Survival after Treatment for Gynaecological Cancer

Survival after Treatment for Gynaecological Cancer:

Dealing with Treatment-Related Morbidity

Edited by

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CHAPTER 1

GYNAECOLOGICAL CANCERS: AN OVERVIEW— EPIDEMIOLOGY, TREATMENT AND SURVIVAL OF GYNAECOLOGICAL CANCERS

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YAA ACHAMPONG,
KONSTANTINOS DOUFEKAS,
ADEOLA OLAITAN

Abstract

There are five gynaecological cancers, which are listed in Table 1, in order of frequency in the United Kingdom.

Cancer Site	Incidence Rates/100,000 population
Uterine cancer	24.9
Ovarian Cancer	22.3
Cervical Cancer	10.4
Vulval Cancer	3.7
Vaginal Cancer	0.9

Table 1. Incidence Rates of Gynaecological Cancers UK (2016) - Cancer Research UK (CRUK).

These cancers vary in their predisposing factors, presentation and treatment approaches, as well as in age-related incidence. Naturally, the impact on a woman's life of the diagnosis of cancer and its treatment will also differ. Individually, gynecological cancers are uncommon but are an important cause of mortality and morbidity in women.

As a multi-modality approach to treatment is often required, it is essential that women with gynaecological malignancies are managed by a multi-disciplinary team (MDT) of experts including site-specialised surgeons, oncologists, pathologists, radiologists and clinical nurse specialists (Heudel et al. 2017, Crawford and Greenberg 2012).

In this chapter, we present a brief overview into each cancer that affects the female reproductive tract.

Endometrial Cancer

This is the commonest gynaecological cancer in the UK, with an estimated 9100 cases diagnosed every year (CRUK). One in 41 women will be diagnosed with this cancer during their lifetime, making it the fourth commonest cancer in women. The incidence rates the UK are highest in females aged 75 to 79 (CRUK).

It is estimated that a third of these cancers are preventable (CRUK , NIH 2018). The main risk factor is obesity (Setiawan et al. 2013, Bhaskaran et al. 2014, Lauby-Secretan et al. 2016). A minority of women have a genetic predisposition, mainly related to the hereditary nonpolyposis colorectal carcinoma syndrome (HNPCC) or Lynch syndrome (Meyer, Broaddus, and Lu 2009).

The commonest presenting factor is post-menopausal bleeding, which occurs in 90% of cases, although in younger patients the presentation may be with heavy, irregular periods (Hacker and Friedlander 2010b).

The diagnosis is made by an endometrial biopsy and radiological assessment is important to plan treatment (Hacker and Friedlander 2010b, Sundar et al. 2017). The majority of women present with early disease and gold standard treatment is a total hysterectomy with removal of the adnexa, and in selected cases, the removal of lymph nodes (Hacker and Friedlander 2010a, Sundar et al. 2017). The minimal access route is preferred as it is associated with less morbidity (Sobiczewski et al. 2005, Obermair et al. 2012, Yu et al. 2005). The role of block dissection of the

pelvic and para-aortic nodes in the management of endometrial cancer has been the subject of much debate (Bogani et al. 2014, Colombo et al. 2016). A large multi-centre trial (ASTEC) concluded that lymph node dissection had no impact on survival (Kitchener et al. 2009). Another similar study also showed that pelvic lymphadenectomy did not improve disease-free or overall survival (Benedetti Panici et al. 2008). These studies have been much criticised, mainly due to the small number of nodes retrieved. (Uccella et al. 2009b, Hakmi 2009, Amant, Neven, and Vergote 2009, Uccella et al. 2009a). A new study (STATEC) is re-examining the role of lymphadenectomy in endometrial cancer (CRUK and UCLCTC).

Even if lymph node dissection is proven to improve survival, there is concern about the potential morbidity, in particular lymphoedema (Frost et al. 2017). There is a move towards sentinel node dissection rather than a block dissection to minimize post-operative morbidity (Suidan et al. 2018, Geppert et al. 2018).

After surgical staging, a decision is made about whether adjuvant therapy is required and this is usually radiotherapy, although chemotherapy is playing an increasingly important role (Hacker and Friedlander 2010a).

Survival rates from endometrial cancer are 78% and with a majority of women expected to survive, treatment-related morbidity must be considered and every effort made to reduce its impact (CRUK).

Ovarian Cancer

About 20 women a day are diagnosed with ovarian cancer, making it the sixth most common cancer in women in the UK (CRUK). Incidence rates for ovarian cancer in the UK are highest in females aged 75-79 years (CRUK).

The symptoms of ovarian cancer are insidious in onset and can mimic benign disease (Olson et al. 2001). As a consequence approximately 60% of women have advanced disease at diagnosis (Doufekas and Olaitan 2014).

The usual approach to treatment is a combination of surgery and chemotherapy (Cho and Nezhat 2017, Fotopoulou et al. 2017). Women with fully surgically staged early disease may avoid chemotherapy but as the majority present with advanced disease, most will require chemotherapy (Trimbos et al. 2003). The aim of surgery is to remove all

visible disease and this may require ultra-radical techniques which may include bowel resection and stomas (Ang et al. 2011, Aletti, Dowdy, et al. 2006, Aletti, Podratz, et al. 2006, Cibula et al. 2018, Fotopoulou et al. 2017). Neoadjuvant chemotherapy with interval cytoreductive surgery has been shown to have equal survival rates to upfront surgery, and may be appropriate in patients not fit for immediate surgery, or whose disease distribution makes complete cytoreduction unachievable (Vergote et al. 2010, Kehoe et al. 2015).

Chemotherapy is platinum-based and the standard approach is a combination of Carboplatin and Paclitaxel (du Bois et al. 2003, du Bois et al. 2005, du Bois et al. 2010). Both drugs cause transient immunosuppression. Paclitaxel also causes paraesthesia which manifests as loss of feeling in the fingers and toes from which the woman might never fully recover (Scripture, Figg, and Sparreboom 2006, Pignata et al. 2006). It also causes alopecia which resolves when the drug is discontinued (Sehouli et al. 2015, Bafaloukos et al. 2010).

In recent years, an improved understanding of ovarian carcinogenesis and the related signaling pathways has led to the development of a new category of agents, known as targeted therapies (Kotsopoulos et al. 2014). Bevacizumab, a monoclonal antibody targeting the Vascular Endothelial Growth Factor (VEGF) receptor, is currently used along with the standard chemotherapy in eligible patients (Burger et al. 2011, Perren et al. 2011).

Only 35% of patients will survive ovarian cancer for more than ten years (CRUK). Despite the fact that survival from ovarian cancer has significantly improved during the last 20 years, the disease remains the leading cause of death from gynaecological malignancies (Doufekas and Olaitan 2014). Often women will have to live with the side effects of surgery or chemotherapy, or face further surgical procedures, which can limit their quality of life. The extended multi-disciplinary team's focus, in addition to detecting recurrence, should be to minimise the impact of treatment-related morbidity on the woman's life.

Cervical Cancer

Cervical cancer is potentially preventable. The introduction of prophylactic vaccinations against the high risk human papilloma virus (HPV), the cause of most cervical cancers, combined with screening for the precursors of cervical cancer has meant that the incidence of this disease is decreasing in developed countries (Harper et al. 2004, Joura et al. 2007, Joura et al.

2015, Vilos 1998, Spitzer 1998). It still remains a major health problem in the developing world (Ferlay et al. 2015).

There were 3126 cases of cervical cancer diagnosed in the UK in 2015 (CRUK). There has been a 5% increase in incidence over the last decade and this may be attributed to poorer uptake of screening or migration by women from countries with no screening program (Guerri et al. 2018).

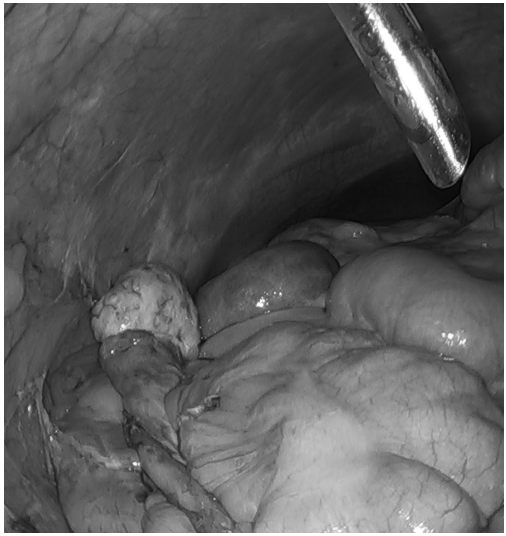
Incidence rates for cervical cancer in the UK are highest in females aged 25 to 29 years (Geppert et al. 2018). A significant proportion of these women will be nulliparous and desirous of fertility.

Screen-detected cancers are usually small and can be treated with fertility-sparing options (Cibula et al. 2018). Larger cancers may require a hysterectomy with the consequent loss of fertility potential (Cibula et al. 2018).

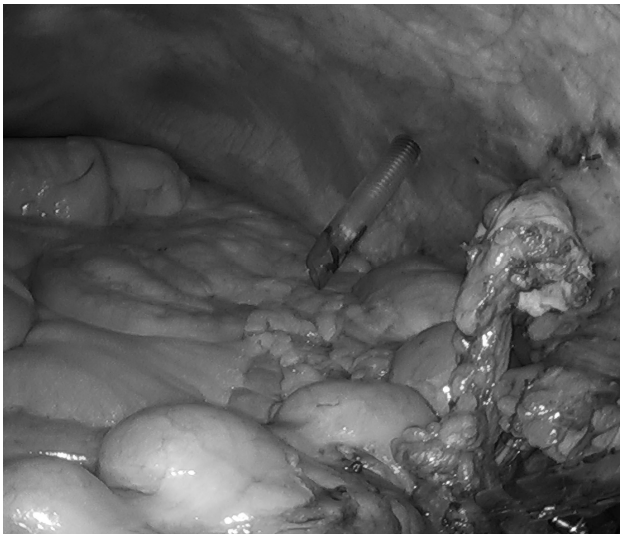
The minimal access approach has been shown to reduce the morbidity of surgery but a recent study has suggested that this may be at the expense of survival (LACC Trial) (Ramirez PT et al. 2018). Inoperable cancers require treatment with chemo-radiation, resulting in loss of ovarian function (Cibula et al. 2018). Laparoscopic ovarian transposition to move the ovaries out of the radiotherapy field can lead to the preservation of ovarian function in up to 65% of women. (Figure 1) (Hwang et al. 2012, Shou et al. 2015, Gubbala et al. 2014).

There are long term effects of pelvic radiotherapy, including an increased risk of a second malignancy (Chaturvedi et al. 2007). There are often profound psychosexual consequences of a diagnosis and treatment of cervical cancer (Park et al. 2007). Treatment should be tailored to the size and prognostic indicators of the tumour and the patients' reproductive wishes where it is safe to do so.

Figure 1: Transposed Ovaries Prior to chemo-radiation for Cervical Cancer (*A. Olaitan archive*)



Right Ovary



Left Ovary

Vulval and Vaginal Cancer

Vulval cancer is uncommon, with around three cases diagnosed every day in the UK, accounting for 1,300 cases each year (CRUK). The rates have increased by 11% over the last decade and this may be related to HPV prevalence (CRUK). It is predominantly a disease of older women, with the highest incidence rates in women aged over 90 years of age (CRUK).

It is estimated that the diagnosis of vulval cancer is delayed by up to six months in 30% of patients due to a combination of patient embarrassment and lack of awareness among health care professionals (Vandborg et al. 2011). Consequently, women may present with large tumours needing more radical treatment (figure 2).

The treatment of vulval cancer is mainly surgical, the aim being to excise the tumour completely with a clear surgical margin of 1cm (Heaps et al. 1990, Gaffney, Werner, and Boothe 2017). The size of the lesion will determine the extent of surgery. In tumours measuring 2cm or less, with a depth of invasion of less than 1mm, involvement of the inguinal nodes nodes is unlikely and inguinal node dissection is not indicated (Gaffney, Werner, and Boothe 2017, Hacker et al. 1984). Larger tumours will require inguinal node dissection, ipsilateral if the lesion is more than one centimeter from midline structures, bilateral if not (Gonzalez Bosquet et al. 2007, Gaffney, Werner, and Boothe 2017).

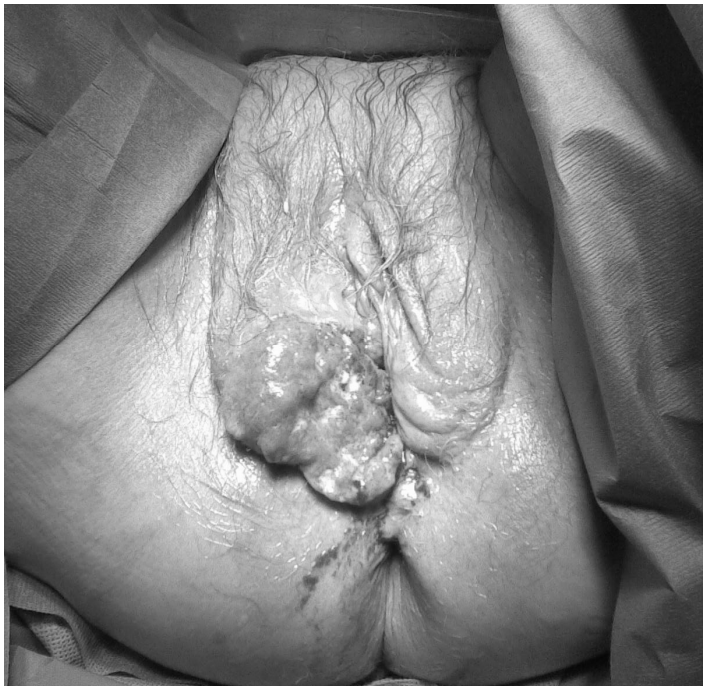
Large radical excisions will require skin grafts or flaps to improve the cosmetic appearance and encourage healing (Saito et al. 2009). Inguinal node dissection carries a 30% risk of lymphedema which, in elderly women, can limit mobility (Huang et al. 2017). Sentinel node detection in eligible women, reduces the risk of lymphedema without compromising survival (Van der Zee et al. 2008, Te Grootenhuis et al. 2016)

Women with close surgical margins or involved nodes will require adjuvant chemo-radiation (Mahner et al. 2015, Faul et al. 1997, Gaffney, Werner, and Boothe 2017, Viswanathan et al. 2013).

Vaginal cancer is even rarer, with 240 new cases diagnosed annually (CRUK). It accounts for less than 1% of all new cancer cases in females in the UK (CRUK). It is also a mainly disease of older women, with incidence rates highest in those aged 80 to 84 years (CRUK). Unlike vulval cancer, incidence rates have remained stable (CRUK). Vaginal cancer is usually treated with chemo-radiation, as achieving surgical

margins while preserving the function of adjacent organs is difficult (Guerri et al. 2018, Hacker 2017).

Figure 2: Vulval Cancer (*A. Olaitan archive*)



Almost two-thirds (64%) of women diagnosed with vaginal or vulval cancer in England survive their disease for five years or more (CRUK).

Conclusion

Gynaecological cancers are, in some cases, potentially preventable and in all cases, curable with minimal morbidity if detected early. Unfortunately, and despite all the advances in screening and prevention, women will continue to present with advanced disease, the treatment of which requires a multimodal approach with consequent treatment-related morbidity. The organs affected and the impact will depend on the cancer and the treatment modality. In the following chapters, we consider the complications and long-term effects of treatment and where appropriate, how to minimise these.

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CHAPTER 2

PSYCHOSEXUAL DIFFICULTIES AFTER GYNAECOLOGICAL CANCER

DR SUE GESSLER

Introduction

The problem

Sexual difficulties are described by many cancer patients (Ananth et al. 2003, Andersen, Anderson, and deProsse 1989, Miles et al. 2007, Flynn et al. 2016) and can persist long after completion of treatment (Greenwald and McCorkle 2008, Stead et al. 2007, Wiggins 2008, Schover et al. 2014). Gynaecological cancer survivors are particularly vulnerable, with a prevalence of sexual difficulties reported as high as 83% (Aerts et al. 2012) and an estimated 50% of women with long-term sexual dysfunction (NCI/NIH 2013). Many women are unaware at the outset of the sexual consequences of their cancer and its treatment (Gessler et al. 2019).

Sexual problems are formally defined by Diagnostic and Statistical Manual-5, as failure of sexual arousal, pelvic pain or pain on intercourse, and female orgasmic disorder (Association 2013). Yet despite widespread understanding by treating teams of sexual difficulties in this population, these remain persistently under-treated (Hill et al. 2011, Candy et al. 2016, Barbera et al. 2017, Schover 2018).

Causes

Physical results of treatment

Treatment for gynaecological cancers is particularly problematic as by their very nature both cancer and treatment damage the major areas of sexual response in the body. Radical hysterectomy disrupts pelvic anatomy

and the local nerve supply to the pelvic floor, affecting sexual arousal, vaginal lubrication and sensation (Jackson and Naik 2006). Loss of internal sensation and lubrication leads to secondary issues where women infer lack of sexual interest from their lack of bodily response and can intensify inhibitory sexual pathways. Radiation damage causes lack of elasticity and scarring to vaginal tissues and stenosis.

Menopause induced by surgery, chemotherapy or radiotherapy leads to vaginal dryness, loss of libido and loss of fertility. Vulvectomy damages or removes labia and other surrounding structures, sometimes including the clitoris.

Formation of ostomies (stomas) can cause body image issues, shame and avoidance, as well as issues with leakage.

Psychological factors

Shame and self-blame can be widespread, especially depending on the patient's beliefs, which can include the belief that they brought their cancer on themselves by stress, or other life-style factors (Ehrenreich 2010). This has been studied particularly in cervical cancer. Waller et al (Waller, Marlow, and Wardle 2007) suggest that shame related to knowledge about the sexually transmitted nature of the Human Papilloma Virus (HPV) can be moderated by the medical team during the initial or later consultations, by offering information at diagnosis and emphasising the common nature of HPV ('It is like the common cold'), before talking about sexual transmission. However, (Flynn et al. 2017) showed that this is less effective in women who have a 'shame-prone' character trait.

Self esteem and body image are often impacted, as well as major changes in, and loss of, role in the home, relationship or at work.

Other responses to physical damage include anxiety, and the secondary anxiety of the partner afraid of damaging a body rendered vulnerable by cancer and its treatments.

Aggravating factors include inflexible sexual attitudes, poor sexual communication skills, feeling stigmatised by cancer, or cancer type, and conflict and dissatisfaction in the woman's intimate relationship (Flynn et al. 2012, Schover 2018).

Protective factors include a positive sexual self-schema, which Carpenter et al (Carpenter et al. 2009) argue helps recovery. It is associated with

more frequent sexual activity, better sexual responsiveness and higher global sexual satisfaction across all disease sites and confounders (Andersen 1994), suggesting that it helps women be resilient to the adverse sexual effects of their cancer.

Although women do resume sexual activity (Stafford and Judd 2010) as frequently as their age-matched cohort (Laumann 1994), they report significant impairment of sexual satisfaction (Gershenson et al. 2007) and responsiveness in longitudinal studies (Gershenson et al. 2007, Lindau, Gavrilova, and Anderson 2007, Hawighorst-Knapstein et al. 2004).

Interventions

Interventions for sexual difficulty after gynaecological cancer include physical, pharmacological and psychological treatments. Physical aids include vaginal dilators, lubricants and clitoral therapy devices (vibrators). Pharmacological treatments include HRT and topical oestrogen to maintain vaginal patency.

Psychological treatments are adapted from those used in the general population, and usually include a full psychosexual assessment, including a sexual history and attitudes before cancer, and should address the physical changes, reconnection with the changed body after treatment, and work on improving couple communication and developing flexibility around sexuality and intimacy (Brotto et al. 2008).

They can be supported and supplemented by written material, but as Schover (Schover 2018) points out, too often leaflets are too general, aimed at the widest possible access and acceptability, hence failing to convey key information in usable form. Sexuality and Cancer: for the woman who has cancer and her partner (Society 2011) is an honourable exception to this criticism, as is ‘Intimacy and Sexuality for Cancer Patients and their Partners’ (Brandenburg 2010), a British publication covering both psychological understanding of sexual response and how it is affected by cancer, as well as highly practical sex therapy techniques.

Online interventions were examined in a systematic review by Kang et al (Kang et al. 2018). For all cancers they found only four articles meeting criteria, but reported the situation as encouraging.

Some websites, such as Will2love.com (Will2Love 2018), can be helpful to both women and professionals. They are informative and normative

especially about women's experience of their bodies, and recent interest in exploring the range of women's sexual responsiveness to genital touching in a non-clinical setting (Herbenick et al. 2018) can be affirming and normalising.

Despite the large literature describing the problem, research into interventions in this population has been underfunded and has largely been confined to small studies. Funding is hard to secure and it is ethically difficult to conduct an randomized controlled trial (RCT) where treatment is denied (Candy et al. 2016).

Evidence for most interventions is moderate. A Cochrane review (Flynn, Kew, and Kisely 2009) found evidence only for topical oestrogen, and rated all studies identified as methodologically poor. A more recent Cochrane review (Candy et al. 2016) found 4218 records of studies of interventions for sexual dysfunction in women after cancer, of which only 11 were found to be eligible for inclusion.

They found weak evidence for testosterone cream and pelvic floor exercises. Of the eight psychological studies, designs and complexity of intervention were so diverse that they were unable to combine for analysis and judge efficacy. They recommend that future studies spend much more time in preparatory stages in intervention development, and that psychotherapeutic and psycho-educational studies follow the Medical Research Council (MRC) guidelines on developing and evaluating complex interventions (Craig et al. 2008).

However, despite the absence of high-level evidence for effectiveness, the clinical demand remains.

A clinically driven approach to the issue has recently led to the development of guidelines for clinical practice in this field. Cancer Care Ontario (CCO) sponsored a systematic review (Barbera 2016) to serve as the evidentiary base and the subsequent guideline (Barbera et al. 2017) has been adopted by the American Society of Clinical Oncology (ASCO) in an adapted and enlarged form (Carter et al. 2018, Schover 2018). The systematic review included 103 studies, which served as the basis for the draft guideline, which was reviewed by an internal expert panel and externally reviewed in targeted peer review. However, most of the evidence was rated as low-to-moderate quality, which would not have been accepted by the Candy et al Cochrane review (Candy et al. 2016).

Their recommendations for women fell into 6 areas.

Sexual Response: Offer psychosocial counselling, aiming to improve desire, arousal and orgasm. There is insufficient evidence to demonstrate superiority of one form over others. Regular stimulation, e.g. masturbation, was also recommended to improve sexual response. No recommendation was made for pharmacological intervention.

Body Image: Offer psychosocial counselling, with partner if possible was recommended, for a minimum of 6 sessions.

Intimacy and Relationships: Offer psychosocial counselling. Studies were highly heterogenous in terms of target (individual, group or couple), type of counselling, number of sessions, follow up and outcome measures and no type could be specified on the evidence.

Overall Sexual Function and Satisfaction: Offer psychosocial counselling (individual, couple or group), but there was no evidence of superiority of any particular type. Physical exercise and pelvic floor physiotherapy might be of benefit.

Vasomotor Symptoms: Hormone replacement therapy (HRT) where oncologically acceptable, up to age 51, and by discussion thereafter, and psychosocial counselling Cognitive Behavioural Therapy (CBT) for symptom management in the absence of HRT.

Genital Symptoms: Women with symptoms of vaginal atrophy be managed in the same way as women without cancer, i.e. initially with vaginal moisturisers. In more severe cases, or if moisturisers are insufficient, vaginal oestrogen was recommended if the cancer is not hormone sensitive. Use of oestrogens in gynaecological cancers requires careful decision-making with the patient and with the oncological team Vaginal dilators were recommended for vaginismus and to prevent vaginal stenosis after radiotherapy for cervical cancer.

Communication about sex in the consultation

Societal assumptions about sex are widespread, affecting both patients and clinicians, for example that older people inevitably give up sex, or that certain cultural groups will have poorer sexual lives. Montgomery (Montgomery 2008) pointed out poor recognition of sexual desire disorders in the general population, and Fromson, (Fromson 2018) against expectation found that more strictly religious members of some religious groups experienced greater sexual satisfaction than more liberal members,