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REVIEW

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The current management of cervical cancer

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Cervical cancer is a common cause of death worldwide. In the developed world, cervical cancer screening has successfully reduced the incidence of and mortality from the disease. Mortality remains high among developing nations. Over the past decade, there have been various developments in management strategies, based on currently available evidence. This review explores such evidence and recommends current management strategies, including fertility-sparing surgical options for early-stage disease.

Introduction

Cervical cancer remains a common malignancy worldwide, although the incidence appears to be falling.[1,2] At the same time, there has been an apparent increase in the incidence of preinvasive disease, cervical intraepithelial neoplasia (CIN), owing to effective cervical cancer screening in the developed world. There is wide variation in both the incidence and the lifetime risk of cervical cancer across different parts of the world (Tables 1 and 2). In England, the incidence of cervical cancer fell from 4467 new cases in 1985 to 2900 in 1995.[3–5] By 2000, this had fallen to 2424 new cases.[6] There are approximately half a million new cases each year worldwide, with 80% occurring in developing nations.[1,5,6] The age distribution rate varies from country to country and between different populations.[6,7] The peak incidence for invasive cancer is between 45 and 50 years of age, although there has been a rise in the 25–34-year age range.[8] The peak incidence of CIN is 25–40 years of age. Currently, the mortality rate from cervical cancer is falling by almost 7% annually in the UK, which has been attributed mainly to the success of the cervical screening programme.[3] Squamous cell carcinoma accounts for the majority of cases of invasive cervical cancer although, since 1998, there has been a significant rise in the proportion of cases of adenocarcinoma and adenosquamous carcinoma.[9,10]

Various aetiological factors have been associated with cervical cancer. Among these are human papillomaviruses (HPVs), smoking, sexual behaviour, immunosuppression (such as women who are HIV-positive and women undergoing renal transplant who are taking immunosuppressants) and combined oral contraceptive pills.[11,12] There is now overwhelming evidence that HPVs are the main cause of both preinvasive and invasive squamous cell carcinoma of the cervix in nearly 100% of cases.[11,13,14] These are mainly the oncological HPVs (HPVs 16, 18, 31, 33, 35).

Staging

Staging is based on clinical evaluation. Apart from stages Ia1 and Ia2 (where histological diagnosis is usually made from a cone or loop cervical biopsy, depending on the depth and horizontal extent of the disease), staging of cervical cancer is clinical, preferably by examination under anaesthesia by an experienced clinician. Thereafter, the stage should not be altered because of subsequent findings. The International Federation of Gynecology and Obstetrics (FIGO) recommends that if there is any doubt as to which stage a particular cancer should be allocated, the earlier stage is mandatory (see Table 3 for FIGO staging).[16]

Cystoscopy is performed to exclude bladder involvement and a rectovaginal examination should be performed to determine the tumour bulk and the presence of any parametrial or pelvic sidewall extension. Other examinations that may be carried out are proctoscopy, sigmoidoscopy, intravenous urography and a chest X-ray.[16] The role of magnetic resonance imaging (MRI) is becoming increasingly important in staging early cervical cancer. MRI is more sensitive than clinical examination in detecting parametrial involvement.[17–19] It is also useful in detecting the presence of regional lymphadenopathy.[19] Extension to the uterine corpus is disregarded because it is impossible to estimate clinically whether or not a cancer of the cervix has extended to the uterine corpus. Figure 1 illustrates the staging of cervical cancer.

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Table 1. Age-standardised incidence rate of cervical cancer, 1988–1992[7]

Population	Incidence rate/100 000 women
Los Angeles:	
Hispanic	17.9
Black	11.6
White (non-Hispanic)	7.2
Harare:	
African	67.2
European	10.4
Israel:	
Jewish	5.3
Non-Jewish	3.0
Singapore:	
Chinese	16.3
Malay	11.1
Indian	8.6
Europe:	
Denmark	15.2
Finland	3.6
Eastern Germany	21.2
The Netherlands	7.1
Sweden	8.0
United Kingdom	12.5[a]
Latin America:	
Colombia, Cali	34.4
Peru, Trujillo	53.5

[a]The age-specific incidence has since fallen in the UK to an average of 9/100 000[3]

Meticulous staging of cervical cancer is important in determining the most appropriate form of treatment, as well as being a prognostic indicator. It is also valuable in comparing therapy results. The stage of the disease also correlates well with the risk of regional lymphatic metastases, as shown in Table 4.

Investigations

Routine blood tests should include a full blood count, urea and electrolyte estimations and liver function tests. A chest X-ray should be performed to exclude pleural effusion and pulmonary metastases. Intravenous urography is not routinely performed, although it may reveal hydronephrosis and hydroureters. Computed tomography and ultrasound scans are usually unable to discriminate between cancer and soft tissue swelling, so are not routinely used in the investigation and staging of cervical cancer. Conversely, MRI is increasingly being used preoperatively for determining tumour size, degree of stromal penetration, parametrial extension and lymph node status.[17–19] MRI poses no radiation risk to the fetus and is particularly useful in determining the spread of disease in pregnant women diagnosed with cervical cancer.

Table 2. Lifetime risk of developing cervical cancer[15]

Country	Risk (%)
UK	1.3
Columbia	5.5
Spain	0.5
Israel	0.5

Management

The management of cervical cancer involves treating both the primary lesion and the potential sites of metastases. The options are:

- surgery
- radiotherapy
- chemotherapy
- a combination of two or more of the above.

In women selected for surgery, adjuvant radiotherapy increases the risk of complications so should be avoided if possible. Accurate staging should, therefore, be obtained before commencing definitive therapy. Surgery or radiotherapy may be used as the primary treatment or in combination, although definitive surgery is usually limited to women with early-stage cervical

Table 3. FIGO staging of cervical cancer[16]

Stage	Features
0	Carcinoma *in situ*, CIN 3
I	Cervical carcinoma confined to the cervix
1a	Microscopic lesion: measured stromal invasion with a maximum depth of 5 mm and a horizontal extension not more than 7 mm
1a1	Stromal invasion ≤3 mm, horizontal spread ≤7 mm
1a2	Stromal invasion 3–5 mm, horizontal spread ≤7 mm
1b	Preclinical lesions greater than Ia2 or visible clinical lesions confined to the cervix
1b1	Clinical lesions ≤4 cm
1b2	Clinical lesions >4 cm
II	Extension beyond cervix, but not to the pelvic side wall or the lower third of the vagina
IIa	Involvement of the upper two-thirds of the vagina
IIb	Parametrial extension but NOT reaching pelvic side wall
III	There is extension to pelvic side wall or lower one-third of the vagina
IIIa	Extension to the lower one-third of the vagina, without involvement of the pelvic side wall
IIIb	Tumour extends to pelvic side wall and/or causes hydronephrosis or non-functioning kidney
IV	Extension beyond true pelvis or involvement of mucosa of the bladder and/or rectum (biopsy proven). A bullous oedema does not permit a case to be allotted to stage IV
IVa	Adjacent organs involvement: bladder, rectum
IVb	Distant metastasis

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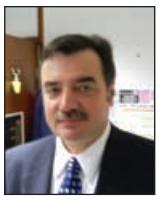

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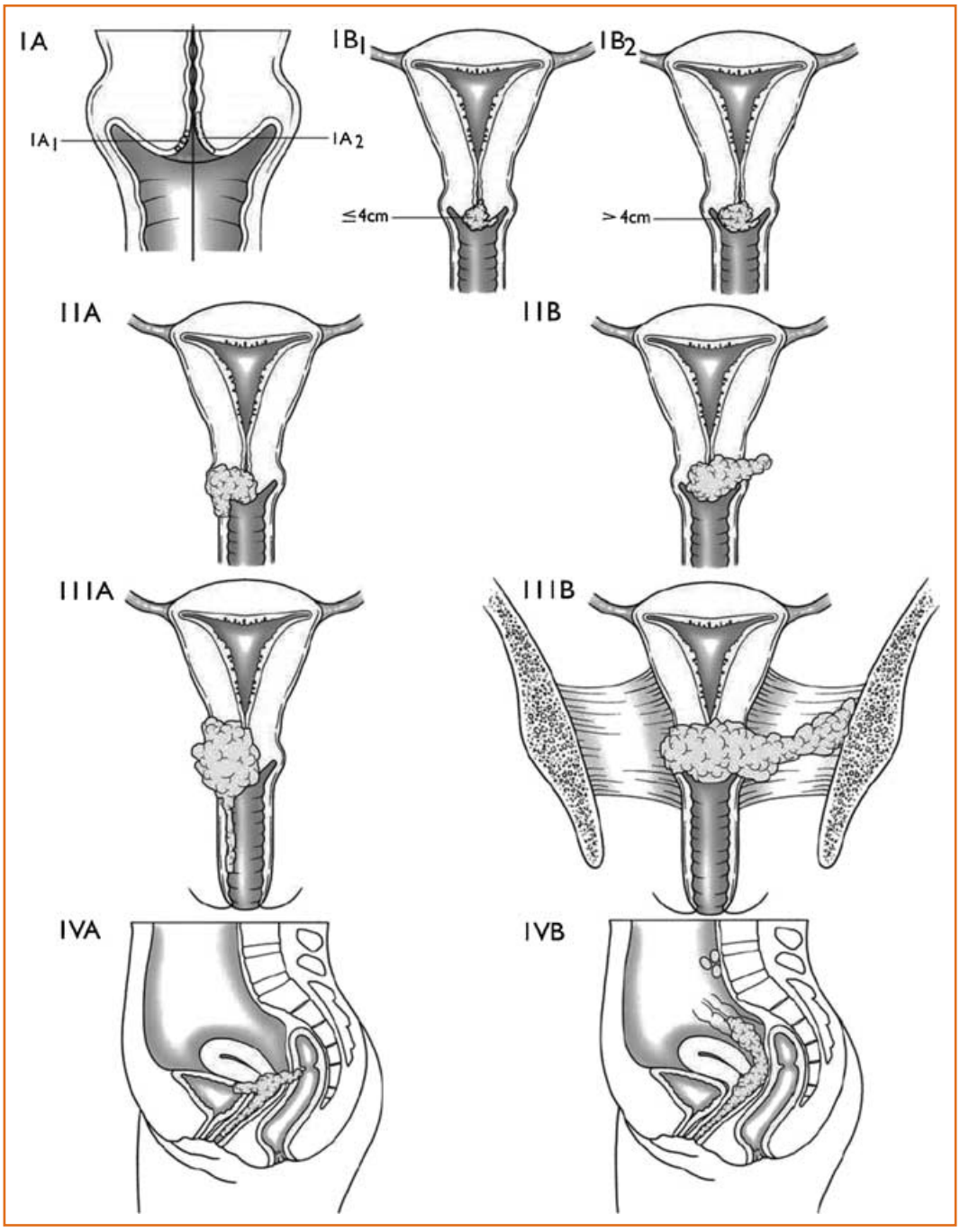


Figure 1. Carcinoma of the cervix uteri: staging cervical cancer (primary tumour and metastases); reproduced with permission from Benedet *et al*.[20]

cancer in whom radiotherapy may be avoided. Chemotherapy can be used concurrently with radiotherapy for cancer of the cervix. It has also been used prior to surgery or radiotherapy as neoadjuvant therapy, and after surgery or radiotherapy as adjuvant therapy.

Factors affecting the management strategy are: stage of the disease, age of the woman, her general condition and her past medical history. Tumour size and volume can be assessed accurately with MRI prior to treatment[17–19] and are important prognostic factors. The treatment modality should be decided after joint consultation with the clinical oncologist and discussion at the multidisciplinary meeting (consisting of the gynaecological oncologists, clinical oncologists, pathologists and radiologists). The treatment goal is either curative or palliative, depending on the

Table 4. Incidence of pelvic lymph node involvement with the stage of the disease[15]

Stage	Positive pelvic nodes (%)
Ia1	<1
Ia2	5
Ib	16
II	30
III	44
IV	55

Table 5. Overall 5-year survival by FIGO stage; reproduced with permission from Benedet *et al.*[20]

Stage	Overall survival (%) at 5 years
Ia1	98.7
Ia2	95.9
Ib1	88.0
Ib2	78.8
IIa	68.8
IIb	64.7
IIIa	40.4
IIIb	43.3
IVa	19.5
IVb	15.0

The overall 5-year survival for all the stages is 69.9%[20]

stage of the disease. Overall 5-year survival by FIGO stage[20] is shown in Table 5.

Stage Ia1 (cervical tumour invading to a depth of 3 mm or less, with horizontal spread not exceeding 7 mm)

The risk of lymph node spread is less than 1%.[21,22] The majority of these cases are usually diagnosed on cone biopsy of the cervix or, more commonly, following large loop excision of the transformation zone (LLETZ). If the excision margins are clear of the disease (and of CIN) no further treatment is necessary. On the other hand, if the excision margins are involved further LLETZ may be performed, or the woman may be offered a simple hysterectomy if she has completed her family. If simple hysterectomy is chosen, a repeat loop or cone biopsy should be performed before proceeding to surgery in order to exclude a more extensive, invasive disease (Figure 2). The significance of lymphovascular space invasion is not mentioned in the staging by FIGO, although it is a poor prognostic factor.[22] It is, therefore, difficult to say whether lymphovascular space invasion should be disregarded when planning treatment for stage Ia1 disease. It is also not known whether lymphovascular space invasion in stage Ia1 increases the risk of lymph node metastases.

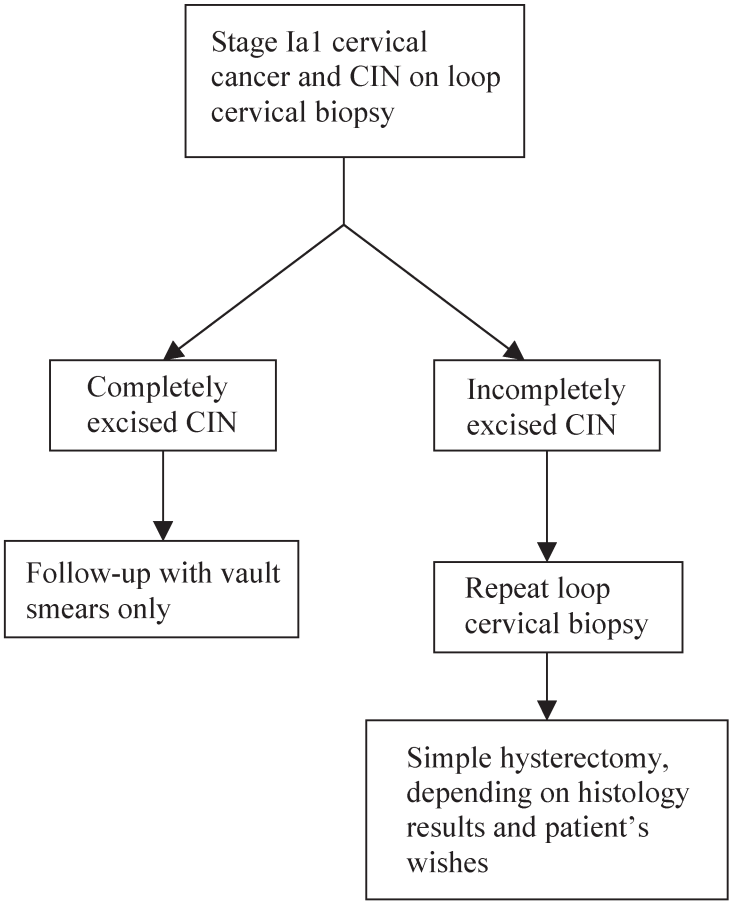
Stage Ia2 (cervical tumour invading to a depth greater than 3 mm, but less than 5 mm, with horizontal spread not exceeding 7 mm)

The risk of lymph node metastases is approximately 5%.[21] There is little evidence for the optimal management of stage Ia2 cervical cancer. Modified radical hysterectomy plus pelvic node dissection has been traditionally used but this is likely to have over-treated women. Conducting randomised controlled trials will be difficult because the number of treatment failures in stage Ia2 disease is small. A simple hysterectomy may be appropriate and even a LLETZ or cone biopsy may be suitable in carefully selected women who wish for more children. The recommended treatment in the USA for stage Ia2 cervical disease is modified radical hysterectomy and pelvic lymphadenectomy,[23] or cervical cone biopsy with extraperitoneal or laparoscopic pelvic lymphadenectomy (if a woman would like more children). Another treatment option for selected women with early-stage, low-volume disease who require fertility preservation is radical trachelectomy with reanastomosis of the vaginal and uterine isthmus and extraperitoneal or laparoscopic pelvic lymphadenectomy.[24] Subsequent mode of delivery will be by elective caesarean section. The treatment for women who are medically unfit should be intracavitary radiotherapy plus external beam radiotherapy.

Stages Ib1–IIa (lesions greater than Ia2 and/or lesions involving the upper vagina)

Stage Ib1 cervical disease is the ideal stage for radical hysterectomy and pelvic lymphadenectomy,

Figure 2. Suggested algorithm for the management of stage Ia1 cervical cancer diagnosed on loop cervical biopsy of the cervix



This algorithm assumes that the invasive focus has been excised at large loop excision of the transformation zone (LLETZ) during colposcopy

although a similar cure rate can be achieved using primary radiotherapy.[25] Surgery is preferable for young women, with the advantages of possible ovarian conservation and preservation of sexual function. Radiotherapy is associated with the increased risk of radiotherapy-induced menopause (radiation effects on the ovaries), vaginal stenosis and the late complication of radiation-induced carcinogenesis. The other potential adverse effects of radiotherapy are cystitis and proctitis, which are both unpleasant and distressing for the woman.

Stages IIb–IVa (parametrial extension up to lesions involving adjacent organs such as the bladder and the rectum)

Radical external beam radiotherapy and concurrent chemotherapy (cisplatin) plus brachytherapy is the core treatment in women with this advanced disease.[26,27] The combination of cisplatin and 5-fluorouracil has also been used as concurrent chemotherapy. They are both radiosensitisers and are associated with reduced disease progression and a longer period of disease remission.[25,28] Cisplatin alone is more effective and more tolerable than the combination of cisplatin and 5-fluorouracil and is also associated with improved disease recurrence-free interval.[28,29]

Stage IVb cervical cancer (distant metastasis)

There is no standard therapy and treatment is mainly palliative with a multidisciplinary approach, including a palliative care team, gynaecological surgeons, oncologists, nurse specialists and occupational therapists. Optimal pain control should be readily achievable. Palliative doses of radiotherapy should be given to achieve reasonable bleeding control if this becomes a major issue.

Recurrent cervical cancer

Management is multidisciplinary and depends on the mode of primary therapy, type of recurrence and the woman's fitness. If there is local pelvic recurrence following primary treatment with radiotherapy, the woman may be suitable for exenterative pelvic surgery. With a central recurrence, exenterative surgery in carefully selected women could give a 5-year survival of 40–60%.[27,30] If there is recurrence after surgery, the usual treatment is radiotherapy with or without platinum-based chemotherapy. The role of chemotherapy is mainly for palliation to relieve symptoms as well as to prolong survival.[31]

Radical hysterectomy and exenterative surgery involving partial resection of the bowel, bladder and/or ureter may be performed in carefully selected women with persistent disease following primary radiotherapy.[32] The morbidity from such extensive surgery is high and few women are suitable for this procedure; however, some may be cured and thus have a good quality of life.

Management of cervical adenocarcinoma

The management strategies for both invasive squamous carcinoma and invasive adenocarcinoma of the cervix are essentially the same stage-for-stage. The incidence of invasive adenocarcinoma of the cervix is probably as high as 20%.[33,34] HPV is frequently associated with adenocarcinoma and, unlike squamous carcinoma, is less related to sexual, reproductive or socioeconomic factors.[35] A 1997 study showed that outcomes of surgery and radiotherapy for stages Ib to IIa cervical cancer (for both squamous carcinoma and adenocarcinoma) were the same in terms of the 5-year survival and disease-free intervals.[25]

Cervical cancer in pregnancy

The incidence of cervical cancer is 1.2 per 10 000 pregnancies.[36] It presents with vaginal bleeding (unrelated to the pregnancy), postcoital bleeding, abnormal vaginal discharge and, rarely, pelvic pain. A significant proportion of cases (approximately 20%) may be asymptomatic.[33,36] If invasive cervical cancer is suspected, a biopsy should be arranged. This should be under general anaesthesia because the cervix is highly vascular during pregnancy and there is a risk of severe haemorrhage.

Cervical cancer staging in pregnancy is always a problem, firstly because of the desire to protect the fetus until viability, and secondly because the oedematous and softening nature of the cervix and pelvic connective tissue makes clinical assessment of the parametria difficult. Colposcopic examination of the cervix is safe during pregnancy, as is MRI. MRI can be used to assess the volume of the disease as well as parametrial spread and lymph node metastases.[37]

Management

The management is the same, stage-for-stage, as for nonpregnant women, although fetal viability is usually an issue. Overall, the prognostic outcome for all stages of the disease is also similar to that for the nonpregnant woman. Management

decisions should be made at a multidisciplinary meeting and discussed with the woman and her partner. The risks involved in prolonging the pregnancy once a diagnosis of invasive cervical cancer has been made should be considered. The general rule is to proceed with treatment without delay if a diagnosis is made before 20 completed weeks of gestation. After 30 weeks, fetal viability may be awaited for a further 2–4 weeks before proceeding with treatment. The dilemma occurs when a diagnosis is made between 20–30 weeks of gestation. There does, however, seem to be a worsening prognosis for women with small stage Ib disease if treatment is delayed to promote fetal viability.[38] Antenatal corticosteroids should be given to promote fetal lung maturity.

In early-stage disease, surgical management is usually chosen. If the fetus is viable, a classical caesarean section can be performed followed by radical hysterectomy and pelvic lymphadenectomy. In advanced-stage disease, where there may be increased risk of severe haemorrhage from the cervix if vaginal delivery is allowed, caesarean section followed by chemoradiotherapy may be the management of choice. Radiotherapy will result in miscarriage if used as the primary mode of treatment in the first trimester (usually after 3–5 weeks). In the second trimester, the pregnancy may be terminated either by medical or surgical methods (depending on the woman's wishes) before radiotherapy is given.

New surgical advances

Radical trachelectomy and Saling procedure

Radical trachelectomy was first developed by Dargent as a modification of the radical vaginal hysterectomy, which was devised by Schauta.[39] It involves removing the cervix, parametria and a cuff of the vagina. Thus, the body of the uterus is preserved for fertility. The procedure is combined with either extraperitoneal or laparoscopic pelvic lymphadenectomy.

Radical trachelectomy is only appropriate for selected women with early-stage cervical cancer (stage Ib1 or less) without vascular space invasion and low-volume disease (confined to the cervix) wishing to preserve their fertility. Compared with radical hysterectomy, the other advantages are reduced blood loss and blood transfusion rate and a shorter hospital stay. Proper and adequate training is required before the procedure can be competently undertaken. The pregnancy rate has been quoted as high as 37% within 1 year of trying to conceive and most women are able to achieve spontaneous conception.[40] Delivery is by elective lower segment caesarean section.

The Saling procedure, performed at the time of radical trachelectomy, may prevent second-trimester miscarriage and prematurity because of cervical weakness.[41] This procedure may also be performed at 12–14 weeks of gestation under general or regional anaesthesia. The vaginal tissue around the cervical os is infiltrated with normal saline, to separate the mucosa and underlying muscle layers. The paravaginal mucosa immediately around the cervix is excised circumferentially to a width of approximately 1.5 cm. This area is then closed with a resorbable monofilament suture in two layers; the deeper layer includes the cervical stroma, while the superficial layer includes the vaginal mucosa. This technique closes the cervical os completely and delivery is performed by elective caesarean section.

Sentinel lymph node

The sentinel lymph node is the first node that drains a primary tumour.[42] Lymphatic drainage occurs in a stepwise fashion. The sentinel lymph node would, therefore, reflect the pathological status of the remaining lymph nodes in the lymphatic basin.[42,43] sentinel lymph node identification in the staging and conservative management of certain malignancies, such as breast cancer, melanoma and vulval cancers, has attracted much interest as a new management tool.[44–46] The sentinel lymph node identification procedure limits the extent of surgical lymph node dissection and thus may help to reduce operative mortality and morbidity.[47] Most women (approximately 85%) have a single sentinel lymph node, but 15% have two or more.[42,43] Effort has focused on implementing less aggressive interventions in gynaecological malignancies in order to reduce extensive radical procedures and reduce morbidity, but little work has been done about lymphatic mapping for cervical cancer.

The future

Combined gene immunotherapy and radiotherapy in locally advanced cancers has a viable future in the management of cervical cancer.[48] The relative ease of access of cervical tumours makes it possible for the direct injection of DNA–liposomal complexes and human leucocyte

antigen. This may promote a favourable cytotoxic immune response, with the potential benefit of reducing the incidence of local and distant recurrence. Gene therapy in cervical cancer is still in the early stage of clinical trial. A randomised controlled trial that compares conventional therapy with immunotherapy in conjunction with conventional therapy, and their effects on the prevention of metastatic spread and disease relapse, is warranted. ■

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