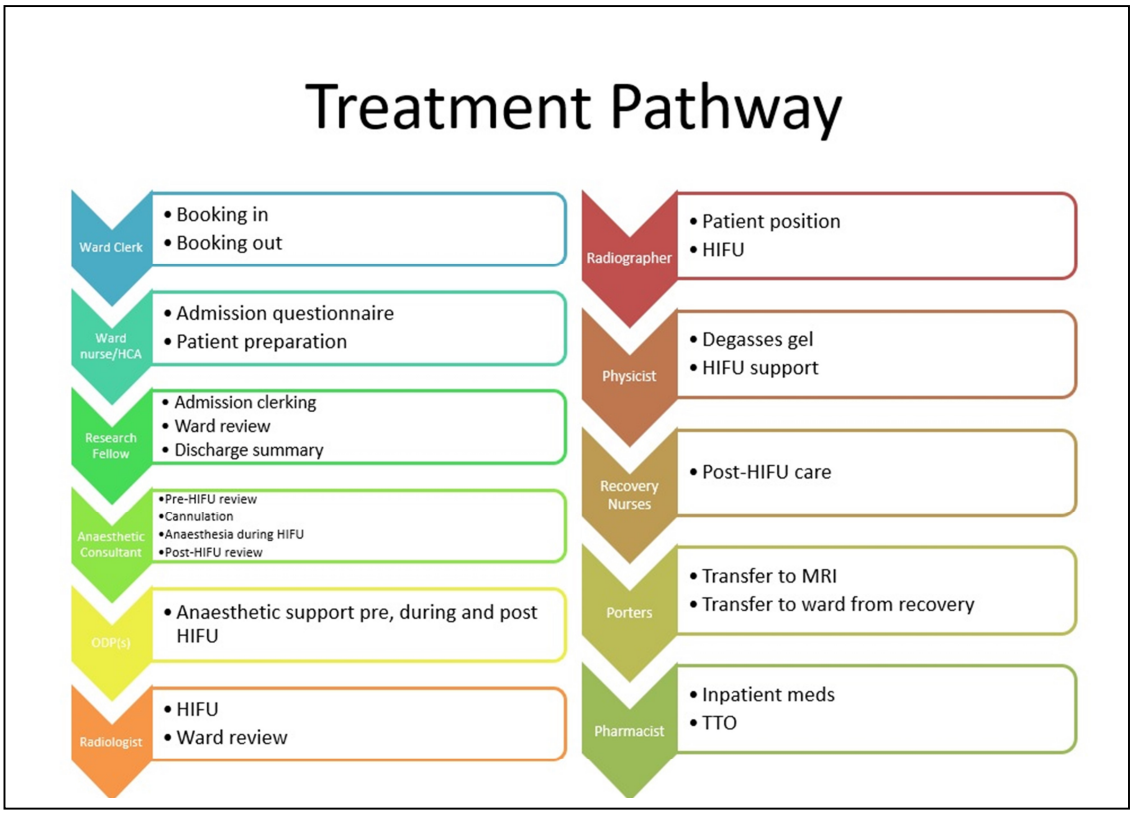


Figure 4.15b Steps required at the treatment visit to achieve MRgHIFU

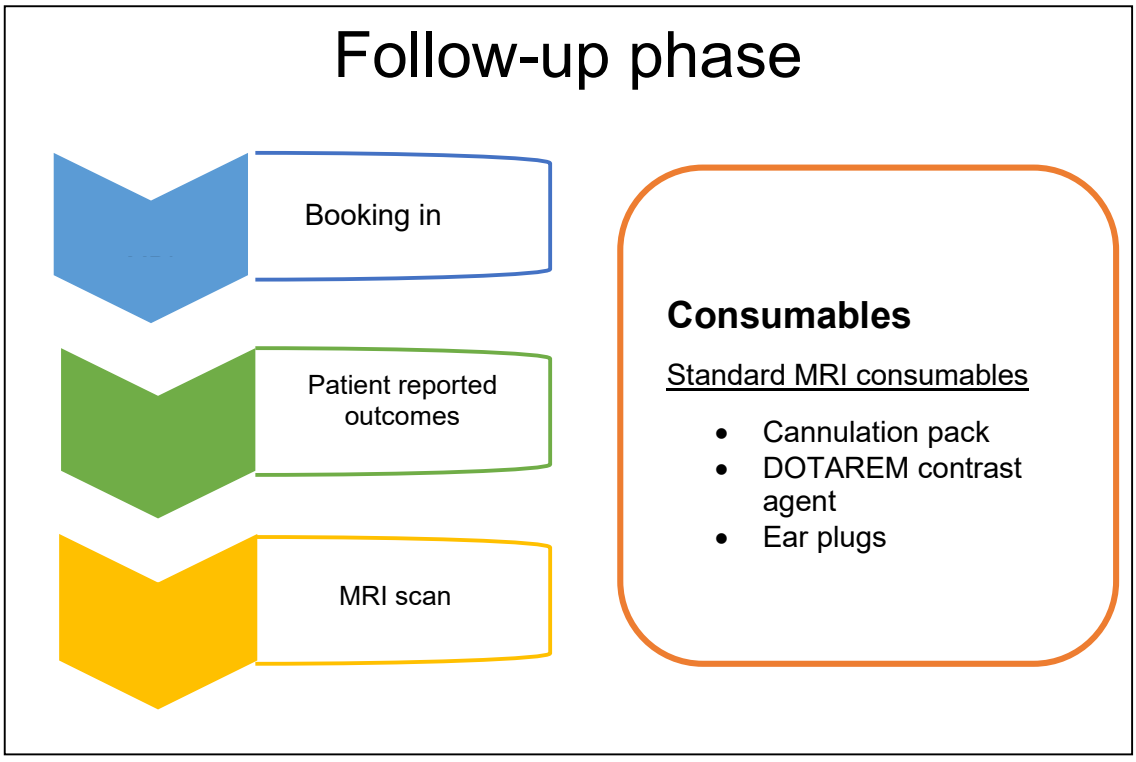


Figure 4.15c Steps outlining staff and consumables for follow-up phase

4.6.1.2 Costing approach

All costs were examined from the NHS providers' perspective and an ingredients approach was used to collect data on resources used. The costs were categorised into three groups: recruitment, treatment and follow up. Follow-up visits for each patient were grouped together for analysis as they were very homogenous and not all patients completed all follow-up end points beyond day 30.

4.6.1.3 Collection and valuation of inputs

The NHS attributing the cost of health and social care Research and Development (AcoRD) tool was used to calculate the overall costs of developing an efficacy trial. Staffing costs were determined using the NHS Unit Costs of Health and Social Care (PSSRU, 2018). Consumables were costed from the Shared Business Services (SBS) costing templates and the RMH materials management MRI procurement costing list. In-patient costs were determined using a combination of the NHS Unit Costs of Health and Social Care [158]and the WHO-CHOICE estimates of cost for inpatient and outpatient health service delivery[159]. **Table 4.14** summarises the collection and valuation of inputs used for the micro costing analysis. Unit costs for all resources were based on the 2018 financial year and calculated in pound sterling

The total cost of each of the step (average across all patients) was then calculated using the following equation:

$$\left(\begin{array}{c}(Staff\ time\ 1\ x\ cost\ per\ minute\ +\ staff\ time\ 2\ x\ cost\ per\ minute\ \ldots) \\ + \\ (Consumable\ 1\ x\ cost\ +\ consumable\ 2\ x\ cost)\end{array}\right)$$

$$\times\ proportion\ who\ have\ the\ step$$

For follow up visit resources, I took the patient requiring the most resources and assumed that would be the "expected" resource as the visits were very homogenous.

Type	Item	Cost (£)	Unit
*Staff	Clinician/Doctor	1.47	minute
	Radiographer	0.60	minute
	Physicist	0.60	minute
	Pharmacist	0.60	minute
	ODP	0.60	minute
	Nurse	0.60	minute
	Health Care Assistant (HCA)	0.35	minute
	Porter	0.35	minute
	Admin	0.35	minute
ΦConsumables	Cannulation pack	0.73	Item
	Catheterisation pack	18.69	Item
	Dressing gown	8.55	Item
	Speculum	0.80	Item
	Ear plugs	0.09	Item
	Gel ice pack	18.00	Item
	MRI Safe electrodes	15.00	Item
	Degassed gel	1.49	Application
	Phone call	0.09	Minute
*Pathology	Blood (FBC/UE&E/LFT/Bone	49.00	Sample
*Procedure	ECG	27.00	Procedure
	MRI - single area with contrast	454.00	Procedure
	Cardiac monitoring	-	Procedure
	Fluid infusion machine	NHS	Procedure
#Drugs	DOTAREM	see MRI	See MRI
	Ondansetron	29.97	Treatment
	Paracetamol	12.00	Treatment
	Normal Saline	2.84	Treatment
	Propofol	15.00	Treatment
	Ramifentanil	25.60	Treatment
	Buscopan	0.29	Treatment
	Bowel Prep	3.39	Treatment
**Other	Excess bed stay	431.00	Night

Table 4.14: Cost inputs used for the micro-costing analysis

Sources:
*Secondary care industry costing tool (AcCORD) 2018
#NICE British National Formulary (BNF) Online
ΦThe Royal Marsden MRI procurement and costing template
**NHS national schedule of reference costs 2017/2018

4.6.1.4 Patient outcome measures

Although quality of life data was collected before and after treatment, data was only available for seven days prior to the procedure. Comparative costs versus primary healthcare attendances and analgesic use that would have been incurred had the patient not participated in the trial was not possible as the trial team became the primary point of contact once patients were recruited. Therefore, it was difficult to compare the effect of treatment on quality of life outcomes and associated cost and so a cost per outcome description was not done.

4.6.2 Results of health-economic evaluation

4.6.2.1 Pathway mapping

The recruitment and screening visit was similar to a generic oncology new outpatient appointment. The screening visit was longer than subsequent follow-up appointments as it involved taking consent and determining the optimal treatment position in the scanner. As expected, the treatment phase of the pathway was the longest and involved the largest number of clinicians and allied health care professionals as well as consumables. The follow-up visits were very homogenous and shorter in duration than other trial-specific visits as patients were familiar with the paperwork to be completed and MRI scanning was standard.

4.6.2.2 Micro-costing Analysis

Table 4.15a and b show the costs incurred for non-treatment and treatment visits respectively. If taken up within a clinical setting, the screening and treatment visit costs would be equivalent to this setting. Differences would be around reduced time for specialist trial consent, reduced interviews for completion of questionnaires before and after treatment, and reduced physicist input on the day of treatment. The follow-up visits were entirely done for assessing trial outcome and were solely a research cost.

Step Name	Cost Type	Type Detail	Activity	Mean Time (min)(mins)/unit	Cost (£)
Book In	Staff	Admin	Patient check-in	5	1.75
Consultation	Staff	Oncologist	Clinical history	16	23.52
	Staff	Oncologist	Telephone consult and questionnaire (D1)	15	22.05
	Staff	Oncologist	Examination	5	7.35
	Staff	Radiologist	Informed consent	13	19.11
	Staff	Anaesthetist	Anaesthetic review	21	30.87
	Staff	Nurse	ECG	10	6
	Staff	Oncologist	Review questionnaire	10	14.7
	Staff	Radiographer	MRI checklist	7	4.2
	Non-staff	Consumables	Speculum	1	0.8
	Non-staff	Equipment	Call	15	1.35
	Non-staff	Equipment	ECG	1	27
Tests	Staff	Radiographer	Cannulation and blood test	5	3
	Staff	Pathology	Bloods test	1	49
MRI	Staff	2x Radiographer	Preparation and positioning (screening)	14	16.8
	Staff	2x Radiographer	Preparation and positioning	7	4.2
	Staff	Radiographer	Scanning	41	24.6
	Staff	Radiologist	Scanning (additional time for screening)	14	20.58
		Radiologist	MR reporting	15	22.05
	Staff	Rad/Oncologist	Results	12	17.64
	Non-staff	Consumables	Dressing gown	1	8.55
	Non-staff	Consumables	Cannulation pack	1	18.69
	Non-staff	Consumables	Ear plugs	1	0.09
	Non-staff	Consumables	Urinary catheter (pelvic - screening)	2	37.38
	Non-staff	Consumables	Degassed gel	1	1.49
	Non-staff	Equipment	MRI scan	1	454
	Non-staff	Drugs	DOTAREM contrast	1	-
	Non-staff	Drugs	Bowel Prep - pelvic	1	3.39
	Non-staff	Drugs	Buscopan	1	-
	Non-staff	Equipment	MRgHIFU Table (screening)	1	-
Trial	Staff	Oncologist	Trial eligibility criteria (screening)	10	14.7
	Staff	Radiologist	Treatment planning (screening)	30	44.1
	Staff	Radiographer	Treatment planning (screening)	30	44.1
	Staff	Physicist	Treatment planning (screening)	30	18
Book out	Staff	Admin	Patient check-out, OPA booking	5	1.75
			Total staff	**470**	**408.32**
			Total non-staff	**-**	**601.74**
			Grand total (scrn)	**-**	**939.41**
			Grand total for D1 (call)	**15**	**23.4**
			Grand total per non-screening visit for D7, 30, 60, 90	**-**	**603.89**

Table 4.15a Costs of non-treatment trial visits (Phase 1 and Phase 3) including screening, day 1, day 30, day 60 and day 90. All are patient-centric costs. Blue highlighted rows were common to Phase 1 and Phase 3.

Step	Cost Type	Type Detail	Activity	Mean Time (mins)/Unit	Cost
Pre-Treatment	Staff	Oncologist	Organising patient admission	15	22.05
	Staff	Radiologist	Treatment planning	30	44.1
	Staff	Radiographer	Treatment planning	30	18
	Staff	Radiographer	MRgHIFU QA	15	9
	Staff	Physicist	MRgHIFU QA	15	9
Admission	Staff	Admin	Patient check in	5	1.75
	Staff	Oncologist	Patient review and trial questionnaire	16	23.52
	Staff	Anaesthetist	Pre-procedure review and cannulation	12	17.64
	Staff	Radiologist	Confirm consent	10	14.7
	Staff	HCA	Admission proforma	15	5.25
	Staff	Nurse	Catheterisation (pelvic)	10	6
	Non-staff	Consumables	Dressing gown	1	8.55
	Non-staff	Consumables	Cannulation pack	1	0.73
	Non-staff	Consumables	Urinary catheter (pelvic)	2	37.38
Treatment	Staff	Porter	Transfer to MRI department	5	1.75
	Staff	2x Radiographer	Preparation and positioning	13	15.6
	Staff	ODP	Patient preparation	17	10.2
	Staff	Radiologist	MRgHIFU Ablation	112	164.64
	Staff	Anaesthetist	MRgHIFU Ablation	112	164.64
	Staff	Radiographer	MRgHIFU Ablation	112	67.2
	Staff	ODP	MRgHIFU Ablation	112	67.2
	Non-staff	Consumables	Dressing gown	1	0.8
	Non-staff	Consumables	Ear plugs	1	0.09
	Non-staff	Consumables	Degassed gel	1	1.49
	Non-staff	Equipment	MRI	1	454
	Non-staff	Drugs	DOTAREM contrast	-	-
	Non-staff	Drugs	Paracetamol	1	12
	Non-staff	Drugs	Normal saline	1	2.84
	Non-staff	Drugs	Propofol	1	15
	Non-staff	Drugs	Ramifentanil	1	25.6
	Non-staff	Equipment	MRgHIFU Table	-	-
	Non-staff	Equipment	Cardiac Monitoring	-	-
	Non-staff	Equipment	IV Fluid Infuser	-	-
Recovery	Staff	Porter	Transfer to recovery	10	3.5
	Staff	Anaesthetist	Recovery handover	10	14.7
	Staff	Nurse	Post-procedure monitoring	21	12.6
	Non-staff	Consumables	Cooling pack	1	18
	Non-staff	Drugs	Ondansetron	1	29.97
Monitoring	Staff	Porter	Transfer to ward	5	1.75
	Staff	Radiologist	Post-ablation review	10	14.7
	Staff	Nurse	Catheter removal	5	3
	Staff	HCA	Post-procedure aftercare	10	3.5
Discharge	Staff	Oncologist	Review and discharge summary	10	14.7
	Staff	Admin	Check out and discharge admin	5	1.75
Bed stay	Other	excess stay	Elective excess bed stay	1	431
			Total staff	**820**	**780.41**
			Total non-staff	**-**	**606.45**
			Grand total (without excess stay)	**-**	**1338.89**
			Grand total (with excess bed stay)	**-**	**1769.89**

Table 4.15b Costs of MRgHIFU on treatment day. Overnight stay was required in 8 of the treatments for patient monitoring after an afternoon treatment session or due to patient locality for national referrals.

4.7 Discussion

4.7.1 Safety of MR guided HIFU

Skin erythema is the commonest reported adverse event in other MRgHIFU series, and it was the commonest adverse event reported in this series. Some degree of skin erythema was seen in half our patients. Moreover, blistering was noted in one case and a grade 2 skin burn with ulceration in a surgical scar in another. A very large series of more than 27,000 patients from 19 centres across China where HIFU was used to treat benign uterine disease indicated that the incidence of skin erythema was 0.32%, skin blistering 0.07% and skin burn 0.14% [160]. This was much lower than in our study, where patients were older, had often received previous radiation at that site, or had distorting surgical scars close to the treatment site. These factors were the likely cause of poorer skin to gel pad contact made than may have been possible with the uterine fibroid treatments where a full prone position was adopted. Factors that have been significantly associated with thermal injury to skin were shown in a univariate logistic regression analysis of 892 cases to be related to sonication time, sonication time per hour, total energy deposited, distance from uterine fibroid ventral side to skin, volume of uterine fibroids, abdominal wall scar, abdominal wall thickness and body mass index (BMI). In a multivariate analysis, however, total energy, abdominal wall scar and abdominal wall thickness were significantly associated with thermal injury [161]. To overcome the problem of abdominal scars, acoustic patches on the skin, which can be used to reflect the ultrasound energy from scars, have been introduced [162]. One study [163] reported that the scar patch provides an effective treatment option for patients with abdominal scars located in the beam path, who were previously excluded from MRgHIFU treatment, given the increased risk of skin burns. Use of a scar patch does not appear to compromise the efficacy of the treatment [164]. We did not use acoustic patches in this study, mainly because we were also limited by anatomical distortion associated with major prior cancer surgery. In the future however, this

may well avoid the higher incidence of skin erythema in our series compared to others.

Fat necrosis has not been formally reported as a side effect of HIFU, though there is a substantial literature on cryolipolysis for cosmetic body sculpting purposes, so the induction of fat necrosis with HIFU is well-established [165-167]. The cosmetic effects of fat necrosis were not a consideration in our cancer patients in whom symptom palliation was an overriding objective.

4.7.2 Symptom control

4.7.2.1 In relation to tumour depth

Better symptom control (pain) was achieved in extra-pelvic compared to intra-pelvic tumours. This was primarily related to the depth of the central pelvic and side-wall recurrences, compared to the depth of extra-pelvic (groin, ischiorectal fossa and limb) recurrences treated. This meant that there was less tissue in the pre-focal area to cause dissipation of ultrasound energy. A retrospective study in pancreatic cancer indicated that tumour ablation correlated negatively with posterior tumour depth, with a 1-cm increase in depth decreasing ablation by 30.7%. At less than 7cm posterior tumour depth (as determined by CT), ablation was nearly 10 times greater as assessed by the non-perfused post treatment volume than at depths > 7 cm [168]. In this series, the depth of the closest tumour border was >8cm for the intra-pelvic lesions and between 3 and 8 cm for the extra-pelvic ones. In addition to tumour depth, experimental data on the layers of fat and water and their thickness indicates that the layering of fat and muscle interfaces may further compromise the thermal energy delivery and result in suboptimal temperature rises at the focus [169]. In all the pelvic tumours treated here, the beam path inevitably traversed fat and gluteal muscle, in a layered arrangement that was often asymmetric in the beam path. This asymmetry is a further disadvantageous

scenario for achieving the desired focal temperatures. In future, use of higher powers and longer focal length transducers will be essential for effective delivery of HIFU to pelvic tumours.

4.7.2.2 In relation to thermal dose

Although no significant V240EM was seen in all the intra pelvic tumours treated, pain responses were evident. This indicates either that a significant V240EM is not necessary for a symptomatic response, or that the HIFU procedure has a powerful placebo effect. In a multicentre randomised controlled trial of 147 patients with painful bone metastases, although there was a clear difference in pain response between those that received real (n=122) vs. sham (n=35) treatments, pain responses were seen in 20% of patients in the placebo arm, with 5.7% showing a complete response [42]. The response rate in this series was greater than this even when ablative temperatures were not reached, suggesting that sub-therapeutic heating changes may well cause physiological changes at a cellular level which results in symptomatic improvement. Alternatively, the thermometry might have been suboptimal because of difficulty in placing the pre-focal monitoring slice away from fat. In some cases (patient 11), this is supported by the clear instance of immediate post-treatment changes on contrast enhanced images in the treated region.

In extra-pelvic tumours, where a V240EM was achieved, this was small compared to the GTV; nevertheless, there was sustained symptom response. It is possible that ablative necrosis and physiological damage to surrounding tissue was attained as demonstrated in uterine fibroid treatments where pain and bleeding improves even though a much smaller volume of the whole fibroid is treated.

4.7.2.3 In relation to imaging changes

The volume of tumour treated in this series was much smaller than the PTV, primarily because much of the tumour was at depth and beyond the reach of the transducer focus. It was always intended merely to ablate the surface of the tumour at a point where contact with neighbouring normal tissue was likely to be the cause of pain, or to cause some debulking effect. The imaging changes were therefore only expected at the site of the ablation and were evident as lack of contrast enhancement in the treated region in 2 cases, and an increase in contrast enhancement in 2 cases, with no visible changes in the remainder. Even in fibroid ablation, where treatments are much simpler and more standardised, it is expected that imaging changes will be seen in a proportion of the tumour only. Typically, ~20% of the treated fibroid shows as a non-perfused volume [170]. In 60 fibroid treatments, Yoon et al [171] showed that where the thermal dose volume obtained from phase-difference MR images during treatment was greater than 27% of the fibroid volume, the ratio of the non-perfused fibroid post-treatment (indicating ablated volume) to thermal dose volume was greater than 1. This means that the extent of ablation achieved was greater than the volume in which an ablative thermal dose was achieved, and indicates some spreading of the thermal effects to surrounding tissue.

Where thermally ablative temperatures (>55^{o}C) were achieved in the extra-pelvic tumours, there was an immediate increase in tumour volume, mainly in the non-perfused compartment, indicative of oedema. Despite lower temperatures with the increased energy delivered in intra-pelvic compared to extra-pelvic tumours, there was a symptomatic improvement in pain in 2 patients with intra-pelvic tumours, which may be attributable to neural damage at the lower temperatures or to a placebo effect.

All tumours increased in volume with time indicating tumour progression, although alterations in the pace of progression cannot be estimated in this pilot study in the absence of a randomized control group. Nevertheless, an improvement in symptoms was achieved in 45% of treatments in this palliative care setting.

4.7.3 Quality-of-Life

4.7.3.1 In comparison to palliative radiotherapy

The same quality of life measures as used for palliative radiotherapy indicated that emotional functioning improved although other measures did not. This supports the view that on-going counselling and hospital visits with health care professionals provides a valuable support system for these patients at the end of their life, despite the additional effort required in keeping these appointments. Most data on alleviation of pain with palliative radiotherapy relates to bone metastases [172]. The impact of palliative radiotherapy on quality of life in pelvic cancer patients is poorly studied. A recent pilot data set from 25 patients where the baseline symptoms were pain (48%), bleeding (40%), bleeding/pain (8%), and intestinal sub-occlusion (4%) showed that the improvement in well-being was 64% and in ability to perform daily activities 48%[173], which mirrors the emotional and physical functioning metrics in my work.

4.7.3.2 In comparison to HIFU treatment of painful bone metastases

HIFU is now a recognised method for treating painful bone metastases [174], and a randomised controlled trial indicated that it was not just a placebo effect [42]. Nevertheless, quality of life in these patients has been insufficiently assessed. An international multicentre trial of 20 patients that used the QLQ-C15-PAL and QLQ-BM22 questionnaires before and on days 7, 14, 30, 60 and 90 post-treatment showed that clinically significant improvements were seen in the QoL scales of physical functioning, fatigue, appetite loss, nausea and vomiting, constipation and

pain in the 53% of patients who were classified as responders at Day 30 but no significant changes were seen in the 47% of patients who were non-responders at this time point [89]. This confirms the validity of HIFU in the treatment armamentarium in the palliative care setting for improving quality of life.

4.7.4 Health economic considerations

This is the first study to prospectively detail the MRgHIFU treatment pathway in the treatment of solid tumours.

As expected, the most resource-intensive phase was the day of treatment which required several hours of clinician and allied health professional time. This included several porters, health care assistants (HCAs), nurses, radiographers, operating department practitioners and doctors. The largest staff costs were attributed to the two consultants (treating radiologist and anaesthetist) followed by the specialist band 8 radiographer as they all had large time commitments before, during and after treatment. Follow-up visits were very homogenous and had much lower costs as the patient visits were shorter but also because less clinician time was needed compared to screening or treatment days. The main costly consumables were related to MRI scanner time.

Staff time during recruitment and screening and during follow-up phases was also influenced by patient status: the severity of their symptoms, ability to cope and support systems at home meant that counselling time was variable. On the day of treatment, patient variation regarding the site of the tumour and the patient's BMI affected the time taken to achieve optimal positioning, anaesthetic requirements and time were consequent on positioning and other co-morbidities, and time required for successful treatment delivery varied with tumour size and location. Fortunately, a range of pelvic tumour sites were treated and patients were treated in supine and prone oblique positions, so the average time obtained for the costings analysis was

a fair representation of the variety of situations that may be encountered when palliating recurrent gynaecological tumours with MRgHIFU.

It is worth noting that in the case of MRgHIFU there is only one treatment visit unlike other palliative interventions where patients attend on a regular basis e.g. weekly visits for up to 18 weeks in the case of palliative chemotherapy or up to five treatments in the case of radiotherapy. Innovations in radiation oncology have usually involved higher costs because of increase planning requirements [175], but recently several trials in breast and prostate cancer have reduced costs dramatically by introducing hypofractionation and reducing the number of visits [176, 177]. Other single-visit thermal ablation treatment trials have dealt mainly with benign conditions: second generation microwave and thermal balloon techniques for heavy menstrual bleeding were shown to be considerably cheaper than hysterectomy, but in the longer term this was offset by the need for re-treatment [178]. A health economic analysis 2411 Chinese women treated with HIFU or surgery for symptomatic uterine fibroids across 20 Chinese hospitals indicated that hospital stay was shorter and that QoL improved more rapidly in patients treated with HIFU [152]. An economic analysis in Ontario compared MRgHIFU to other established therapies for treatment of symptomatic uterine fibroids and concluded that it may be a cost effective treatment modality with potential implementation resulting in cost savings of up to $4.15 million [179], warranting further comparison in a randomise controlled trial. Both the recruitment and screening phase and the treatment phase steps of this trial would be within a clinical costs domain, although when established and streamlined the process would require less staff time. The follow-up visits in this study, as with other studies are comparable to other clinical trials and represent research costs. In a solely clinical setting, follow-up would likely require one visit to assess for early toxicity and efficacy at Day 30.

4.7.5 Limitations

Several of the limitations were outlined in previous relevant sections of the discussion however, the main limitations of this study is the low number of patients treated. As a result, statistically significant conclusions cannot be drawn and all statistics were descriptive in nature and micro-costing only partial as comparative analysis could not be carried out.

4.8 Conclusion

Magnetic resonance high intensity focused ultrasound ablation is a novel and potentially effective treatment approach for recurrent gynaecological cancer with a robust safety profile and acceptable cost. The ability to accurately target tumours with a limited risk to previously irradiated surrounding normal tissue makes it an attractive therapy. It is distinguishable by live feedback during treatment and the non-invasive nature compared to other ablative therapies.

This study, albeit small in the number of patients treated has shown that MRgHIFU is feasible in the treatment of extra-pelvic recurrent gynaecological cancer, is associated with little in terms of unexpected or severe side effects and can be integrated to the clinical cancer-pathway. The current technology is limited by its inability to target deep tumours within the pelvis such as vaginal vault and pelvic side wall disease which is rather disappointing as these are the common sites of recurrence. It does however show promise in the treatment of recurrent tumours outside the deep pelvis and potentially other solid tumours such as sarcomas. If MRgHIFU is to be integrated and studied in the setting of pelvic tumours, then further pre-clinical research is required to try and improve the focusing array. A different treatment approach might be required e.g. transvaginal ablation; however this would make it more invasive.

This application of MRgHIFU as a treatment of recurrent pelvic gynaecological cancer was the first of its kind and the results can guide the direction and design of future trials to implement it in the cancer treatment pathway of gynaecological and other tumour types.

4.9 Key Points

- It was feasible to treat pelvic recurrences of gynaecological malignancy safely (skin erythema being the main adverse event), and achieve pain responses in 45% (5 of 11) of cases.

- There was no relationship between thermal dose delivered and symptom response in this pilot cohort.

- Other than pain, improvements in quality of life were evident in emotional functioning but not in physical functioning or other metrics.

- Extra-pelvic metastases showed greater reductions in enhancement on contrast-enhanced MRI post-treatment than intra-pelvic ones although measurement variability was high.

- Health economic evaluation indicated high costs for a single visit on the day of the procedure with low costs for subsequent follow-up.

Chapter 5 – Conclusions and Future Direction

5.1 Management of recurrent gynaecological cancer with curative intent

Once gynaecological malignancy has recurred following primary treatment, the likelihood of cure is small and mainly limited to cases where the recurrence is confined to the pelvis. As radiation is normally part of the primary treatment, re-irradiation has only been employed cautiously in recurrent pelvic disease, and not necessarily with curative intent. Exenterative surgery therefore has been the main approach at cure in these patients, but carries substantial morbidity (e.g. loss of normal continence mechanisms) with impact on quality-of-life (e.g. stoma care) so that its benefits need to be balanced against the potential for cure. Because outcomes of exenterative surgery rely predominantly on site and location of the relapse, skill of the surgeon and the overall aggressiveness of the disease, the prognostic factors that currently influence the decision for exenteration for curative purposes are tumour size [5, 6] and time to recurrence of less than 2 years [54]. The use of adjuvant treatments as described in this thesis have the potential to modify outcomes.

Although rigorous patient selection is undertaken prior to PE, data from my thesis indicate that surgery results in an involved margin in almost a third of cases in line with previously reported data. While post-operative radiation is recognized as an acceptable form of disease modification for the involved margin in the radiation naïve setting, concerns about toxicity have hindered its use in the previously irradiated pelvis. My dosimetric studies have demonstrated that SBRT can be utilised to deliver ablative doses not just to the margin but to nearby area of high risk after PE while minimising dose to the surrounding OARs. This may translate into a

tolerable and effective treatment modality for this group of patients to achieve longer term local control or even cure. Patient selection is key and current surgical advances including intra-operative histopathological assessment and fiducial marker insertion could facilitate target volume delineation during radiation planning. Although prospective clinical studies are required to assess toxicity and efficacy before its adoption, such trials are not likely to be viable in part due to the low number of patients undergoing PE but also due the heterogeneity of the patient, tumour and histopathological characteristics to draw concrete conclusions. It is therefore important to thoroughly counsel patients before and after SBRT treatment plans are designed to discuss potential morbidity and the uncertainties surrounding its impact on quality-of-life in this setting.

In the radiation naïve locally recurrent gynaecological cancer where brachytherapy is not an option, chemoradiation remains the standard of care. However, clinical outcomes remain worse compared to disease amenable to brachytherapy where dose to macroscopic disease is boosted to > 78 Gy. Several studies have explored the role of newer radiation techniques to escalate dose in a similar fashion to BT but few studies have compared those with current established practices such as SIB and sequential VMAT and no studies have done so while differentiating between CRD and PSWD. My studies demonstrate that SBRT and PBT allow dose escalation with good tumour coverage while respecting dose constraints for previously irradiated OARs. In CRD, PBT offers improved lower dose to OARs due to the difference in planning technique unlike SBRT where a low-dose radiation bath occurs from the treatment arc. In cases of PSWD where the recurrence is close to the sciatic nerve, SBRT is recommend as it offers better nerve sparing unless a single field technique is used for PBT which requires further exploration as this was not in the remit of my thesis. SBRT is established internationally but in the UK is currently only commissioned with stringent criteria which limits its use to nodal recurrences in the previously irradiated pelvis. Moreover, there is currently little

experience of PBT in the treatment of either primary or recurrent gynaecological cancer in the UK with only one NHS centre treating patients. Although there is little data on cost effectiveness of newer radiation techniques particularly PBT, cost analysis by Mahmoud et al reveals comparable costs between IMRT and SBRT in the USA for treating gynaecological cancer which may justify delivering an ablative dose with SBRT. Further dose escalation remains possible with isotoxic planning with an individualised treatment plan taking into account patient OAR anatomy to escalate or de-escalate dose where a one-size-fits-all approach is not viable as demonstrated from the early halting of the phase II trial of SBRT as a boost in cervical cancer by Albuquerque. The REGENCY study will aim to assess and document toxicity of this SBRT technique in this group of patients prior to a establishing a phase III prospective randomised trial to assess efficacy.

The current status of HIFU means that its use as an adjunctive treatment to PE is not justified. Complete disease ablation in the pelvis in a palliative setting would need to be demonstrated first. This would then require a proper phase II toxicity trial before a randomised Phase III trial in the palliative setting before even considering asking it in the adjuvant/curative setting. Moreover, we only demonstrated that HIFU is feasible outside the true pelvis with the current technology so technological improvements to enable effective targeting of deeper tissues would need to be proven first.

5.2 Management of recurrent gynaecological cancer with palliative intent

Palliative PE should only be considered when disease-related morbidity is uncontrollable with other therapeutic modalities. Therefore, for palliating symptoms from recurrent gynaecological malignancy, other modalities such as chemotherapy and radiotherapy are first-line. When disease in widespread, and symptoms are

multi-site, palliative chemotherapy may be indicated. Radiotherapy is indicated for controlling symptoms induced by local or distant recurrences that are directly related to the site of recurrence such as pain or bleeding. Newer techniques such as SBRT are helpful here as dose distributions can be limited to reduce toxicity.

SIB/SBRT/PBT for true “palliation” would be of dubious ethics unless we want to achieve longer term control in metastatic disease where the primary in pelvis is controlled. As the required palliative radiation doses to the pelvis can be delivered with traditional 3D conformal or even virtual simulation, none of the radiation treatment modalities described in this thesis are currently acceptable in the palliative setting.

HIFU is now used clinically for palliation of pain in patients with bone metastases. The mechanism by which pain palliation is successfully achieved with this technique is not yet fully understood. At the simplest level, a very precise focal thermal burn of periosteal nerve endings disrupts the perception of pain. However, periosteal destruction of C-fibres has not been definitively demonstrated in *in vivo* treatments. Other postulated mechanisms include localised denervation of the target by reducing the density of nociceptive fibres present: unmyelinated nerve fibres have been shown to be particularly vulnerable to thermal injury in non-HIFU treatments [180]. Direct sonication of neuronal structures *in vivo* also has been shown to result in demyelination and neural degeneration [181]. At lower temperatures, reversible blockade of nerve action potential conduction occurs [182, 183], particularly in unmyelinated fibres. Debulking of tumour by HIFU is also claimed to reduce pain [174].

The use of HIFU for symptom palliation requires careful patient selection. Matching the symptom to the site of disease is a primary consideration. As the technique is very precise, the ideal situation is where a tightly focussed thermal injury is likely to address the cause of the symptom, e.g. proximity of the tumour to innervated

tissues such as periosteum and peritoneum. Where recurrent disease is multisite, the utility of symptom palliation with HIFU is less likely to be successful as the perception of pain tends to move from the treated primary site of recurrence to the secondary site with no overall benefit to the patient. Other considerations in patient selection are disease location; lesions deep in the pelvis are more difficult to treat effectively because of attenuation of the HIFU energy in the pre-focal tissues. This is a particular problem where the pre-focal tissues are predominantly fat [184] for instance in high BMI patients. Finally, if bowel cannot be avoided in the pre-focal beam, there is a risk of fistulae formation.

HIFU procedures require anaesthesia because the thermal burns are painful at the time of delivery. Furthermore, the length of time of a procedure (on average 1 hr treatment time in our series) requires that a patient does not move because each planned treatment cell is delivered with millimetre accuracy. It is unreasonable to expect patient compliance with staying still for this length of time, particularly if placed in an uncomfortable position within an MRI scanner. The use of general anaesthesia with remote access to the patient inside the scanner bore in the magnet room is not ideal, so latterly we adopted a system of spinal or epidural anaesthesia. The use of anaesthesia elevates the procedure from a simple out-patient procedure to a day case admission, with the attendant resource requirements as set-out in the health economics analysis. In future, shorter more streamlined procedures may reduce requirements for hospital admissions. The resource implications will need to be carefully evaluated against the potential advantages of this treatment in a palliative care setting.

Although the HIFU treatments described in this thesis were performed under MRI guidance, options such as ultrasound guidance also exist [185]. These ultrasound guided HIFU systems do not offer the possibility of real-time temperature mapping, but allow much more patient access and flexibility in patient positioning.

Transducers with longer focal lengths are becoming available that will address the possibility of treating deeper lesions and electronically steerable arrays will allow greater angulation of the beam to ensure greater coverage.Finally, a big step forward would be in the development of transvaginal transducers for treating lesions in and around the vagina. Transrectal HIFU probes already exist for treating prostate cancer and are widely used for this purpose [186], while transurethral probes are now being trialled [187]. The much larger population eligible for these treatments in prostate cancer has driven these developments, which in future could be successfully adapted to specialist requirements for patients with recurrent gynaecological cancers.

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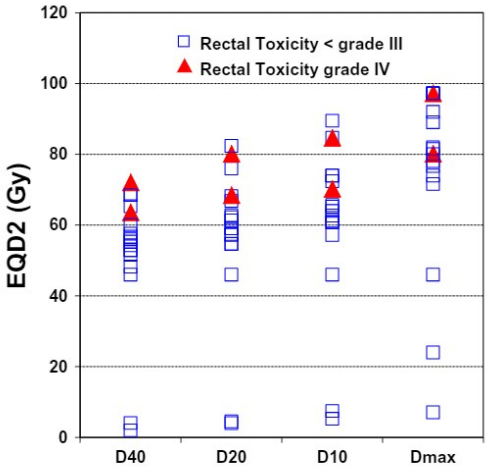
Appendices

Appendix 1.1 FIGO Staging for gynaecological cancers – adapted from *Bhatla, N. et al. (2019) Revised FIGO staging for carcinoma of the cervix uteri. Int. J. Gynecol. Obstet. 145, 129–135.*

FIGO Stage	Cervix	Endometrial	Ovarian
IA	Invasive carcinoma diagnosed by microscopy	Invasive carcinoma < one half of myometrium	I: Tumour confined to one ovary of fallopian tube with no malignant cells in the ascires of peritoneal washings
IB	Invasive carcinoma limited to the cervix with deepest invasion ≥5 mm	Invasive carcinoma > half of myometrium	Tumour limited to both ovaries or fallopian tubes
IC	-	-	IC1: surgical spill, IC2: capsule rupture or tumour on ovarian/fallopian surface, IC3: malignant cells in ascites or peritoneal washings
IIA	Involvement limited to upper two thirds of the vagina	II: Cervical stroma invasion	Extension to the uterus
IIB	Parametrial involvement		Extension to other intraperitoneal tissue
IIIA	Involvement of lower third of the vagina	Spread to serosa or to fallopian tubes/ovaries	Involvement of retroperitoneal nodes or microscopic extrapelvic peritoneal involvement
IIIB	Extension to the pelvic wall and/or hydronephroris	Vaginal involvement	Macroscopic peironteal metastatsis < 2cm beyond the pelvis
IIIC	Involvement of pelvic or paraaortic lypmh nodes	Involvement of pelvic or paraaortic lypmh nodes	Macroscopic peironteal metastatsis > 2cm beyond the pelvis
IVA	Spread to adjacent organs	Spread to adjacent organs	Pleural effusion with positive cytology
IVB	Spread to distant organs	Spread to groin nodes or distant organs	Spread to groin nodes or extra-abdominal organs

Rectum

STUDY	SITE	FRACTN	CONSTRAINTS	DOSE-VOLUME
MICHALSKI REVIEW 2010				Wachter, Cozzarini, Fiorino, Tucker
RTOG0415	Prostate	1.8-2Gy per fraction	RTOG 94-06 (conformal)	D15% < 75Gy D25% < 70Gy D35% < 65Gy D50% < 60Gy Mean dose ≤ 52.5 Gy
BRACHY				
EMBRACE II	Cervix	EBRT + BT	GEC-ESTRO	D2cc Aim < 65 Gy Limit <75 Gy
Georg 2012	Cervix	45-50.4#25 7x4 BT	GEC-ESTRO	≥G2 toxicity D2cc 5% 67, 10% 78, 20% 90 D1cc 5% 71, 10% 87, 20% 104 D0.1cc 5% 83, 10% 132, 20% 186
Mazeron EMBRACE	Cervix	EBRT+ IUBT	GEC-ESTRO	D2cc < 65 two time lower risk of proctitis compared to D2cc >75 Gy ≥G2 toxicity D0.1cc Proctitis 79.7Gy Bleeding 80.7Gy Stenosis 75.6Gy Fistulae 84.1Gy D2cc

				Proctitis 66.2Gy Bleeding 66.9Gy Stenosis 65.5Gy Fistulae 70.6Gy
SEQUENTIAL				
Guckenberger 2010	CX/END	50in25		 **Fig. 3.** Gy equivalent total doses (EQD_2) for the rectum/sigmoid were accumulated for the conventionally fractionated and the SBRT series: doses for patients with (red rectangle) and without (blue square) grade IV intestino-vaginal fistula are shown.
SBRT				
Musunuru 2015 + Alayed 2018	Prostate	40in5 25in5 pelvis		V38 strong predictor of rectal toxicity Rectum V28<15%, V35 <5% Bladder V25 <15% Bowel V25 < 20cc

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Bowel

STUDY	SITE	CONSTRAINTS	FRACT	DOSE-VOLUME
Gallagher 1986	All Pelvis	RTOG0415	Variable	Mild Diarrhoea 158cc 45 Gy Responsive Diarrhoea 138cc 60 Gy Obstruction 317cc 55 Gy
Kavanagh 2010	Review		Variable	Individual bowel delineation Dmax 15Gy to <120cc Bowel sac V45 <195cc SBRT Dmax <30 Gy
McDonald 2015	Bladder	Gallagher Kavanagh	55Gy in 20F 64Gy in 32F	Threshold 25% to maintain low ≥ G2 Bowel toxicity V30 178 V45 139 V50 127 V55 155 V60 98
Huang 2007	Gynae		Surgery vs No surgery RT + HDR IUBT	Grade 2 – 3 Toxicity, Significant increase in ≥ G2 V60-V100 V40 489 V50 385 V60 307 V70 262
Roeske 2003	Gynae		IMRT 45Gy 1.8Gy/F	Table 5 Dosimetric factors associated with clinically si univariate analysis Parameter n % $Vol_{SB,25}$ ≤602 13 >602 37 3 $Vol_{SB,50}$ ≤563 13 >563 37 3 $Vol_{SB,75}$ ≤396 13 >396 37 3 $Vol_{SB,100}$ ≤195 13 >195 37 3 $Vol_{SB,110}$ ≤19 38 2 >19 12 5 $Vol_{R,25}$ ≤50 5 >50 45 3 $Vol_{R,50}$ ≤50 5 >50 45 3 $Vol_{R,75}$ ≤63 25 1 >63 25 3 $Vol_{R,100}$ ≤63 25 2 >63 25 3 $Vol_{R,110}$ ≤7 38 2 >7 12 5 $Vol_{R,X}$, rectal volume (cc) receiving X% o greater, $Vol_{SB,X}$, small bowel volume (cc) receiv dose or greater.
BRACHYTHERAPY				
EMBRACE II	Cervix		EBRT + IUBT	No relation between D2cc and bowel morbidity from EMBRACE GEC-ESTRO Sigmoid D2cc Aim < 70, Limit < 75 Gy Bowel D2cc Aim <70 Gy, Limit <75 Gy

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GU/Bladder

STUDY	SITE	FRACT	CONSTRAINTS	DOSE-VOLUME
Viswanathan 2010/RTOG0415	Pelvic	Variable	RTOG0415	D15% < 80Gy D25% < 75Gy D35% < 70Gy D50% < 65Gy Mean dose ≤ 51 Gy
BRACHYTHERAPY				
EMBRACE II	Cervix	EBRT + IUBT	GEC-ESTRO	D2cc Aim < 80Gy, Limit <90 Gy
Georg 2012	Cervix	45-50.4#25 7x4 BT	GEC-ESTRO	≥G2 toxicity D2cc 5% 70Gy, 10% 101Gy, 20% 134Gy D1cc 5% 71Gy, 10% 116Gy, 20% 164Gy D0.1cc 5% 61Gy, 10% 178Gy, 20% 305Gy

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Appendix 3.2

REGENCY Feasibility Questionnaire

REGENCY: A Phase II trial of stereotactic radiotherapy for recurrent gynaecological cancer

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REGENCY Trial Synopsis

Introduction:

Isolated pelvic recurrence following surgery occurs in approximately 10-15% patients with cervical and endometrial cancer.In cervical cancer, there are 40-70% survival rates for central disease treated with radiotherapy but only 0-30% for sidewall involvement. Similarly, for endometrial cancer, 3 year survival rates are 70-80% for small vaginal recurrences suitable for a brachytherapy boost, but bulky central disease has lower control rates of 40-50% and historically only 8-15% for lateral relapse. Toxicity can be high with grade 3 bowel complications up to 18-30% reported when external beam radiotherapy alone or interstitial brachytherapy is used. Therefore isolated pelvic disease can potentially be cured but the current radiation treatments have a high risk of toxicity and limited effect for larger tumours unsuitable for brachytherapy.

Stereotactic radiotherapy has the potential for enabling dose escalation by reducing the OAR doses while allowing tumour dose hetereogeneity in a similar approach to brachytherapy. Several small case series have reported local control rates of 70-100% and low toxicity when SBRT is used for patients with primary cervical or endometrial cancer not suitable for brachytherapy and for recurrent disease including the sidewall.

In cervical cancer the OAR dose tolerances for intrauterine brachytherapy are internationally established and an isotoxic approach is used to determine prescription dose and fractionation. It is feasible to use a similar approach with an SBRT boost with equivalent tolerances for OAR values. We have completed a dosimetric feasibility study for patients with sidewall recurrence and with central disease. The results have been used to derive the planning targets for this study and to assess impact of variable GTV-PTV margins depending on SBRT technique.

Design & Treatment:
This is a multicentre, phase II study planned to open in approximately 7-10 UK sites. 46 patients with recurrent and primary gynaecological cancer not suitable for brachytherapy due to previous surgery or tumour topography will be treated with IMRT followed by a SBRT boost.

Treatment Schedule:

Phase One: IMRT to pelvis (+/- PAN) with 45Gy in 25 fractions

Integrated nodal boost 55 Gy in 25# for PET positive nodes (<2cm)

Phase Two: SBRT boost to GTV

For 17.5-22.5 Gy in 5 fractions using online image guidance with either Cyberknife or Linear accelerator delivered SBRT

Dose determined by OAR tolerances on Phase 2 plan

- dose limits have been developed for 5 fractions SBRT
- Aiming for >72 Gy (EQD2-10) total median GTV dose

Study aims:

To assess the outcomes of treating recurrent or primary gynaecological cancer not suitable for brachytherapy with IMRT followed by a stereotactic boost

To correlate toxicity with OAR dosimetry

Key Inclusion criteria:

- Previous total or sub-total hysterectomy
- Recurrent gynaecological cancer planned for radical radiotherapy to pelvis
  - central pelvic recurrence
  - pelvic sidewall recurrence
- Primary cervical or vaginal cancer not suitable for brachytherapy (e.g. previous subtotal hysterectomy, bulky vaginal cancer)
- Have a performance status of 0 - 2 and demonstrate adequate organ function.

Key Exclusion criteria:

- Previous radiotherapy to abdomen or pelvis
- Para-aortic nodes above renal vessels; no more than 3 involved nodes on PET scan

Questionnaire

We would be grateful for your help to assess the feasibility of conducting the proposed study and would appreciate it if you could complete the following brief questionnaire

Interested in participating as a trial site □ **Yes** □ **No**

Contact Information:		
• Principal Investigator	Name:	
	Address:	

	Contact number:	
	Fax number:	
	Email:	
• Trial Coordinator	Name:	
	Address:	
	Contact number:	
	Fax number:	
	Email:	

Recruitment Feasibility Questions:		
1. How many patients with isolated pelvic recurrence of gynaecological cancer or primary cancer not suitable for brachytherapy do you see at your institution per year?	_____ Patients per year	
2. Based on the attached study summary and key inclusion / exclusion criteria, please estimate the number of eligible patients that you might see per year?	_____ Eligible patients / year	
3. What percentage of these eligible patients do you expect would be willing to participate in this study? *(tick only one)*	□ 0-20% □ 21-40% □ 41-60%	□ 61-80% □ 81-100%
4. Do you think there is sufficient outcome data already available that we should proceed directly to a randomised trial?	□ Yes □ No Why? _____ _____	
5. Are you taking part in any other conflicting studies in this field?	□ Yes □ No If yes please specify how many: _____	
6. Do you anticipate any problems recruiting to this trial?	□ Yes □ No If yes please specify reason: __ _____.	
7. What is your current standard of care for this group of patients?	*Phase One* Technique: _____ Dose _____Gy ___ fractions Nodal boost? □ Yes□ No *Phase Two* Technique: _____ Dose _____Gy ___ fractions	
8. Do you use fiducial markers in routine treatment of this patient population?	□ Yes □ No If no, will you use them for SBRT? _____	
9. Is your centre currently delivering or planning	□ Yes	

to start SBRT for pelvic disease either for gynaecology or other tumour sites?	□Within SABR Commissioning through Evaluation (CtE) □Within 12 months □No
10. What SBRT technique do you use?	□Cyberknife □ Linear accelerator
11. Are you currently using SBRT for gynaecological cancer in any clinical scenario?	□Re-irradiation sidewall □Re-irradiation central pelvis □Primary RT sidewall □Primary RT central pelvis □Nodal metastasis Other – please specify
12. Please use this space for any additional comments you may have related to the proposed study design or your interest in this trial.	

Please return completed forms to alexandra.taylor@rmh.nhs.uk or rm-ctu@rmh.nhs.uk by
Friday 1st December
If you require any further information please contact RM-CTU on the above email or Tel: 02089 156503

Appendix 3.3

The ROYAL MARSDEN
NHS Foundation Trust

REGENCY
Stereotactic radiotherapy for recurrent gynaecological cancer

	Phase II single-arm multi-centre study
Target Population	Women with recurrent or primary gynaecological cancer planned for radical radiotherapy not accessible with brachytherapy Target sample size: 46 patients 7-10 UK radiotherapy centres
Study Intervention	Radical radiotherapy to pelvis with dose escalation to macroscopic disease Phase one: IMRT 45 Gy in 25 fractions Phase two: Stereotactic radiotherapy boost: 17.5-22.5 Gy in 5 fractions Dose determined by organ at risk dose constraints (isotoxic planning)
Key trial assessments	3 monthly clinical review and toxicity assessment for two years MRI scan and CT-PET scan at 3 months and 12 months after RT QoL questionnaires at baseline, 3, 6, 12 and 24 months after RT Central collection of radiotherapy planning data ?CTC Collection
Outcome measures	Primary endpoint: Local control at 12 months Secondary endpoints: PFS, OS G2+ GI and GU late toxicity Correlation of toxicity with DVH parameters Quality of life up to 24 months ?CTC exploratory component
Statistical analysis	Percentage with local control at 12 months after RT OS, PFS: Kaplan-Meier analysis Toxicity analysis: summary statistics
Sample size assumptions	Site distribution: central 80%, sidewall 20% Central disease (primary): 37 patients, Alpha 0.05, 80% power; 12 month local control > 55% assuming true rate 75% Sidewall (exploratory): 9 patients, 50% power; local control >25 assuming the true rate 50%.
Timings of trial	August 2018 Trial set-up+ RT Quality assurance programme Feb 2019 – Jan 2021 Patient recruitment Mar 2023 Last recruited patient 24 months review June 2022 Commence Data analysis

Appendix 4.1

RECOMMENDATION FOR LOW RESIDUE DIET PRIOR TO YOUR

MRgHIFU TREATMENT

Breads, flours and cereals

Foods to choose:

- White flour and products such as breads, scones, crackers, rolls, crumpets, bagels, muffins, pancakes, dumplings, Yorkshire puddings and pizza bases
- Ground oatmeal porridge
- Cornflakes
- Rice cereals
- Cornflour
- Chapatti/naan flour N ^{O} I

Foods to limit:

- Breads such as granary, seeded, wholegrain and wholemeal
- Rye breads
- Crispbreads
- Malted fruit bread
- Wholewheat breakfast cereals such as Shredded Wheat@, Weetabix@ and Muesli
- Crunchy cereal bars
- Tortilla chips
- Twiglets@

Vegetables

Foods to choose:

- Peeled and deseeded vegetables
- Remove tough stems, skins, husk, etc.
- Cook until soft and easily mashed, or pureed

Foods to limit:

- Corn
- Pips
- Tough skins of vegetables such as: skins of baked potatoes, cucumber, bell peppers and tomato
- Green vegetables such as: broccoli, sprouts, leeks, spring greens, curly kale, okra, pak choi
- Onions

Pasta and rice

Foods to choose:

- Well cooked, soft white pasta and noodles
- Well cooked, soft white rice and Basmati rice

Foods to limit:

- Wholemeal pasta
- Wholegrain and wild rice

Pulses

Foods to choose:

- Hummus
- Refried beans and other pureed beans
- Smooth dhal

Foods to limit:

- Whole beans
- Lentils and peas, especially baked beans
- Red kidney beans, soya beans and green beans

Fruit

Foods to choose:

- Peeled and soft fruit without pips or pith
- Cooked or tinned fruit
- Soaked or cooked and softened dried fruit
- Avocado (smooth guacamole)
- Fresh fruit smoothies (without pips)
- Fruit jellies, compotes and jams without pips
- Smooth fruit juice

Foods to limit:

- Fruits with seeds, pips, pith, hard skins or fibres, such as berries, kiwifruit, citrus fruits, grapes, rhubarb and plantain
- Unpeeled fruit such as apples, pears, peaches and nectarines
- Raw or dried fruit such as prunes, figs, dates and apricots
- Mixed dried fruit
- Jams or fruit spreads containing seeds, pips or tough skins

Nuts and seeds

Foods to choose:

- Smooth nut and seed butters and spreads such as peanut, pumpkin, sunflower seed, almond, cashew nut, hazelnut and pistachio
- Finely ground nuts and seeds. For example, almond flour
- Tahini

Foods to limit:

- All whole nuts and seeds
- Crunchy peanut butter
- Nut roast

Protein foods

Foods to choose:

- Tender meats (baked or poached), with the fat trimmed
- Poultry with skin removed
- Fish
- Eggs

Cakes and biscuits

Foods to choose:

- Plain flour sponges

- Biscuits such as chocolate, ginger, wafers and shortbreads
- Cakes such as Madeira, carrot, Swiss roll and teacakes - Danish pastries without dried fruit

Foods to limit:

- Fruit cake or biscuits containing hard pieces of dried fruit or fruit peel, nuts and seeds

Miscellaneous

Foods to choose:

- Barley sugars
- Caramels - Jellies
- Boiled sweets
- Honey
- Lemon curd
- Seedless spreads
- Marmite@
- Prawn crackers

Foods to limit:

- Bombay mix
- Chocolate with nuts or dried fruit
- Yoghurt with seeds, nuts or dried fruit
- Wholegrain mustard
- Hot and spicy foods
- Fizzy drinks and beer
- Coffee—try to drink less than four cups per day

A suggested meal plan

Breakfast ideas:

- Cereal and milk. For example, oatmeal porridge, corn flakes, rice breakfast cereals.
- Fresh peeled or stewed peeled fruit. Tinned fruit or fruit juice, or a fruit smoothie without pips.
- White bread or toast, butter or margarine, seedless jam or marmite.

Lunch ideas:

- White sandwiches or rolls filled with lean meat, tinned fish, meat paste, cheese or boiled egg.
- Scrambled, boiled or poached egg on toast.
- Yoghurt without seeds or nuts.
- Fruit as for breakfast.

Dinner ideas:

- Tender, lean meat or fish, cheese or egg dishes.
- White pasta, rice or peeled potatoes, well cooked.
- Vegetables, well cooked. Remove all tough parts and skins. Choose larger portions from the lower fibre varieties.
- Milk puddings. For example, custard, yoghurt and rice pudding.
- Sponge puddings and sauce, jelly and ice cream.

Appendix 4.3a Brief Pain Inventory

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

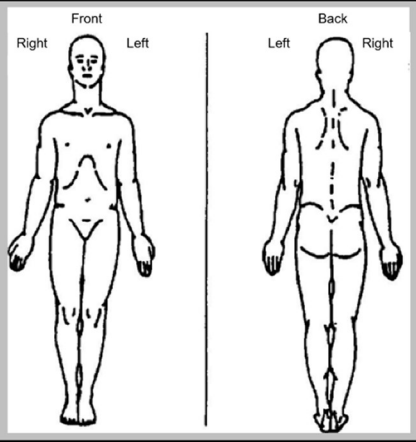
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ___/___/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Appendix 4.3b QLQ-C15-PAL

ENGLISH

EORTC QLQ-C15-PAL (version 1)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋
Today's date (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you

15. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4.3c EQ-5D-5L

CCR 4360: HIFU Gynae Study: Subject: □□□□□□□□□

EQ-5D-5L

Patient DOB: _____/_____/_____

Date completed: _____/_____/_____

Cohort 1: ▫ Screening

Cohort 2: ▫ Screening ▫ Treatment (Day 0) ▫ Day 7 ▫ Day 30

▫ Day 60 ▫ Day 90

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

Please turn over

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

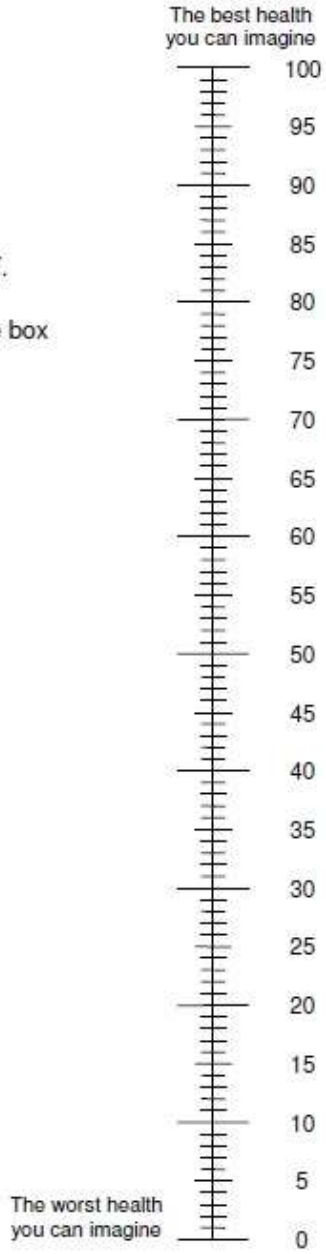
I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

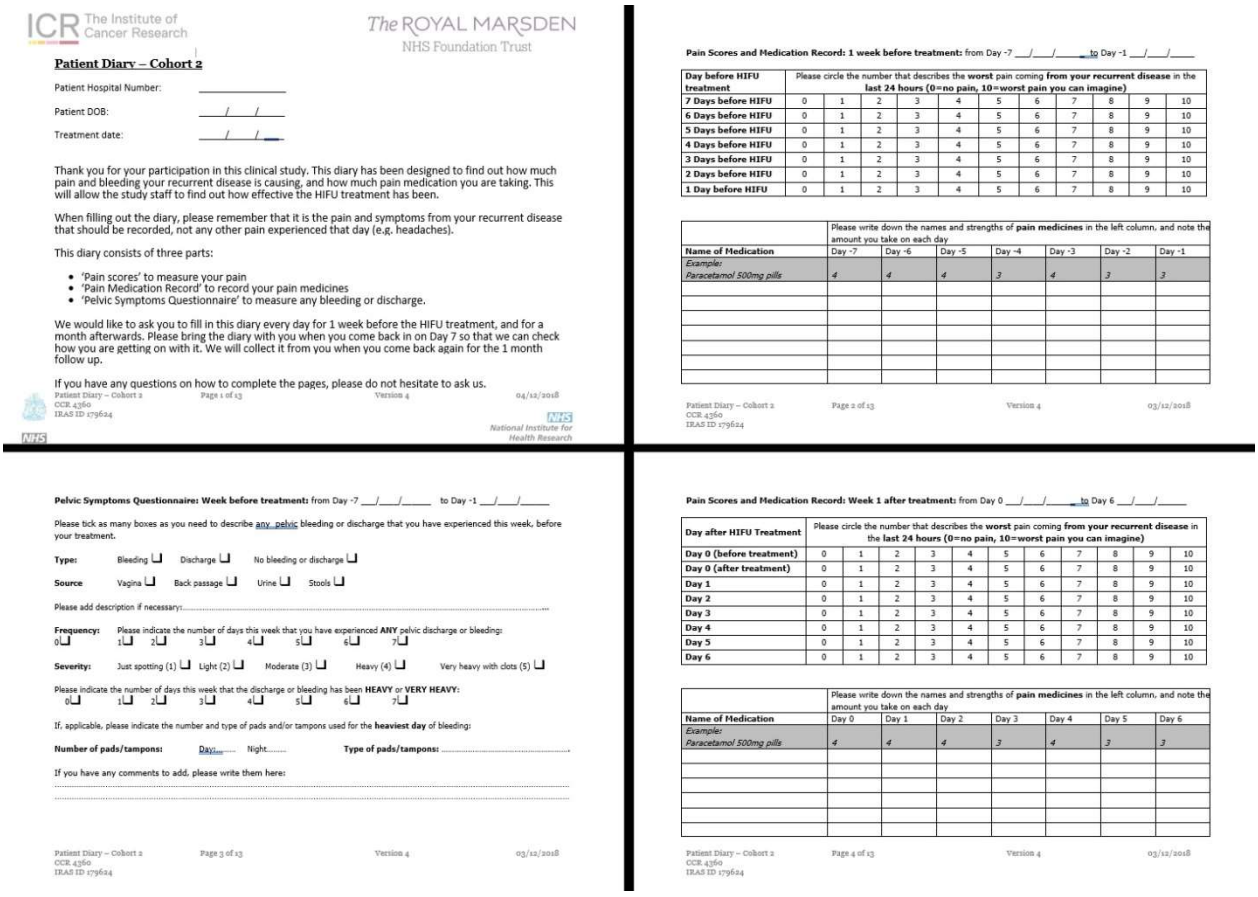
We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 4.4 Patient Diary – showing first four pages which are repeated for 5 weeks.



ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

Patient Diary – Cohort 2

Patient Hospital Number: _____

Patient DOB: ___/___/____

Treatment date: ___/___/___

Thank you for your participation in this clinical study. This diary has been designed to find out how much pain and bleeding your recurrent disease is causing, and how much pain medication you are taking. This will allow the study staff to find out how effective the HIFU treatment has been.

When filling out the diary, please remember that it is the pain and symptoms from your recurrent disease that should be recorded, not any other pain experienced that day (e.g. headaches).

This diary consists of three parts:

- 'Pain scores' to measure your pain
- 'Pain Medication Record' to record your pain medicines
- 'Pelvic Symptoms Questionnaire' to measure any bleeding or discharge.

We would like to ask you to fill in this diary every day for 1 week before the HIFU treatment, and for a month afterwards. Please bring the diary with you when you come back in on Day 7 so that we can check how you are getting on with it. We will collect it from you when you come back again for the 1 month follow up.

If you have any questions on how to complete the pages, please do not hesitate to ask us.

Patient Diary – Cohort 2 CCR 4360 IRAS ID 179624 Page 1 of 13 Version 4 04/12/2018

NHS National Institute for Health Research

Pain Scores and Medication Record: 1 week before treatment: from Day -7 ___/___/_____ to Day -1 ___/___/_____

Day before HIFU treatment	Please circle the number that describes the **worst** pain coming **from your recurrent disease** in the **last 24 hours (0=no pain, 10=worst pain you can imagine)**										
7 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
6 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
5 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
4 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
3 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
2 Days before HIFU	0	1	2	3	4	5	6	7	8	9	10
1 Day before HIFU	0	1	2	3	4	5	6	7	8	9	10

	Please write down the names and strengths of **pain medicines** in the left column, and note the amount you take on each day						
Name of Medication	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1
Example: Paracetamol 500mg pills	*4*	*4*	*4*	*3*	*4*	*3*	*3*

Patient Diary – Cohort 2 CCR 4360 IRAS ID 179624 Page 2 of 13 Version 4 03/12/2018

Pelvic Symptoms Questionnaire: Week before treatment: from Day -7 ___/___/_____ to Day -1 ___/___/_____

Please tick as many boxes as you need to describe any pelvic bleeding or discharge that you have experienced this week, before your treatment.

Type: Bleeding ☐ Discharge ☐ No bleeding or discharge ☐

Source Vagina ☐ Back passage ☐ Urine ☐ Stools ☐

Please add description if necessary:.....

Frequency: Please indicate the number of days this week that you have experienced **ANY** pelvic discharge or bleeding:
0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

Severity: Just spotting (1) ☐ Light (2) ☐ Moderate (3) ☐ Heavy (4) ☐ Very heavy with clots (5) ☐

Please indicate the number of days this week that the discharge or bleeding has been **HEAVY** or **VERY HEAVY:**
0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

If, applicable, please indicate the number and type of pads and/or tampons used for the **heaviest day** of bleeding:

Number of pads/tampons: Day:..... Night..... **Type of pads/tampons:** .....

If you have any comments to add, please write them here:

.....

.....

Patient Diary – Cohort 2 CCR 4360 IRAS ID 179624 Page 3 of 13 Version 4 03/12/2018

Pain Scores and Medication Record: Week 1 after treatment: from Day 0 ___/___/_____ to Day 6 ___/___/_____

Day after HIFU Treatment	Please circle the number that describes the **worst** pain coming **from your recurrent disease** in the **last 24 hours (0=no pain, 10=worst pain you can imagine)**										
Day 0 (before treatment)	0	1	2	3	4	5	6	7	8	9	10
Day 0 (after treatment)	0	1	2	3	4	5	6	7	8	9	10
Day 1	0	1	2	3	4	5	6	7	8	9	10
Day 2	0	1	2	3	4	5	6	7	8	9	10
Day 3	0	1	2	3	4	5	6	7	8	9	10
Day 4	0	1	2	3	4	5	6	7	8	9	10
Day 5	0	1	2	3	4	5	6	7	8	9	10
Day 6	0	1	2	3	4	5	6	7	8	9	10

	Please write down the names and strengths of **pain medicines** in the left column, and note the amount you take on each day						
Name of Medication	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Example: Paracetamol 500mg pills	*4*	*4*	*4*	*3*	*4*	*3*	*3*

Patient Diary – Cohort 2 CCR 4360 IRAS ID 179624 Page 4 of 13 Version 4 03/12/2018

Publications arising from this work

Manuscripts published

Imseeh, G. Giles, S. Taylor, A. Brown, M. Rivens, I. Gordon-Williams, R. ter Haar, G. and deSouza, NM. **Feasibility of Palliating Recurrent Gynaecological Tumours with MRgHIFU: Comparison of Symptoms, Quality-of-Life and Imaging Response in Intra- and Extra-Pelvis Disease.** Int J Hyperthermia. 2021 – in print.

Giles SL, Rivens I, Imseeh G, Brown MRD, Taylor A, ter Haar GR, deSouza, NM **Magnetic Resonance Guided High Intensity Focused Ultrasound (MRgHIFU) for Treating Recurrent Gynaecological Tumours: Effect of Pre-Focal Tissue Characteristics on Target Heating.**. Journal of Imaging and Interventional Radiology (2020); 3:1-6.

Giles SL, Imseeh G, Rivens I, Ter Haar GR, Taylor A, deSouza NM. **MR guided high intensity focused ultrasound (MRgHIFU) for treating recurrent gynaecological tumours: a pilot feasibility study.** Br J Radiol. 2019 Jun;92(1098):20181037. doi: 10.1259/bjr.20181037. Epub 2019 May 14.

Manuscripts in preparation

Imseeh G, Barton DPJ, Kolomainen D, Bryan S, Fernandes A, Llewelyn M, Ash J, Sohaib A, deSouza NM, Taylor A. **Studying patterns of relapse after pelvic exenteration for recurrent gynaecological cancer and defining high risk target volumes for post-operative re-irradiation using 3-dimensional tumour mapping.**

Imseeh G, Amin K, Birnstein D, Llewellyn M, deSouza NM, Taylor A **A dosimetric study of tumour dose escalation for central and pelvic side wall recurrent gynaecological cancer not suitable for brachytherapy: comparing simultaneous integrated boost volumetric arc therapy versus sequential stereotactic radiotherapy and proton beam therapy.**

Abstracts

G Imseeh, S Giles, I Rivens, A Taylor, G ter Haar, E Scurr, NM deSouza. **Imaging and pain response in extra vs intra-pelvic recurrent gynaecological tumours treated with MR guided HIFU: a pilot study.** Proceedings of the Annual Meeting of the ISMRM-ESMRMB (2020), Virtual. p.4752

G Imseeh, DPJ Barton, M Llewelyn, J Ash, A Fernandes, A Taylor. **Feasibility of post-operative stereotactic ablative radiotherapy (SABR) using cyberknife for positive margins after pelvic exenteration for gynaecological malignancy** International Journal of Gynecologic Cancer Nov 2019, 29 (Suppl 4) A120; DOI: 10.1136/ijgc-2019-ESGO.166

G Imseeh, DPJ Barton, D Kolomainen, S Bryan, A Fernandes, J Ash, A Sohaib, NM de Souza, A Taylor. **Using 3-dimensional tumour mapping to study patterns of relapse after pelvic exenteration for gynaecological malignancy** International Journal of Gynecologic Cancer Nov 2019, 29 (Suppl 4) A65; DOI: 10.1136/ijgc-2019-ESGO.86

G Imseeh, DPJ Barton, D Kolomainen, S Bryan, A Fernandes, J Ash, A Sohaib, NM de Souza, A Taylor **Patterns of Recurrence Following Pelvic Exenteration: Defining High Risk Target Volumes for Post-operative Re-irradiation** BGCS 2019, Cambridge, UK

S Giles, J Winfield, I Rivens, K De Paepe, V Morgan, G Imseeh, G ter Haar, A Taylor, NM deSouza. **Feasibility of MR guided High Intensity Focused Ultrasound (MRgHIFU) for treating recurrent gynecological tumours: comparing T2W imaging and diffusion weighted imaging (DWI) for treatment planning** Proceedings of the Annual Meeting of the ISMRM-ESMRMB (2018), Paris. p.4048.

S Giles, I Rivens, K De Paepe, V Morgan, G Imseeh, G ter Haar, A Taylor, NM deSouza. **Feasibility of MR guided High Intensity Focused Ultrasound (MRgHIFU) for treating recurrent gynecological tumours: a pilot study** Proceedings of the Annual Meeting of the ISMRM-ESMRMB (2018), Paris. p.4047.