

5. Gynaecological cancers

Cervix cancer

Background

Patients presenting with small volume International Federation of Gynaecologists and Obstetricians (FIGO) stage IB1 and IIA disease can be treated either by radical hysterectomy and lymphadenectomy or radical radiotherapy as primary procedures. The two approaches have equivalent survival rates (Level 1b).^{1,2}

The combination of surgery and radiotherapy increases morbidity and should be avoided if possible.^{1,3} Postoperative chemoradiotherapy is indicated for patients with poor prognostic features discovered at surgery (positive nodes, positive margins or extensive lymphovascular space involvement) (Level 1b).²⁻⁴

Local control and survival are increased by the addition of concomitant chemotherapy in all stages, although the benefit may be smaller when only one node is positive or when the tumour size is <2 centimetres (cm) (Level 1b).²⁻¹¹

Randomised studies of radiotherapy have used fractionation regimens of 40–50.4 Gray (Gy) in daily 1.8–2 Gy fractions over 4–5.5 weeks (Level 1b).^{1-3,12,13} Both early and late toxicity are increased when chemotherapy is added (Level 1b).^{2,12,14}

Overall treatment time, including intracavitary brachytherapy (ICBT), should not exceed 56 days for squamous carcinoma (Level 1b).^{2,15-19} Haemoglobin levels during treatment are prognostic, with the best outcomes in those whose haemoglobin remains greater than 12 grams per decilitre (g/dl) throughout treatment (Level 2b).^{2,20}

Small-volume parametrial disease can be often be encompassed within the brachytherapy dose-envelope using a combination of interstitial and intracavitary brachytherapy (ISBT and ICBT) (Level 2b).² Alternatively, a simultaneous integrated intensity-modulated radiotherapy (IMRT) planned external beam radiotherapy (EBRT) boost can be considered (Level 2b).² Boosting parametrial disease conventionally with three-dimensional conformal radiotherapy (3D-CRT) or parallel opposed fields with midline blocking does not usually allow organs at risk (OAR) constraints to be met and is not recommended (Level 1b).^{2,21,22}

Evidence from cohort series supports the use of image-guided brachytherapy (IGBT) to reduce late toxicities and facilitate delivery of >80–85 Gy (combined external beam and brachytherapy equivalent dose in 2 Gy per fraction [EQD2]).^{23,24} Dose constraints to OARs have been published based on organ volume rather than point doses (Level 2b).^{2,25} These doses can only be achieved within normal tissue constraints when doses of <50 Gy are delivered by external beam radiotherapy.

Currently, there is no evidence of improvements in survival to support the routine use of neoadjuvant or adjuvant chemotherapy in addition to primary chemoradiotherapy. This question is being addressed by two international trials: Cisplatin and Radiation Therapy with or without Carboplatin and Paclitaxel in Patients with Locally Advanced Cervical Cancer (OUTBACK) and Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer (INTERLACE).^{26,27}

Treatment technique

The planning target volume (PTV) for treating pelvic malignancy normally encompasses the lymphatic drainage of the true pelvis and may be extended further, depending on the extent and type of malignancy, to include the para-aortic nodes, the inguinal nodes or the vagina.²⁸

Nodal atlases have been developed to assist in the outlining of the female pelvis.^{29,30} Significantly less toxicity is seen if EBRT is delivered using IMRT or volumetric-modulated arc therapy (VMAT) rather than 3D-CRT (Level 2b).^{2,31}

Recommendations

Post-operative external beam:

40 Gy in 20 fractions over 4 weeks (Grade A)
 45 Gy in 25 fractions over 5 weeks (Grade A)
 50 Gy in 25 fractions over 5 weeks (Grade A)
 50.4 Gy in 28 fractions over 5.5 weeks (Grade A)

Delivered with weekly concurrent cisplatin 40 milligrams per metre squared (mg/m²) (Grade A)

Definitive primary treatment

External beam radiotherapy:

40 Gy in 20 fractions over 4 weeks (Grade A)
 45 Gy in 25 fractions over 5 weeks (Grade A)
 50 Gy in 25 fractions over 5 weeks (Grade A)
 50.4 Gy in 28 fractions over 5.5 weeks (Grade A)

Delivered with weekly concurrent cisplatin 40 mg/m² (Grade A)

Involved pelvic and para-aortic lymph nodes should receive:

57–60 Gy in 28 fractions over 5.5 week using a simultaneous integrated boost (Grade C)

Parametrial disease that cannot be encompassed by ICBT and ISBT may receive:

57–60 Gy in 25–28 fractions over 5–5.5 weeks
 65 Gy in 28 fractions over 5.5 weeks using a simultaneous integrated boost (Grade C)

EBRT should be followed by image-guided brachytherapy so that a total dose of 80–85 Gy EQD2 is delivered to the high-risk clinical target volume (CTV) (Level 2b).

This is achieved with:

45 Gy in 25 fractions over 5 weeks external beam followed by high-dose rate (HDR) 28 Gy in 4 fractions (Grade B)

Other fractionation schedules in use for brachytherapy after the external beam schedules given above are:

HDR: 6–7.5 Gy per fraction for 3–5 fractions (Grade C)

Pulsed dose rate (PDR): 17 Gy per fraction at 1 Gy per hour for 2 fractions, 7–10 days apart (Grade C)

Overall treatment time, including brachytherapy should be no more than 56 days for squamous cancers (Level 1b)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

Endometrial cancer

Adjuvant therapy in operable disease

The majority of patients present with organ-confined disease and surgery is the primary treatment.

Trials of pelvic radiotherapy consistently show a reduction in local recurrences but no overall survival benefit.^{32–37} The Vaginal Brachytherapy Versus Pelvic External Beam Radiotherapy for Patients with Endometrial Cancer of High–Intermediate Risk (PORTEC 2) trial showed equivalent outcome for patients with some intermediate risk features who received either adjuvant vaginal brachytherapy (VBT) or external beam radiotherapy.³⁵ The long-term pelvic side-effects in the brachytherapy group were less than with external beam. The PORTEC 3 trial has investigated the benefit of concurrent chemoradiotherapy and adjuvant chemotherapy compared to adjuvant radiotherapy alone, which has been the current standard of care. This shows an advantage for the combined approach in stage III patients after hysterectomy.^{36,37}

Recommendations

High-risk patients

Postoperative adjuvant external beam radiotherapy:

46 Gy in 23 fractions over 4.5 weeks (Grade A)

48.6 Gy in 27 fractions over 5.5 weeks (Grade A)

Other schedules in use include 45 Gy in 25 fractions (Grade D) and 50.4 Gy in 28 fractions (Grade D)

Stage III patients should receive chemoradiation with cisplatin followed by adjuvant carboplatin and paclitaxel (Grade A)

Vault brachytherapy may follow the above schedules in patients with cervical involvement although there is no strong evidence base for this practice:

HDR: 8 Gy at 5 millimetres (mm) in 2 fractions (Level 1b)

PDR: 19 Gy at 5 mm at 1 Gy per hour given in 1 fraction (Level 1b)

Intermediate risk patients

Vaginal vault brachytherapy:

HDR:

21 Gy at 5mm in 3 fractions over 3 weeks (Grade A)

12–30 Gy at 5 mm in 3–8 fractions (Grade C)

PDR: 28 Gy at 5 mm in 1 Gy pulse per hour given in 2 fractions delivered in 7–10 days (Level 1b)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

Definitive radiotherapy for inoperable disease

Endometrial carcinoma may be inoperable because of medical co-morbidity or advanced disease stage. Accurate staging can be achieved using magnetic resonance imaging (MRI). Radiotherapy can control stage I and II disease and may have a role in more advanced cases (Level 2a).^{38,39}

Recommendations

Brachytherapy alone

HDR:

36 Gy in 5 fractions (Grade C) prescribed to the uterine serosa
37.5 Gy in 6 fractions (Grade C) prescribed to the uterine serosa

Combination therapy

External beam:

45 Gy in 25 fractions over 5 weeks (Grade C)
50 Gy in 25 fractions over 5 weeks (Grade C)

Brachytherapy:

HDR:

28 Gy in 4 fractions (Grade C) prescribed to the uterine serosa
25 Gy in 5 fractions (Grade C) prescribed to the uterine serosa

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

Endometrial carcinoma: salvage

Recurrent uterine corpus carcinoma in a previously unirradiated pelvis can be treated, and sometimes salvaged, with radiotherapy (external beam alone, external beam combined with brachytherapy or brachytherapy alone). Data of any sort are sparse, with no randomised trials. Doses of greater than 60 Gy EQD2 including brachytherapy should be delivered, provided rectal and bladder constraints are respected (Level 2c).^{40,41}

Vulva

Adjuvant therapy in operable disease

For those with operable vulval cancer, surgical resection of the primary with inguinal lymphadenectomy remains the treatment of choice.⁴²

Adjuvant radiotherapy may be considered for those with incomplete resection, two or more positive lymph nodes or any extracapsular spread. Concurrent chemotherapy with cisplatin is used, but without a strong evidence base to support it (Grade C).² The Gronigen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS – II) study is comparing surgery with either definitive radical radiotherapy or radical chemoradiotherapy where sentinel lymph node metastases <2 mm are detected.⁴³

Recommendation**Postoperative radiotherapy to vulva, pelvic and inguinal nodes:**

45 Gy in 25 fractions over 5 weeks (Grade C)

50 Gy in 25 fractions over 5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

Inoperable vulval carcinoma

Data in this area are sparse with no randomised studies. Potential therapeutic options include definitive chemo-radiotherapy, treating the primary and nodes. Consideration should then be given to surgical removal of residual disease or a second phase of radiotherapy with electrons or brachytherapy.⁴⁴

Recommendation**Inoperable vulval cancer:**

45 Gy in 25 fractions over 5 weeks (Grade C)

50 Gy in 25 fractions over 5 weeks (Grade C)

50.4 Gy in 28 fractions over 5.5 weeks (Grade C)

External beam radiotherapy may be given with weekly cisplatin 40 mg/m² (Grade C)

The primary and involved nodes should be boosted using electrons, simultaneous integrated boost (SIB) with IMRT or brachytherapy to deliver a total dose of 60–65 Gy EQD2 (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

Vaginal carcinoma

The rarity of vaginal carcinoma has led to therapy recommendations being derived from single institution series accrued over many years and extrapolation from cervical carcinoma data with no randomised trials. Therapy with EBRT in combination with either ISBT or ICBT is accepted practice with doses of between 70–80 Gy EQD2 appearing to confer survival advantage (Level 4).⁴⁵ The addition of concurrent chemotherapy appears to deliver a survival advantage (Level 4).⁴⁶

Recommendation**Definitive therapy of vaginal carcinoma:**

45–50 Gy in 25 fractions over 5 weeks (Grade C)

Followed by ISBT or ICBT HDR 18.75–20 Gy in 5 fractions (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.²

References

1. Landoni F, Maneo A, Colombo A *et al.* Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. *Lancet* 1997; **350**(9077): 535–540.
 2. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
 3. Sedlis A, Bundy BN, Rotman MZ, *et al.* A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* 1999; **73**(2): 177–183.
 4. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010; **(1)**: CD009285.
 5. Whitney CW, Sause W, Bundy BN *et al.* Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999; **17**(5): 1339–1348.
 6. Rose PG, Bundy BN, Watkins EB *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; **340**(15): 1144–1153. [erratum in *N Engl J Med* 1999; **341**(9): 708]
 7. Morris M, Eifel PJ, Lu J *et al.* Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; **340**(15): 1137–1143.
 8. Keys HM, Bundy BN, Stehman FB *et al.* Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999; **340**(15):1154–1161. [erratum in *N Engl J Med* 1999; **341**(9): 708].
 9. Thomas GM. Improved treatment for cervical cancer – concurrent chemotherapy and radiotherapy. *N Engl J Med* 1999; **340**(15): 1198–1200.
 10. Rose PG, Bundy BN. Chemoradiation for locally advanced cervical cancer: does it help? *J Clin Oncol* 2002; **20**(4): 891–893.
 11. Eifel PJ, Winter K, Morris M *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004; **22**(5): 872–880.
 12. Peters WA 3rd, Liu PY, Barrett RJ 2nd *et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000; **18**(8): 1606–1613.
 13. Monk BJ, Wang J, Im S *et al.* Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol* 2005; **96**(3): 721–728.
 14. Vale CL, Tierney JF, Davidson SE, Drinkwater KJ, Symonds P. Substantial improvement in UK cervical cancer survival with chemoradiotherapy: Results of a Royal College of Radiologists' audit. *Clin Oncol (R Coll Radiol)* 2010; **22**(7): 590–601.
 15. The Royal College of Radiologists. *The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions*, Third edition. London: The Royal College of Radiologists, 2008
-

16. Chatani M, Makayoshi Y, Masaki N, Inoue T. High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation. *Strahlenther Onkol* 1997; **73**(7): 379–384.
17. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix part I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **32**(5): 1275–1288.
18. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. *Radiother Oncol* 1992; **25**(4): 273–279.
19. Delaloye JF, Coucke PA, Pampallona S, De Grandi P. Effect of total treatment time on event-free survival in carcinoma of the cervix. *Gynecol Oncol* 1996; **60**(1): 42–48.
20. Winter WE 3rd, Maxwell GL, Tian C *et al*. Association of hemoglobin level with survival in cervical carcinoma patients treated with concurrent cisplatin and radiotherapy: A Gynecologic Oncology Group study. *Gynecologic Oncol* 2004; **94**(2): 495–501.
21. Mohamed S, Kallehaug J, Fokdal L, Lindegaard JC, Tanderup K. Parametrial boosting in locally advanced cervical cancer: combined intracavitary/interstitial brachytherapy versus intracavitary brachytherapy plus external beam radiotherapy. *Brachytherapy* 2015; **14**(1): 23–28.
22. Huang E-Y, Lin H, Hsu HC *et al*. High external parametrial dose can increase the probability of radiation proctitis in patients with uterine cervix cancer. *Gynecol Oncol* 2000; **79**(3): 406–410.
23. Mazon R, Castelnau-Marchand P, Dumas I *et al*. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiother Oncol* 2015; **114**(2): 257–263.
24. Rijkmans EC, Nout RA, Rutten IH *et al*. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol* 2014; **135**(2): 231–238.
25. Potter R, Georg P, Dimopoulos JC *et al*. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2001; **100**(1): 116–123.
26. <https://clinicaltrials.gov/ct2/show/NCT01414608> (last accessed 26/9/16)
27. <https://clinicaltrials.gov/ct2/show/NCT01566240?term=interlace&rank=2> (last accessed 13/10/16)
28. Yap ML, Cuartero J, Yan J *et al*. The role of elective para-aortic lymph node irradiation in patients with locally advanced cervical cancer. *Clin Oncol (R Coll Radiol)* 2014; **26**(12): 797–803.
29. Taylor A, Rockall AG, Powell ME. An atlas of the pelvic lymph node regions to aid radiotherapy target volume definitions. *Clin Oncol (R Coll Radiol)* 2007; **19**(7): 542–550.
30. Small W Jr, Mell LK, Anderson P *et al*. Consensus guidelines for delineation of the clinical target volume for intensity-modulated pelvic radiotherapy in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008; **71**(2): 428–434.
31. Hasselle MD, Rose BS, Kochanski JD *et al*. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011; **80**(5): 1436–1445.
32. ASTEC study group, Kitchener H, Swart AM, Qian Q *et al*. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009; **373**(9658): 125–136.

References

33. Creutzberg CL, Nout RA, Lybeert ML *et al.* Fifteen-year radiotherapy outcomes of the randomised PORTEC-1 trial for endometrial carcinoma. *Int J Rad Oncol Biol Phys* 2011; **81**(4): e631–e638.
 34. Keys HM, Roberts JA, Brunetto VL *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**(3): 744–751.
 35. Nout RA, Smit VT, Putter H *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**(9717): 816–823
 36. <https://clinicaltrials.gov/ct2/show/NCT00411138?term=PORTEC+3&rank=1> (last accessed 26/9/16)
 37. de Boer SM, Powell ME, Mileskin L *et al.* PORTEC study group: Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018; **19**(3): 295–309.
 38. Churn M, Jones B. Primary radiotherapy for carcinoma of the endometrium using external beam radiotherapy and single line source brachytherapy. *Clin Oncol* 1999; **11**(4): 255–262.
 39. Gill BS, Kim H, Houser C *et al.* Image-based three-dimensional conformal brachytherapy for medically inoperable endometrial carcinoma. *Brachytherapy* 2014; **13**(6): 542–547.
 40. Vargo JA, Kim H, Houser CJ *et al.* Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification. *Radiother Oncol* 2014; **113**(1): 126–131.
 41. Jerezek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. *Int J of Radiat Oncol Biol Phys* 2000; **48**(2): 405–413.
 42. Van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulval cancer. *Cochrane Database Syst Rev* 2011; **5**: CD002224.
 43. <https://clinicaltrials.gov/ct2/show/NCT01500512?term=GROINSS&rank=1> (last accessed 26/9/16)
 44. Moore DH, Ali S, Koh WJ *et al.* A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynaecological oncology group study. *Gynecol Oncol* 2012; **124**(3): 529–533.
 45. Beriwal S, Bhatnagar A, Heron DE *et al.* High-dose-rate interstitial brachytherapy for gynecological malignancies. *Brachytherapy* 2006; **5**(4): 218–222.
 46. Rajagopalan MS, Xu KM, Lin JF, Sukumvanich P, Krivak TC, Beriwal S. Adoption and impact of concurrent chemoradiation therapy for vaginal cancer: A National Cancer Data Base (NCDB) Study. *Gynecol Oncol* 2014; **135**(3): 495–502.
-