

Uterine Cancer Treatments

A Review of the Bio-Medical Evidence

The Women's Health Council
Comhairle Shláinte na mBan



Research Summary 2009

This fact sheet is intended to inform women recently diagnosed with cancer of the treatments available to them, and to provide up-to-date, high quality evidence of their effectiveness to those involved in receiving or providing treatment.

Uterine cancer statistics

Both the incidence and mortality rates of uterine cancer in Ireland are very similar to the European Union average rates (EU25) (Ferlay *et al.*, 2007). The number of women diagnosed with uterine cancer has been slowly increasing over the ten years, with a high of 302 women diagnosed in 2005, although this decreased to 291 women in 2006. There was a sharp increase in the number of women dying from uterine cancer from 62 in 2005 to 87 in 2006. However, the decrease in mortality since 2006 is predicted to continue over the next several years.

Figure 1 Uterine cancer incidence in Ireland (NCRI, 2008)

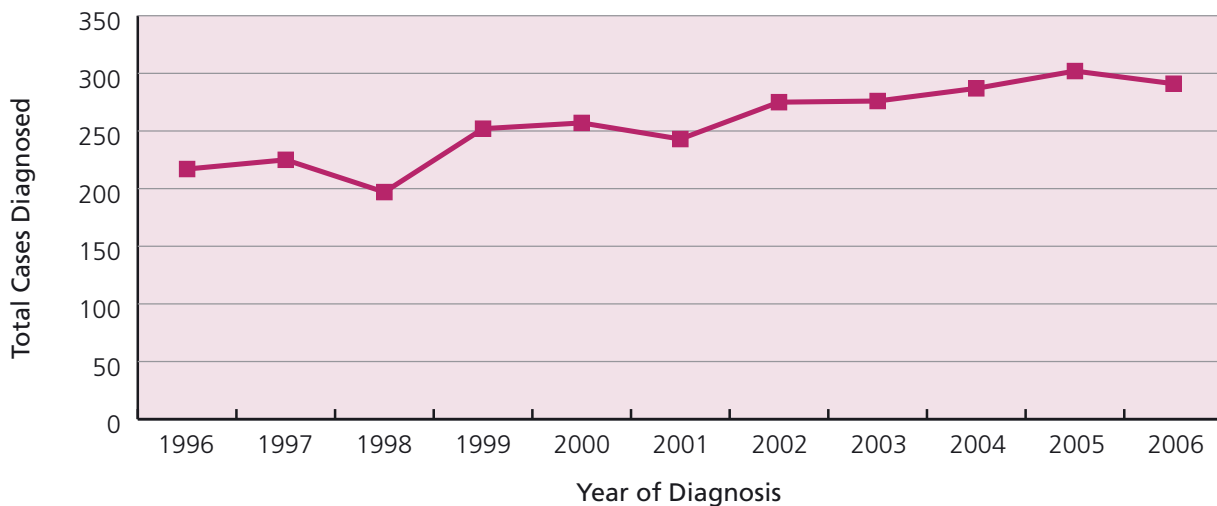


Figure 2 Uterine cancer mortality in Ireland (CSO, 2008; O’Lorcain et al., 2006)

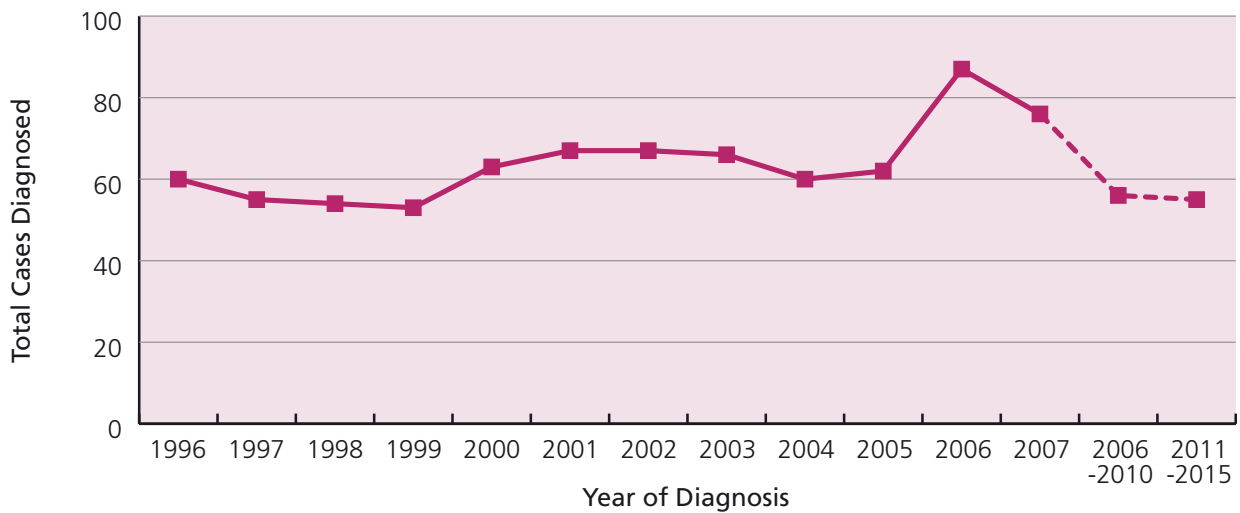
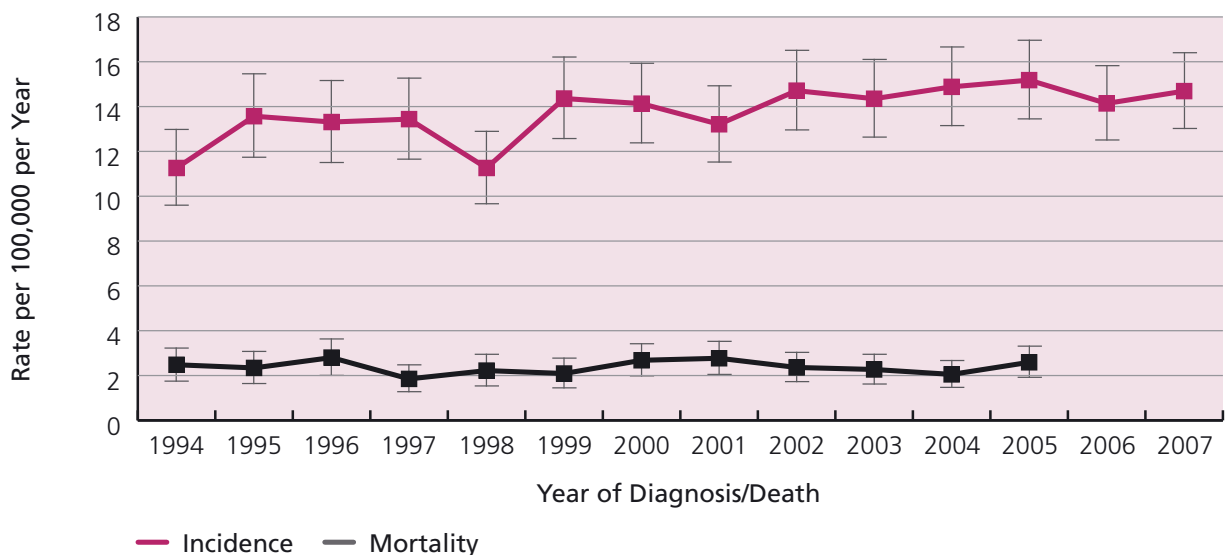


Figure 3 Uterine cancer rate and mortality rate in Ireland (NCRI, 2009)



The five-year survival in women with uterine cancer has shown very slight improvement from 72.9% for women diagnosed in 1995-1999, to 74.1% for women diagnosed in 2000-2004 (NCRI, 2008). Cancer survival depends on the stage of the cancer at diagnosis and the age of the women. For example, the relative five-year survival for women with early (stage 0-2) uterine cancer is 82.3% but 31.5% for women diagnosed with advanced (stage 3-4) uterine cancer (NCRI, 2008). The five-year relative survival for women aged 15-49 diagnosed with uterine cancer is 79.2%, 80.6% among women aged 50-69, and 62% among women aged 70 and older (NCRI, 2008).

What is it?

Uterine cancer may also be referred to as womb cancer. The lining of the womb is called the endometrium, and endometrial cancer is the commonest type of uterine cancer. Uterine cancer mainly affects post-menopausal women. Almost 90% of uterine cancer cases present in women aged over 50.

Risk factors

Increasing risk	Decreasing risk
Increasing age	Combined oestrogen-progestogen oral contraceptive pill
Being overweight	Physical activity
Having a late menopause (after age 52)	Parity
Never having been pregnant	
Starting periods early in life (early menarche)	
Having longer than average periods	
Failing to ovulate (release an egg every month)	
Infertility	
Race	
Family history	
Genetic – presence of HNPCC gene	
A high fat diet	
Diabetes	
Tamoxifen (a treatment sometimes used for breast cancer)	

What are the symptoms?

Common symptoms

- Abnormal bleeding from the vagina, especially in postmenopausal women. Abnormal bleeding may be due to other conditions such as endometriosis (when the lining of the womb starts to grow outside of the womb), or fibroids (non-cancerous tumours of the muscle of the womb).

Less common symptoms

- Pain in the abdomen, back or legs.
- Pain or bleeding during intercourse or when urinating.
- A change in bowel habits (such as constipation).
- Weight loss.
- The womb may feel enlarged or swollen.

Treatment options

Surgery is normally the first treatment used for uterine cancer, and may be the only treatment required if the cancer is completely contained within the uterus. Additional treatments that may be required include **radiotherapy**, **chemotherapy** and **hormone therapy**. Radiotherapy may be used when surgery is not possible, or it may be used before or after having surgery as an adjuvant* treatment. Chemotherapy is sometimes used to help control advanced uterine cancer. Hormone therapy is normally used to slow down the progression of advanced uterine cancer. Hormone therapy has an established role in recurrent and advanced disease, but not for adjuvant treatment (i.e. high risk and stage I and II cancers).

Stage and grade of uterine cancer

Staging of the cancer determines the size of the cancer and how far it has spread.

Table 1 FIGO staging system for uterine cancer

Stage 1	Cancer is confined to the uterus
1a	The cancer is only in the inner lining (endometrium) of the uterus
1b	The cancer has grown into the muscle wall (myometrium) of the uterus, but no more than halfway
1c	The cancer has grown more than halfway into the muscle wall of the uterus
Stage 2	Cancer has spread to the cervix
2a	The cancer has grown into the glands covering the cervix
2b	The cancer has grown into the muscle (stroma) of the cervix
Stage 3	Cancer is more advanced but still remains within the pelvis
3a	The cancer has grown up to the ovaries or cancer cells have escaped into the abdomen (cancer cells in ascites or peritoneal washings)

* Adjuvant treatment is treatment given in addition to the main treatment to try to prevent cancer from returning.

3b	The cancer has grown down into the vagina
3c	The cancer has spread to nearby lymph glands
Stage 4	The cancer has spread to other parts of the body
4a	The cancer has spread to the bowel or bladder
4b	The cancer has spread to other organs that are further away, such as the lungs, liver, bones or brain.

Grading of the cancer cells is conducted under a microscope. The appearance of the cancer cells indicates how quickly the cancer may develop or spread. Cancer cells may be graded:

Table 2 Grades of uterine cancer

1 (low-grade)	The cancer cells look like the normal uterine cells. They usually grow slowly and are less likely to spread.
2 (moderate-grade)	The cancer cells look more abnormal than low-grade cells.
3 (high-grade)	The cancer cells look very abnormal. They are likely to grow quickly and are more likely to spread.

Surgery

Early stage uterine cancer

Most women with uterine cancer are advised to have a total hysterectomy, with the uterus and both ovaries removed. Around one in ten women with stage 1 uterine cancer treated with surgery alone will have a recurrence of their cancer (Kong *et al.*, 2007).

During surgery lymph nodes around the uterus may be removed and checked for signs of cancer. The procedure is called a 'lymphadenectomy' (pronounced: LIM-fa-deh-NEK-toh-mee). Results from the 'ASTEC' trial recently suggested that although lymphadenectomy to remove some lymph nodes is useful to determine the stage of the cancer, removing all the pelvic lymph nodes offers no benefit in survival in women with early uterine cancer (ASTEC, 2009). The removal of all the pelvic lymph nodes substantially increases the risk of lymphoedema (swelling) in the legs.

Laparoscopic (keyhole) surgery may offer similar survival rates to laparotomic surgery (surgical incision through abdominal wall). Although laparoscopy takes slightly longer to perform, there is significantly less blood loss and fewer complications during and after the operation (Palomba *et al.*, 2009).

Advanced uterine cancer

Of the women diagnosed with uterine cancer, around one in four have an advanced stage of the cancer (Kendrick *et al.*, 2007). Women with stage 3 uterine cancers are generally treated with surgery, after which they undergo post-operative treatment with chemotherapy and/or radiotherapy. Surgery, which aims to remove as much of the cancer as possible**, has been shown to significantly increase survival time compared to women who did not have surgery (Kendrick *et al.*, 2007). Numerous factors should be considered before deciding on this type of surgery, such as the individual's age, general health and the extent of the cancer.

Radiotherapy

Women with stage 1 uterine cancer have a low-risk of recurrence of their cancer. However, some women with stage 1 uterine cancer have a higher risk of recurrence (those with stage 1c or grade 3 cancers). For these women, radiotherapy after surgery is normally offered.

Pelvic external beam radiotherapy after surgery may reduce the risk of cancer recurring, in some cases by 72% compared to women who have surgery alone (Kong *et al.*, 2007). However, external beam radiotherapy is associated with risk of damage and toxicity and should be avoided in stage 1 uterine cancer with low-risk (such as stage 1a, 1b, and grade 1 and 2 cancers) (Kong *et al.*, 2007).

New evidence suggests that internal radiotherapy called 'brachytherapy' may be a better treatment for reducing recurrence of uterine cancer. Results from the 'PORTEC-2' trial recently reported vaginal recurrence of 0.9% among women treated with brachytherapy and 2% among women treated with pelvic external beam radiotherapy (Nout *et al.*, 2009). Brachytherapy also has a lower toxicity rate and shorter treatment duration compared to external beam radiotherapy (Jolly *et al.*, 2005).

Both pelvic external beam radiotherapy and brachytherapy reduce the risk of the cancer recurring, although their benefit on overall survival in early stage uterine cancer is limited (Kong *et al.*, 2007; ASTEC/EN.5 writing committee, 2009).

The effectiveness of intensity modulated radiotherapy (IMRT) in treating gynaecological cancers such as uterine cancer is currently being investigated (Fyles, 2009). This treatment delivers a radiation beam that is shaped to fit the cancer more precisely. This allows a higher dose of radiation to be delivered to the cancer while limiting damage to the healthy surrounding area.

** This type of surgery is known as cytoreductive surgery or debulking surgery and is used to remove as much of the tumour as possible.

Chemotherapy

There is currently no standard chemotherapy regimen for treating uterine cancer. Platinum drugs, anthracyclines and paclitaxel currently appear to be the most effective chemotherapy regimens (Humber *et al.*, 2006).

Chemotherapy is usually used to treat advanced uterine cancer and uterine cancer that has come back after initial treatment. The use of chemotherapy is limited due to the adverse effects associated with it. When a combination of two or more drugs are given at the same time the adverse effects are more frequent and more severe and may require treatment to be delayed or stopped. The addition of paclitaxel to cisplatin and doxorubicin showed no benefit in recurrence-free survival, but was associated with increased toxicity (Homesley *et al.*, 2008).

Treatment with chemotherapy combined with radiotherapy (chemoradiation) is currently being investigated in clinical trials. One recent study of advanced stage uterine cancer found overall survival 3 years after treatment with adjuvant*** chemotherapy was only 33%, 70% among women treated with adjuvant radiotherapy only, and 79% among women treated with both adjuvant chemotherapy and radiotherapy (Alvarez Secord *et al.*, 2007). Further research is required to determine the optimal sequencing and types of chemotherapy and radiotherapy (Alvarez Secord *et al.*, 2007).

A recent randomised controlled trial suggests that chemotherapy with doxorubicin and cisplatin is more effective than pelvic external beam radiography when treating women with advanced stage uterine cancer. However, only 63% of women completed the prescribed chemotherapy treatment mainly due to the adverse effects experienced (Randall *et al.*, 2006).

Hormone therapy

Hormone therapy is mainly used to slow the progression of advanced uterine cancer. The effectiveness of hormone therapy can depend on the presence of hormone receptors in the cancer cells. Approximately one in four (25%) tumours respond well to treatment with hormone therapy drugs (CancerHelp UK, 2009).

Just over 10% of women diagnosed with uterine cancer are premenopausal. Hormone therapy may be a useful treatment for women with early stage, low-grade uterine cancer who wish to preserve their fertility. A recent review reported that 51% of young women treated with hormone therapy had a complete and lasting response, 25% had a temporary response and the remaining 24% showed no response to treatment. After completing their family, standard surgical treatment can be carried out (Chiva *et al.*, 2008).

*** Adjuvant treatment is treatment given in addition to the main treatment to try to prevent cancer from returning.

Side effects of hormone therapy may include feeling sick, tiredness, water retention, hot flushes or sweating, breast discomfort and a decreased desire for sex (CancerHelp UK, 2009).

Research on hormone therapies for uterine cancer is currently ongoing. The most common hormonal treatment is with progesterone-like drugs called progestins. Research on the effectiveness of selective oestrogen-receptor modulators, aromatase inhibitors and gonadotrophin-releasing hormone agonists is also currently being investigated (Temkin & Fleming, 2009).

Experimental Treatment

Improved understanding of the molecules involved in the growth of uterine cancer has led to the development of targeted therapies. Targeted therapies use drugs to block the growth of cancer by interfering with specific molecules involved in their development and growth.

Numerous drugs are currently being investigated for their effectiveness in treating uterine cancer. Early studies have shown encouraging results for some targeted therapy drugs (Temkin & Fleming, 2009). Clinical trials are now being conducted to investigate their effectiveness in uterine cancer patients.

Specialist Cancer Centres

There is good evidence that people who have surgical treatment for many of the common cancers in centres with higher throughput, experience better quality of care and better survival rates. As a result of "The National Cancer Strategy: A strategy for cancer control in Ireland" published in 2006, the HSE has designated eight hospitals across Ireland as Specialist Cancer Centres. These Specialist Cancer Centres will provide treatment for all forms of cancer. As each Specialist Cancer Centre serves a large population the care provided is more specialised, clinicians and clinical teams gain greater experience, and the diagnosis and planning of treatment are conducted by multidisciplinary teams. These Specialist Cancer Centres will provide care informed by evidence-based guidelines, effective audit and quality assurance programmes, and closer collaborations between clinicians and researchers.

Conclusion

There are many factors to consider during the decision-making process regarding treatment for cancer. These include the type of cancer, the size of the tumour, the stage of the cancer, the grade of the cancer cells, the age of the women and whether she has a desire to have children, or if she is postmenopausal, and also the overall health of the women and her personal preference. These factors will be discussed between the woman and her specialist cancer treatment team to decide on the most appropriate treatment plan.

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Notes

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The Women's Health Council's "Cancer Treatments: A review of the Bio-Medical evidence on Breast, Ovarian and Cervical Cancer" is available on the Women's Health Council website: <http://www.whc.ie>

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