AN OVERVIEW OF TREATMENT FOR INVASIVE CERVICAL CANCER

Jim Nicklin  Gynaecologic Oncology, Royal Brisbane and Women’s Hospital, Herston, Queensland
Email: jnick@bigpond.net.au

Abstract

Treatment of cervical cancer varies depending on stage and patient factors. Comprehensive management is best provided within a well resourced multidisciplinary team. Micro-invasive disease is largely managed surgically. Treatment for stage IA2 disease involves radical clearance around the primary disease and pelvic lymphadenectomy. Stage IB1 and non-bulky stage IIA disease can be treated with radical hysterectomy or chemoradiation. Important developments in the surgical management of patients with this stage of disease include radical trachelectomy, nerve sparing and laparoscopic techniques, and sentinel node identification and resection. For patients with stage IB2 and bulky stage IIA disease there are four valid management options. These include primary chemoradiation, radical hysterectomy and lymphadenectomy +/- adjuvant chemoradiation, neoadjuvant chemotherapy followed by radical surgery and chemoradiation followed by completion hysterectomy. The mainstay of treatment for patients with stage IIB – IVA disease is chemoradiation. Timely completion of treatment and the maintenance of haemoglobin between 12-14 g/dL are associated with optimal results. The role of surgery in advanced disease is controversial. There may be some role for the resection of bulky pelvic and para-aortic lymph nodes prior to chemoradiation. With the advent of sophisticated imaging modalities of CT, MRI and PET scanning, the role of pre-treatment surgical staging via a retroperitoneal or laparoscopic approach is more controversial. There is some role for primary exenterative surgery in selected patients with stage IVA disease involving either bladder or bowel mucosa. Treatment of patients with stage IVB and recurrent disease is highly individualised and may involve surgery, chemotherapy or radiotherapy.

The treatment of cervical cancer varies, depending upon stage of disease and patient factors. Comprehensive management of the full spectrum of disease can only be provided in the context of a well resourced multidisciplinary team, including specialist gynaecologic pathologists, subspecialty trained surgeons, medical oncologists, radiation oncologists, palliative care specialists, nursing and allied health professionals.

**Micro-invasive disease (FIGO stage IA1 and IA2)**

Micro-invasive disease is by definition microscopic disease, usually arising in a background of high grade intra-epithelial neoplasia. The diagnosis can be subtle and cannot be made on anything less than a cone biopsy or equivalent excisional treatment. Ideally, the entire cone specimen should be extensively embedded and sectioned and reviewed by an expert gynaecological pathologist. Stage IA1 is defined as measured invasion of stroma no greater than 3mm in depth and no wider than 7mm. Stage IA2 is defined as invasion of stroma greater than 3mm, but no greater than 5mm, and width no greater than 7mm. The distinction is quite important with respect to the risk of nodal involvement. FIGO staging does not distinguish between squamous and glandular lesions.

For patients with stage IA1 disease, the risk of pelvic nodal disease is less than 1%. Patients can be treated with a simple hysterectomy or cone biopsy if reproductive potential is required. Conisation alone is safe therapy where the cone margins are negative, there is no lymph-vascular space invasion and the endocervical curettings are negative. Cumulative data would suggest that these recommendations can be safely applied to both squamous and glandular lesions.

For patients with stage IA2 disease, there is a larger tumour volume and greater depth of invasion. The risk of pelvic lymph node involvement is of the order of 4-8%. There is an imperative to ensure not only an adequate margin around the primary tumour, but to also treat the pelvic lymph nodes. It may be possible to achieve an adequate margin around the primary tumour with cone biopsy or hysterectomy, however commonly a modified radical hysterectomy or trachelectomy (depending upon reproductive requirements) is performed to ensure adequate clearance. A pelvic lymphadenectomy is also necessary because of the risk of nodal disease.

**Stage IB1 and non-bulky IIA disease**

There are two main options for treatment of stage IB1 and non-bulky IIA disease; surgery or chemoradiation. The benchmark for surgery is radical hysterectomy and pelvic lymphadenectomy. This operation refers to an en bloc excision of the uterus with the parametrium to the level of the internal iliac artery, the uterosacral ligaments one third to half way to the sacrum, and the upper part of the vagina. The pelvic lymphadenectomy includes all the fibro-fatty-lymphatic tissue between the internal iliac/obliterated umbilical artery, the obturator nerve, the deep circumflex iliac vein, the genito-femoral nerve and the common iliac nodes +/- sacral nodes. A modified radical hysterectomy may be used for smaller primary lesions and is defined as resection of the parametrium to the level of the ureters and the uterosacral ligaments, divided some 2-3cm from the cervix and a smaller cuff...
of vagina. The extent of surgery can be largely tailored to the size of the tumour, with a view to attaining margins of at least 1cm.

Recent developments in the surgical management of cervical cancer include the incorporation of minimal access and laparoscopic techniques. Laparoscopic assisted radical vaginal hysterectomy and total laparoscopic radical hysterectomy (including the incorporation of robotics) have been demonstrated to be feasible with reduced blood loss, longer operating times, shorter hospitalisation, and faster recovery. A randomised trial comparing laparoscopic radical hysterectomy and open surgery has recently commenced (www.ClinicalTrials.gov, Identifier: NCT00614211). Another development in the surgical management is the nerve-sparing radical hysterectomy. The technique involves identification and clearance of the hypogastric nerve under the ureter and lateral to the uterosacral ligaments, the inferior hypogastric plexus in the lateral parametrium and the distal inferior hypogastric plexus in the posterior vesico-uterine ligament. This latter technique is reportedly associated with less voiding, defaecation and sexual dysfunction.

An option for patients who are desirous of retaining reproductive potential, is radical trachelectomy (in conjunction with a pelvic lymphadenectomy). This provides radical clearance around the primary tumour without removing the corpus. Radical tracheectomy is usually confined to smaller cancers <2cm with no lymph-vascular space invasion and can be performed via either a vaginal or abdominal approach. A more detailed review of this treatment has been included elsewhere in this issue. There are no randomised trials comparing radical tracheectomy with standard surgical treatment, however retrospective observational series have demonstrated the procedure to be safe and feasible with an acceptable “take-home baby rate”.

A novel, experimental approach to the management of the pelvic lymph nodes is sentinel node biopsy. The rationale for this approach is the belief that there is an orderly sequence of metastatic spread from the primary site to identifiable sentinel nodes and then to second echelon and subsequent nodal groups. This approach has become increasingly accepted in the management of breast cancer, cutaneous melanomas and even vulval cancer. In the context of treating cervix cancer, technetium-99 radiocolloid and Patent Blue vital dye is injected around the tumour. The sentinel node is identified at the time of surgery by colour and increased radioactivity on a gamma probe. Several studies have demonstrated that detection and removal of sentinel nodes is feasible and safe, particularly in patients with smaller tumours. Although over 800 have been reported in the world literature, this is an experimental surgical protocol and randomised trials comparing it with full pelvic lymphadenectomy are still some way off.

The second option for treatment of early stage disease is primary chemoradiation. The survival outcomes for surgery and radiotherapy are identical. There has been only one randomised study comparing hysterectomy and tailored adjuvant radiotherapy with primary radiotherapy alone for women with stage IB1 to IIA disease. In the study, 109 out of 228 (47.8%) patients had bulky disease >4cm and were stratified by cervical diameter. There was a very high rate of adjuvant radiotherapy in the surgery arm (64%) and the five year survival rates and disease free survival were not significantly different (83% and 74%). There was a significantly higher rate of severe morbidity (predominantly urological and gastro-intestinal) in the surgery (plus tailored radiotherapy) v the radiotherapy arm (28% v 12%, p = 0.0004).

The superiority of chemoradiation over radiation alone in treating women with both early and advanced cervical cancer has been demonstrated in several randomised trials and in a meta-analysis. Consequently, chemoradiation has become the standard of care. Of note, few patients in the combined trials had early stage disease such as in the population under consideration. Survival is so good in this group that the addition of chemotherapy provides a small marginal benefit.

The advantage of surgery is as follows:
1. Preservation of ovarian function in pre-menopausal women.
2. Preservation of vaginal function and length.
3. More comprehensive evaluation and capacity for resection of bulky pelvic lymph nodes.
4. Determination of extent of nodal metastases allows individualisation of radiotherapy field.

The advantage of primary chemoradiation is as follows:
1. Avoids the demonstrated morbidity of combined radical treatments.
2. Avoids the need for surgery, particularly for patients with significant medical co-morbidities.

Treatment decisions in this group ultimately come down to patient factors, patient and physician preference and local resources and expertise.

**Stage IB2 and bulky stage IIA**

For patients with bulky stage IB and IIA disease there are four valid options for management:
1. Primary chemoradiation.
2. Radical hysterectomy and lymphadenectomy, plus adjuvant chemoradiation.
3. Neoadjuvant chemotherapy followed by radical surgery.
4. Chemoradiation followed by completion hysterectomy.

Primary chemoradiation is a predominant mode of treatment in the developed world. The addition of concurrent chemotherapy to radiotherapy has been associated with significant survival benefits in many randomised studies. The benefits of the addition of chemotherapy are more marked for earlier stage disease. A more detailed discussion of chemoradiation is included in the next section.

Primary surgery followed by chemoradiation allows removal of large, potentially radiation resistant tumours,
may obviate the need for brachytherapy, allows for removal of bulky retroperitoneal lymph nodes, and may allow for transposition and preservation of ovarian function and tailored adjuvant chemoradiation. The risk of major morbidity is increased with the combination of radical therapies. To minimise the risk of morbidity the following techniques have been advocated:

1. Restricting lymphadenectomy to debulking of enlarged nodes only, on the understanding that radiation to the nodal bed will sterilise the vast majority of microscopic metastases.

2. Limiting the radiation to a smaller central field where a comprehensive lymphadenectomy has been performed and no nodal metastases found.

3. Use of carefully planned conformal radiotherapy field and belly board to minimise gut morbidity.

The rationale of neoadjuvant chemotherapy is sound. Numerous non-randomised studies demonstrate that squamous cell carcinoma of the cervix is usually sensitive to cisplatin-containing regimens. Delivery of these regimens is feasible and safe and is associated with downsizing of tumours with increased resectability of bulky tumours. A recent Cochrane meta-analysis from 18 trials involving 2074 patients found a high degree of heterogeneity in chemotherapy regimes and trial design. However, it was noted that trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m²/week tended to show a survival advantage for neoadjuvant chemotherapy. The authors concluded only that timing and dose intensity of cisplatin-based neoadjuvant chemotherapy had an important impact on benefits for women with locally advanced cervical cancer and that further investigation was warranted.15

Historically, a completion hysterectomy following radiotherapy was often planned in this patient population in the era before chemoradiation. The rationale was that bulky, often hypoxic tumours were found to extend laterally and superiorly to the tumouricidal, isodose radiation curves of the brachytherapy devices post external beam radiation. Up to one half of specimens were found to contain viable tumour at the completion of radiation. A single randomised study comparing radiation with and without extra-fascial hysterectomy demonstrated a trend towards a lower recurrence rate in the surgery arm (15 v 27%), with much stronger trends for larger tumours, but the difference was not statistically significant.16 Consequently, even before chemoradiation replaced radiotherapy alone as the standard of care, the routine practice of completion hysterectomy largely fell out of favour. However, Nijhuis et al advise careful evaluation for viable tumour and biopsy of the cervix eight to ten weeks post treatment to identify patients who may benefit from salvage surgery.17 Multiple series have subsequently been published reporting the role of completion hysterectomy following chemoradiation in patients with disease ranging from stage 1B1 to IVA.18 This treatment certainly has a role in the multi-modality management of cervical cancer, most notably in patients with surgically-resectable, viable disease post-chemoradiation, in patients with anatomical distortions of the lower genital tract due to fibroids or tumour which may compromise brachytherapy and possibly in larger tumours.

**Stage IIB, III and IVA disease**

The mainstay of treatment for patients with locally advanced disease is combination external beam irradiation and brachytherapy with concomitant sensitising chemotherapy. The superiority of chemoradiation over radiation alone has been demonstrated in multiple randomised studies and a meta-analysis.14,19-23,24,25 The optimal chemoradiation regimen has not been determined as the radiation regimen used in each of the trials was different. The conclusion of the Cochrane review was that radiation with sensitising chemotherapy, whether with or without cisplatin, was associated with a significantly improved overall survival and progression free survival, with a significant reduction in both loco-regional and distant recurrence rates. There was a significantly greater incidence of haematological and gastro-intestinal toxicity, with poor reporting of late effects of treatment. Treatment related deaths were rare. The greatest beneficial effect was noted in trials that included the higher proportion of patients with early stage disease.14

From several retrospective studies it is apparent that timely completion of chemoradiation is associated with improved local control of disease and survival.24,25 Ideally, treatment should be completed within six to eight weeks. Treatment durations of greater than eight to ten weeks were shown to be associated with higher rates of loco-regional recurrence and poorer survival.24,25

Anaemia is common in patients with advanced cervical cancer and has been demonstrated to be associated with compromised outcomes.26,27 Thus, anaemia is a credible target for therapeutic interventions to improve clinical outcomes. The optimal haemoglobin level during treatment is thought to be between 12 and 14 g/dL.28 Experimental strategies to correct anaemia during treatment using either blood transfusions or recombinant erythrocyte erythropoietin have been studied.29-31 Erythropoiesis stimulating agents used in this manner have been associated with increased thromboembolic events. The optimal regimen to maintain haemoglobin levels during treatment is yet to be determined.

**The role of surgery in advanced stage disease**

Bulky, malignant, retroperitoneal nodes on the pelvic side wall and in the aortic area are potentially resistant to standard doses of (chemo) radiation and a likely site of treatment failure. Retrospective studies of debulking of grossly involved nodes prior to radiation have shown some improvement in outcome compared to radiation treatment alone.32-34 Although chemoradiation is the new standard of care, it is likely that pre-treatment resection of bulky nodes, particularly via a retro-peritoneal approach, will provide some therapeutic advantage.

With the advent of the sophisticated imaging modalities of CT, MRI and PET scanning capable of detecting occult para-aortic and distant metastases, the place of routine
staging surgery is reduced. Surgical staging may be accomplished via either a trans-peritoneal or extra-peritoneal approach, using either laparoscopy or laparotomy. Multiple studies have demonstrated that such an approach is feasible and potentially more accurate than imaging techniques. However, this must be balanced against the delay in institution of chemoradiation and particularly the GIT morbidity of combined radical modality therapy. A single randomised study comparing clinical staging to pre-treatment surgical staging, via either a laparoscopic or an extra-peritoneal open approach, was terminated prematurely when interim analysis demonstrated significantly worse progression-free and overall survival in the surgical arm.\(^9\)

For selected patients with primary malignant involvement of the bladder or rectal mucosa, particularly with evidence of fistula formation and without evidence of significant distant disease, there is a place for exenterative surgery and reconstruction.

### Stage IVB disease

For all intents and purposes, disseminated disease is incurable. Treatment is palliative and quality of life is of paramount importance. Specific treatments are directed at symptom relief. For patients with significant vaginal bleeding, palliative radiotherapy is usually appropriate. Any place for chemotherapy is determined by the extent and type of symptoms and patient wishes.

### Recurrent disease

The treatment of recurrent disease is determined by the extent and distribution of disease, the interval to recurrence, the modality used to treat the primary disease and patient wishes. For patients with an isolated central recurrence of disease, particularly following chemoradiation, there is a place for exenterative surgery. Surgery may also be appropriate for isolated, late, pulmonary metastases or nodal metastases. Radiotherapy may be useful to palliate pain or bleeding in the pelvis and at other sites.

Multiple chemotherapeutic drugs, including ifosfamide, paclitaxel, topotecan and vinorelbine have been tested as single agents and in combination with cisplatin in patients with disseminated cervical cancer. Only the combination of cisplatin and topotecan was shown to have a survival advantage over single agent cisplatin (9.4 versus 6.5 months). While there was significantly greater toxicity in the combination regimen, there was no significant difference in quality of life.\(^36,37\)

### Conclusions

The treatment of cervical cancer frequently involves carefully integrated, multi-modal therapies which optimise survival and minimise morbidity. Early stage disease is usually amenable to surgery alone. More advanced stage disease will usually require multi-modal therapy often including chemoradiation +/- surgery. A multi-disciplinary team provides the full spectrum of expertise and services to manage patients with all stages of cervical malignancy. Furthermore, this therapeutic model provides continuity of care, particularly with respect to recurrent disease and complications of treatment.

### References

5. Inoue T. Prognostic significance of the depth of invasion relating to nodal metastases, parametrial extension, and cell types. A study of 628 cases with Stage IB, IIa, and IIb cervical carcinoma. Cancer 1984;54:3035-42.


