

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

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