NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of high dose rate (HDR) brachytherapy for carcinoma of the cervix.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2005

Procedure name

High dose rate brachytherapy
HDR afterloading brachytherapy
HDR Intracavitary radiation therapy

Specialty societies

Royal College of Obstetrics and Gynaecology
British Gynaecological Cancer Society
Royal College of Radiologists

Description

Indications:

In the UK as many as 3000 women are diagnosed with cancer of the cervix each year. There are two main types. The most common, squamous cell carcinoma, usually develops from the cells which cover the outer surface of the cervix (ectocervix), within the so-called transformation zone The other, adenocarcinoma, usually develops from the glandular cells which line the cervical canal (endocervix). The stage of a cancer is defined by its size and by the extent of spread beyond the cervix. The initial treatment of cervical cancer is dictated by a number of factors, including the stage of the disease at presentation.

The most common symptoms of cervical cancer are abnormal vaginal bleeding or discharge and discomfort during intercourse.

Current treatment and alternatives

Cancer of the cervix can be treated with surgery, radiotherapy, chemotherapy or a combination of these treatments. The choice of treatment will depend mainly upon

the stage of the cancer. Surgery is often the main treatment for cancer of the cervix in its early stages (where cancer is found only in the cervix). Chemotherapy is occasionally used before surgery, shrinking the cancer and make the operation simpler. However, it is mainly given in combination with radiotherapy either as a primary therapy or after surgery.

Brachytherapy is a form of radiation treatment where radioactive sources are placed on or into cancer tissues. Therapy can be given in low medium or high dose rates. There is no universally accepted definition of these rates, but in principle the higher the dose rate the more radiation is delivered in a shorter time (although total doses may in fact be lowest with high dose rate therapy). Low dose rate brachytherapy was the first internal radiation system developed in which radiation is delivered slowly, or at a low dose rate. In order to administer a radiation dose that will eliminate the cancer, the instruments need to be in place for an extended period of time, with applicators inserted into the vagina for 2 to 3 days.

In order to eliminate the radiation hazard to staff, and to reduce the length of inpatient treatment, with requirement for isolation of the patient, and thus improve patient acceptability of treatment, high dose rate (HDR) brachtherapy was developed., Whilst the same treatment may be used for palliation of advanced disease, this overview refers only to HDR brachytherapy used with the intent to cure cervical cancer.

What the procedure involves:

In HDR Brachytherapy an implant containing a high dose of radioactivity (microselectron) is inserted into the cervix and this is left in place typically for a few minutes, and then removed. These treatments are often repeated several times, a few days apart, and are usually given as an outpatient. Ultra sound guidance may be used during the planning of the treatment. This intervention gives a high dose of radiation to the cervix and the area close by, but only a low dose to tissues and organs more than a few centimetres away. Practically all high dose rate brachytherapy is given in conjunction with external beam radiation therapy (EBRT).

Efficacy:

Across the randomised controlled trials comparing patients treated with HDR and LDR brachytherapy, the overall survival (across all stages of disease) with HDR ranged from 68%[1] to 54%[2], at three and five years follow up respectively. The corresponding survival following LDR brachytherapy was 71%[1] and 55%[2] to the same follow up time. Similarly, disease free survival was achieved with HDR brachytherapy in 65%[1] to 69%[3] of patients with stage II disease at three and five years respectively, while the rate was found to be 76%[1] and 87%[3] for LDR brachytherapy treated patients respectively. For patients with stage III cancer, disease free survival following HDR brachytherapy was 74%[1] and 51%[3] at three and five years, while this outcome was achieved in 59%[1] and 60%[3] of LDR brachytherapy treated patients. None of these differences between groups were significantly different

In randomised controlled trial comparing 31 patients receiving HDR brachytherapy to 29 having Medium dose rate (MDR) treatment overall five year survival (across all stages) was 61% Vs 63% (p=0.9839). In the same study local disease free survival achieved in 67% of HDR brachytherapy cases compared to 78% in MDR treated patients (p=0.8603)[4]

The pattern of treatment failure across HDR treated patients from randomised controlled trials and case series found distant failures occurred in 6% (15/236) [2], 19% (372/1992)[5], 22% (43/200)[6] and (25/112) [1], 25% (figures not reported) [3] of cases. Where the outcome was reported, local recurrence occurred in 6% (7/112) [1], 18%

(not reported) [3], 21% (415/1992) [5], and 22% (51/236) [2], with follow up ranging from 3 to 10 years.

Safety:

Complications have been reported using a range of outcome measures across the studies. Serious complications that required subsequent surgery occurred in between 2%[5] and 6% (11/200) [6] of cases from two case series.

In a large case series with a median 8 year follow up period the overall complication rate was 35% and radiation therapy oncology group grade 3 or 4 complications occurred in 7% of cases[5]. In a randomised controlled trial comparing HDR and MDR brachytherapy the grade 2 complication rate among HDR treated patients was 13% (4/31) [4].

Where reported separately, rectal complications (all grades) were reported in between 4%[3] and 20% (22/112) [1] of cases, and bladder complications between 4% (8/200) [6] and 24%[7] of cases.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high dose rate brachytherapy for all gynaecological malignancies. Searches were conducted via the following databases, covering the period from their commencement to 20/05/2005. MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with carcinoma of the cervix
Intervention/test	High dose rate brachytherapy with curative intent
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on four randomised controlled trials [1-4] and three case series[5-7]

Existing reviews on this procedure

No systematic reviews or evidence based guidelines on ultrasound-guided minimally invasive breast surgery were identified during the literature search.

Table 1 Summary of key efficacy and safety findings on curative high dose rate (HDR) brachytherapy for carcinoma of the cervix.

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
El-Baradie M M (1997)(4) Randomised controlled trial Japan n=60 (31 HDR brachytherapy) Concurrent EBRT for all cases except stage Ia HDR brachytherapy at 32Gy per four fractions T1 and 2, 30Gy per four fractions T3, and 22.5Gy per 3 fractions in T4. MDR brachytherapy at 35.6GY per four fractions, 34Gy per four fractions, and 25.5 Gy per three fractions, respectively Age =61 years, Stage I =12, stage II =22, stage III = 23, stage IV =3. Median follow up = 2 years, (maximum 5 years)	**Survival** 5 year actuarial survival Overall survival was 61% in the HDR brachytherapy group, and 63% I the MDR group (p=0.9839) Stage HDR MDR I and II 74% 69% III and IV 32% 57% Absolute figures not reported Overall loco-regional disease free survival was 67% in the HDR brachytherapy group, and 78% in the MDR group (p=0.8603) Stage HDR MDR I and II 85% 83% III and IV 54% 75% Absolute figures not reported	**Complications** The five year cumulative complication rate was 14% in the HDR group and 7% in the MDR group (p=0.4466) In The HDR arm there were grade 2 complications in 13% (4/31) of cases, three rectal complications and one with paralytic ileus. In the MDR arm there were grade 2 complications in 3% (1/29) of cases (rectal bleeding). There was also grade 3 complications in 3% (1/29) of cases (rectal and bladder fistulae).	Staging using the Union Internationale Contre le Cancer TNM classification (1987) Allocation to treatment group using random number table No details of concealment of allocation or blinding stated.

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Patel F D (1993)(2) Randomised controlled trial India n=482 (236 HDR Brachytherapy) Concurrent EBRT for all cases, identical treatment method and dose (within each group) Previously untreated patients with invasive squamous small cell carcinoma of the uterine cervix Staging according to International Federation of Gynecology and Obstetrics system Patients were randomised using alternative allocation stratified for stage. Two subgroups were established. Group 1: early stage patients, with growths <3cms where predominant treatment was brachytherapy Group 2: stage III patients and early stage patients with groups >3cm in diameter where EBRT was the predominant therapy HDR therapy with 9.5Gy in 4 fractions (group 1), or 9Gy in 2 fractions (group 2) Stage I =74, stage II = 183, stage III = 225 Follow up = 3 years minimum.	**Survival** In group 1, 5 year overall survival was 71.9% in LDR brachytherapy patients and 81.7% with HDR. Stage HDR LDR I 85.0% 81.0% II 71.3% 66.4% Absolute figures not reported. In group 2, 5 year overall survival was 55.1% in LDR brachytherapy patients and 53.6% with HDR. Stage HDR LDR I 74.6% 69.9% II 62.5% 60.1% III 42.6% 50.0% Absolute figures not reported. **Pattern of failure** In group 1, of patients treated with HDR brachytherapy 6%(2/34) demonstrated distant failure, 6% (2/34) had loco-regional recurrence, and 6% (2/34) had combined local and distant recurrence. For LDR brachytherapy patients the rates were 11% (4/36), 8% (3/36), and 3% (1/36) respectively. In group 2, of patients treated with HDR brachytherapy 6%(13/202) demonstrated distant failure, 24% (49/202) had loco-regional recurrence, and 2% (4/202) had combined local and distant recurrence. For LDR brachytherapy patients the rates were 8% (17/210), 21% (44/210), and 1% (2/210) respectively.	**Complications** Complications were classified according to the Radiation Therapy Oncology Group morbidity scoring scheme Site of complication / Rate HDR group / Rate LDR group Rectosigmoid – all: 6% (15/236) P<0.001 / 20% (49/246) Rectosigmoid – Grade 3 to 5: <1% (1/236) P > 0.05 / 2% (6/246) Symptoms 6 to 14 months post therapy Bladder – all: 15% (17/236) / 24 % (26/246) Bladder – Grade 3 to 5: 0% / 0% Small intestine – all: 0% / 0% Small intestine – Grade 3 to 5: 0% / 0% No reported cases of intestinal obstruction, or small bowel per	No comparison made of baseline demographic or clinical characteristics Different treatment regimens for based on stage and tumour size. EBRT given concurrently with HDR brachytherapy in group 1, and before HDR brachytherapy in group 2. No details of blinding to treatment allocation (probably not practical) or for outcome assessment Statistical significance of differences between groups for overall complication rate are not given HDR insertions achieved under anaesthesia, and vaginal packing to displace the bladder and rectum.

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Lertsanguansinchai P (2004)(1) Randomised controlled trial Thailand n=221 (112 HDR Brachytherapy) Concurrent EBRT for all cases, no concurrent or adjuvant chemotherapy was allowed Patients with carcinoma of the uterine cervix staged according to the International Federation of Gynaecology and Obstetrics system Dose schedules and fraction of brachytherapy depended on the dose at point A delivered by EBRT before central shielding There were no significant differences between the groups in terms of baseline demographics stage IB1=9, stage IB2 = 3, stage IIA = 3, stage IIB = 125, stage IIIB =81 Median follow up = 3.1 years (for HDR group)	**Survival** 3 year overall survival was 70.9% in LDR brachytherapy patients and 68.4% with HDR. Stage HDR LDR IIB 64.5% 73.8% IIIB 70.8% 62.9% Absolute figures not reported. 3 year pelvic control rate was 89.1% in LDR brachytherapy patients and 86.4% with HDR. Stage HDR LDR IIB 80.6% 88.3% IIIB 93.7% 92.8% Absolute figures not reported. 3 year relapse free survival rate was 69.9% in LDR brachytherapy patients and 69.9% with HDR. Stage HDR LDR IIB 65.1% 75.9% IIIB 74.1% 58.9% Absolute figures not reported. No statistically significant differences between treatment modalities, or for subgroups based on stage Comparison between LDR and HDR groups of stage I and IIA was not performed owing to small number of patients in these groups **Pattern of failure** In the group of patients treated with HDR brachytherapy 22%(25/112) had distant metastases, 6% (7/112) had loco-regional recurrence, and 4% (5/112) had combined local and distant recurrence. In the group of patients treated with LDR brachytherapy 18%(20/109) had distant metastases, 6% (7/109) had loco-regional recurrence, and 2% (2/109) had combined local and distant recurrence.	**Complications** Complications were classified according to the Radiation Therapy Oncology Group morbidity scoring scheme Overall complications were seen in 35% (39/112) of the HDR patients and 47% (51/109) of the LDR patients Site of complication / Rate HDR group / Rate LDR group Rectum - all 20% (22/112) 32% (35/109) Rectum – Grade 3 or 4 4% (5/112) <1% (1/109) Bladder – all 15% (17/112) 24 % (26/109) Bladder – Grade 3 or 4 <1% (1/112) 3% (3/109) Small intestine – Grade 3 or 4 4% (4/112) 0% (0/109) No statistically significant difference in grade 3 or 4 complications was found between the treatment groups either overall or by site.	Randomisation with stratification for age ± 50 years and stage of cancer Vaginal gauze packing used to increase the distance from the brachytherapy source to the rectal and bladder wall. There was a 12% (27/221) loss to follow up rate post treatment in the study which may have provided a higher overall survival rate than other studies Authors state that the optimal dose fractionation schedule has yet to be established

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Hareyama M (2002)(3) Randomised controlled trial Japan n=132 (61 HDR Brachytherapy) Concurrent EBRT for all cases HDR brachytherapy at 29Gy per five fractions stage IIa, 23Gy per three or four fractions stage IIb, and 17.3Gy per two or three 3 fractions in stage III. Patients with invasive carcinoma of the uterine cervix, staged by palpation, cystoscopy, and proctoscopy Age =64 years, stage II =48, stage III = 84. Follow up = 3.9 years (median)	**Treatment dynamics** The time required for one treatment was 15 to 20 minutes. **Survival** 5 year disease free survival Stage HDR LDR II 69% 87% III 51% 60% Absolute figures not reported. No statistically significant differences between treatment modalities. 5 year pelvic recurrence free survival Stage HDR LDR II 89% 100% III 69% 70% Absolute figures not reported. No statistically significant differences between treatment modalities **Pattern of failure** In the group of patients treated with HDR brachytherapy 7% (4/61) died from independent causes, and 44% (27/61) of cases from tumour. Of these 25% had distant metastases, 18% pelvic recurrence, and 10% paraaortic lymph node metasteses. In the group of patients treated with LDR brachytherapy 7% (5/71) died from independent causes, and 30% (21/71) of cases from tumour. Of these 24% had distant metastases, 13% pelvic recurrence, and 11% paraaortic lymph node metasteses. There was no significant difference in the pattern of failure between the groups	**Complications** Complications were classified according to the Radiation Therapy Oncology Group late radiation morbidity scoring scheme Overall complication rate at 5 years for grade 3 and above complications (those requiring treatment) were 10% (6/61) in the HDR brachytherapy group and 13% (9/71). There were no significant differences in the rate of complications either overall, on in the subgroups of stage II or stage III cancer Site of complication / Rate HDR group / Rate LDR group Rectum 3.5% 8.7% Bladder 4.0% 1.6% Small intestine 2.4% 7.5% Absolute figures not reported. No statistically significant differences between treatment modalities	2% (2/132) of patients were lost to follow up and were analysed as having uncontrolled pelvic disease Method of randomisation used was based on alternate months of birth No details given of blinding of outcome assessments Authors state that study might not have sufficient power to detect differences in survival between groups No definition given of type of treatment required for the complications reported. Complication rates may be effected by the timing of the external beam radiation therapy and brachytherapy.

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Lorvidhaya V (2000)(5) Case series (retrospective) Thailand n=1992 (who completed therapy of 2063) Cases of carcinoma of the cervix. Staging according to international federation of gynaecology and obstetrics included Chest X-rays, intravenous pyelography, and blood chemistries. Stage Ia =2, Ib =211, IIa =225, IIb =902, IIIa =14, IIIb =675, IVa =16, IVb =16, unstaged =2. Squamous cell carcinoma =83%, adenocarcinoma =9% Age =49 years. Follow up = 8 years (median)	**Survival** 5 year actuarial survival Overall disease free survival was 54.0%, and overall survival rate was 68.2% Stage / disease free / overall Ib / 79.5% / 86.3% IIa / 70.0% / 81.1% IIb / 59.4% / 73.0% IIIa / 46.1% / 50.3% IIIB / 32.3% / 47.8% IVa / 7.8% / 7.8% IVb / 23.1% / 30.8% Absolute figures not reported **Tumour size** Patients with tumour size <3cm tended to have better disease free survival (79.1%) than those with tumours sized 3 to 6 cm (51.1%) or >6 cm (44.4%). No statistical comparison reported. **Recurrence** The pattern of failure in all patients showed a local recurrence in 20.8% (415/1992) of patients and metastases in 18.7% (372/1992), with 4.0% (79/1992) having both local recurrence and metastases.	**Complications** Late complications were graded by the radiation therapy oncology group (RTOG) criteria The overall complication rate for any grade (1 to 4) complication in the bowel or bladder was 35.1% Overall moderate to severe complications (RTOG grade 3 or 4) occurred in 7.0% of cases 1.9% of patients required surgery for bowel obstruction, severe rectal bleeding, and or stenosis.	No survival data reported on stage Ia cases, perhaps these 2 cases were among the 4% of initial cohort that didn't complete therapy Significant patient selection with patients with Stage Ib and early IIa who had good performance status selected out for radical surgery (irrespective of tumour size) Stage IIb to IIB cases also received chemotherapy depending on the protocol. Almost all patients treated as outpatients Patients with Haemoglobin levels <10gm% received packed red blood cells until the level rose above this threshold. For disease free survival patients who died from unknown cause were analysed as having died from the disease. Not clear what fraction of study cohort late complications were assessed in.

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Chantini M (1994)(6) Case series (prospective) Japan n=200 Cases with carcinoma of the intact uterine cervix, staging using UICC 1987 classification. Investigations used included cystoscopy, proctoscopy, intravenous pyelography abdominal CT scan, bone scan , and rectosigmoidoscopy for all advanced cases. Stage Ia =8, Ib =22, IIa =22, IIb =53, III =85, IV =10. Sqaumous cell carcinoma = 96% (192/200), Age <60 years =41%, >60 years =59%. Concurrent EBRT in all patients except stage Ia Follow up =10 years (99% of cohort)	**Survival** Cause specific survival Stage 5 yr 10yr Ia 100% 100% Ib 90% 90% IIa 76% 76% IIb 84% 84% III 54% 46% IV 20% 20% (p=0.0001) Actuarial survival Stage 5 yr 10yr Ia 100% 84% Ib 86% 78% IIa 64% 64% IIb 76% 68% III 42% 36% IV 20% 20% The site of recurrence was analysed up to the last follow-up time, and was found to be distant metastasis in 22% (43/200), and central recurrence (paraaortic lymph node metastasis) 14% (27/200). **Prognostic factors** Multivariate analysis of determinant of tumour specific death found the following factors to be significant. Cancer stage (p=0.0001), age (p=0.0114), and haemoglobin value ((p=0.0005).	**Complications** Almost all complications at the rectum developed after three years, while those concerning the bladder were recorded over 9 years. Severe complications requiring treatment (medical or surgical) Site of complication rate Rectum 7% (14/200) Bladder 4% (8/200) Sigmoid colon <1% (1/200) Small intestine 3% (5/200) Of these, severe complications requiring surgery were recorded in 3% (5/200) of cases in the rectum, 3% (5/200) of cases in the small intestine, and <1% (1/200) of cases in the sigmoid colon	Relatively dated study and technology may have evolved since 1982 (last case) Complications and secondary intervention required is not clearly defined No definition of case selection process The dose and fraction regimen of HDR brachytherapy varied between stages of cancer at baseline

Abbreviations used: Computed tomography – CT, External beam radiation therapy - EBRT, Low Dose Rate - LDR, High dose rate - HDR

Study Details	Key efficacy findings	Key safety findings	Comments
Nakano T (2004)(7) Case series Japan n=1148 Histologically confirmed squamous cell carcinoma of the uterine cervix staged according to the International Federation of Gynaecology and Obstetrics system Concurrent EBRT given in all cases HDR brachytherapy at 29Gy per five fractions stage IB to II with small tumour, 24Gy per four fractions stage II medium to large tumour and stage III small tumours, and 15Gy per three fractions in stage III medium to large and all stage IV cases. Most treatment was delivered within a 6 week period after initiation Stage IB =146, IIA =44, IIB =261, IIIA =9, IIIB =545, IVA =72. IVB =71. Age =60 years (range 25-95). Follow up = 22 years (median for surviving patients)	**Survival** Overall survival to last follow up was 19% (223/1148). 35% (399/1148) of cases had died of cervical carcinoma. Overall survival Stage 5 yr 10yr IB 88% 74% II 69% 52% III 66% 42% IIA 21% 17% IVB 10% 4% Absolute figures not reported Cause specific survival Stage 5 yr 10yr IB 94% 89% II 80% 74% III 66% 59% IIA 32% 32% IVB 12% 5% Absolute figures not reported There was a significant difference in treatment outcome depending on tumour size for stage II and stage III disease	**Complications** Late complications were graded by the radiation therapy oncology group (RTOG) criteria Number of complications at 20 years of follow up Site of complication events Rectosigmoid colon 184 Bladder 151 Small intestine 87 Number of grade 3 to 5 complications at 20 years of follow up Site of complication events Rectosigmoid colon 35 Bladder 8 Small intestine 42 The dominator available at 20 years was not stated Actuarial complication rate at 20 years Site of complication events Rectosigmoid colon 23% Bladder 24% Small intestine 16% Absolute figures not reported Actuarial grade 3 to 5 complication rate at 20 years Site of complication events Rectosigmoid colon 5.3% Bladder 1.3% Small intestine 8.3% Absolute figures not reported	Prospective follow up with >70% undergoing annual inpatient evaluation Status outcome was available for 98% of patients Patients who died without complications were censored at the time of death, and survivors without complications were censored at the date of last follow up. Not clear if how many patients were available for analysis of rate of complications No details given of order of HDR brachytherapy and EBRT treatment.

Validity and generalisability of the studies

- Considerable variation in dose of HDR brachytherapy between studies and within studies depending on tumour stage.
- Some studies offered concomitant chemotherapy in some cancer stages depending on the protocol used.
- Concomitant EBRT given to nearly all cases (except some stage Ia cases) but order of therapy and timing varied between studies
- Different staging definitions have been developed over time.
- Inconsistent methods of complication outcome assessment between studies
- Some studies selected patients with stage I or IIa disease for inclusion as being high risk surgical candidates.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr Peter Hoskins, Dr Susan Davidson, Dr Jane Orton, Dr Peter Blake, Dr Anthony Branson, Prof. John Shepherd.

- Advisors considered HDR brachytherapy for Cervical malignancies an established procedure or a minor variation on an established procedure.
- Reported adverse events include diarrhoea, bleeding, colitis, and cystitis, and also fistulae requiring surgery.
- Theoretical adverse events suggested by advisors include a higher incidence of late complications of the bowel, bladder, and rectum.
- Potential audit criteria include tumour control, quality of life, and tissue toxicity
- Concurrent chemotherapy can be added to standard radiotherapy
- Centres offering LDR brachytherapy are having to chose between HDR or pulse dose rate brachytherapy delivery as the LDR and MDR machines and caesium sources are being phased out by the manufacturer
- Training may be needed for staff to convert to HDR technique, and new types of applicator
- CT scanning may help planning the procedure to ensure the correct dose is delivered, and 3D imaging techniques may be beneficial.
- There is a decreasing demand for brachytherapy services for cervical cancer
- It is thought that HDR brachytherapy will be provided at a minority of hospitals at specialist radiotherapy centres.

Issues for consideration by IPAC

- HDR brachytherapy can also be used as a palliative therapy in end stage cervical cancer.
- There are various sites of gynaecological malignancies (for example vaginal, endometrial) for which HDR brachytherapy can be a treatment option. Need to consider how generalisable guidance on this topic can be, or whether to widen the scope of this guidance with a systematic review.

References

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(5) Lorvidhaya V, Tonusin A, Changwiwit W, Chitapanarux I, Srisomboon J, Wanwilairat S et al. High-dose-rate afterloading brachytherapy in carcinoma of the cervix: an experience of 1992 patients. International Journal of Radiation Oncology, Biology, Physics 46(5):1185-91, 2000.

(6) Chatani M, Matayoshi Y, Masaki N, Teshima T, Inoue T. Long term follow-up results of high-dose rate remote afterloading intracavitary radiation therapy for carcinoma of the uterine cervix. Strahlentherapie und Onkologie Vol 170(5)()(pp 269-276), 1994 1994;(5):269-276.

(7) Nakano T, Kato S, Ohno T, Tsujii H, Sato S, Fukuhisa K et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer 103(1):92-101, 2005.

Appendix A: Additional papers on curative high dose rate (HDR) brachytherapy for carcinoma of the cervix not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
el Baradie M, Inoue T, Inoue T, Murayama S, Tang JT, Yamazaki H et al. HDR and MDR intracavitary treatment for carcinoma of the uterine cervix. A prospective randomized study. Strahlentherapie und Onkologie 173(3):155-62, 1997.	RCT n=22 FU=1.6yrs	Have larger RCTS	Overall 3 year survival 62% for HDR and 68% for MDR Rectal and bladder complication rate 29% at 3 years for both groups
Tanaka E, Oh RJ, Yamada Y, Shiomi H, Nakamura S, Shimamoto S et al. Prospective study of HDR (192Ir) versus MDR (137Cs) intracavitary brachytherapy for carcinoma of the uterine cervix. Brachytherapy 2(2):85-90, 2003.	RCT n=54 FU=3.7yrs	Have larger RCTS	Overall 3 year cause free survival 85 to 0% for HDR and 100 to 40% for MDR (p=0.45) Grade 2 or 3 complication in 11% HDR and 4% MDR
Chen M-S, Lin F-J, Hong C-H, Tu C-P, Lan J-H, Tang SG et al. High-dose-rate afterloading technique in the radiation treatment of uterine cervical cancer: 399 cases and 9 years experience in Taiwan. International Journal of Radiation Oncology, Biology, Physics Vol 20(5)()(pp 915-919), 1991 1991;(5):915-919.	NRCT n=399 FU=5yrs	Non-randomised trial where RCTs are available	Greater initial complete response, local control, and survival rate better with HDR than LDR but not statistically significantly
Okkan S, Atkovar G, Sahinler I, Oner DF, Koca A, Koksal S et al. Results and complications of high dose rate and low dose rate brachytherapy in carcinoma of the cervix: Cerrahpasa experience. Radiotherapy & Oncology 67(1):97-105, 2003.	NRCT n=293 FU=4.5yrs	Non-randomised trial where RCTs are available	5 year pelvic control rate 73 to 65% with HDR and 86 to 53% with LDR. Grade 2 to 4 complications at 14% with HDR and 19% with LDR (p>0.05)
Kucera H, Potter R, Knocke TH, Baldass M, Kucera E. High-dose versus low-dose rate brachytherapy in definitive radiotherapy of cervical cancer. Wiener Klinische Wochenschrift 113(1-2):58-62, 2001.	NRCT n=189 FU=2.8yrs	Non-randomised trial where RCTs are available	Actuarial survival was 58% after HDR and 51% after LDR. Grade 3 or 4 complication rate after HDR 3% bladder, 4% bowel 6% rectum.
Arai T, Nakano T, Morita S, Sakashita K, Nakamura YK, Fukuhisa K. High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. Cancer 69(1):175-80, 1992.	NRCT n=1022 FU=9+yrs	Non-randomised trial where RCTs are available	10 year survival rate with HDR 75 to 10%, and 83 to 10% with LDR Grade 4 complication rate with HDR 2% rectosigmoid, <1% bladder, <1% small bowel
Petereit DG, Sarkaria JN, Potter DM, Schink JC. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: Analysis of tumor recurrence - The University of Wisconsin experience.	NRCT n=173	Non-randomised trial where RCTs are	No difference in survival, pelvic control, relapse free survival, or distant

International Journal of Radiation Oncology, Biology, Physics Vol 45(5)()(pp 1267-1274), 1999 1999;(5):1267-1274.	FU=1.8yrs	available	metasteses between HDR and LDR No safety data
Hsu WL, Wu CJ, Jen YM, Yen SH, Lin KT, Ger LP et al. Twice-per-day fractionated high versus continuous low dose rate intracavitary therapy in the radical treatment of cervical cancer: a nonrandomized comparison of treatment results. International Journal of Radiation Oncology, Biology, Physics 32(5):1425-31, 1995.	NRCT n=149 FU=4yrs	Non-randomised trial where RCTs are available	Five year survival was 68% in HDR (6 fractions) 78% HDR (4 fractions) and 90% LDR. Grade 2 and 3 complications lower in HDR with 4 fractions 11% Vs 6 fractions 26% not significant difference
Kim WC, Kim GE, Suh CO, Loh JJ. High versus low dose rate intracavitary irradiation for adenocarcinoma of the uterine cervix. Japanese Journal of Clinical Oncology 31(9):432-7, 2001.	NRCT n=70 FU=3.5yrs	Non-randomised trial where RCTs are available	Overall 5 year cause free survival 87 to 44% for HDR and 73 to 36% for LDR (p>0.05) Late complication rate was 27% with HDR and 12% LDR
Patel FD, Rai B, Mallick I, Sharma SC. High-dose-rate brachytherapy in uterine cervical carcinoma. International Journal of Radiation Oncology, Biology, Physics Vol 62(1)()(pp 125-130), 2005 Date of Publication: 01 MAY 2005 2005;(1):125-130.	NRCT n=121 FU=3yrs	Non-randomised trial where RCTs are available Comparing number of fractions	Five year disease free survival was 62% with HDR Risk of grade 3 or greater complication was 3%
Busch M, Meden H, Meibodi F, Duhmke E, Kuhn W. Long term results of definitive radiotherapy for cervical carcinoma using four applications of high dose rate afterloading. Cancer 86(8):1520-7, 1999.	Case series n=73 FU=?	Case series where there is a larger series or longer follow up available	Five year survival rates with HDR ranged from 55 to 30% (depending on stage) The number of afterloading fractions was an independent predictor of local tumour control
Ogawa Y, Nemoto K, Kakuto Y, Ariga H, Matsushita H, Takeda K et al. Results of radiation therapy for uterine cervical cancer using high dose rate remote after loading system. Tohoku Journal of Experimental Medicine 199;(4):229-238.	Case series n=442 FU=5 yrs	Case series where there is a larger series or longer follow up available	Five year overall survival rates with HDR was 60% The incidence of all complications was 16%
Chiou JF, Liu MT, Lai YL, Chang KH. High-dose-rate afterloading brachytherapy in carcinoma of the uterine cervix. Journal of the Formosan Medical Association 92(2):165-73, 1993.	Case series n=321 FU=5 yrs	Case series where there is a larger series or longer follow up available	Five year overall survival rate was 55% The rate of complications was 4% to 8 years
Souhami L, Corns R, Duclos M, Portelance L, Bahoric B, Stanimir G. Long-term results of high-dose rate brachytherapy in cervix cancer using a small number of fractions. Gynecologic Oncology Vol 97(2)()(pp 508-513), 2005 2005;(2): 508-513.	Case series n=282 FU=7.2yrs	Case series where there is a larger series or longer follow up available	The overall survival was 57% at 5 years, 52% at 10 years and 47% at 15 years Actuarial gastrointestinal complication rate was

			15%
Busch IM, Duhmke E, Kuhn W, Teichmann A. Definitive radiation therapy in the treatment of carcinoma of the uterine cervix. Treatment results and prognostic factors. Strahlentherapie und Onkologie Vol 167(11)()(pp 628-637), 1991 1991;(11):628-637.	Case series n=219 FU=5yrs	Case series where there is a larger series or longer follow up available	Five year survival rates with HDR ranged from 90 to 0% (depending on stage) Severe late complications occurred in 6% of cases to 5 years
Potter R, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: Report on the Vienna University Hospital findings (1993-1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiotherapie Vol 4(2)()(pp 159-172), 2000 2000;(2):159-172.	Case series n=189 FU=2.8yrs	Case series where there is a larger series or longer follow up available	At 34 months pelvic control and disease specific survival were 78% and 69% respectively Grade 3 or 4 complications were 4% for the bowel, 3% for the bladder, 6% for the rectum and 31% for the vagina
Selke P, Roman TN, Souhami L, Freeman CR, Clark BG, Evans MD et al. Treatment results of high dose rate brachytherapy in patients with carcinoma of the cervix. International Journal of Radiation Oncology, Biology, Physics 27(4):803-9, 1993.	Case series n=187 FU=3yrs	Case series where there is a larger series or longer follow up available	Five year actuarial survival with HDR brachytherapy ranged from 72 to 45% (depending on stage) 8% of cases suffered grade 3 or 4 complications
Kataoka M, Kawamura M, Nishiyama Y, Hamada K, Hamamoto K, Matsu-Ura S. Results of the combination of external-beam and high-dose-rate intracavitary irradiation for patients with cervical carcinoma. Gynecologic Oncology 44(1):48-52, 1992.	Case series n=220 FU=5yrs	Case series where there is a larger series or longer follow up available	Five year survival rates with HDR ranged from 89 to 17% (depending on stage) 8% of cases had serious intestinal complications
Wang C-J, Leung SW, Chen H-C, Sun L-M, Fang F-M, Changchien C et al. High-dose-rate intracavitary brachytherapy (HDR-IC) in treatment of cervical carcinoma: 5-year results and implication of increased low-grade rectal complication on initiation of an HDR-IC fractionation scheme. International Journal of Radiation Oncology, Biology, Physics Vol 38(2)()(pp 391-398), 1997 1997;(2):391-398.	Case series n=173 FU=5 to 7.8 yrs	Case series where there is a larger series or longer follow up available	Overall 5 year actuarial survival rate was 58%, and pelvic control rate 83% Bladder complications were seen in 9% of patients
Hammer J, Zoidl JP, Altendorfer C, Seewald DH, Track C, Stummvoll W et al. Combined external and high dose rate intracavitary radiotherapy in the primary treatment of cancer of the uterine cervix. Radiotherapy & Oncology 27(1):66-8, 1993.	Case series n=153 FU=5.3yrs	Case series where there is a larger series or longer follow up available	Five year survival rates with HDR ranged from 79 to 41% (depending on stage) Grade 3 or 4 complications were seen in <1% of cases
Demanes DJ, Rodriguez RR, Bendre DD, Ewing TL. High dose rate transperineal interstitial brachytherapy for cervical cancer: high pelvic control and low complication rates. International Journal of Radiation Oncology, Biology, Physics 45(1):105-12,	Case series n=62	Case series where there is a larger series or longer	The overall local control rate was 94%, and actuarial disease free survival 48%. Grade 3 or 4

1999.	FU=3.3yrs	follow up available	morbidity occurred in 7% of patients
Abitbol AA, Wolfson AH, Lewin AA, Houdek PV, Laufer KA, Brandon AH et al. Management of stage I-B, II-A, and II-B carcinoma of the cervix with high-dose-rate brachytherapy: Initial results of an institutional clinical trial. American Journal of Clinical Oncology: Cancer Clinical Trials Vol 19(3)()(pp 223-228), 1996 1996;(3):223-228.	Case series n=24 FU=2.2yrs	Case series where there is a larger series or longer follow up available	Overall 2 year survival was 74% 8% of cases suffered uterine perforation during insertion, but no reported vaginal fistula or gastrointestinal or bladder damage

Appendix B: Literature search for curative high dose rate (HDR) brachytherapy for carcinoma of the cervix.

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases. For all other databases a simple search strategy using the key words in the title was employed.

Procedure Number: 305	**Procedure Name: HDR brachytherapy for gynaecological malignancies**
Database: Medline	**Date searched: 20/06/2005**

1. brachytherapy/
2. brachytherap$.tw.
3. (intracavitary adj3 radiotherap$).tw.
4. gammamed.tw.
5. gamma med.tw.
6. or/1-5
7. (high adj2 dose adj2 rate$).tw.
8. hdr.tw.
9. 7 or 8
10. 6 and 9
11. exp genital neoplasms, female/
12. ((malignan$ or carcinoma$ or cancer$ or neoplasm$ or tumor$ or tumour$) adj5 (vulva$ or cervi$ or endometr$ or ovar$ or vagina$ or uter$)).tw.
13. 11 or 12
14. 10 and 13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized controlled trials/
18. random allocation/
19. double blind method/
20. single blind method/
21. or/15-20
22. animals/ not human/
23. 21 not 22
24. clinical trial.pt.
25. exp clinical trials/
26. (clin$ adj25 trial$).ti,ab.
27. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
28. placebos/
29. placebo$.ti,ab.
30. random$.ti,ab.
31. research design/
32. or/24-31
33. 32 not 22
34. 33 not 23
35. comparative study/
36. exp evaluation studies/
37. follow up studies/
38. prospective studies/
39. (control$ or prospectiv$ or volunteer$).ti,ab.
40. or/35-39
41. 40 not 22
42. 41 not (23 or 34)
43. 23 or 34 or 42
44. 14 and 43
45. limit 44 to yr=1990 - 2005

Action	Comments	Version searched (if applicable)	Date searched
Search for similar NICE topics	LDR and HDR brachytherapy for prostate cancer		20/06/2005
Consult notification and specialist advisors questionnaires for additional papers	See questionnaires in folder for multiple extra papers		20/06/2005
Conduct general internet search for background	Basic overview for lay person of the procedure		20/06/2005
Search for Cochrane systematic review	Adjuvant radiotherapy for Stage I endometrial cancer		20/06/2005
ASERNIP website	Nothing relevant found		20/06/2005
FDA website	Nothing relevant found		20/06/2005
Search conferences websites	Nothing relevant found		20/06/2005
Search Databases:			
The Cochrane Library	31 results found	Issue 2 2005	21/06/2005
CRD Databases	7 results found		21/06/2005
Embase	230 results found	1980 to 2005 Week 25	21/06/2005
Medline	270 results found	1966 to June Week 2 2005	20/06/2005
Premedline	6 results found	June 20, 2005	21/06/2005
CINAHL	5 results found	1982 to June Week 3 2005	21/06/2005
BLIC (limit to current year only)	7 results found		21/06/2005
National Research Register	1 record found	Issue 2 2005	21/06/2005
Controlled Trials Registry	1 result found		21/06/2005