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Cervix cancer

Background

Patients presenting with small-volume International Federation of Gynecology and Obstetrics (FIGO) Stages 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; 120 g/l) throughout treatment (Level 2b).[2,20]

Parametrial disease can be encompassed within the brachytherapy dose envelope using a combination of interstitial brachytherapy (ISBT) and ICBT (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 >85 Gy (combined external beam and brachytherapy equivalent dose in 2 Gy per fraction [EQD2]).[23,24] Dose constraints to OAR 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 (EBRT).

There is no evidence to support the routine use of adjuvant chemotherapy following primary chemoradiotherapy. The OUTBACK trial (cisplatin and radiation therapy with or without carboplatin and paclitaxel in patients with locally advanced cervical cancer)[26] failed to demonstrate an improvement in either overall survival or progression-free survival in keeping with earlier studies. In contrast, however, the INTERLACE study recently presented in abstract form suggests there may be an advantage for selected patients, which may change this view once the full results are published.[27]

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Treatment technique

The clinical target volume (CTV) for treating pelvic malignancy normally encompasses the lymphatic drainage of the cervix pelvis including the internal, external and common iliac nodes and presacral nodes. This 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 intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) rather than 3D-CRT (Level 2b).[2,31]

Recommendations

Definitive primary treatment

External beam radiotherapy:

- 45 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/m^2 (Grade A)

Involved pelvic and para-aortic lymph nodes should receive:

- 55–60 Gy in 25–28 fractions over 5.5 weeks using a simultaneous integrated boost (Grade C)

Brachytherapy[32]

The high total doses required of 85–90 Gy to the high-risk CTV (HR-CTV) D90 are achieved by adding to the external beam schedules above:

- High-dose rate (HDR) brachytherapy 28 Gy in 4 fractions (Grade B)
- For small-volume tumours (<30 ml) a 3-fraction schedule may be considered (7.7 Gy × 3)

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

Postoperative external beam:

- 45 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/m^2) (Grade A)

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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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.[33–36] 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 EBRT.[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 with adjuvant radiotherapy alone, which has been the current standard of care. This shows an advantage for the combined approach in Stage III and serous histology after hysterectomy.[36]

A more sophisticated approach using molecular classification of the tumour has been proposed and is under evaluation in clinical trials but as yet the evidence is not sufficiently robust to be considered a standard of care.

Recommendations

High-risk patients

Postoperative adjuvant EBRT:

- 46 Gy in 23 fractions over 4.5 weeks (Grade A)
- 45 Gy in 25 fractions over 5 weeks (Grade A)
- 48.6 Gy in 27 fractions over 5.5 weeks (Grade A)
- 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 mm in 2 fractions (Level 1b)

Intermediate-risk patients

Vaginal vault brachytherapy:

- HDR: 21 Gy at 5 mm in 3 fractions over 2–3 weeks (Grade A)

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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 Stages I and II disease and may have a role in more advanced cases (Level 2a).[37,38]

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).[39,40]

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.[41]

Adjuvant radiotherapy may be considered for those with positive resection margins, two or more positive lymph nodes or any extracapsular spread. Concurrent chemotherapy with

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cisplatin is used, but without a strong evidence base to support it (Grade C). The Gronigen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-II) compared surgery with either definitive radical radiotherapy or radical chemoradiotherapy where sentinel lymph node metastases <2 mm were detected.[42] Inguinofemoral radiotherapy to a dose of 50 Gy is a safe alternative to inguinofemoral lymphadenectomy for micrometastases <2 mm but inguinofemoral lymphadenectomy is recommended for macrometastases (Grade C).

Recommendations

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 chemoradiotherapy, treating the primary and regional nodes. Consideration should then be given to surgical removal of residual disease or a second phase of radiotherapy with electrons or brachytherapy.[43]

Recommendations

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)
- EBRT may be given with weekly cisplatin 40 mg/m^2 (Grade C)
- The primary and involved nodes should be boosted using a simultaneous integrated boost (SIB) with VMAT or brachytherapy to deliver a total dose of 60–68 Gy EQD2[44] (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 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).[46,47]

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Recommendations

Definitive therapy of vaginal carcinoma:

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

Followed by HDR brachytherapy: note the lower vagina is less tolerant of very high doses. A total EQD2 dose of 70–80 Gy should be the aim:

• Upper vagina: 24–28 Gy in 4 fractions (Grade C)
• Lower vagina: 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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