Endometrial Cancer in Obese Women

1. Introduction

Obesity is now affecting 25% of adults in the UK and predisposes women to endometrial as well as other cancers. In 2007, the UK government-commissioned Foresight report predicted that if no action were taken, 60% of men, 50% of women and 25% of children would be obese by 2050. Excess body weight is known to be associated with an increased risk of many malignancies and the risk of endometrial cancer is strongly associated with obesity. Obesity is predominantly associated with type 1 (endometroid) endometrial cancers rather than type 2 (non-endometroid type such as serous or carcinosarcoma) endometrial cancer; however, both sub-types are increased with obesity. Risk of endometrial cancer is increased in women with a body mass index (BMI) greater than 30 kg/m² and the risk increases linearly with increasing BMI. In the UK, approximately 50% of endometrial cancers are attributable to obesity.

Endometrial cancer is the fourth most common cancer in women in the UK with 7536 cases diagnosed in 2007, accounting for around 5% of all female cancers. The incidence of endometrial cancer is rising in postmenopausal women, but 5-year survival rates have improved to more than 77%, although women from deprived backgrounds have up to a 4% lower 5-year survival. In the UK, the incidence of uterine cancer remained stable between 1975 and 1993, but increased by more than 40% between 1993 and 2007. The incidence rates peak between the ages of 60 and 79, the age range within which the largest increases have occurred, with rates doubling since 1975, rising from 40 to over 75 in every 100,000 women in 2007.

Standard treatment for endometrial cancer is surgery (historically total abdominal hysterectomy and bilateral salpingo-oophorectomy, removal of uterus, cervix, tubes and ovaries, with or without lymph node dissection) with adjuvant treatment in the form of radiotherapy and/or chemotherapy as indicated. Preoperative assessment of endometrial cancer may be problematic in obese women. A magnetic resonance imaging (MRI) scan is often used for assessment of endometrial cancer, but many scanners have a weight limit which prohibits scanning morbidly obese patients.

A BMI >30 kg/m² indicates obesity and is associated with an increased risk of perioperative complications, while a BMI >40 kg/m² is described as morbid obesity and is associated with higher rates of complications. Obesity is associated with numerous disorders, notably diabetes, hypertension and cardiovascular disease. In morbidly obese women, perioperative complications such as obstructive sleep apnoea, arrhythmias, acute cardiac events and venous thrombotic events are more common. Obese and morbidly obese women are therefore likely to require more detailed preoperative assessment to reduce the sequelae of co-existing morbidity and more intensive postoperative care. The challenges of perioperative care for such patients are likely to impact on medical, nursing and psychosocial resources. Thus, treatment for endometrial cancer needs to be reassessed in the complex and increasingly common situation of the obese older woman with this disease.

2. Surgery

Laparoscopic hysterectomy and bilateral salpingo-oophorectomy has been demonstrated to be the surgical technique of choice for women with endometrial cancer in three large randomised controlled trials. In an American randomised controlled trial, the Gynecologic Oncology Group (GOG) LAP2 study, all women underwent pelvic and para-aortic lymphadenectomy at the time of hysterectomy and bilateral salpingo-oophorectomy, while in an Australian, New Zealand and Hong Kong randomised controlled trial women could be excluded for lymph node staging if they were obese, had early-stage disease or were medically unfit (52% had lymphadenectomy). In a Dutch randomised controlled trial, women had only hysterectomy and bilateral salpingo-oophorectomy.
Laparoscopic hysterectomy has the benefits of shorter hospitalisation, reduced analgesic requirements, superior quality of life scores and resumption of daily activities. Laparoscopic surgery by experienced surgeons did not result in any more significant intraoperative complications than open surgery. All patient-reported outcome measures were significantly better after laparoscopic surgery in women with BMIs less than 35 kg/m². In both the GOG and the Dutch study, women with high BMIs had a higher conversion rate from laparoscopic to open surgery. In the GOG trial, there were significantly more postoperative events after abdominal hysterectomy, but this was not the case in the other two randomised controlled trials. In the GOG study, 26.5% of women with a BMI of 34–35 kg/m² were converted to open procedures and 57.1% of women with a BMI greater than 40 kg/m² were also converted to open surgery. In the Dutch study, a BMI over 35 kg/m² was associated with a conversion rate of 32.3%. These trials reported conversion rates in thin patients of 17.5% and 6.5% respectively, perhaps reflecting the inclusion of pelvic and para-aortic lymphadenectomy in the American study and not in the Dutch study. In the Australian study, the conversion rate was low for all procedures at 3.6% and not reported in relation to BMI.

In a case series from the Hammersmith hospital with highly trained laparoscopic surgeons, the conversion rate to open surgery in 191 women undergoing laparoscopic hysterectomy and salpingo-oophorectomy for endometrial cancer which included 60% patients with a BMI ≥ 30 was 1.04%. Bijen et al. performed a randomised controlled trial on the outcomes from laparoscopic hysterectomy for endometrial cancer. The conversion rate for women over 70 years of age was the same as for younger women (10.5%); however, there was a significant difference in women with a BMI >35 kg/m². The estimated risk of conversion from laparoscopy to laparotomy increases with BMI, with a steep rise in women with a BMI >35 kg/m². The major complication rate in women with BMI >35 kg/m² undergoing laparoscopic surgery was similar to open surgery (25%). The authors concluded that it was not cost-effective to perform laparoscopic hysterectomy in high-BMI women. However, it is of note that the conversion rate in this study was much higher than in the other studies mentioned, which would account for the lack of cost-effectiveness.

Laparoscopic hysterectomy has been demonstrated to improve patient-reported outcomes compared with open surgery in the short term but there is no significance difference other than body image at 6 months. In a randomised controlled trial of the use of laparoscopic hysterectomy for treatment of endometrial cancer, both in the early phase of recovery and 6 months postoperatively, patients who had laparoscopic hysterectomy reported significantly greater improvement in quality of life measures from baseline compared with those who had an open hysterectomy, in all subscales apart from emotional and social wellbeing.

Many authorities recommend modified apronectomies to improve surgical access and reduce long-term wound morbidity in morbidly obese women. These retrospective case series report significantly lower wound complication rates compared with mid-line laparotomy alone. Apronectomy was associated with a four-fold reduction in wound morbidity compared with standard laparotomy approach. Surgical time for hysterectomy combined with apronectomy in women who are obese is significantly prolonged compared with hysterectomy alone, with an American case series reporting the following surgical times: median 265 minutes (range 171–355) compared with 168 minutes (range 40–368), i.e. an average additional operating time of more than one and a half hours. However, Umeadi reported a UK case series of apronectomies at the time of hysterectomy; in this series, surgery time was median 167 minutes (range 120–522), which is equivalent to the hysterectomy-only group in the American case series. Hysterectomy combined with apronectomy has been shown to result in prolonged hospitalisation.

Vaginal hysterectomy and bilateral salpingo-oophorectomy performed under regional anaesthesia may be an alternative route for surgery in obese women not fit for general anaesthetic. However, this route does not allow direct visualisation of the peritoneal surfaces and can be challenging in very obese postmenopausal women. Surgical times are significantly prolonged in obese patients. In addition, abdominal hysterectomy in obese women is known to have a high morbidity, with a significant increase
in wound infection, wound separation and re-hospitalisation compared with surgery in the non-obese.26–28 This is not surprising as a recent report suggests that tissue antibiotic levels may be sub-therapeutic in obese women when given in standard doses.29 One of the advantages of laparoscopic hysterectomy in obese women is the low rate of wound infection compared with laparotomy.30 Obesity-related wound complications after colectomy were estimated to be 60% more frequent compared with non-obese cases, and were estimated to increase hospital costs by US$17,324 per case in the US in 2011.31 Similarly, the increased estimated costs of obesity-related wound infections in cholecystectomy and appendicectomy were estimated to be US$1,109 and US$666 in another recent study by the same group.32 To date there are no published reports on the economic impact on health services of hysterectomy in relation to obesity either in the US or UK.

One of the major controversies in the management of endometrial cancer is the role of lymph node dissection (pelvic and possibly para-aortic) at the time of surgery. Lymph node dissection may be used for accurate staging of endometrial cancer or may have a therapeutic role. The therapeutic role of lymphadenectomy is still not proven in prospective trials; however, some retrospective reports suggest a therapeutic benefit for patients with high-risk early-stage endometrial cancer.33 In morbidly obese women, the addition of lymphadenectomy may result in more complications owing to difficulties with surgery in this group of women, and possibly higher conversion rates for laparoscopic procedures. In a retrospective case series, the median duration of hysterectomy without lymphadenectomy in women with a BMI >35 kg/m² was 145 minutes (range 40–335) at laparotomy and 203 (range 94–330) at laparoscopy.21 Median laparoscopic operating times in women with a high BMI were significantly longer (95 minutes) than low-BMI women (60 minutes).20 In the LAP2 randomised controlled trial that included lymphadenectomy on all patients, a high BMI was also associated with prolonged surgery and higher conversion rates to open surgery.14 In the Australasian randomised controlled trial, lymphadenectomy was optional in high-BMI women.15

3. Primary radiotherapy

Endometrial cancer is radiosensitive and radiotherapy may be used as a sole treatment modality. Although there have been no direct comparisons of primary radiotherapy with surgery in women with local disease and significant comorbidities, early case series suggest that primary radiotherapy has inferior survival rates compared with hysterectomy, with the risk of intrauterine recurrence. Radiotherapy as primary treatment of endometrial cancer is only considered in exceptional cases; recurrence rates of up to 18% have been reported in these patients in a recent retrospective study.34

Radiotherapy is administered either as a combination of external beam radiotherapy and brachytherapy or as brachytherapy alone.34 The justification for using external beam radiotherapy is that some patients have occult pelvic sidewall disease, particularly with high-grade tumours, and its inclusion might improve outcomes. The inclusion of external beam radiotherapy might be considered over-treatment in early-stage low-grade disease. However, reports suggest a 5–20% rate of late radiation toxicity when combining external beam and intracavitary radiotherapy.18

External beam radiotherapy of the pelvis in obese patients is also complicated by anatomical changes in these patients owing to the amount of adipose tissue. The target organ may shift, resulting in a reduced dose being delivered to it. Higher failures with radiotherapy to pelvic cancers have been reported in prostate cancer.36 Image-guided planning and treatment may overcome some of these problems.

The majority of early publications report on low-dose-rate (LDR) brachytherapy with later studies reporting on high-dose-rate (HDR) brachytherapy. HDR offers the benefit of shorter treatment times. These case series tend to include women who are unfit for surgery owing to medical comorbidities – including significant obesity – and the majority of published case series were conducted prior to computerised radio-planning. In these case reports, death rates owing to intercurrent disease were high, but reported disease-specific 5-year survival rates35 were similar to surgical cure rates.
4. Progestogens

Many clinicians faced with the dilemma of low-grade endometrial cancer in women with morbid obesity and comorbidity are prepared to use progestogens, particularly administered by intrauterine system (IUS), as a conservative management of disease. However, there are no large case series reporting on the outcome of such medical management as a primary treatment and the long-term outcome of such management is unclear. There are several small case series of using either the oral route or IUS to administer progestogens in young women with severe endometrial atypia or low-grade endometrial cancer who wish to preserve their fertility. The results of these studies are heterogeneous and may not necessarily apply to obese patients with endometrial cancer.

Studies in a recurrence setting (irrespective of the patient’s weight) with high-dose oral progestogens report an objective response rate from 11% to 25%. Most responses are partial and of relatively short duration, although some patients remain free of disease progression for more than 12 months.

5. Cancer prevention and survivorship

The association between obesity, the resultant metabolic changes and endometrial cancer is well established. The rationale for prevention of endometrial cancer is based on our understanding of the cellular and molecular pathways involved in this cancer. Use of the combined contraceptive pill is associated with reduction in risk of developing endometrial cancer; however, the pill may not be safe for use in obese women (UKMEC). Use of the Mirena IUS, weight loss, exercise and use of oral hypoglycaemic drugs (e.g. metformin) for control of diabetes have all been suggested as a means of prevention of endometrial cancer in obese women. Bariatric surgery that results in sustained weight loss has also been linked with reduction in risk of developing cancer, more noticeably in women.

The Cancer Reform Strategy (2007) outlined the need for a National Cancer Survivorship Initiative to improve the care and support provided for those living with and beyond cancer. Women with endometrial cancer will require generic physical/psychological support after initial treatment in keeping with the survivorship agenda. Women who are significantly overweight are likely to benefit from tailored lifestyle interventions to enhance general wellbeing and to reduce the risk of recurrence.

Obesity is associated with non-cancer-related comorbidities such as diabetes, cardiovascular disease, hypertension and pulmonary disease that might also have a negative impact on morbidity and survival. In two US surveys of endometrial cancer survivors, obesity was associated with a low level of physical activity, poor physical functioning, fatigue and pain. Obese endometrial cancer survivors often have comorbidities restricting their lifestyle, and this has a negative impact on quality of life measures.

The growing evidence base suggests that obesity has a negative impact not only on cancer-related outcomes but also on women’s global wellbeing. Weight management should be advocated as an important component of the NHS survivorship agenda. Despite the adverse effects of obesity in cancer survivors, only five studies have assessed weight management in cancer populations. Two of these studies looked mainly at survivors who had completed active treatment, and reported that individual dietary counselling provided by a dietician was effective in promoting weight loss. Three studies have shown that physical exercise reduces the risk of cancer recurrence and overall survival in breast and colon cancer. A study in breast and prostate cancer survivors suggested that the optimum time to influence lifestyle changes was shortly after diagnosis and that lifestyle interventions are more likely to be sustained in women. In a small randomised controlled trial of 45 obese women surviving endometrial cancer, a counselling programme including a psychologist and dietician improved eating behaviour and emotional wellbeing but not quality of life.

In July 2011, the UK government set out a framework for delivery of public health, entitled ‘Healthy lives, healthy people. White Paper: Update and way forward’, in which prevention of obesity and lifestyle initiatives become the responsibility of public health through local authorities. Lifestyle changes were to be encouraged within this framework, and the Department of Health published physical activity...
guidelines including specific recommendations for the elderly and obese. These themes were endorsed in the RCOG’s Expert Advisory Group report in July 2011, ‘High Quality Women’s Health Care: A proposal for change’, which promotes a life-course approach, in tandem with primary care strategies to promote better health by reducing obesity. The multidisciplinary gynaecological oncology team needs to exploit the opportunity of lifestyle changes in women undergoing treatment and subsequent follow-up within the new survivorship agenda.

6. Opinion

Surgery for endometrial cancer in obese patients presents challenges to surgeons, anaesthetists and nursing teams. Laparoscopic surgery is the optimum approach in order to minimise postoperative wound complications and encourage early discharge from hospital. Surgery, whether laparoscopic or open, is challenging and is very much dependent on the expertise of the operator. High conversion rates in morbidly obese patients in some randomised controlled trials of laparoscopic hysterectomy illustrate that the choice of surgical route has to be carefully considered depending on available local expertise. Abdominoplasty at open procedures is time consuming but reduces perioperative morbidity, and the morbidity of such procedures is likely to be reduced by an experienced surgeon. Ideally, all gynaecological cancer centres should offer expertise in surgery for morbidly obese women to their networks, as individual units are unlikely to develop such experience. Centres should encourage training in operative techniques that enhance skills in laparoscopic surgery and abdominoplasty. There are no data currently available to evaluate the clinical or cost effectiveness of robotic surgery in the management of these women.

Laparoscopic or open surgery in morbidly obese women exerts demands on the local health economy: preoperative investigations can be extensive, the duration of surgery can be prolonged, patients often require high-dependency postoperative care, surgical wards need specific equipment for such patients, and hospitalisation can be prolonged. At present, there is no enhanced tariff for hysterectomy in morbidly obese women compared with women of low BMI. Centralisation of surgery of morbidly obese women with endometrial cancer is likely to reduce morbidity, but delivering such a quality service needs to be recognised by an uplift in tariff/revenue for such complex cases. Thought should also be given to investment in training of surgeons in appropriate technologies such as laparoscopic surgery to deal with the increasing number of morbidly obese patients.

Primary radiotherapy may be a viable treatment modality in patients with significant comorbidities and a prospective nationwide registry of such cases should be considered. Finally, the gynaecological oncology community needs to develop a definitive study of progestogens, administered either orally or by IUS, for the primary treatment of low-grade endometrial cancers in obese women with comorbidities precluding surgery before their use in this setting becomes commonplace.

Specific patient-centred information is needed for obese women undergoing management for endometrial cancer. Furthermore, the optimum timing and nature of interventions to promote better lifestyles needs to be ascertained in clinical trials, as there is limited evidence for such strategies, particularly in gynaecological oncology.

References


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