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Endometrial cancer

1 Background information

Quick info:

Scope:
- diagnosis, staging, management, and follow-up of endometrial carcinoma in primary and secondary care
- adults over age 18 years
- investigation of post-menopausal bleeding (PMB) to diagnose endometrial cancer
- therapeutic options including surgical intervention, radiotherapy, chemotherapy, and brachytherapy
- gives consideration to management of pain related to the condition and to the treatment
- other care maps to consider when viewing this care map include the 'Menstrual cycle irregularities and post-menopausal bleeding (PMB)' care map and the 'End of life care' care map

Out of scope:
- diagnosis and management of uterine sarcoma

Definition:
- endometrial cancer:
  - most common type is endometrioid adenocarcinoma, which is composed of malignant glandular epithelial elements
  - clear-cell and serous carcinoma of the endometrium are tumours that are histologically similar to those noted in the ovary and the fallopian tube
  - in approximately 75% of patients with endometrial adenocarcinoma, the invasive neoplasm is localised to the uterus at diagnosis (stage I) [1-3]
- PMB – defined as the occurrence of vaginal bleeding 6 months or more after a woman’s last menstrual cycle

Incidence:
- in western Europe and North America, endometrial cancer is the most common gynaecological malignancy [1,4]
- in women in the UK, endometrial cancer is the fourth most common cancer with 7,536 cases diagnosed in 2007, compared to 45,700 women diagnosed with breast cancer in 2007 [1]
- in the UK in 2008, 1,741 deaths from corpus uteri cancer were reported, accounting for only 2.3% of all cancer deaths in UK females [1]
- the incidence in older women (age 60-69 years) increased in the UK by 19% between 1993 and 2001 [4]
- incidence of endometrial cancer is rising in postmenopausal women but five-year survival rates have improved to more than 75% [1]
- 93% of cases are diagnosed in women age 50 years or older [1]
- in the European Union (EU), about 81,500 women are affected every year [3]
- the median occurrence is at age 63 years, while more than 90% of women diagnosed are age 50 years or older [3]
- the majority of endometrial cancers occur after menopause, but up to 25% of cases may be premenopausal [3]

Prognosis:
- the five-year survival for stage I patients is 90% [3] compared with 25% for women diagnosed with stage IV [1]

Risk factors:
- greater than age 50 years
- obesity
- nulliparity
- late menopause
- diabetes mellitus (DM)
- prolonged, unopposed oestrogen exposure
- tamoxifen
- oestrogen-only hormone replacement therapy (HRT)
- polycystic ovaries
- hereditary non-polyposis colon cancer (HNPCC; Lynch syndrome)

NB: This information appears on each page of the care map.

References:
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2 Information resources for patients and carers

Quick info:
Patients and carers in England can access this care map through NHS Choices at http://healthguides.mapofmedicine.com/choices/map/endometrial_cancer1.html

The following resources have been produced by organisations certified by The Information Standard:

• 'Abdominal hysterectomy – information, symptoms and treatment' (URL) from Bupa at http://www.bupa.co.uk
• 'Cancer of the womb' (URL) from Macmillan Cancer Support at http://www.macmillan.org.uk
• 'Coping with womb cancer' (URL) from Cancer Help UK at http://www.cancerhelp.org.uk
• 'Endometrial Cancers' (URL) from Datapharm at http://www.medguides.medicines.org.uk
• 'External radiotherapy for womb cancer' (URL) from Cancer Help UK at http://www.cancerhelp.org.uk
• 'Stages of womb cancer' (URL) from Cancer Help UK at http://www.cancerhelp.org.uk
• 'Treatment for womb cancer' (URL) from Cancer Help UK at http://www.cancerhelp.org.uk
• 'Uterine (Endometrial) cancer' (PDF) from Patient UK at http://www.patient.co.uk
• 'Womb (endometrial and uterine) cancer' (URL) from Cancer Help UK at http://www.cancerhelp.org.uk
• 'Womb cancer – information, symptoms and treatment' (URL) from Bupa at http://www.bupa.co.uk

The following resource has been written or recommended by national policy bodies or guideline producers whose content has informed this care map:

• 'Referral for suspected cancer: information for the public' (PDF) from National Institute for Health and Clinical Excellence (NICE) at http://www.nice.org.uk/

Information for carers and people with disabilities is available at:

• 'Caring for someone' (URL) from Directgov at http://www.direct.gov.uk
• 'Disabled people' (URL) from Directgov at http://www.direct.gov.uk

Patient stories describing their care journeys are available at 'Healthtalkonline' (URL) from DIPEX at http://www.healthtalkonline.org.

Explanations of clinical laboratory tests used in diagnosis and treatment are available at 'Understanding Your Tests' (URL) from LabTestsOnline-UK at http://www.labtestsonline.org.uk.

The Map of Medicine is committed to providing high quality health and social care information for patients and carers. For details on how these resources are identified, please see Map of Medicine Patient and Carer Information.

NB: This information appears on each page of this care map.

3 Updates to this care map

Quick info:
Date of publication: 31-Oct-2011

Interim update:
The care map has been updated in line with the following guideline:


Date of publication: 29-Apr-2011

Interim update:
The use of quality assured transvaginal ultrasound and pipelle endometrial biopsy in primary care has been updated according to feedback from the National Cancer Action Team.

Date of publication: 31-Jan-2011

Interim update:
This care map has been updated according to feedback from the National Cancer Action Team.

Date of publication: 29-Oct-2010

Three floating nodes now appear at the top of each care map page. These provide:

• easy access to scope and background information on each page of the care map whilst reducing repetition between nodes
• easy access to patient resources/leaflets
• information on care map updates

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This care map was published by International. A printed version of this document is not controlled so may not be up-to-date with the latest clinical information.
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This care map was created in line with the following guidelines:


Further information was provided by the following references: [1,4-6,11-14,18-29,32-34]. For further information, please see the care map's Provenance.

The care map has been completely restructured and redrafted in line with the new methodology and to bring in line with current clinical practice.

NB: This information appears on each page of this care map.

4 Endometrial cancer - clinical presentation

Quick info:

Patients with endometrial cancer may present with:

- postmenopausal bleeding (PMB) – the most common presentation in 90% of patients [3];
  - commonly defined as the onset of vaginal bleeding 6 months after a woman's last period [6] – the Scottish Intercollegiate Guidelines Network (SIGN) adapt a definition of PMB as the occurrence of vaginal bleeding 12 months or more after the cessation of periods [7]
  - alterations in the menstrual cycle
- intermenstrual bleeding in pre-menopausal females – see the [Menstrual cycle irregularities and post-menopausal bleeding (PMB)] care map
  - postcoital bleeding
  - vaginal discharge
  - abdominal or pelvic mass
  - unscheduled bleeding for women on hormone replacement therapy (HRT)

Symptoms of more advanced disease include:

- pelvic pain
- weight loss
- shortness of breath
- haematuria
- renal failure
- back pain
- bowel syndromes

NB: Only 10% of patients presenting with PMB have endometrial cancer [3].

References:


5 History

Quick info:
In patients presenting with post-menopausal bleeding (PMB), assess the pattern of bleeding, eg:
- light, intermittent
- heavy
- recurrent
- persisting

Review possible risk factors of endometrial cancer, including:
- age – the probability of endometrial cancer being present in women with post-menopausal bleeding increases after age 50 years
- tamoxifen therapy – clinicians should be aware that post-menopausal women receiving tamoxifen therapy, particularly for longer than five years, are at increased risk
- oestrogen-only hormone replacement therapy (HRT):
  - abnormal bleeding in post-menopausal women receiving HRT can be caused by any of the following, which should be considered as differential diagnoses:
    - poor compliance, especially related to omission of progestogens
    - poor gastrointestinal (GI) absorption (for oral preparations), eg due to malabsorption symptoms
    - medication interactions
    - coagulation defects
    - other gynaecological disorders
- hereditary non-polyposis colorectal cancer (HNPCC)
- obesity
- patients with diabetes mellitus (DM)
- women with hypertension
- a past history of hyper-oestrogenism (endogenous or exogenous)

Assessing abnormal bleeding in women using HRT:
- enquire whether bleeding pattern is abnormal:
  - unscheduled bleeding is the term used to describe:
    - breakthrough bleeding occurring in females on cyclical HRT
    - any bleeding in females on tibolone (Livial)
  - any bleeding in females on continuous combined HRT (can take up to 6 months for amenorrhoea to develop)
- for sequential regimens abnormal bleeding may:
  - be heavy or prolonged at the end of or after the progestogen phase
  - occur at any time (breakthrough bleeding)
- for continuous combined regimens abnormal bleeding may occur after:
  - the first six months of treatment
  - amenorrhoea has been established
- assess for any other related symptoms or contributory factors associated with endometrial cancer

Consider using the following questions in the assessment:
- when does bleeding occur with respect to the oestrogen and the progestogen phase?:
  - women on sequential regimens should ideally not experience withdrawal bleeding before completion of the progestogen component of the preparation
  - how long does the bleeding last and how heavy is it?
  - was there a period of amenorrhoea before HRT was started?
  - is there a problem that suggests poor compliance?
  - is there a reason to suspect poor GI absorption?

NB: There is no evidence of an increased risk of endometrial cancer in women using combined HRT.
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6 Examination

Quick info:
Perform a full physical examination.
A full pelvic examination should be performed on women presenting with post-menopausal bleeding at some stage during their assessment – this should include speculum examination of the cervix.
This information was drawn from the following references:

7 Consider differential diagnosis

Quick info:
Other causes of abnormal findings include:
• atrophic vaginitis [7]
• cervical and endometrial polyps [7]
* cervical cancer – see the 'Cervical dysplasia and cancer' care map [7]
• vulval cancer [8]

Abnormal bleeding in post-menopausal women receiving hormone replacement therapy (HRT) can be caused by any of the following, which should be considered as differential diagnoses [7]:
• poor compliance, especially related to omission of progestogens
• poor gastrointestinal absorption (GI) (for oral preparations), eg due to malabsorption syndromes
• medication interactions
• coagulation defects
• other gynaecological disorders

References:

8 Consider urgent referral to a gynaecologist

Quick info:
GPs should take the following into account when considering referral [7]:
• patterns of bleeding
• the relationship of bleeding to use of hormone replacement therapy (HRT)
• patient preferences
Consider referral to an emergency gynaecology unit if the patient has anaemia or heavy bleeding [6].
Consider urgent referral (within two weeks) if the patient:
• has a suspicious cervix [6]
• presents with postmenopausal bleeding (PMB), and is not on hormone replacement therapy (HRT) [8,9]
• is on HRT and presents with persistent or unexplained postmenopausal bleeding after cessation of HRT for 6 weeks [8,9]
• is taking tamoxifen and presents with postmenopausal bleeding [8,9]
• presents with persistent intermenstrual bleeding and a negative pelvic examination [8,9]
• presents with a palpable abdominal or pelvic mass is suggestive of cancer [8,9]
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If ready access to quality assured transvaginal ultrasound and pipelle endometrial biopsy is available in primary care, this is an acceptable alternative to referral to a secondary care rapid access clinic for the assessment of post-menopausal bleeding or suspicious intermenstrual bleeding [6].

The risk of endometrial cancer in non-HRT users complaining of PMB and in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation [7].

Patient information can be found [The Eve Appeal](URL) [6].

References:

10 Investigation in all women with post-menopausal bleeding (PMB), including those on HRT

Quick info:
Transvaginal ultrasound is the investigation of choice in women with post-menopausal bleeding (PMB) women [7]:
• it helps to identify those at higher risk of endometrial cancer who require further investigation
• it should be considered as the first-line procedure in all women with PMB and in women using hormone replacement therapy (HRT)

Reference:

11 Investigation in asymptomatic post-menopausal women not on HRT

Quick info:
Investigation in asymptomatic postmenopausal women who are not receiving hormone therapy:
• transvaginal sonography (TVS) is routinely performed as part of a pelvic sonogram in postmenopausal women referred for a variety of symptoms, eg suspicion of a pelvic mass [11]
• if endometrial thickness is between 5mm and 11mm, further investigation should be based on clinical opinion regarding risk of underlying pathology [6]
• if endometrial thickness is above 11mm, consider further investigation with hysteroscopy/biopsy [6]

References:

12 Investigation in post-menopausal women on tamoxifen

Quick info:
Patients using tamoxifen:
• women taking tamoxifen on a long-term basis are at increased risk of endometrial cancer [7]
• hysteroscopy with biopsy is the preferred first-line of investigation if the patient is symptomatic and on tamoxifen regardless of endometrial thickness [6]
• unnecessary investigation should be avoided in patients using tamoxifen in the absence of vaginal bleeding [7]:
• there are risks associated with further investigation
• both the clinician and patient should be vigilant for post-menopausal bleeding while receiving tamoxifen treatment
• endometrial thickness increases with long term tamoxifen use and should be taken into account for investigations [6]
• one study indicates an endometrial thickness of more than 5mm can warrant further diagnostic testing in women with tamoxifen-induced postmenopausal bleeding [12]

References:
Endometrial cancer


13 Investigation in pre- and peri-menopausal women

Quick info:
Investigation in pre- and peri-menopausal women [6]:
- there is a low threshold for proceeding to histological assessment for women with abnormal bleeding

Reference:

14 Transvaginal ultrasound (TVUS)

Quick info:
Transvaginal ultrasound (TVUS):
- is the first-line procedure to identify which women with post-menopausal bleeding (PMB) are at higher risk of endometrial cancer (where sufficient local skills and capacity exist) [7].
- and outpatient endometrial biopsy, eg Pipelle, should be considered for initial assessment [6].
- is an effective method of assessing endometrial thickness and morphology [6].
- can reliably assess endometrial thickness and morphology of the endometrium [7].
- thickening of the endometrium may indicate the presence of pathology
  - the mean endometrial thickness in post-menopausal women is much thinner than in pre-menopausal women [7].
  - TVUS can be used to identify women with PMB with thin endometrium who are therefore unlikely to have significant endometrial disease
  - a threshold of more than 5mm can be used to indicate the likelihood of endometrial cancer
  - in women using sequential hormone replacement therapy (HRT) with PMB, the mean endometrial thickness is greater than in women with PMB not using sequential HRT [7];
  - therefore, abnormal endometrial thickness in non-sequential HRT users with PMB can be an indicator of endometrial disease
  - there is insufficient data to assess the normal endometrial thickness in postmenopausal women though some suggest abnormal endometrial thickness can be indicated above 8mm [13,14].
  - in patients on sequential HRT, TVUS measurements should take place during the first half of the cycle where possible [7];
  - the endometrial thickness should be at its thinnest early in the cycle [6].
- studies indicate however, TVUS changes in specificity and sensitivity [6] and have limited accuracy in assessing [15]:
  - cervical extension
  - parametrial invasion
  - lymphadenopathy
- presence of the following can make interpretation difficult [6]:
  - fibroids
  - presence of fluid in the cavity and other morphological changes
- staff undertaking TVUS should be trained to ensure a consistent and acceptable level of performance [7].

Endometrial cancer can be excluded when endometrial tissue thickness threshold is:
- less than 3mm (Scottish Intercollegiate Guidelines Network [SIGN]) recommendation [7] or less than 4-5mm [6] in females who:
  - have never used hormone replacement (HRT)
  - have not taken HRT for 1 year or more are using continuous combined HRT
- 5mm or less in females with unscheduled bleeding who [7]:
  - currently use sequential combined HRT
  - have used sequential combined HRT in the last year

References:
[14] Saksouk FA. Endometrium, Carcinoma. [Internet]. Omaha, NE: eMedicine [accessed 18 October 2010].
15 Consider ultrasound and biopsy, and hysteroscopy if necessary

Quick info:
Initial assessment:
- in the UK, most women will be assessed in rapid access clinics using ultrasound and outpatient endometrial biopsy [6]

Hysteroscopy:
- is the 'gold standard' of investigation in women taking tamoxifen who experience post-menopausal bleeding or in post-menopausal women considered to be at high risk of endometrial cancer [6,7]
- is well-tolerated [6]
- is easily performed [6]
- however, should be considered if Pipelle biopsy is not feasible, or if symptoms persist despite negative Pipelle [6]
- may be useful in evaluating the endometrium for lesion, eg polyps, if the patient has persistent or recurrent undiagnosed bleeding [2]

Outpatient hysteroscopy [36]:
- all gynaecological units should provide a dedicated outpatient hysteroscopy service to aid the management of women with abnormal uterine bleeding
- ensure a nurse chaperone is available, regardless of the gender of the clinician
- the healthcare professional should have necessary skills and expertise to carry out the hysteroscopy
- analgesia:
  - avoid routine opiate use before procedure as it may cause adverse effects
  - to reduce pain in the immediate postoperative period, advise women with contraindications to consider taking standard doses of non-steroidal inflammatory drugs (NSAIDs) around one hour prior to their scheduled appointment
- local anaesthesia should be available for cervical dilatation:
  - prior to hysteroscopy:
    - consider topical application of local anaesthesia to the ectocervix where application of a cervical tenaculum is necessary
    - routine administration of intracervical or paracervical local anaesthesia should be used where larger diameter hysteroscopes are being employed (outer diameter greater than 5mm) and where the need for cervical dilatation is anticipated, eg cervical stenosis
    - give consideration to the route of administration of intracervical and paracervical local anaesthetic, particularly in postmenopausal women
    - routine administration of intracervical or paracervical local anaesthetic is not indicated to reduce the incidence of the vasovagal reactions
  - during hysteroscopy:
    - local anaesthetic applied into or around the cervix is associated with a reduction of the pain experienced during outpatient hysteroscopy
    - instillation of local anaesthetic into the cervical canal does not reduce pain during diagnostic outpatient hysteroscopy but may reduce the incidence of vasovagal reactions
- conscious sedation:
  - should not be routinely used in outpatient hysteroscopic procedures – it has no advantage over local anaesthesia in terms of pain control and the woman's satisfaction
  - can result in life-threatening complications – if procedures are to be undertaken under conscious sedation, appropriate monitoring and staff skills are mandatory
- technique:
  - vaginoscopy reduces pain during diagnostic rigid outpatient hysteroscopy and should be the standard, especially where:
    - insertion of a vaginal speculum is anticipated to be difficult
    - blind endometrial biopsy is not required
- type of hysteroscope:
  - miniature hysteroscopes (2.7mm with a 3-3.5mm sheath) should be used for diagnostic outpatient hysteroscopy as they significantly reduce the discomfort experienced by the woman
  - there is insufficient evidence to recommend 0° or fore-oblique optical lenses (ie 12°, 25°, or 30° off-set lenses) for routine outpatient hysteroscopy – choice of hysteroscope should be left to the discretion of the operator
  - flexible hysteroscopes are associated with less pain during outpatient hysteroscopy compared with rigid hysteroscopes, however, rigid hysteroscopes may provide:
    - better images
    - fewer failed procedures
    - quicker examination time
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- reduced cost
- distension medium:
  - uterine distension with normal saline allows improved image quality and allows outpatient diagnostic hysteroscopy to be completed more quickly compared with carbon dioxide

Facilities to perform hysteroscopy and curettage under general anaesthetic (GA) should be available for when the outpatient procedure is not possible, or the patient has a strong preference for a GA [7].

NB: where Pipelle biopsy has failed, inpatient hysteroscopy under GA should be considered, as outpatient hysteroscopy will also likely be associated with a failed outcome [7].

References:

16 High risk

Quick info:
High-risk findings [6,7]:
- the finding of an endometrial thickness above the relevant cut-offs (4-5mm) indicates that there is a risk of abnormality significant enough to warrant further investigation

References:

17 Low risk

Quick info:
Low-risk findings [7]:
- if the clinician and the patient judge that the level of reassurance and reduced risk are acceptable following a transvaginal ultrasound (TVUS) (measurement of 4-5mm or less [less than 3mm according to Scottish Intercollegiate Guidelines Network recommendations]), no further action needs to be taken [6,7]
- consider carrying out a biopsy if symptoms persist despite a normal scan or if there is a history of heavy/recurrent bleeding [6]

References:

18 Positive results

Quick info:
Clinical nurse specialist review [35]:
- Improving Outcome Guidance requires a nurse specialist to be present at the time of discussing the diagnosis
- the nurse specialist can assess:
  - information needs
  - social issues
  - financial issues
  - additional support needs from primary care
- patients who receive such support and information from a clinical nurse specialist report better understanding regarding the diagnosis and treatment options who do not receive such care

Reference:
20 Consider hysteroscopy if necessary

Quick info:

Hysteroscopy and biopsy (with curettage):
- is the preferred technique to detect polyps and other benign lesions [7]
- should be offered on an outpatient basis [36]

Outpatient hysteroscopy [36]:
- all gynaecological units should provide a dedicated outpatient hysteroscopy service to aid the management of women with abnormal uterine bleeding
- ensure a nurse chaperone is available, regardless of the gender of the clinician
- the healthcare professional should have necessary skills and expertise to carry out the hysteroscopy
- analgesia:
  - avoid routine opiate use before procedure as it may cause adverse effects
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    - flexible hysteroscopes are associated with less pain during outpatient hysteroscopy compared with rigid hysteroscopes, however, rigid hysteroscopes may provide:
      - better images
      - fewer failed procedures
      - quicker examination time
      - reduced cost
    - distension medium:
      - uterine distension with normal saline allows improved image quality and allows outpatient diagnostic hysteroscopy to be completed more quickly compared with carbon dioxide

Consider inpatient hysteroscopy (with general anaesthesia) if [6]:
- Pipelle biopsy is not feasible
- symptoms persist despite negative biopsy
Endometrial cancer

References:

21 Follow-up
Quick info:
Follow-up [7]:
• further investigation is justified if the clinician, the patient or both are not satisfied with this level of reassurance
• investigation should include an endometrial biopsy to obtain a histological assessment
• the Scottish Intercollegiate Guidelines Network (SIGN) suggest considering re-investigation of recurrent post-menopausal bleeding after six months
Reference:

22 Follow-up
Quick info:
Follow-up:
• if symptoms persist, an endometrial biopsy to obtain a histological assessment is strongly indicated [6]
• the Scottish Intercollegiate Guidelines Network (SIGN) suggest considering re-investigation of recurrent post-menopausal bleeding after six months [7]
References:

23 Positive results
Quick info:
Clinical nurse specialist review [35]:
• Improving Outcome Guidance requires a nurse specialist to be present at the time of discussing the diagnosis
• the nurse specialist can assess:
  • information needs
  • social issues
  • financial issues
  • additional support needs from primary care
• patients who receive such support and information from a clinical nurse specialist report better understanding regarding the diagnosis and treatment options who do not receive such care
Reference:

25 Follow-up
Quick info:
Follow-up:
• if symptoms persist, an endometrial biopsy to obtain a histological assessment is strongly indicated [6]
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Key Dates

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Evidence summary for Endometrial cancer

This pathway has been developed according to the Map of Medicine editorial methodology (http://mapofmedicine.com/whatisthemap/editorialmethodology). The content of this pathway is based on high-quality guidelines [2,3,7-10,15-17,30,31,36] and critically appraised meta-analyses and systematic reviews [21,23,25,26]. Practice-based knowledge has been added by contributors with front-line clinical experience [6,18], including any literature endorsed by the contributor group [1,4,5,11-14,19,20,22,24,27-29,32-35].

Search date: Jun-2010

References

This is a list of all the references that have passed critical appraisal for use in the care map Endometrial cancer

<table>
<thead>
<tr>
<th>ID</th>
<th>Reference</th>
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<tr>
<td>6</td>
<td>Contributors representing the National Cancer Action Team. 2010.</td>
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ID Reference
http://www.ncbi.nlm.nih.gov/pubmed/19553814?dopt=Citation

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