Diagnosis and management of cervical cancer

Patrick Petignat,[1] Michel Roy[2]

[1]Senology and Gynaecological Oncology Unit, Geneva University Hospitals, 1211 Geneva 14, Switzerland

[2]Gynaecologic Oncology Service, CHUQ, Laval University, Quebec, Canada

Correspondence to: P Petignat
patrick.petignat@hcuge.ch

BMJ 2007;335:765-8
doi:10.1136/bmj.39337.615197.80

Cervical cancer is the second most common cancer in women worldwide, with more than half a million new cases diagnosed in 2005.[1] The disease disproportionately affects the poorest regions—more than 80% of cases are found in developing nations, mainly in Latin America, sub-Saharan Africa, and the Indian subcontinent.[1] Cervical cancer is an important cause of early loss of life as it affects relatively young women. Important advances have taken place in the diagnosis and treatment of this cancer in recent years. Surgery or chemoradiotherapy can cure 80-95% of women with early stage disease (stages I and II) and 60% with stage III disease (table).[2-5]

Sources and selection criteria

We searched the literature to identify all relevant articles published from 1966 to March 2007 (PubMed and Cochrane database) using a combination of the terms "cervical cancer", "diagnosis", and "management". Variables of interest were cervical cancer, surgery, chemotherapy, radiotherapy, chemoradiotherapy, complications of treatment, recurrence, and follow-up. Much of the clinical management discussed in this review was based on meta-analyses, systematic reviews, and phase III randomised controlled trials (RCTs).

What causes cervical cancer?

Infection with high risk types of human papillomavirus is the main cause of cervical cancer.[6] This has obvious implications for primary prevention (vaccination) and secondary prevention (screening) of this disease.

How does cervical cancer spread and what are the symptoms?

Cervical cancer usually originates in the transformation zone of the cervix, and spreads to regional lymph nodes. Parametrial invasion is also common. Clinical presentation depends mainly on the location and extent of disease. Precancerous changes or very early stage disease are usually asymptomatic and are detected on a cervical smear. Symptoms usually appear when the tumour causes spontaneous or contact bleeding, or pain if lymph nodes are involved. Other symptoms include serosanguineous foul smelling vaginal discharge or backache.

How is cervical cancer diagnosed?

When a lesion is visible with the naked eye, conisation is contraindicated, and a cervical biopsy will usually provide the diagnosis. Conisation is indicated when frank invasion cannot be ruled out by a colposcopically directed biopsy, or when colposcopy is unsatisfactory and the results of a smear test show a high grade lesion.

Pathology

Squamous cell carcinoma accounts for about two thirds of all cervical cancers. Adenocarcinoma has many histological variations and is found in 15-25% of cases. Unusual histological variants include clear cell carcinoma, neuroendocrine carcinoma, and adenosquamous carcinoma. Tumour grade (well differentiated, moderately differentiated, and poorly differentiated), depth and width of invasion, and presence (or absence) of invasion of lymphovascular space are prognostic factors that should be adequately assessed.

Cervical cancer is a clinically staged disease

The International Federation of Gynaecology and Obstetrics (FIGO) staging system is the most commonly used (table).[7] It takes into account the results of the physical examination, colposcopy, histopathology (cervical biopsy or conisation), radiography (for example, chest radiography, intravenous pyelography, and barium enema), and endoscopy (for example, cystoscopy or sigmoidoscopy). Suspected invasion of the bladder or the rectum should be confirmed by biopsy.

Current controversies in cervical cancer

Should information obtained from imaging or surgical investigations (or both) be included in a new FIGO classification? Would this improve survival?

Can we safely omit full pelvic dissection in patients with stage IA2-IB1 disease who have a negative sentinel lymph node biopsy result?

Does neoadjuvant chemotherapy have a role in the treatment of this disease?

Are the benefits and effects on long term prognosis equal for laparoscopy and laparotomy?

What is the value of imaging techniques?

Computed tomography or magnetic resonance imaging is often used to define lymph nodes status and to assess the extent of local disease.[8] Because they rely on size and morphological criteria to recognise lymph node metastases, it is difficult to identify normal sized nodal metastases using these methods. A recent prospective study with histopathological results as a reference found that combined positron emission tomography and computed tomography may be useful for detecting smaller nodal metastases.[9]

What is the value of surgical staging?

Surgical staging includes pelvic lymphadenectomy and para-aortic lymphadenectomy. Many investigators have reported excellent results after surgical staging, but the only RCT found no survival advantage of surgical staging over clinical staging.[10] A non-randomised comparison of extraperitoneal and transperitoneal surgical staging found that both techniques had similar accuracy and surgical complications, but a lower rate of enteric complications after irradiation was noted with the extraperitoneal approach.[11] Laparoscopic extraperitoneal approaches may take advantage of both laparoscopy and retroperitoneal dissection.[12] Compared with FIGO clinical staging, surgical staging improved the accuracy of diagnosis in 24% of stage IB tumours, 52% of stage II tumours, and 45% of stage IIIB tumours.[13]

Is clinical staging still the gold standard?

Evidence now shows that computed tomography, magnetic resonance imaging, positron emission tomography, and surgical staging are better than clinical staging for identifying the true extent of the disease. However, none of these methods has been incorporated into the FIGO staging system yet. The main reason is that cervical cancer is most prevalent in developing countries, and staging methods should be universally available, standardised, and comparable around the world. There is also still a lack of consensus about the best imaging modality and the value of surgical staging. Future FIGO staging systems may consider incorporating some of these investigations into the classification.[14]

International Federation of Gynaecology and Obstetrics (FIGO) staging classification (FIGO 1995, Montreal): cervical carcinoma[7]

Stage	Details
0	Carcinoma in situ
IA1	Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal
	invasion ≤3 mm in depth and ≤7 mm in horizontal spread
IA2	Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal
	invasion >3 mm and ≤5 mm in depth and ≤7 mm in horizontal spread
IB1	Invasive carcinoma, confined to cervix, microscopic lesion >IA2 or clinically visible lesion ≤4 cm in greatest dimension
IB2	Invasive carcinoma, confined to cervix, clinically visible lesion >4 cm in greatest dimension
IIA	Tumour extension beyond cervix to vagina but not to lower third of vagina. No parametrial invasion
IIB	Tumour extension beyond cervix. Parametrial invasion but not to pelvic side wall and not to lower third of vagina
IIIA	Tumour extension to lower third of vagina but not to pelvic side wall
IIIB	Tumour extension to pelvic side wall or causing hydronephrosis or non-functioning kidney
IVA	Tumour invasion into bladder or rectum
IVB	Distant metastasis

Managing early stage disease

FIGO stage IA1

Patients with stage IA1 disease should be diagnosed on the basis of conisation using a technique that does not result in cauterised margins, which may obscure surgical margins. If the lymphovascular space is not involved, these patients have less than a 1% risk of lymph node spread. These women can be treated conservatively by simple hysterectomy or by conisation, if they wish to preserve fertility.[15] The importance of involvement of the lymphovascular space in stage IA1 disease is not clear, but most practitioners favour radical surgery or radiation if it is present.

FIGO stage IA2, IB1, and IIA (figure)

Radical hysterectomy is the treatment of choice for young healthy patients because it preserves ovarian function. Radiotherapy is thought to be equally effective for patients with early stage disease. An RCT comparing primary surgery with primary radiotherapy in 347 patients with stage IB-IIA cervical cancer showed that disease free and overall survival for the two groups were the same.[2]

Is fertility sparing surgery an option?

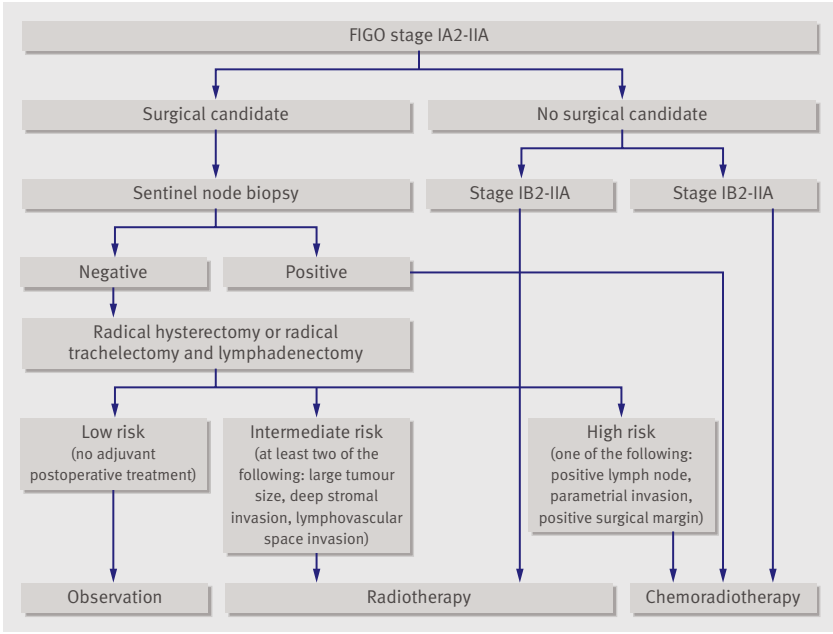
Radical trachelectomy involves removal of the cervix with parametrial tissue after pelvic lymphadenectomy. It is a curative procedure designed to retain fertility in young women with early stage cervical cancer. About 50% of women with cervical carcinoma are under 40 and may be eligible for this treatment.[16] To date, more than 350 cases have been reported. Cure rates are comparable to radical hysterectomy, and women who later try to conceive have more than 50% chance of pregnancy.[17] Radical trachelectomy is emerging as an acceptable alternative for patients with early stage cervical cancer who wish to preserve fertility.

What is the role of sentinel lymph node biopsy in cervical cancer?

The goals of sentinel lymph node mapping are to avoid complete pelvic lymphadenectomy and to identify alternative lymphatic drainage sites. Preliminary results of observational studies have shown that when a sentinel lymph node is metastatic on frozen section, radical surgery can be omitted in favour of radiochemotherapy.[18] Whether full pelvic lymphadenectomy can safely be omitted after a negative sentinel lymph node biopsy is still unclear.

FIGO stage IB2 (figure)

Patients with stage IB2 disease (tumour >4 cm) are poor candidates for primary radical surgery because most will ultimately need adjuvant radiotherapy. Chemoradiotherapy is the treatment of choice. An RCT showed that adding weekly cisplatin to pelvic radiotherapy before hysterectomy reduced the risk of



Algorithm for the treatment of early stage cervical cancer

recurrence of disease and death in women with stage IB2 cervical cancer compared with radiotherapy and hysterectomy alone.[19]

When should adjuvant radiotherapy be added?

Patients with early stage disease have an intermediate risk of recurrence postoperatively if they have two of the following factors: large tumour size, deep stromal invasion, or involvement of the lymphovascular space. An RCT evaluating 277 women with stage IB disease (radiotherapy versus "no further treatment") and at least two risk factors showed that adjuvant radiotherapy decreased the rate of recurrence and improved disease free survival. However, the two groups showed no overall difference in survival.[20] Therefore, despite the positive findings, options regarding adjuvant radiotherapy for surgical patients with selected risk factors remain debatable.

When should chemoradiotherapy be added?

Patients with early stage disease have a high risk of recurrence postoperatively if they have one of the following risk factors: positive nodes, parametrial invasion, or positive surgical margins. Such patients should receive adjuvant cisplatin based chemoradiotherapy after hysterectomy, as shown by an RCT.[21]

ONGOING RESEARCH PRIORITIES

To determine strategies for successfully implementing vaccination, including low cost vaccines for countries in the developing world

To identify which resources most effectively fill healthcare needs in low resource settings, where patients often have more advanced disease at diagnosis

To develop and evaluate therapeutic vaccines to cure precancerous lesions or achieve remission of advanced cervical cancer, or both

To develop and test antiangiogenic agents for patients with metastatic disease

Managing advanced stage disease

FIGO stage IIB, III, and IVA

Three RCTs have shown that improvements in progression free survival and overall survival are greater for chemoradiotherapy than for radiation alone in patients with locally advanced stage IIB-IVA disease.[3 4 22] Benefits have been confirmed by a Cochrane review.[5] Platinum based chemoradiotherapy is now the standard of care for these patients. The role of neoadjuvant chemotherapy followed by radical surgery is currently being studied by the European Organisation for Research and Treatment of Cancer.

FIGO stage IVB

Treatment is only palliative in patients with stage IVB disease, so quality of life and toxicity profiles must influence the choice of treatment. The only RCT to identify a chemotherapy regimen that gave these patients an overall survival advantage and that included quality of life measurements compared cisplatin with cisplatin plus topetecan.[23] Progression free survival and overall survival favoured combination chemotherapy, but toxicity was more common, although it did not significantly reduce quality of life.[23]

Follow-up

The aim of follow-up is to detect relapse at a stage where salvage treatment has the best chance of being effective and to monitor and treat treatment related toxicity. Most recurrences occur in the first two years after primary treatment. Physical examination includes rectovaginal examination, nodal assessment (especially supraclavicular), and cervical smears. Examinations should be performed every three to four months in the first three years.[24] Thereafter, they should be performed every six months and after five years annually. Pain, vaginal bleeding, and gastrointestinal or genitourinary dysfunction must be investigated.

Treating recurrent disease

Recurrent cervical cancer is almost always incurable and less than 5% of patients who develop recurrence are alive at five years. Patients who develop pelvic recurrence after radical hysterectomy may be salvaged with chemoradiotherapy if they have not previously been irradiated.[25] Central pelvic recurrences after radiation or chemoradiotherapy may undergo curative surgery with pelvic exenteration in the absence of metastatic disease.[25]

Conclusions

Over the past few years, in most industrialised countries women with cervical cancer have benefited from improved imaging techniques, better treatments (including chemoradiotherapy), and more conservative surgical approaches. In low resource settings—where facilities for radiology, chemoradiotherapy, and supportive care are limited or unavailable—it is

ADDITIONAL EDUCATIONAL RESOURCES

Information resources for healthcare professionals

American Cancer Society—Nationwide community based voluntary health organisation dedicated to eliminate cancer through research, education, and service (www.cancer.org)

National Cancer Institute—US federally funded research and development centre (www.cancer.gov/cancerinfo/types/cervical)

World Health Organization—Agency of the United Nation coordinating authority on international public health (www.who.int/reproductive-health/publications/cervical_cancer_gep/)

International Agency for Research on Cancer—Intergovernmental agency forming part of the World Health Organization (http://screening.iarc.fr/cervicalindex.php)

BMJ Clinical Evidence—International source of the best available evidence on the effects of common clinical interventions (www.clinicalevidence.com/ceweb/conditions/woh/0818/0818-get.pdf)

Information resources for patients

Gynecologic Cancer Foundation National Cervical Cancer Campaign—This campaign aims to eliminate cervical cancer through increased education, outreach, and enhanced communication between women and their healthcare providers (www.cervicalcancercampaign.org/)

National Women's Health Resource Center—Independent health information source for women (www.healthywomen.org/)

CancerHelp UK—Information service about cancer and cancer care for people with cancer and their families (www.cancerhelp.org.uk)

National Cervical Cancer Coalition—Non-profit organisation dedicated to serving women with or at risk of cervical cancer and human papillomavirus infection (www.nccc-online.org)

important to identify which resources fill healthcare needs most effectively and to consider alternative approaches. In the near future, the best way to improve mortality and morbidity from cervical cancer will probably be to focus on primary prevention with prophylactic vaccines against human papillomavirus.

We thank Martin Tramer for his constructive comments.

Contributors: This paper was jointly written by PP and MR. PP is guarantor.
Funding: No external funding.
Competing interests: None declared.
Provenance and peer review: Commissioned; externally peer reviewed.

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SUMMARY POINTS

Cervical cancer disproportionately affects women in developing countries, which have no effective screening systems

Cervical biopsy is the most important investigation in diagnosing cervical cancer

Cervical cancer is a clinically staged disease

Fertility sparing surgery (conisation or radical trachelectomy (excision of the cervix)) is an option for women with early stage disease

Chemoradiotherapy is the standard of care for locally advanced and early stage cancers with poor prognostic factors

Chemotherapy is palliative only in patients with recurrent or metastatic disease

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