Cervical cancer and HPV - Management

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What are the clinical features that are suspicious of cervical cancer?

Many women with cervical cancer will be asymptomatic and are diagnosed through the NHS Cervical Screening Programme because of abnormal cervical cytology, and subsequent colposcopy and biopsy. For more information, see the CKS topic on Cervical screening.

- Consider the possibility of cervical cancer in a woman who has any of the following nonspecific symptoms:
  - Intermenstrual bleeding.
  - Postcoital bleeding (risk of cervical cancer increases with age).
  - Postmenopausal bleeding.
  - Blood-stained vaginal discharge.
  - Pelvic pain/dyspareunia.
- Rarely, women may present with advanced cancer with such symptoms as pelvic discomfort or pain, renal failure, leakage of urine or faeces from a fistula, lymphoedema, or severe haemorrhage.
- On examination:
  - The cervix may appear inflamed or friable and bleed on contact (although the most likely cause for this will be *Chlamydia trachomatis*; see Differential diagnosis).
  - There may be a visible ulcerating or fungating lesion or a foul-smelling serosanguineous vaginal discharge.

Basis for recommendation

Nonspecific symptoms

- Information on the clinical features of cervical cancer is based on expert opinion in guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008], a clinical review [Blomfield, 2007], and a systematic review on post-coital bleeding [Shapley et al, 2006].

- Studies have shown that 16–32% of women with early-stage cervical cancer have symptoms at presentation [SIGN, 2008].

- However, symptoms of cervical cancer are non-specific. For example, the prevalence of post-coital bleeding in the community is 0.7–0.9% [SIGN, 2008]. A systematic review included 16 studies of women with cervical cancer and found that the prevalence of post-coital bleeding varies between 0.7% and 39% [Shapley et al, 2006].

  - It is not known how many women with post-coital bleeding in the community who present to primary care are referred to secondary care [Shapley et al, 2006].

  - On average, only 2% of women seen in secondary care with post-coital bleeding have cervical cancer. The likelihood that a woman in the community with post-coital bleeding has cervical cancer is [SIGN, 2008]:

  - 1 in 44,000 if 20–24 years of age.

  - 1 in 56,000 if 25–34 years of age.

  - 1 in 2800 if 35–44 years of age.

  - 1 in 2400 if 45–54 years of age.

Signs

- Information on clinical signs is based on expert opinion in guidelines from SIGN [SIGN, 2008] and clinical reviews [Blomfield, 2007; Petignat and Roy, 2007].

- Large tumours may become infected and produce an offensive serous discharge [Blomfield, 2007].

Advanced cancer

- The description of symptoms of advanced cancer is based on expert opinion in guidelines from SIGN [SIGN, 2008] and a clinical review [Blomfield, 2007].

Should I take a cervical cytology sample?

- **Unscheduled cervical screening is not recommended** in any situation, including when the woman has symptoms of possible gynaecological cancer. Urgent referral and assessment of the cervix is required.

  - If a cervical cytology sample is taken:

  - Referral should not be delayed until results are available.

  - A negative test result should not be considered definitive and the results should not be relied upon in any circumstances.

- For information on scheduled screening through the NHS cervical screening programme, see the CKS topic on Cervical screening.

Basis for recommendation

This recommendation is based on expert consensus in the *Colposcopy and programme management: guidelines for the NHS cervical screening programme* [NHS Cancer Screening Programmes, 2010] and referral guidelines for suspected cancer from the National Institute for Health and Clinical Excellence (NICE) [National Collaborating Centre for Primary Care, 2005].

- An unscheduled cervical sample is also not recommended by the Scottish Intercollegiate Guidelines Network [SIGN, 2008].

What other causes of non-specific symptoms should I consider?

Consider the following causes of non-specific symptoms:

- **Sexually transmitted infections.** Cervicitis or pelvic inflammatory disease may present with vaginal discharge associated with post-coital or intermenstrual bleeding, dysuria, deep dyspareunia, or lower abdominal pain. It is most commonly caused by *Chlamydia trachomatis*, and less commonly by *Gonorrhoeae neisseria*.

  - Cervicitis caused by chlamydia (or less commonly by gonorrhoea) is characterized by an inflamed cervix which bleeds easily and may be associated with a mucopurulent discharge.

- Pelvic inflammatory disease caused by chlamydia (or less commonly by gonorrhoea) is characterized by lower abdominal pain, with or without fever. Cervicitis may be seen, and adnexal tenderness and cervical excitation found on bimanual palpation.

- For further information on the diagnosis, investigation, and management of sexually transmitted infections, see the CKS topics on Chlamydia - uncomplicated genital, Gonorrhoea, Pelvic inflammatory disease and Vaginal discharge.

- **Endometrial cancer** may present with postmenopausal bleeding.

- **An ectropion or cervical polyps** may cause post-coital bleeding.

- **Hormonal contraception** may cause unscheduled bleeding, particularly when first prescribed.

- Unscheduled bleeding is common with *all* forms of hormonal contraception during the first 3 months of use.

- Notable bleeding is also common in the first 6 months of use with the levonorgestrel-releasing intrauterine system (LNG-IUS) or progestogen-only implants.

Basis for recommendation

Clinical features of differential diagnoses

- Information on the clinical differential diagnosis of cervical cancer is based on guidelines published by the Health Protection Agency (HPA) [HPA, 2007], the Faculty of Sexual and Reproductive Healthcare (FSRH, formerly the Faculty of Family Planning and Reproductive Healthcare [FFPRHC]), the British Association for Sexual Health and HIV [FFPRHC and BASHH, 2006], the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008], and a systematic review that found post-coital bleeding may be associated with a cervical ectropion or a cervical polyp [Shapley et al, 2006].

Hormonal contraception

- This information on hormonal contraception and intermenstrual bleeding is based on expert advice in guidelines published by the Faculty of Sexual and Reproductive Healthcare Clinical

Effectiveness Unit, in collaboration with the Royal College of Obstetricians and Gynaecologists [FSRH and RCOG, 2009].

Who should I refer on suspicion of cervical cancer?

Where appropriate, exclude other diagnoses that may cause non-specific symptoms that may be presenting features of cervical cancer, for example hormonal contraception or sexually transmitted infection (see Differential diagnosis). Always consider the need for a pregnancy test.

- Refer for *fast-track colposcopy* all women in whom there appears to be a visible suspicion of cervical cancer, or an abnormal cervical cytology sample. Do *not* delay referral because of a previously negative cervical cytology result.

- Refer *urgently* to gynaecology (within 2 weeks) postmenopausal women who:

  - Have *not* received hormonal replacement therapy and have vaginal bleeding.

  - Have persistent or unexplained vaginal bleeding after cessation of hormone replacement therapy for 6 weeks.

- Refer to gynaecology or genitourinary medicine clinic, premenopausal women who have:

  - Persistent intermenstrual bleeding, post-coital bleeding, or blood-stained vaginal discharge, *and*

  - Infection has been excluded *or* infection had been treated, but the bleeding has continued for 6–8 weeks post treatment.

  - Polyp, ectropion, cervicitis, or warts.

  - Consider urgent referral (within 2 weeks) for women with persistent intermenstrual bleeding and a negative pelvic examination.

- Hormonal contraception commonly causes unscheduled bleeding, and clinical judgement is necessary. Always exclude infection. Consider referral to a gynaecologist (within 2 weeks) if there are features in the history that raise the possibility of cervical cancer:

  - The woman has not participated in the national cervical screening programme.

- Bleeding continues beyond 3 months (6 months may be acceptable if the woman is using the levonorgestrel-releasing intrauterine system [LNG-IUS] or progestogen-only implants).

- The woman has new symptoms or a changed bleeding pattern.

- The woman has tried contraceptive modification but unscheduled bleeding persists.

Basis for recommendation

Pregnancy exclusion

- This recommendation to rule out pregnancy is based on expert advice from guidelines published by the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit in collaboration with the Royal College of Obstetricians and Gynaecologists [FSRH and RCOG, 2009].

Referral for signs of cervical cancer

- The National Institute for Health and Clinical Excellence (NICE) advises urgent referral for all women in whom examination of the cervix raises the suspicion of cervical cancer [NICE, 2005].

Referral for postmenopausal bleeding

- Both guidelines from NICE [NICE, 2005] and from the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008] advise urgent referral for all women with postmenopausal bleeding. NICE adds that if a woman on hormone replacement therapy still has bleeding after cessation of hormone replacement therapy for 6 weeks, an urgent referral should be made [NICE, 2005].

Referral for post-coital bleeding, intermenstrual bleeding, and blood-stained vaginal discharge

- These referral recommendations are based on guidelines from SIGN [SIGN, 2008] and guidelines on the *Clinical practice guidance for the assessment of young women aged 20-24 with abnormal vaginal bleeding* developed by a working subgroup of the Advisory Committee on Cervical Screening and published by the Department of Health [DH, 2010].

- The scope of the guidelines from SIGN is for women of all ages, whereas the Department of Health guidelines are focussed on younger women who are not yet eligible for cervical screening. Although SIGN did not discuss intermenstrual bleeding, its recommendations do not contradict the Department of Health guidelines; therefore CKS have extrapolated the recommendations from the Department of Health to all women [DH, 2010].

- Neither guidelines discuss the management of blood-stained vaginal discharge. However, CKS considers this symptom should be managed as for intermenstrual bleeding.

- NICE also advises considering urgent referral for all women with persistent intermenstrual bleeding and a negative pelvic examination [NICE, 2005].

Excluding infection

- Guidelines on the *Clinical practice guidance for the assessment of young women ages 20–24 with abnormal vaginal bleeding* developed by a working subgroup of the Advisory Committee on Cervical Screening and published by the Department of Health [DH, 2010] recommend taking swabs or for sexually transmitted infection or referring to a genito-urinary medicine clinic all women 20–24 years of age with post-coital bleeding, and referring them to gynaecology or genito-urinary medicine if the bleeding persists for 6–8 weeks after treatment.

- Guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008] recommend testing all premenopausal women for *Chlamydia trachomatis*.

Referral for cervical ectropion or cervical polyps

- Referral recommendations are based on guidelines published by the Department of Health [DH, 2010]. Although post-coital bleeding is often attributed to the existence of a cervical ectropion or cervical polyps, a systematic review found little evidence for this [Shapley et al, 2006]. The review reported:

- A cross-sectional study that included 151 women with a large cervical ectropion found that only 5% reported post-coital bleeding [Goldacre et al, 1978]. The author commented that a cervical erosion should not be assumed to be the cause of post-coital bleeding.

- Two studies found an association between post-coital bleeding and cervical polyps:

- One study of 134 women with post-coital bleeding found that 5% had a cervical polyp [Rosenthal et al, 2001].

- Another study of 248 women with post-coital bleeding found that 13% had a cervical polyp [Selo-Ojeme et al, 2004].

- However, the authors commented that these studies lacked controls and suffered from selection bias.

- CKS has therefore advised referral to a gynaecologist for management of these conditions and exclusion of another underlying cause (including cervical cancer).

Women taking hormonal contraception

- Recommendations for considering referral in women receiving hormonal contraception is based on expert opinion from guidelines published by the Department of Health [DH, 2010] and guidelines from the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit in collaboration with the Royal College of Obstetricians and Gynaecologists [FSRH and RCOG, 2009].

Cervical cancer and HPV - Management

View full scenario

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How can cervical cancer be prevented?

- Where appropriate, encourage women to:

- Participate in the NHS cervical screening programme — available to women 25–64 years of age in England. See the CKS topic on Cervical screening.

- Receive immunization with the human papillomavirus (HPV) vaccine — available as Cervarix® (bivalent vaccines, part of the Childhood Immunisation Programme) or Gardasil® (quadrivalent vaccine, available on private prescription).

- For optimum effectiveness, the HPV vaccination must be given before the woman becomes sexually active.

- For more information, see the section on Immunization schedule in the CKS topic on Immunizations - childhood.

▪ Inform women about practising safe sex and the use of condoms. Explain that:

- Condom use may lower the risk of HPV, but does not offer full protection, as HPV can infect areas not covered by a condom.

- Condoms also protect against other sexually transmitted diseases, which are a risk factor for progression of cervical cancer (for example HIV).

- Limiting the number of sexual partners reduces potential exposure to HPV infection.

▪ Screening for HPV is not currently used in routine practice.

Basis for recommendation

Human papillomavirus (HPV) immunization

▪ Human papillomavirus vaccines are intended to be prophylactic, not therapeutic. Protection rates are lower in women who have already been infected with the vaccine-related genotypes [WHO, 2007]. It is therefore important to vaccinate girls before they become sexually active [DTB, 2008]. The National Childhood Immunization Programme offers immunization for girls of 12–13 years of age [DTB, 2008].

▪ Controlled trials have indicated that the two vaccines currently available (Cervarix® [bivalent] and Gardasil® [quadrivalent]) were highly effective [WHO, 2007]. Studies found:

- 90% fewer persistent infections with genotypes 16 or 18.

- Almost 100% fewer moderate or severe cervical lesions.

- Almost 99% fewer genital warts (when the quadrivalent vaccine was used).

▪ A multi-site study of HPV type-specific prevalence in women with cervical cancer, cervical intraepithelial neoplasia, and normal cervical cytology in England found that non-vaccine HPV types (that is types 16 and/or 18) were found in 60% of women with mild dyskaryosis or less, but in fewer than 20% of women with cervical cancer. The authors commented that these results suggested that the HPV vaccine should have a marked impact on cervical disease in England [Howell-Jones et al, 2010].

▪ It is not known how long protection lasts and whether booster doses are necessary [DTB, 2008]. Levels of antibodies to HPV are low or non-existent after infection, because HPV only has a mucosal phase and not a bloodstream phase. Levels of antibody after vaccination are much higher than after natural infection. This differs from other viral vaccines, and therefore it is not possible to predict from experience the expected length of time for protection against HPV infection [WHO, 2007].

- A follow-up study of 383 women who had received three doses of HPV-16/18 virus-like particle vaccine and 393 women who had received a placebo found sustained high levels of antibodies at 4.5 years of follow up [Harper et al, 2006].

- A follow-up study of 17622 women who had received the quadrivalent vaccine found that the vaccine had provided sustained protection for 42 months [The Future I/II Study Group, 2010].

▪ There is some cross-protection against other genotypes from both the bivalent and the quadrivalent vaccines [WHO, 2007].

- Bivalent vaccine: cross-protection demonstrated against two other genotypes has been demonstrated in HPV-naive women.

- Quadrivalent vaccine: neutralizing antibodies against genotypes 31 and 45 have been demonstrated.

Safer sex measures

▪ This information is based on expert advice from the Centers for Disease Control and Prevention [CDC, 2009] and the World Health Organization [WHO et al, 2007].

Human papillomavirus screening

▪ HPV screening or testing is not presently used in routine practice. However, the potential benefits of introducing HPV testing into the cervical screening programme are currently under investigation [NHS Cancer Screening Programmes, 2010]. HPV testing may be used:

o In women who have either a borderline or mild dyskaryosis result:

o This is called 'HPV triage'. Under the current cervical screening programme, women with these abnormalities are recalled every 6 months and/or have colposcopy, often generating anxiety. However, only 15–20% of these women will need treatment for cervical intraepithelial neoplasia 2 (CIN 2) or worse. If the woman does not have a high-risk strain of HPV present, then there is only a negligible risk that she will need treatment. Preliminary results from the sentinel site pilot studies suggest that management could be tailored to these two groups of women, depending on whether they are at high or negligible risk. Those at negligible risk could return to the normal recall programme, whereas those at high risk would have immediate colposcopy [NHS Cancer Screening Programmes, 2008].

o In women who have had treatment for CIN:

o This is called 'test of cure'. Of women who develop cervical cancer in the UK, 16% have had previous treatment for CIN. After treatment for CIN, women are tested for both abnormal cells (cervical cytology) and HPV. If these tests are negative, then the woman is returned to the normal screening programme instead of being followed up with annual screening for 10 years.

o Research is continuing to determine the optimum time to do these tests. Expert opinion in guidelines for the NHS cervical screening programme is that there is some evidence to suggest that the HPV test should be done 6 months after treatment for CIN, followed by a combined cervical cytology and HPV test 12–18 months after treatment. If all three of these tests are negative, then the woman may be returned to routine recall [NHS Cancer Screening Programmes, 2010].

o The potential benefits of population screening are also being investigated, although it is not currently recommended for routine use. It is likely that HPV testing may be particularly useful because of its high negative

predictive value. This means that a high proportion of women with a negative test result do not have CIN, and there is a high probability that this result is correct. Good evidence from a randomized controlled trial [Kitchener et al, 2009] indicates that HPV testing combined with cervical cytology is not cost effective. However, the trial highlighted the possibility of initial HPV testing with cervical cytology reserved for women who have a positive HPV result. HPV testing does not seem to cause significant psychosocial distress.

Cervical cancer and HPV - Management

View full scenario

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How is cervical cancer staged in secondary care?

Cervical cancer is staged on clinical findings using the FIGO (Fédération Internationale des Gynaecologistes et Obstetristes) criteria. Treatment is defined according to the stage of the disease. It is acknowledged that clinical staging alone is inaccurate, and in the UK clinicians allow information obtained from modern medical imaging, as well as FIGO staging, to influence their management. However, the FIGO system remains to allow comparisons to be made worldwide, as most cervical cancer occurs in developing countries.

- **Stage 0:** cervical intraepithelial neoplasia (CIN) 3: carcinoma in situ; pre-invasive cancer.
- **Stage I:** the cancer remains within the cervix and uterus.
  - **Stage IA:** diagnosed only by microscopy.
  - Stage IA1: measured stromal invasion of not more than 3 mm in depth, and extension of not more than 7 mm.
  - Stage IA2: measured stromal invasion of between 3 mm and 5 mm in depth, and extension of not more than 7 mm.
  - **Stage IB:** clinically visible lesions confined to the cervix, or preclinical cancers greater than 1A.

- Stage IB1: clinically visible lesions not more than 4 cm in the greatest dimension.

- Stage IB2: clinically visible lesions more than 4 cm in the greatest dimension.

- **Stage II:** the cancer has begun to spread into the tissues surrounding the cervix.

- Stage IIA: no obvious parametrial involvement (the parametrium is the connective tissue of the pelvic floor extending from the fibrous subserous coat of the supracervical portion of the uterus, laterally between the layers of the broad ligament).

- Stage IIB: obvious parametrial involvement.

- **Stage III:** the cancer has spread within the pelvis.

- Stage IIIA: the tumour involves the lower third of the vagina but not the pelvic side wall.

- Stage IIIB: spread to the pelvic side wall. Includes hydronephrosis and non-functioning kidney.

- **Stage IV:** the cancer has spread to other body organs beyond the pelvis or has involved the mucosae of the bladder or rectum.

- Stage IVA: spread of the growth to adjacent organs.

- Stage IVB: spread to distant organs.

[Pugh, 2000; Petignat and Roy, 2007; Cancer Research UK, 2010b]

Basis for recommendation

This information is from expert review articles [Blomfield, 2007; Petignat and Roy, 2007].

How is cervical cancer treated in secondary care?

Staging is based on the FIGO staging system that is universally used worldwide. In the UK, computed tomography, magnetic resonance imaging, and positron emission tomography (PET) are also used to assess the extent of the disease. Decisions on treatment are made based on the extent of the disease.

- **In women with cervical intraepithelial neoplasia (CIN)** (FIGO stage 0):

o Colposcopy.

o Biopsy and histological analysis.

o If moderate to severe abnormalities are found: excision or ablation.

- **In women with early cervical cancer** (FIGO stages IA1, IA2, and IB1):

o Surgery is the treatment of choice for women with early cervical cancer:

o Simple hysterectomy or radical hysterectomy, depending on the stage of cancer.

o If there is pelvic lymph node involvement, concomitant chemotherapy and radiotherapy may be used.

o If the woman wishes to preserve her fertility, then options (depending on the stage and whether lymphatic-vascular space invasion is present) include:

o Radical trachelectomy (removal of the upper vagina, the cervix with parametrial tissue after pelvic lymphadenectomy, with preservation of the uterus). Pelvic lymphadenectomy may be done laparoscopically.

o Cold-knife conization, or large-loop excision of the transformation zone (LLETZ), with or without pelvic lymph node dissection.

- **In women with late cervical cancer** (FIGO stages IB2, IIA, IIB, IIIA, IIIB and IVA):

o Combined chemotherapy and radiotherapy is the treatment of choice.

o Surgery is not suitable because of the risk of positive margins (that is there are cancer cells at the edge of the tissue that has been removed) and positive lymph nodes.

- **In women with advanced cervical cancer** (FIGO stage IVB):

o Only palliative treatment is possible.

o Platinum-based combination chemotherapy has potential benefits for some women.

- **In women who are pregnant:**

o If the woman has early-stage disease (FIGO stages IA1, IA2, IB):

o If before 16 weeks' gestation, immediate treatment is advised.

o If after 16 weeks' gestation, delivery may be delayed until the fetus has matured.

o If the woman has late-stage disease (FIGO stage IB2 or more advanced):

o If before 20 weeks' gestation, immediate delivery and treatment of disease is advised.

o If after 20 weeks' gestation, delivery and treatment should be initiated within 4 weeks. Consideration for delay should be based on the gestational age and the woman's wishes.

- **If the cervical cancer recurs,** then the options are:

o Surgery (salvage): pelvic exenteration is possible if the relapse is confined to the central pelvis and chemotherapy and radiotherapy have failed.

o Chemotherapy — palliative.

o Supportive care only.

Basis for recommendation

Treatment of non-pregnant women

- This information is based on guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008], a summary of the SIGN guidelines [James et al, 2008], the European Society for Medical Oncology (ESMO) clinical recommendations for diagnosis treatment and follow up [Haie-Meder et al, 2009], information from *Drug and therapeutics bulletin* [DTB, 2008], and a clinical review [Blomfield, 2007].

Treatment of pregnant women

- This information is based on guidelines from SIGN [SIGN, 2008].

Treatment of recurrent disease

- This information is based on guidelines from SIGN [SIGN, 2008].

What specific problems are associated with advanced cervical cancer?

Women with incurable cervical cancer should be managed on an individual basis with the primary healthcare professional as part of a multidisciplinary team. For general information on primary care management at the end of life, see the CKS clinical category on Palliative care.

Primary care clinicians should be aware of the distressing problems that are associated specifically with advanced cervical cancer for whom the following treatments may be appropriate.

- **Pain** — early specialist referral for consideration of:
  - Nerve-blocking procedures in addition to analgesics.
  - Spinal therapy (using opiates, local anaesthetics, and clonidine) to provide regional blockade for pelvic pain, pain from bony metastases, or neuropathic pain.
  - Percutaneous cementoplasty for bony metastases.
- **Renal failure** due to ureteric obstruction — options include:
  - No treatment.
  - Percutaneous nephrostomy.
  - Retrograde stenting.
- **Bleeding and thrombosis** problems:
  - **Deep vein thrombosis** — low-molecular-weight heparin is more effective than oral anticoagulants.
  - **Minor vaginal bleeding** — may respond to oral or topical tranexamic acid or radiotherapy.
  - **Massive haemorrhage** may occur due to erosion of a major artery, and may lead to death. Relieve distress promptly and discuss management with the multidisciplinary team. Consider using midazolam for its anxiolytic effect,

or diamorphine for its hypotensive effect, if admission is not deemed to be appropriate.

- **Malodour** — management is dependent on the cause.

  - If due to necrotic tissue. consider surgical debridement.

  - If it is due to fistula-related faecal incontinence, consider referral for defunctioning colostomy.

  - If it is due to fistula-related urinary incontinence, consider referral for bilateral percutaneous nephrostomy.

- **Lymphoedema** of the legs.

  - Refer to a specialist for consideration of conservative treatments, such as decongestant lymphatic therapy with compression bandaging, manual lymph drainage, and massage, and ensure good skin care and exercise.

  - Ensure prompt treatment of cellulitis.

  - Give advice about avoidance of injury.

Basis for recommendation

These recommendations are based on expert opinion in guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) [SIGN, 2008].

Low-molecular-weight heparin

- This recommendation is based on expert opinion in guidelines from the SIGN [SIGN, 2008] and is based on the results of a randomized controlled trial. People with cancer who had also had a deep vein thrombosis or a pulmonary embolism were randomized to receive either low-molecular-weight heparin (dalteparin) for 5–7 days followed by a coumarin derivative for 6 months (338 people) or low-molecular-weight heparin (dalteparin) alone for 6 months (338 people). It was found that dalteparin alone was more effective at reducing the risk of recurrent thromboembolism without increasing the risk of bleeding [Lee et al, 2003].