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REVIEW ARTICLE

Image-guided high-dose-rate brachytherapy in inoperable endometrial cancer

^{1,2}P DANKULCHAI, MD, ¹J PETSUKSIRI, MD, ¹Y CHANSILPA, MD and ²P J HOSKIN, MD

¹Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

²Mount Vernon Cancer Centre, Northwood, Middlesex, UK

Address correspondence to: Dr Pittaya Dankulchai

E-mail: pittaya.dan@mahidol.ac.th

ABSTRACT

Inoperable endometrial cancer may be treated with curative aim using radical radiotherapy alone. The radiation techniques are external beam radiotherapy (EBRT) alone, EBRT plus brachytherapy and brachytherapy alone. Recently, high-dose-rate brachytherapy has been used instead of low-dose-rate brachytherapy. Image-guided brachytherapy enables sufficient coverage of tumour and reduction of dose to the organs at risk, thus increasing the therapeutic ratio of treatment. Local control rates with three-dimensional brachytherapy appear better than with conventional techniques (about 90–100% and 70–90%, respectively).

Endometrial cancer is the third most common cancer among females in the world, following breast cancer and cervical cancer. In 2008, the world incidence rate for new cases of uterine cancer was 157 and 175 per 100,000 population in higher and lower Human Development Index (HDI), respectively.¹ In 2008, the corresponding mortality rates of uterine cancer were 8 and 36 per 100,000 population in higher and lower HDI, respectively. Uterine cancer is the second most prevalent cancer among females in the USA. There were 47,130 new cases diagnosed in 2012.² This cancer is usually treated with surgery, radiotherapy (with or without chemotherapy) or hormonal therapy. Cancer of the uterine corpus is initially staged and treated at surgery. Standard surgical treatment consists of total hysterectomy plus bilateral salpingo-oophorectomy and peritoneal washing with or without locoregional lymphadenectomy. After surgery for intermediate- and high-risk endometrial cancer, the locoregional recurrence rate is still significant, and thus adjuvant radiotherapy is considered in this group. The 5-year locoregional recurrence rate with adjuvant radiotherapy is <5%.^{3–6}

In inoperable endometrial cancer for patients with comorbidities or advanced age, radiation therapy remains the only curative option. In the past, low-dose-rate (LDR) brachytherapy with radium-226 was used in combination with external beam radiotherapy (EBRT).^{7–17} More recently, LDR brachytherapy has been replaced by high-dose-rate (HDR) brachytherapy with iridium-192 after loading.^{18–24} Image-

guided brachytherapy (IGBT) using CT and MRI have been used for treatment planning in both EBRT and brachytherapy incorporating three-dimensional (3D) techniques. In cervical cancer, both the European gynaecological (GYN) Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO) network group and American Brachytherapy Society have developed guidelines for IGBT in cervical cancer. They show that the therapeutic ratio, relating target coverage and sparing of normal organs at risk (OAR) can be significantly improved.^{25–28} However, there is little evidence on the role of IGBT for the treatment of inoperable endometrial cancer. The objective of this article is to review the applicators and brachytherapy techniques, target volume definition and dose prescription, results and the future of radical IGBT in inoperable endometrial cancer.

STATEMENT OF SEARCH STRATEGY USED AND SOURCES OF INFORMATION

A systematic literature search was carried out through PubMed using the key words: “high dose rate”, “brachytherapy”, “inoperable”, “endometrial” and “cancer”. Abstracts and full text manuscripts were reviewed. Moreover, additional articles and textbooks were also considered.

APPLICATORS AND BRACHYTHERAPY TECHNIQUES

Applicators are an important factor in brachytherapy. There are two different types of applicators for brachytherapy in

inoperable endometrial cancer, either standardized fixed applicators or individualized packing methods.²⁹

Standardized applicators

The Rotte endometrial applicator or Rotte “Y” applicator (Figure 1a) was developed by Professor Dr Karstan Rotte of the University of Frauenklinik, Würzburg, Germany. This device consists of two rigid applicators with a curved end to reach the two uterine horns; to increase dose at the uterine fundus, a third applicator should be added at the midpoint between the two rigid applicators. The insertion of this applicator is easy and convenient. The two rigid applicators can be locked in position with a single action, and then vaginal gauze packing can keep the applicators in the appropriate place. The dose distribution with this applicator provides optimal dose in the craniocaudal and lateral directions that depends on the thickness of the uterine wall, but the dose distribution may be suboptimal in the antero-posterior direction. It may be a problem for the tolerance dose of the bladder and rectum surrounding this direction. Moreover, in the case of cervical extension, two ovoids or a ring applicator can be added to provide optimal dose to encompass the whole cervix. This will also have an effect on the dose to the bladder and rectum. A tandem using a vaginal cylinder applicator may also be considered for insertion in the case of cervical and vaginal involvement.

Individual packing methods

The classic Heyman packing technique for radium-226 treatment of endometrial cancer was introduced by Heyman of Radiumhemmet³⁰ in 1930 (Figure 1b). Later, Simon *et al*³¹ modified this for after loading using a hollow plastic tube extending from the capsule. More recently, different sizes of capsules with long thin flexible tubes have been introduced. The advantage of this applicator is that we can modify the individual packing with capsules to adapt the appropriate dose distribution for each patient.

The technique of Heyman packing is more demanding than the Rotte “Y” applicator requiring accurate insertion of up to 18

individual capsules into the uterine cavity. However, as a technique, it can provide better individualized dose distribution than standard applicators.

A comparison of these techniques is shown in Table 1.

TARGET VOLUME DEFINITION

There is no official consensus regarding definition of the gross tumour volume (GTV) and clinical target volume (CTV) in brachytherapy for endometrial cancer. Only four reports on image-based brachytherapy planning in endometrial cancer discuss the definition of target volume.^{32–35} Weitmann *et al*³² described the findings of transvaginal ultrasound or hysteroscopy in patients without MRI and high-intensity area on T_2 weighted MR images as GTV. Ohkubo *et al*³³ also mentioned GTV defined from MRI as the visualized tumour on T_2 weighted images. All four studies introduced a definition of CTV that consists of the whole uterus and cervix, but three^{32,34,35} additionally defined the upper vagina as included in CTV. Beriwal *et al*³⁵ used a CTV including the upper 3 cm of the vagina. In 2011, Petric *et al*³⁶ modified the target volume for inoperable endometrial cancer from GEC-ESTRO recommendations for cervical cancer brachytherapy. Based on these evidence-based articles, they concluded that the GTV and adjacent layers of the uterine wall have a high risk of recurrence as high-risk (HR) CTV. If a tumour is located in only the superficial region, the internal half of the uterine wall is included as (HR CTV), but if a tumour is located in the outer half of the uterine wall, the HR CTV has to be extended to serosa. They introduced the idea that this target volume should be taken into account so that a sufficiently high dose in excess of 80–90 Gy in equivalent dose in 2-Gy fractions (EQD2) (D90) is given for treatment. Moreover, they defined an intermediate-risk (IR) CTV as the entire uterus and areas, which might have a significant microscopic tumour load, which should receive 60 Gy in EQD2 (D90). Figure 2 presents an example of delineation based on the definitions used in these studies.

In addition, normal organs, including the bladder, rectum, sigmoid and bowel, were delineated according to the GYN GEC-ESTRO recommendations for 3D image-based brachytherapy on cervical cancer.^{25,26}

Dose prescription

Weitmann *et al*³² prescribed a dose to the CTV of 42 Gy in six fractions of HDR brachytherapy delivering 1–3 fractions per week and a total EQD2 with an α/β ratio of 10 of 59.5 Gy. They attempted to encompass CTV with 7 Gy and GTV with 10 Gy isodose, so that the total EQD2 of both targets were 59.5 and 100 Gy, respectively. 3 of 16 patients were treated in combination with EBRT to the pelvis of 30–40 Gy. The dose constraints of OAR were kept at <5 Gy per fraction (70% of 7 Gy) for bowel and 6 Gy per fraction (85% of 7 Gy) for bladder and rectum. Unfortunately, Ohkubo *et al*³³ used two-dimensional (2D) treatment planning with reference to CT images, because the 3D treatment planning system was not obtainable, but they retrospectively analysed for the tumour and OAR using CT images. They defined the uterine reference points as the maximal distance between the applicator tube and the external uterine

Figure 1. Applicators for brachytherapy in uterine cancer: (a) Rotte “Y” applicator; (b) Heyman packing applicator.

Table 1. Comparison of the standardized applicator (Rotte “Y”) and individual packing applicator (Heyman)

Aspects	Standardized applicator	Individual packing applicator
Insertion	Easy and convenient	Difficult
	Need to know the length of uterine cavity	Need more skill and experience
Optimization	Difficult owing to only 1–3 channels	Easy, depends on place of applicators
Dose distribution	Optimal dose in craniocaudal and lateral directions	Better individually appropriate dose distribution
	Suboptimal in the anteroposterior direction	
	May be a problem for the tolerance dose of the organs at risk	

border on CT images, which were then set on orthogonal radiographic films. Moreover, they prescribed a dose to these reference points of 24 Gy in 4 fractions; 9 of 10 patients also received EBRT to the whole pelvis in 50 Gy with central shielding at 30.6 Gy. Coon et al³⁴ treated 31 patients with 2D planning and 18 patients with 3D planning of brachytherapy. Those treated with 3D brachytherapy received a dose of either 20 Gy in five fractions twice a day (b.i.d.) with 45–50 Gy external beam to the whole pelvis or 35 Gy in five fractions b.i.d. when treating without EBRT. Another publication by Niazi et al³⁷ did not provide the definition of target volume, but some patients were prescribed a dose to the surface of the uterus based on MR images. They did not issue the dose per fraction of brachytherapy in their study, but prescribed a median HDR dose as 23.9 Gy in 3 fractions, and 8 of 30 patients were treated in combination with EBRT in 42 Gy. They also adjusted brachytherapy dose based on the size and shape of the uterus and extension of the tumour that was detected on MR images.

Volume definition

MRI is recognized as a valuable imaging modality in the staging of endometrial cancer. MRI is considered an essential part of the pre-operative diagnostic workup in endometrial cancer for planning of the surgical procedure and radiotherapy technique,^{38–42} as defined in the guidelines of the European Society of Urogenital Imaging. In addition, all information from

diagnostic procedures, such as hysteroscopy or transvaginal ultrasound, should be included in assessing the patient and the required volumes for high-dose radiotherapy.

MRI is the best imaging modality for planning 3D brachytherapy for inoperable endometrial cancer. The GTV is demonstrated by a high intensity area on T_2 weighted MR images. The CTV consists of two target volumes: the HR CTV, which is GTV plus adjacent layers of uterine wall representing a high-risk volume, which should receive >80–90 Gy to the D_{90} in EQD2; and the IR CTV, which is the whole uterus and the cervix, with or without the upper part of the vagina representing areas of potential microscopic disease, which should receive at least 60 Gy to the D_{90} in EQD2.

CT may also be used to locate the target volume and OAR, but the definition of target volumes is different from MRI planning, as the GTV and HR CTV cannot be defined on the CT images; therefore, we conclude that the CTV on CT planning is the same as the IR CTV on MRI planning (to receive at least 60 Gy to the D_{90} in EQD2).

A volume, which encompasses the whole uterus and cervix, with or without upper vagina, is complex, and it may be difficult to cover this with the prescribed dose in all patients and remain within dose constraints for OAR. This applies especially to the

Figure 2. Examples of the delineation regarding the studies on CT (a) and MRI (b). CTV, clinical tumour volume; GTV, gross tumour volume; HR CTV, high-risk clinical tumour volume; IR CTV, intermediate-risk clinical tumour volume.

sigmoid and rectosigmoid regions, which are frequently located close to the superior and posterior uterine wall and have a lower tolerance dose than the bladder, which may also be in close apposition to the uterus. Tumours located in the anterosuperior region of the uterine wall present a particularly difficult challenge often requiring compromise of tumour dose to remain within reasonable tolerance doses for surrounding organs as shown in Figure 3. This problem may in part be overcome by designing additional needles placed into the uterine muscle wall to provide additional flexibility in conforming the high dose distribution to encompass the target volumes within the dose constraints of OAR.

There is uncertainty regarding the dose constraints of the OAR, when using varying EBRT and HDR brachytherapy schedules. This should be extrapolated from an absolute dose for each schedule using an EQD2 total dose, including the dose from both EBRT and HDR brachytherapy. At the moment, there is no evidence base for the dose constraints of the OAR in endometrial cancer brachytherapy. However, since the OAR are the same, it is reasonable to extrapolate from the experience in cervical cancer brachytherapy. Georg *et al*⁴³ established the dose–response relationships for late side effects of the OAR in cervical cancer brachytherapy and proposed that a threshold dose of 78 and 101 Gy EQD2 related to a 10% probability of Grade 2 or more of late rectal and bladder side effects, respectively. There was no dose–response analysis for late sigmoid morbidities because the incidence was too low for analysis. Thus, the dose constraints of sigmoid colon may be assumed to be the same as those for the rectum.

OUTCOMES

Only two studies have reported the results of IGBT in inoperable endometrial cancer (Table 2). The first publication was the study of Weitmann *et al*³² from the Medical University of Vienna, Austria. 16 patients with locally confined endometrial carcinoma received 3D HDR brachytherapy with modified Heyman packing method based on MRI and CT planning. The median follow-

up of this study was 47 months after completion of radiotherapy. 13 of 16 uterine cancer patients were treated with curative intent and had an excellent local control rate at last follow-up (100% at 4-year local control rate). In this series, 4-year disease-specific survival was 100% and 4-year overall survival was 39% (5 of 13 patients) with the majority of deaths caused by intercurrent diseases. No severe acute or late side effects were reported. There were a few cases of acute and late bladder side effects, and some patients developed mild late vaginal morbidity (Table 2).

Coon *et al*³⁴ reported the results of 3D HDR in inoperable endometrial cancer. Only 18 of 49 patients (36.7%) were treated with 3D planning and Y-applicator placement in this series. The median follow-up was 33 months for all cases, but only 5 months in 3D planning cases. The 3-year local control for all cases was 93.9%, whereas the 3- and 5-year actuarial cause-specific survival rates and overall survival rates were 93%, 87%, 83% and 42%, respectively. There was no report of acute severe morbidity; however, a 13% incidence of late side effects confined to the 2D planning cases was seen.

Most publications of radical radiotherapy in endometrial carcinoma use LDR brachytherapy and 2D planning. A small number of HDR brachytherapy reports in endometrial cancer are found.^{33,44–52} When we compare the results from these publications, the local control rate and side effect profile of 3D planning seems better than 2D planning as shown in Table 2, and this may also lead to a better overall survival rate. However, this conclusion should be regarded with caution in view of the small selected numbers of patients included.

CONCLUSION

The results of 2D brachytherapy in inoperable endometrial cancer have been established with local control rates of 70–80%. IGBT can now be used in the treatment of inoperable endometrial cancer with curative aim and to increase the dose coverage. The local control rates of 3D brachytherapy (approximately 90–100%) appear better than in 2D (70–90%), but there is no formal comparison, and numbers in both groups are too small for a meaningful statistical analysis. Image-based planning enables adequate coverage of tumour and the identification of the OAR for which tolerance doses are defined; thus, the therapeutic ratio of treatment is increased. The definition of CTV and dose prescription remains inconsistent. The whole uterus, whole cervix, with or without upper vagina should be considered as the CTV and should receive 60 Gy EQD2 to the *D*₉₀ with CT planning. With MR planning, this will be equivalent to the IR CTV. We are able to apply the GEC-ESTRO recommendations in 3D brachytherapy for cervical cancer to delineate the GTV (high intensity area on *T*₂ weighted) and HR CTV (GTV plus adjacent layers of uterine muscle) to receive 100 Gy and >80–90 Gy EQD2 to the *D*₉₀ on MRI planning, respectively. The dose constraints of the rectum and sigmoid colon should be considered as 78 Gy EQD2 to the dose to 2cc of OAR (*D*_{2cc}), while the threshold dose of the bladder is around 100 Gy EQD2 to the *D*_{2cc} for a 10% probability of Grade 2 and more late side effects. Long-term follow-up of image-guided 3D brachytherapy in endometrial cancer is required to confirm our conclusions.

Figure 3. An example of the dose coverage of target volume with high dose for sigmoid and rectosigmoid colon (arrow) in a case of tumour location at anterosuperior uterine wall.

Table 2. Comparison of the radical radiotherapy in inoperable endometrial cancer with two-dimensional (2D) and three-dimensional (3D) high-dose-rate (HDR) brachytherapy in the literature

Author	Patient No.	Applicators	Dose prescription	Total dose in EQD2 ($\alpha/\beta = 10$)	Local control rates	Severe late complication rates (Grade 3–4) (%)
2D HDR						
Taghian et al ⁴⁴	104	NA	NA	NA	87.6% at 5 years 85.1% at 10 years	17
Rouanet et al ⁴⁵	250	NA	NA	NA	75.9% at 5 years	3
Nguyen et al ⁴⁶	27	Tandem alone or one tandem and ovoid applicators	HDR alone: 20 Gy/2–3 Fr or EBRT WP 42 Gy + HDR 20 Gy/2–3 Fr	HDR alone: 27.4 Gy, or EBRT + HDR: 69.4 Gy	85.2% at 4 years	11
Knocke et al 1995 and 1997 ^{47,48}	280	One channel intracavitary and intravaginal applicators	4–5 Fr $\times$ 8.5 Gy	52.4–65.5 Gy	75.4% at 5 years 70% at 10 years	5.2
Kucera et al ⁴⁹	228	One-channel intracavitary and intravaginal applicators	4–5 Fr $\times$ 8.5 Gy	52.4–65.5 Gy	76.6% at 5 years 73.9% at 10 years	4.6
Nguyen and Petereit ⁵¹	36	One tandem and ovoid or cylinder applicators	5 Fr $\times$ 9 Gy	71.3 Gy	88% at 3 years	21
Fusco et al ⁵⁰	41	NA	EBRT WP 45–50 Gy + HDR 2–3 $\times$ 6–8 Gy	68.3–86 Gy	NA	10 (GI: Grade 2–3)
Inciura et al ⁵²	29	Three-channel intrauterine applicators	EBRT WP 16 Gy + HDR 5 Fr $\times$ 10 Gy	99.3 Gy	82.8% at 5 years	0 (Grade 1–2: 13.8%)
Ohkubo et al ³³	10	Rotte “Y” applicator	EBRT WP 30–30.6 Gy + HDR 4 Fr $\times$ 6 Gy (retrospective dose analysis in 3D)	62 Gy	100% at 5 years	0
3D HDR						
Weitmann et al ³²	13	Norman–Simon applicators with Heyman packing	6 Fr $\times$ 7 Gy to CTV (whole uterus, cervix and upper vagina)	59.5 Gy	100% at 4 years	0
Coon et al ³⁴	18	Rotte “Y” applicators	EBRT WP 45–50 Gy + HDR 5 Fr $\times$ 4 Gy, or HDR 5 Fr $\times$ 7 Gy b.i.d alone to CTV (whole uterus, cervix and upper vagina)	EBRT + HDR: 69.3–74.6 Gy, HDR only: 49.6 Gy	93.9% at 3 years	0 (13% was reported in 2D cases of this study)

b.i.d, twice daily; CTV, clinical target volume; EBRT, external beam radiotherapy; EQD2, equivalent dose in 2-Gy fractions; Fr, fraction; GI, gastro-intestinal system; NA, not available; WP, whole pelvis.

REFERENCES

- Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol* 2012; **13**: 790–801. doi: [10.1016/S1470-2045\(12\)70211-5](https://doi.org/10.1016/S1470-2045(12)70211-5)
- Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012; **62**: 220–41. doi: [10.3322/caac.21149](https://doi.org/10.3322/caac.21149)
- Eifel PJ. Intracavitary brachytherapy in the treatment of gynecologic neoplasms. *J Surg Oncol* 1997; **66**: 141–7.
- Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000; **355**: 1404–11.
- Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004; **92**: 744–51. doi: [10.1016/j.ygyno.2003.11.048](https://doi.org/10.1016/j.ygyno.2003.11.048)
- Nout RA, Smit VT, Putter H, Jurgensliemk-Schulz IM, Jobsen JJ, Lutgns LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010; **375**: 816–23. doi: [10.1016/S0140-6736\(09\)62163-2](https://doi.org/10.1016/S0140-6736(09)62163-2)
- Kucera H. The treatment of inoperable endometrial cancer by means of intracavitary radiotherapy. [In German.] *Geburtshilfe Frauenheilkd* 1980; **40**: 432–6.
- Kucera H, Unel N, Weghaupt K. Fractionated short-time-afterloading with high dose rates in ambulant treatment of inoperable cancer of the uterine corpus. [In German.] *Geburtshilfe Frauenheilkd* 1983; **43**: 456–60.
- Grigsby PW, Kuske RR, Perez CA, Walz BJ, Camel MH, Kao MS, et al. Medically inoperable stage I adenocarcinoma of the endometrium treated with radiotherapy alone. *Int J Radiat Oncol Biol Phys* 1987; **13**: 483–8.
- Varia M, Rosenman J, Halle J, Walton L, Currie J, Fowler W. Primary radiation therapy for medically inoperable patients with endometrial carcinoma—stages I-II. *Int J Radiat Oncol Biol Phys* 1987; **13**: 11–15.
- Wang ML, Hussey DH, Vigliotti AP, Benda J, Wen BC, Doornbos JE, et al. Inoperable adenocarcinoma of endometrium: radiation therapy. *Radiology* 1987; **165**: 561–5. doi: [10.1148/radiology.165.2.3659385](https://doi.org/10.1148/radiology.165.2.3659385)
- Sipila P, Kauppila A. Intracavitary irradiation of endometrial carcinoma using a high-intensity 60Co afterloading method. *Acta Oncol* 1989; **28**: 601–5.
- Lehoczy O, Bosze P, Ungar L, Tottosy B. Stage I endometrial carcinoma: treatment of nonoperable patients with intracavitary radiation therapy alone. *Gynecol Oncol* 1991; **43**: 211–16.
- Rose PG, Baker S, Kern M, Fitzgerald TJ, Tak WK, Reale FR, et al. Primary radiation therapy for endometrial carcinoma: a case controlled study. *Int J Radiat Oncol Biol Phys* 1993; **27**: 585–90.
- Kupelian PA, Eifel PJ, Tornos C, Burke TW, Delclos L, Oswald MJ. Treatment of endometrial carcinoma with radiation therapy alone. *Int J Radiat Oncol Biol Phys* 1993; **27**: 817–24.
- Pernot M, Hoffstetter S, Peiffert D, Guillemain F, Carolus JM, Verhaeghe JL, et al. Pre-operative, post-operative and exclusive irradiation of endometrial adenocarcinoma. *Strahlenther Onkol* 1994; **170**: 313–21.
- Chao CK, Grigsby PW, Perez CA, Camel HM, Kao MS, Galakatos AE, et al. Brachytherapy-related complications for medically inoperable stage I endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 1995; **31**: 37–42. doi: [10.1016/0360-3016\(94\)00399-6](https://doi.org/10.1016/0360-3016(94)00399-6)
- Kucera H, Sagl R, Skodler W, Weghaupt K. Afterloading short-term irradiation of inoperable uterine cancer. [In German.] *Geburtshilfe Frauenheilkd* 1986; **46**: 515–19.
- Kucera H, Weghaupt K. Treatment of inoperable endometrial carcinoma with intracavitary high-dose rate iridium irradiation. [In German.] *Strahlenther Onkol* 1988; **164**: 508–14.
- Kucera H, Vavra N, Weghaupt K. Value of irradiation alone of generally inoperable endometrial cancer with high dose rate iridium 192. [In German.] *Geburtshilfe Frauenheilkd* 1990; **50**: 610–13.
- Weiss E, Arnold-Bofinger H, Hirnle P. Primary radiotherapy of endometrial carcinoma. [In German.] *Zentralbl Gynakol* 1995; **117**: 481–5.
- Bond MG, Workman G, Martland J, Clinkard JE, Carey BM, Rothwell RI, et al. Dosimetric considerations in the treatment of inoperable endometrial carcinoma by a high dose rate afterloading packing technique. *Clin Oncol (R Coll Radiol)* 1997; **9**: 41–7.
- Petereit DG, Sarkaria JN, Chappell RJ. Perioperative morbidity and mortality of high-dose-rate gynecologic brachytherapy. *Int J Radiat Oncol Biol Phys* 1998; **42**: 1025–31.
- Nag S, Erickson B, Parikh S, Gupta N, Varia M, Glasgow G. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys* 2000; **48**: 779–90.
- Haie-Meder C, Potter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005; **74**: 235–45.
- Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; **78**: 67–77.
- Viswanathan AN, Thomadsen B. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy* 2012; **11**: 33–46.
- Viswanathan AN, Beriwal S, De Los Santos JE, Demanes DJ, Gaffney D, Hansen J, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy* 2012; **11**: 47–52.
- Potter R, Haie-Meder C. *Endometrial cancer*. Leuven, Belgium: ACCO; 2002.
- Heyman JRO, Benner S. The Radiumhemmet experience with radiotherapy in cancer of the uterus: classification, method of treatment and results. *Acta Radiol Excerpt* 1941; **22**: 12–98.
- Simon N, Silverstone SM, Roach LC. Afterloading Heyman applicators. *Acta Radiol Ther Phys Biol* 1971; **10**: 231–8.

32. Weitmann HD, Potter R, Waldhausl C, Nechvile E, Kirisits C, Knocke TH. Pilot study in the treatment of endometrial carcinoma with 3D image-based high-dose-rate brachytherapy using modified Heyman packing: clinical experience and dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2005; **62**: 468–78.
33. Ohkubo Y, Kato S, Kiyohara H, Tsuruoka I, Tamaki T, Noda SE, et al. Dose volume analysis of radiotherapy for inoperable patients with stage I-II endometrial carcinoma. *J Radiat Res* 2011; **52**: 666–73.
34. Coon D, Beriwal S, Heron DE, Kelley JL, Edwards RP, Sukumvanich P, et al. High-dose-rate Rotte “Y” applicator brachytherapy for definitive treatment of medically inoperable endometrial cancer: 10-year results. *Int J Radiat Oncol Biol Phys* 2008; **71**: 779–83.
35. Beriwal S, Kim H, Heron DE, Selvaraj R. Comparison of 2D vs. 3D dosimetry for Rotte “Y” applicator high dose rate brachytherapy for medically inoperable endometrial cancer. *Technol Cancer Res Treat* 2006; **5**: 521–7.
36. Petric P, Limbergen EV, Haie-Meder C. Adaptive contouring of the target volume and organs at risk. In: Akila N, Viswanathan CK, Erickson BE, Potter R, eds. *Gynecologic radiation therapy*: Berlin/Heidelberg, Germany: Springer-Verlag; 2011. pp. 99–118.
37. Niazi TM, Souhami L, Portelance L, Bahoric B, Gilbert L, Stanimir G. Long-term results of high-dose-rate brachytherapy in the primary treatment of medically inoperable stage I-II endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1108–13. doi: [10.1016/j.ijrobp.2005.04.036](https://doi.org/10.1016/j.ijrobp.2005.04.036)
38. Haldorsen IS, Salvesen HB. Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques. *Clin Radiol* 2012; **67**: 2–12. doi: [10.1016/j.crad.2011.02.018](https://doi.org/10.1016/j.crad.2011.02.018)
39. Kinkel K, Forstner R, Danza FM, Oleaga L, Cunha TM, Bergman A, et al. Staging of endometrial cancer with MRI: guidelines of the European Society of Urogenital Imaging. *Eur Radiol* 2009; **19**: 1565–74. doi: [10.1007/s00330-009-1309-6](https://doi.org/10.1007/s00330-009-1309-6)
40. Manfredi R, Gui B, Maresca G, Fanfani F, Bonomo L. Endometrial cancer: magnetic resonance imaging. *Abdom Imaging* 2005; **30**: 626–36. doi: [10.1007/s00261-004-0298-9](https://doi.org/10.1007/s00261-004-0298-9)
41. Peungjesada S, Bhosale PR, Balachandran A, Iyer RB. Magnetic resonance imaging of endometrial carcinoma. *J Comput Assist Tomogr* 2009; **33**: 601–8. doi: [10.1097/RCT.0b013e31818d4279](https://doi.org/10.1097/RCT.0b013e31818d4279)
42. Taieb S, Rocourt N, Narducci F, Ceugnart L. Endometrial cancer imaging. [In French.] *Bull Cancer* 2012; **99**: 13–20.
43. Georg P, Potter R, Georg D, Lang S, Dimopoulos JC, Sturdza AE, et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2012; **82**: 653–7. doi: [10.1016/j.ijrobp.2010.12.029](https://doi.org/10.1016/j.ijrobp.2010.12.029)
44. Taghian A, Pernot M, Hoffstetter S, Luporsi E, Bey P. Radiation therapy alone for medically inoperable patients with adenocarcinoma of the endometrium. *Int J Radiat Oncol Biol Phys* 1988; **15**: 1135–40.
45. Rouanet P, Dubois JB, Gely S, Pourquier H. Exclusive radiation therapy in endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 1993; **26**: 223–8.
46. Nguyen C, Souhami L, Roman TN, Clark BG. High-dose-rate brachytherapy as the primary treatment of medically inoperable stage I-II endometrial carcinoma. *Gynecol Oncol* 1995; **59**: 370–5. doi: [10.1006/gyno.1995.9960](https://doi.org/10.1006/gyno.1995.9960)
47. Knocke TH, Kucera H, Weidinger B, Holler W, Potter R. The results of primary HDR-afterloading brachytherapy in corpus carcinoma. [In German.] *Strahlenther Onkol* 1995; **171**: 195–201.
48. Knocke TH, Kucera H, Weidinger B, Holler W, Potter R. Primary treatment of endometrial carcinoma with high-dose-rate brachytherapy: results of 12 years of experience with 280 patients. *Int J Radiat Oncol Biol Phys* 1997; **37**: 359–65.
49. Kucera H, Knocke TH, Kucera E, Potter R. Treatment of endometrial carcinoma with high-dose-rate brachytherapy alone in medically inoperable stage I patients. *Acta Obstet Gynecol Scand* 1998; **77**: 1008–12.
50. Fusco V, Troiano M, Corsa P, Raguso A, Lioce M, Lauriola P, et al. Radiotherapy alone in endometrial neoplasms. The authors’ own experience. [In Italian.] *Radiol Med* 1998; **95**: 640–6.
51. Nguyen TV, Petereit DG. High-dose-rate brachytherapy for medically inoperable stage I endometrial cancer. *Gynecol Oncol* 1998; **71**: 196–203. doi: [10.1006/gyno.1998.5148](https://doi.org/10.1006/gyno.1998.5148)
52. Inciura A, Atkocius V, Juozaityte E, Vaitkiene D. Long-term results of high-dose-rate brachytherapy and external-beam radiotherapy in the primary treatment of endometrial cancer. *J Radiat Res* 2010; **51**: 675–81.