Implementing image-guided brachytherapy for cervix cancer in the UK
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Abbreviations

3D three-dimensional
ABS American Brachytherapy Society
BED biologically effective dose
CT computed tomography
D2cc dose to the most exposed 2 cm³ of an organ at risk
D90 the isodose that includes 90% of the target
DVH dose-volume histogram
EBRT external beam radiotherapy
EMBRACE European study on MRI-guided brachytherapy in locally advanced cervical cancer
EQD2 equivalent dose in 2 Gy fractions
EUD equivalent uniform dose
GEC-ESTRO Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology
GTV gross tumour volume
HDR high dose rate
HR-CTV high-risk clinical target volume
ICRU International Commission on Radiation Units and Measurements
IGBT image-guided brachytherapy
IR-CTV intermediate-risk clinical target volume
LDR low dose rate
LQ linear-quadratic
MRI magnetic resonance imaging
OAR organs at risk
PDR pulsed dose rate
RCR The Royal College of Radiologists
STIC-PDR supporting costly innovative techniques; pulsed dose rate
T1/2 half time for repair
TRAK total reference air kerma
US ultrasound
V100 volume receiving 100% of prescribed dose
WP working party
Foreword

The use of brachytherapy in the treatment of cervical cancer is essential and while the development of external beam radiotherapy (EBRT) has advanced in recent years, the use of brachytherapy had not progressed in the same way. However, during the last few years, concepts for three-dimensional image-based treatment planning in cervix cancer brachytherapy have been developed. In 2005, recommendations for three-dimensional image-based brachytherapy were published by the Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) and have now become the standard.

This document reviews the evidence for the benefit of image-guided brachytherapy for cervix cancer and also provides guidance on equipment, dose prescription and techniques and the training and resources required to implement image-guided brachytherapy for cervix cancer.

The College would like to thank Li Tee Tan (Chair), Peter Blake, Peter Hoskin, Susan Davidson, Adrian Rathmell, Margaret Bidmead, Chris Lee and Mary Wilkins for their work in producing the document.

Jane Barrett
Dean of the Faculty of Clinical Oncology
The Royal College of Radiologists
Executive summary

Brachytherapy is crucial for the cure of cervix cancer with radiotherapy. The standard technique consists of standard doses prescribed to a fixed point and the use of plain X-ray imaging for treatment planning.

In 2005, the European brachytherapy society (Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology, GEC-ESTRO) published recommendations for the use of image-guided brachytherapy for cervical cancer. The guidelines have subsequently been endorsed by both GEC-ESTRO and the American Brachytherapy Society (ABS) as the new international standard for brachytherapy for cervix cancer.

This report reviews the evidence for the benefit of image-guided brachytherapy for cervix cancer.

The report also provides guidance on equipment, dose prescription and techniques and the training and resources required to implement image-guided brachytherapy for cervix cancer.
Implementing image-guided brachytherapy for cervix cancer in the UK

1 Introduction

The standard treatment of locally advanced cervical cancer is external beam radiotherapy (EBRT) with concomitant cisplatin chemotherapy followed by brachytherapy. Over the past two decades, there have been major advances in the planning, prescription and delivery of EBRT. The use of cross-sectional imaging and three-dimensional (3D) conformal treatment planning is now routine practice in most radiotherapy departments, resulting in improved dose to tumour target while reducing dose to organs at risk (OAR).

In contrast, the prescription of brachytherapy is still largely based on systems originally developed in the early 20th century. For cervix cancer brachytherapy, the most commonly used system is the Manchester point A system, originally proposed in the 1930s with standard doses prescribed to a fixed point regardless of tumour topography and doses to OAR, and the use of plain X-ray imaging for treatment planning.

There are several possible reasons for the lack of development of brachytherapy treatment when compared to EBRT.

- The clinical results of brachytherapy have traditionally been superior to EBRT, although its application is usually limited by the size of the tumour. There has therefore been less impetus for development.
- The opportunity for dose optimisation is limited with traditional low dose rate (LDR) techniques.
- The use of modern imaging techniques with traditional applicator designs has been suboptimal due to excessive artefact.

With the advent of high dose rate (HDR) equipment and artefact-free applicators compatible for use with computed tomography (CT) and magnetic resonance imaging (MRI), the possibility for image-guided 3D dose optimisation for brachytherapy treatment is now achievable.

Recently, a working group from the European brachytherapy society (Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology, GEC-ESTRO) published recommendations on contouring of tumour target and OAR as well as dose volume parameters to be reported for image-guided brachytherapy (IGBT) for locally advanced cervix cancer. These recommendations are mainly derived from retrospective single institution experience from Vienna with a MRI-based HDR brachytherapy technique with combined intracavitary and interstitial capability. The major advantage of the technique is the possibility to conform the dose to the anatomy of each patient to take into account the tumour volume and topography, and the position of OAR. The guidelines have been endorsed by both GEC-ESTRO and the American Brachytherapy Society (ABS) as the new international standard for brachytherapy for cervix cancer.

A collaborative European prospective observational study on MRI-guided brachytherapy in locally advanced cervix cancer (EMBRACE) is now under way to evaluate the implementation of these guidelines within a multi-centre setting.

In July 2008, The Royal College of Radiologists (RCR) set up a working party (WP) to facilitate the implementation of IGBT for cervix cancer in the UK. The aims of the WP were:

- To recommend minimum standards for a cervix cancer brachytherapy service in the UK which are in keeping with international recommendations
- To provide national guidance to promote and support the development of an IGBT service for cervix cancer.

The specific tasks undertaken by the WP were:

- To survey the opinions of oncology centres in the UK regarding the implementation of IGBT for cervix cancer
- To evaluate the evidence for the benefit of IGBT for cervix cancer
- To produce guidance on equipment, dose prescription and techniques
- To identify training requirements and competency assessment for IGBT
- To undertake a cost analysis of IGBT
- To develop a strategy to roll out IGBT across the UK.
2 Survey of current practice

An RCR survey of practice in the UK in 2004 estimated that nationally, less than 1,000 cervix cancer patients per year were treated with primary non-surgical radical treatment involving brachytherapy. Forty-two centres with brachytherapy facilities were involved in the survey; of these, 40 centres treated gynaecological cancers and gynaecological applications represented 40–100% of the workload in the centres.

A new survey of practice in 2008 was undertaken as part of the work of this WP. Questionnaires were sent to 46 centres known to offer brachytherapy for cervix cancer. Replies were received from all 46 centres. The results are summarised under the following headings.

2.1 Brachytherapy equipment

In 2004, 25 (63%) centres were treating gynaecological cancers with LDR equipment while 15 (37%) were using HDR equipment. Owing to the cessation of production of the LDR Selectron machine, all the centres using LDR equipment were considering a future replacement with HDR or pulsed dose rate (PDR) equipment. At the time of the survey, 23 centres were intending to change to HDR, one centre was continuing LDR until 2014 and another was considering PDR.

In the current survey, 21 (46%) centres are still using LDR equipment for treating gynaecological cancers. Twenty-four (52%) centres are now using HDR equipment, while one (2%) centre has both. Of the 21 centres with LDR equipment, 14 are planning to change to HDR equipment, four to PDR equipment while three centres are undecided. The one centre with both LDR and HDR equipment will replace the LDR machine with a PDR machine.

2.2 EBRT planning

The local control of cervix cancer depends on both EBRT as well as brachytherapy. Several studies have shown that the use of standard bony landmarks for EBRT planning in cervix cancer frequently results in geographical miss, resulting in an adverse impact on local tumour control. Despite this, a survey of UK practice in 2003 found that only five (of 49 = 10%) centres were using 3D planning for cervix cancer. It is likely that limited access to CT for EBRT planning has contributed to the slow implementation of 3D planning for cervix cancer.

In recent years, however, most centres in the UK have acquired dedicated CT simulators for radiotherapy planning. The WP therefore included a question on EBRT planning in the current survey to see if the availability of up-to-date equipment has changed practice. In 2008, 31 (67%) centres are now planning EBRT for cervix cancer using cross-sectional CT images. However, 15 (33%) centres are still using standard bony landmarks for planning cervix cancer. In 12 centres, such planning is carried out on a virtual simulator where 3D information is available and customised fields can therefore be applied.

The use of standard bony landmarks for planning EBRT for cervix cancer is not recommended in view of the risk of geographical miss.

2.3 Brachytherapy planning

The current survey showed that in 2008, the majority (34 = 74%) of centres in the UK use orthogonal X-rays for planning brachytherapy for cervix cancer. Twelve (26%) centres have access to CT for brachytherapy planning. Only two (4%) centres have access to MRI for brachytherapy planning.

Of the 34 centres which currently use plain X-rays for brachytherapy planning, 20 hope to have access to CT for brachytherapy planning within the next five years while nine also hope to have access to MRI. Only one centre stated that it will continue to use plain X-rays for brachytherapy planning while nine centres are undecided. Overall, 36 (78%) centres in the UK should be using CT (27 centres) and/or MRI (19 centres) for brachytherapy planning within five years.

2.4 Applicator design

The current survey showed that the most common (36 = 78%) brachytherapy technique used in the UK for treating cervix cancer is the tandem and ovoids. Five (11%) centres use the tandem and ring while two (4%) use a line source. Three centres (7%) use the line source as well as tandem and ovoids. Eighteen (39%) centres (12 tandem-ovoids, 5 tandem-ring, and 1 tandem ± ovoids) have no plans to change their brachytherapy technique in the foreseeable future. Twelve (26%) centres plan to change to the tandem-ring applicator. One centre (2%) intends to introduce the line source in addition to tandem and ovoids while another (2%) intends to
introduce the tandem-ring in addition to tandem-ovoids. Fourteen (30%) centres are undecided whether to change their brachytherapy technique.

2.5 Implementation of IGBT

Thirty-eight (83%) centres will be using or hope to use IGBT for cervix cancer within five years. Only eight (17%) centres are uncertain whether to implement IGBT; the reasons for their hesitancy are given in Table 2.1. The most commonly cited reasons are lack of CT/MR compatible applicators, lack of access to MRI for brachytherapy planning and lack of training in MR interpretation for tumour target delineation. Four respondents were uncertain of the benefit of IGBT for cervix cancer.

Table 2.1. Reasons for not implementing IGBT

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of CT/MR compatible applicators</td>
<td>5</td>
</tr>
<tr>
<td>Lack of appropriate planning software</td>
<td>1</td>
</tr>
<tr>
<td>Lack of access to CT for brachytherapy planning</td>
<td>1</td>
</tr>
<tr>
<td>Lack of access to MRI for brachytherapy planning</td>
<td>5</td>
</tr>
<tr>
<td>Limited access to operating theatres</td>
<td>2</td>
</tr>
<tr>
<td>Lack of brachytherapy physicists</td>
<td>2</td>
</tr>
<tr>
<td>Insufficient experience of MR interpretation for tumour target delineation</td>
<td>5</td>
</tr>
<tr>
<td>Unproven benefit</td>
<td>4</td>
</tr>
</tbody>
</table>
The benefits of cross-sectional imaging instead of orthogonal X-rays for the planning of brachytherapy can be considered under the following headings:

- Accurate verification of applicator position
- Accurate definition of normal tissue dosimetry
- Opportunity for conformal dose distributions to tumour volume and OAR
- Opportunity for dose escalation.

3.1 Accurate verification of applicator position

Uterine perforation is a recognised complication of tandem insertion during brachytherapy for cervix cancer. A recent study from Toronto found that CT-detected perforation was present in 8% (8/98) of insertions where the oncologist was clinically confident of correct tandem placement. If undetected, this could potentially result in excessive doses to loops of bowel in close proximity to the tip of the tandem. Intraoperative ultrasound (US) guidance has been shown to improve the accuracy of tandem placement and is useful for difficult insertions. Postoperative imaging (CT or MRI) cannot be used to aid tandem placement but will allow the oncologist to identify misplaced applicators and modify treatment appropriately by repositioning the applicator or altering the source loading.

3D imaging (CT, MRI or US) should be routinely used to verify the position of the applicator within the uterine canal.

3.2 Accurate definition of normal tissue dosimetry

In 1985, the International Commission on Radiation Units and Measurements (ICRU) proposed standard bladder and rectal reference points for reporting the absorbed dose to OAR during brachytherapy for gynaecological cancers. The incorporation of these points into routine clinical practice has not been universal. This is partly because several studies have shown that the doses at the ICRU bladder and rectal reference points significantly underestimate the maximum doses to these organs. Most studies have shown poor correlation between the ICRU bladder dose and the incidence of late bladder complications, although attempts to correlate the ICRU rectal dose and the risk of rectal complications have been more successful.

In EBRT, the use of point doses for normal tissue dosimetry has largely been abandoned in favour of dose-volume histograms (DVHs). Similar developments are under way in cervix cancer brachytherapy. Correlation of DVH parameters with clinical data on toxicity is limited at present but the early evidence suggests a consistency between reports from different institutions which should allow absolute OAR dose constraints to be identified.

The reporting of OAR point doses is the minimum requirement for any brachytherapy treatment. For more complete reporting, the use of DVHs is recommended.

3.3 Opportunity for conformal dose distributions to tumour volume and OAR

One of the major advantages of modern brachytherapy machines (HDR and PDR) is the flexibility to adjust source dwell positions and dwell times to conform the dose distribution to the topography of the tumour target and the position of OAR. Several studies have compared the brachytherapy dose distributions produced using such 3D optimisation with conventional X-ray based planning. All have shown that 3D optimisation improves tumour target dose coverage while reducing the dose to OAR. At present, it is recommended that dose conformation is achieved by an iterative process, with clinical and physics input, rather than using the prescriptive algorithms available in some treatment planning systems.

There are few published reports on the clinical impact of improved dose conformation on local control and toxicity. The seminal paper was published in 2007 by Pötter et al from Vienna who reported the first single-institution experience with MRI-based IGBT in a large consecutive patient population (145 patients). They reported a three-year pelvic control rate of 96% for tumours 2–5 cm in diameter and 90% for tumours >5 cm in diameter, with a three-year actuarial rate of Grade 3–4 bowel and urinary toxicity of 2%, with the introduction of systematic MRI-based planning. While these results are impressive, they are limited to a single-centre experience which may not be reproducible. Recently however, Tan et al reported the Addenbrooke’s experience with CT-based IGBT in a small
cohort of patients (28 patients) with shorter follow-up (10–44 months). The three-year pelvic control rate was 96% (100% for tumours 2–5 cm in diameter and 75% for tumours >5 cm in diameter), which was equivalent to a statistically significant improvement of 20% compared to a previous cohort treated with a conventionally planned triple source LDR brachytherapy technique, while the rate of Grade 3–4 bowel and urinary toxicity was unchanged (16% for the X-ray planned cohort, 14% for the CT-planned cohort).

Dose conformation with IGBT leads to improved local control and reduced toxicity and should be implemented as soon as is reasonably achievable.

3.4 Opportunity for dose escalation

The correlation between higher doses to point A and improved local tumour control is well established. Historically, the doses given in UK centres have been lower than those in European or American institutions and this is reflected in lower tumour control rates for UK cervix cancer patients.

As CT is more commonly available for radiotherapy planning than MRI, the Vienna group has compared the potential for dose escalation with CT and MRI-based brachytherapy planning. They found that compared to conventional planning with X-rays, it was possible to increase the dose to 95% of the target volume by 124% using CT-based planning, and 138% using MRI-based planning, without exceeding the tolerance dose of the rectum and bladder. They reported a 20% increase in local control using MRI-based IGBT compared to a previous cohort of patients treated in 1993–1997, which they attributed to dose escalation and improved tumour coverage including interstitial brachytherapy where appropriate.

Dose escalation with MRI-based IGBT leads to improved local control without increasing toxicity and should be implemented as soon as is reasonably achievable.
4 Recommendations on equipment, dose prescription and techniques

4.1 Equipment – HDR versus PDR

The principles of IGBT have been successfully applied to both HDR\textsuperscript{28,30} and PDR\textsuperscript{29,31} techniques. HDR brachytherapy is now an established option for cervix cancer brachytherapy and the initial concerns about late toxicity have not been substantiated\textsuperscript{42}. Treatment times are short and day-case treatment is therefore feasible. However, treatment has to be given in multiple fractions which could have an impact on operating theatre time unless a cervical sleeve is used. In addition, the treatment rooms require considerable shielding which could have significant impact on installation costs.

In contrast, PDR brachytherapy was originally developed to simulate conventional LDR brachytherapy which has a theoretical radiobiological advantage over HDR brachytherapy. Published schedules\textsuperscript{29,31} tend to describe single treatments given at dose rates in the region of 0.5–1 Gy/h over 2–4 days. At present, there are little clinical data on its efficacy in terms of local tumour control and toxicity and the results of the French multicentre prospective study (STIC-PDR)\textsuperscript{43} are awaited.

While this report is primarily concerned with cervix cancer brachytherapy, the bulk of brachytherapy treatments for gynaecological cancers comprise vault brachytherapy for endometrial cancer. The impact of the longer treatment times of PDR compared to HDR in this group of patients has significant implications for patient throughput and resource requirements, including numbers of machines, bed-days and staffing. It is possible that centres deciding to opt for PDR equipment for treating cervix cancer will also require HDR equipment for vault brachytherapy.

The principles of IGBT are applicable to both HDR and PDR techniques. Choice of equipment will depend on local resource implications.

4.2 Dose-fractionation schedules

In switching over from LDR to HDR or PDR techniques, many clinicians will no longer have the familiarity of experience to guide their dose prescription and modifications. The GEC-ESTRO guidelines\textsuperscript{2} recommend that the linear-quadratic (LQ) model should be routinely used to compare the effects of different dose rates and fraction sizes, assuming an $\alpha/\beta$ ratio of 10 Gy for tumour target volumes and 3 Gy for OAR. For clinical use, the WP felt that the concept of the equivalent dose in 2 Gy fractions (EQD2) is probably more easily understood than biologically effective dose (BED) or equivalent uniform dose (EUD) due to its similarity to EBRT regimes.

A worksheet for calculating EQD2 for different dose fractionation schedules is available from GEC-ESTRO\textsuperscript{2}. However, caution is necessary when using these formulae as many of the radiobiological assumptions involve theoretically derived values. Comparison of HDR schedules is relatively straightforward as the only radiobiological assumption required is the $\alpha/\beta$ ratio. For PDR brachytherapy, the radiobiological parameters necessary to calculate the EQD2 include the $\alpha/\beta$ ratio, the half time for repair (T1/2), the number of pulses, pulse interval and pulse time. The lack of knowledge about T1/2 values for human tissues is probably the largest area of uncertainty in PDR brachytherapy and the GEC-ESTRO guidelines\textsuperscript{2} recommend treatment schedules with pulse sizes of 0.5 to 1.5 Gy repeated every one to three hours.

A comparison of the EQD2 for some LDR, HDR and PDR dose-fractionation schedules is given in Table 4.1.
Table 4.1. EQD2 for some typical LDR, HDR and PDR schedules

<table>
<thead>
<tr>
<th></th>
<th>Point A EQD2 (Gy_{eq})</th>
<th>OAR EQD2 (Gy_{eq})*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 Gy in 25#</td>
<td>50.4 Gy in 28#</td>
</tr>
<tr>
<td>LDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 Gy @ 1.3 Gy/h</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>25 Gy @ 1.7 Gy/h</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>27 Gy @ 1.3 Gy/h</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>27 Gy @ 1.7 Gy/h</td>
<td>81</td>
<td>86</td>
</tr>
<tr>
<td>HDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Gy in 2#</td>
<td>64</td>
<td>69</td>
</tr>
<tr>
<td>21 Gy in 3#</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>28 Gy in 4#</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>PDR **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 Gy @ 1 Gy/h (25 h total)</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>25 Gy @ 1.25 Gy/h (20 h total)</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>27 Gy @ 1 Gy/h (27 h total)</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>27 Gy @ 1.35 Gy/h (20 h total)</td>
<td>79</td>
<td>84</td>
</tr>
</tbody>
</table>

* Assumes dose to OAR from brachytherapy = 70% of prescribed dose to point A

** Assumes 1 pulse/h lasting 15 minutes each

When implementing HDR or PDR brachytherapy, the use of published dose-fractionation schedules with documented clinical data on local control and toxicity is recommended.
4.3 Dose specification and reporting

Different dose parameters for recording and reporting are required for volume-based IGBT planning compared to dosimetry based on point doses and plain X-rays. The GEC-ESTRO guidelines\(^2\) include a comprehensive list of recommendations for recording and reporting 3D gynaecological brachytherapy which are summarised in Table 4.2.

Table 4.2. GEC-ESTRO recommendations for recording and reporting 3D gynaecological brachytherapy\(^2\)

<table>
<thead>
<tr>
<th>Clinical situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy and pathology</td>
</tr>
<tr>
<td>Clinical and imaging dimensions and volume of macroscopic tumour at diagnosis and at time of brachytherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3D sectional imaging technique and contouring procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy technique</td>
</tr>
<tr>
<td>Radionuclide; source type; source strength; applicator type; afterloading method</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment prescription and treatment planning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicator reconstruction, standard loading pattern, dose specification, optimisation method</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Reference Air Kerma (TRAK)</td>
</tr>
<tr>
<td>Dose at point A (right, left, mean)</td>
</tr>
<tr>
<td>D100, D90 for gross tumour volume (GTV), high-risk clinical target volume (HR-CTV) and intermediate-risk clinical target volume (IR-CTV)</td>
</tr>
<tr>
<td>Dose to bladder and rectum for ICRU reference points</td>
</tr>
<tr>
<td>D0.1cc, D1cc, D2cc for OAR (eg, rectum, sigmoid, bladder, vagina)</td>
</tr>
<tr>
<td>D5cc, D10cc for OAR if contouring of organ walls is performed</td>
</tr>
</tbody>
</table>

Complete description of time–dose pattern: physical and biologically weighted doses

\((\alpha/\beta=10 \text{ Gy for GTV and CTV}; \alpha/\beta=3 \text{ Gy for OAR}; T1/2=1.5 \text{ h for GTV, CTV and OAR})\)

While these recommendations are important for research and comparison between institutions, the sheer amount of data collected may be overwhelming to those seeking to implement 3D brachytherapy for the first time. The WP therefore recommends the following dose parameters as the minimum required for clinical practice as they have been shown to be the most clinically relevant.

- For all brachytherapy treatments (X-ray or CT/MRI planned)
  - Physical dose to point A (Gy)
  - EQD2 to point A (Gy\(_{\alpha/\beta=10}\)).
For volume-based image-guided dosimetry

- **D90** (the minimum dose to 90% of the tumour target volume, Gy$_{\alpha/\beta10}$) for the high-risk clinical target volume (HR-CTV)

  The intermediate-risk clinical target volume (IR-CTV), which is equivalent to the 60 Gy volume for LDR brachytherapy,
  has not been included as it is not a commonly used concept in UK practice. Moreover, it has been recommended that dose
  optimisation of the target should mainly be guided by the dose given to the HR-CTV as the dose constraints for the IR-CTV
  are easier to fulfill

- **D2cc** (minimum dose to the most exposed 2 cm$^3$ of OAR, Gy$_{\alpha/\beta3}$) for bladder, rectum and bowel.

For point-based dosimetry planned on X-rays

- Dose to ICRU bladder and rectal reference points (Gy$_{\alpha/\beta3}$).

The V100 (volume receiving 100% of the prescribed dose) is not included in the GEC-ESTRO recommendations but is a useful
parameter for comparing the quality of a dosimetry plan for individual patients and should also be recorded.

The reporting of the physical dose and EQD2 to point A, the D90 and V100 for the HR-CTV, and the D2cc for OAR, is the
minimum requirement for IGBT.

### 4.4 Dose targets and constraints

The following dose targets and constraints are recommended by the WP.

- For the tumour, the EQD2 to point A and/or D90 should be 75–80 Gy$_{\alpha/\beta10}$ in order to maintain similar local control rates to
  historical UK series. The international recommendation by both GEC-ESTRO and the ABS is for a tumour EQD2 of 85–90 Gy$_{\alpha/\beta10}$
  – this is higher than the doses traditionally used in the UK and should be applied with caution in association with detailed
  attention to OAR doses and careful monitoring of morbidity rates.

- For OAR, the absolute dose constraints have not been established. The following dose constraints from the EMBRACE study
  protocol have been included as a guide:

  - Rectum: 70–75 Gy$_{\alpha/\beta3}$
  - Sigmoid/bowel: 70–75 Gy$_{\alpha/\beta3}$
  - Bladder: 90–95 Gy$_{\alpha/\beta3}$.

  The compromise between dose to tumour versus dose to OAR should be taken by the clinician in discussion with the patient.

**In implementing HDR or PDR brachytherapy, the minimum EQD2 to point A and/or D90 should be 75–80 Gy$_{\alpha/\beta10}$. Dose escalation
to 85–90 Gy$_{\alpha/\beta10}$ with MRI-based IGBT is recommended as soon as is reasonably achievable.**

### 4.5 Imaging – CT versus MRI

It is well recognised that MRI is superior to CT for the imaging of cervix cancer as it offers detailed information about the extent of the
gross tumour volume (GTV) within the cervix and uterus as well as any extra-cervical extension. However, most UK centres do not
have ready access to MRI for radiotherapy planning. The Vienna group has compared CT versus MRI–based contouring of tumour
target (GTV, HR-CTV and IR-CTV) and OAR. They found no significant differences between CT and MRI in the volume of or the
dose to the OAR. For tumour targets, however, the CT contours tended to overestimate the width of the tumour, resulting in an
apparent reduction in D90. (Alternatively, this would lead to increased dose to OAR if the D90 was optimised.) CT was unable to
differentiate between GTV and CTV; however, this may not be clinically significant as the target dose is prescribed to the HR-CTV and
the GTV should therefore receive a higher dose. CT was also unable to differentiate between the apex of the cervix and uterine tissue;
again, this may not be clinically significant if a standard loading pattern is used (with the tandem loaded to the tip) as the cervix apex
will invariably be included in the high dose region.

Implementing image-guided brachytherapy for cervix cancer in the UK
The clinical results previously discussed in Section 3.3 suggest that for optimal dose optimisation and/or dose escalation, MRI-based IGBT is the gold standard resulting in superior local control rates, particularly for large tumours, and lower toxicity rates.\textsuperscript{33} However, excellent local control rates can be achieved for tumours 2–5 cm in diameter with the CT-based technique.\textsuperscript{34} This is probably because the risk of geographical miss is minimal in smaller tumours and dose escalation is unlikely to be necessary. The WP therefore recommends that centres without access to MRI for brachytherapy planning should not delay implementation of IGBT for cervix cancer but should proceed with the CT-based technique, perhaps in conjunction with a diagnostic MRI before brachytherapy to assess extent of residual tumour and response to EBRT.\textsuperscript{44}

\textit{MRI-based IGBT is recommended for optimal local tumour control and late toxicity rates. For tumours ≤5 cm in diameter, excellent local control can be achieved with CT-based IGBT and is an acceptable interim solution.}

4.6 Applicator design

The Vienna brachytherapy technique utilises a tandem-ring applicator instead of the more common tandem-ovoids applicator. A modelling study\textsuperscript{45} exploring the optimal dwell positions for brachytherapy for cervix cancer found that in the majority of patients, the optimisation programme favoured dwell positions closer to the cervix and closer to the perimeter of the vagina; that is, a configuration that resembled the ring rather than ovoids. However, several studies\textsuperscript{27,29,46} have shown that dose optimisation with tandem-ovoids applicators also results in improved tumour target coverage and/or reduced dose to OAR. Although clinical data are not yet available, it is likely that this will lead to a beneficial effect on local control and toxicity. The addition of interstitial brachytherapy to intracavitary brachytherapy\textsuperscript{47} further improves tumour coverage for patients with insufficient response and/or unfavourable topography after EBRT while limiting the dose to OAR. Preliminary results suggest that excellent local control can be achieved without increasing toxicity.\textsuperscript{48}

\textit{The principles of IGBT are applicable to both tandem-ring and tandem-ovoids applicators. For tumours with unfavourable topography after EBRT, the addition of interstitial needles is recommended.}
5 Training requirements and competency assessment

The use of IGBT for cervix cancer incorporates new concepts which may be unfamiliar to clinicians and physicists. The following have been identified as learning objectives for those wishing to implement the technique for the first time:

- Target volume delineation (MRI and/or CT)
- Applicator reconstruction (CT and/or MRI)
- Dose evaluation
- Dose optimisation
- Dose modification
- Quality assurance.

In addition, there are a number of logistical and practical issues that are necessary to ensure a safe and comfortable patient journey.

At present, the main resources for learning are teaching courses and practical workshops run by various organisations including ESTRO, ABS, individual institutions and manufacturers of brachytherapy equipment. Tools for competency assessment are currently lacking and developments in this area are urgently needed. Meanwhile, centres are encouraged to progress towards common techniques, prescription, dosimetry and quality assurance, as recommended in the 2007 RCR document on brachytherapy services in the UK.5
6 Cost analysis of IGBT

The cost of implementing IGBT can be considered under the following headings:

- Fixed costs
- Semi-fixed costs
- Variable costs.

Fixed costs are those which do not vary over a wide range of volume of activity. For cervix cancer brachytherapy, these include the cost of:

- The brachytherapy equipment
- Equipment housing, including bunker shielding
- The treatment planning system
- Maintenance and service charges
- Regular source replacement.

Semi-fixed costs are costs that do not vary over a range of volume of activity but will have a stepped increase when a critical volume of activity is exceeded. These costs include:

- Staff costs – oncologists, physicists, radiographers, nurses
- Equipment costs, including number of applicators
- Theatre sessions, including anaesthetic time.

Variable costs alter according to the volume of activity and are therefore dependent on patient numbers and the dose-fractionation schedule. The costs include bed-days, theatre and treatment room consumables, applicator sterilisation and the imaging costs of CT and/or MRI.

In assessing these costs, it is necessary to consider not only the financial cost of equipment and manpower but also the cost in terms of staff time. For example, a HDR service involving multiple fractionated treatments has increased cost in terms of an oncologist's time (for applicator insertion, volume delineation and plan evaluation) as well as a physicist's time (for dosimetry planning). In contrast, a PDR service is less demanding of an oncologist's time but is more demanding of a physicist's time, even with the reduced requirement for dosimetry planning, as several machines will be required for the same number of patients resulting in additional requirements for machine calibration and quality assurance checks after every source change. For oncologists, the amount of time necessary to deliver an IGBT service with individualisation of treatment for patients should be reflected in their job plans.

The cost of implementing an IGBT service for cervix cancer should also take into account the cost of training, maintenance of competency and regular updating of skills. It will also be necessary to consider the impact of ongoing developments on future practice; for example, optimal applicator design and imaging technique. Moreover, the magnitude of the benefit in terms of improved local control and reduced toxicity is such that it should be reflected in the tariffs for payment to encourage rapid implementation of the technique in UK centres.
The implementation of IGBT for cervix cancer may seem daunting to centres which have no experience of the technique. However, the benefits of IGBT can be considered at four levels of complexity as discussed in Chapter 3. Each of these levels of benefit has different resource implications for implementation. A summary of these resources is given in Table 7.1.

Table 7.1. Minimum requirements to achieve benefit of IGBT

<table>
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<tr>
<th>BENEFIT</th>
<th>MINIMUM RESOURCES REQUIRED</th>
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<tr>
<td></td>
<td>Equipment</td>
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<tr>
<td>I. Verification of applicator position</td>
<td>Any</td>
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<tr>
<td>II. Accurate definition of OAR doses</td>
<td>Any</td>
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<tr>
<td>III. Conformation of dose distribution</td>
<td>HDR/PDR</td>
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<tr>
<td>IV. Dose escalation</td>
<td>HDR/PDR</td>
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</table>

Level I and II benefits can be achieved with the standard resources available in all radiotherapy centres as they are applicable to any equipment and any 3D imaging technique. Departments should therefore consider implementing this in the near future. Level III benefit should also be achievable in any centre with HDR or PDR equipment and access to CT for radiotherapy planning. The principles are applicable to standard metal applicators but additional training is required for staff to develop the necessary competencies. However, the gain in terms of improved local control without increased toxicity for tumours ≤5 cm in diameter is such that centres with HDR or PDR equipment should give urgent consideration to implementing this as soon as possible. Level IV benefit is the most resource intensive requiring access to MRI for brachytherapy planning and MR compatible applicators as well as additional training for staff, and it is unlikely that many centres will be able to implement this in the near future. However, this benefit may only be applicable to large tumours >5 cm in diameter or those with unfavourable topography after EBRT. Centres unable to offer Level IV benefit should consider referring such patients to neighbouring centres with the facility until their own service is established. Networks and commissioning bodies may have to decide whether a regional service for this group of patients will be more cost-effective.
8 References


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