



Tumour Review

Improving outcomes for older women with gynaecological malignancies

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ABSTRACT

The incidence of most gynaecological malignancies rises significantly with increasing age. With an ageing population, the proportion of women over the age of 65 with cancer is expected to rise substantially over the next decade. Unfortunately, survival outcomes are much poorer in older patients and evidence suggests that older women with gynaecological cancers are less likely to receive current standard of care treatment options. Despite this, older women are under-represented in practice changing clinical studies. The evidence for efficacy and tolerability is therefore extrapolated from a younger; often more fit population and applied to in every day clinical practice to older patients with co-morbidities. There has been significant progress in the development of geriatric assessment in oncology to predict treatment outcomes and tolerability however there is still no clear evidence that undertaking a geriatric assessment improves patient outcomes. Clinical trials focusing on treating older patients are urgently required. In this review, we discuss the evidence for treatment of gynaecological cancers as well as methods of assessing older patients for therapy. Potential biomarkers of ageing are also summarised.

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Introduction

Incidence and survival in older patients

The EURO CARE project [1], which assesses cancer survival across Europe over time, demonstrated that although for almost all cancers there was a continued improvement in outcomes over time, the rate of progress was slower in older patients – in particular for patients with gynaecological malignancies. However, of note, if older patients with a gynaecological cancer survived the first year after diagnosis, the prognosis for this group was similar to middle-aged patients [2].

The majority of gynaecological cancers (ovarian, endometrial, vulval) are diagnosed in postmenopausal women [3–5]. For cervical cancer, in addition to the incidence peak at age 30–34, there is a second rise in incidence above the age of 70 [6]. The incidence of endometrial cancer peaks in the 70–74 age group (94.1 per 100,000). Between 1993 and 2009, the incidence of endometrial cancer in women over the age of 75 rose by 43%

[4,7] and two thirds of deaths from endometrial cancer occur in women over the age of 70 [4].

Ovarian cancer is predominantly a disease of older women; in the UK, around half of all diagnoses are in women over the age of 65 [8] and the median age at diagnosis is 64.7 [9]. This is similar in the USA where 44% of all ovarian cancer cases occur in women over the age of 65 and the median age at diagnosis of 63 [10]. Over the past 20 years, significant advances in the management of ovarian cancer have led to the improved survival rates in all groups with the notable exception of those over the age of 80 [1]. For example, in the UK, the mean 1-year survival for stage IV ovarian cancer patients of all ages is 51.0% but this dramatically falls to 35.7% for women over the age of 70 [11]. The fundamental issue of worsening outcomes with increasing age is applicable worldwide [12].

With an ageing population, although the overall incidence of cancer is not projected to change, the proportion of patients over the age of 65 is expected to rise. For example, in the UK by 2030, 67.5% of all female cancer patients will be over the age of 65 [7]. Survival rates are summarised in Table 1. The UK survival statistics for gynaecological malignancies are known to be poorer compared to the results of other developed countries. Of concern, is the fact that this difference is magnified further for older patients [11]. For example, a woman over the age of 70 diagnosed with stage

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Table 1
UK Age-specific relative survival at 1 and 5 years by tumour type.

Cancer Type	1-year age-specific relative survival (%)	5-year age-specific relative survival (%)
Cervical [6]		
50–59 years	85.2	59.1
70–79 years	70.0	34.0
Endometrial [98]		
55–59 years	95.6%	86.2
75–79 years	86.5	67.7
Ovarian [3]		
55–59 years	85.9	47.0
75–79 years	56.6	24.5

III ovarian cancer in Canada has an expected 1-year survival of 74% compared to just 57% in the UK [11].

Potential reasons for poor survival

The reasons for poorer outcomes in older patients with gynaecological cancers are not fully understood. It has been postulated that delayed presentation for a multitude of psychosocial reasons leading to advanced stage at diagnosis, increasing comorbidities, relative under-treatment as well as potentially adverse tumour biology in cancers diagnosed in older women may all play a role.

A report from the International Cancer Benchmarking Group demonstrated that more advanced stage at ovarian cancer diagnosis was associated with increasing age [9,11]. Furthermore, it has been shown that older patients were significantly less likely to be referred for investigations such as abdominal ultrasound or to a gynaecologist in the year preceding a diagnosis of ovarian cancer [13]. One study reported that the median time for a 75-year old woman to be referred for further investigation following the reporting of symptoms was 20 weeks [13]. Older women with endometrial cancer are more likely to be diagnosed with a later stage and present as an emergency, both factors known to be associated with worse outcomes [14].

The treatment plan for older women is often different compared to younger patients. For example, older patients with cervical cancer are more likely to receive primary radiotherapy rather than surgery, less likely to undergo a radical hysterectomy, lymphadenectomy, adjuvant radiotherapy or brachytherapy [15,16]. In advanced disease, 12.1% of patients over 80 years old compared to 3.9% under 50 years old ($p < 0.0001$) received no anticancer treatment. Adjusting for stage and treatment, disease-specific mortality was increased in those over the age of 70 [16]. Evaluation of data from the SEER database (1992 and 2002) demonstrated that women over the age of 65 were less likely to undergo radical surgery for endometrial cancer [17]. A retrospective study of 20,468 women from the USA National Cancer Database demonstrated that, adjusting for prognostic factors, women between the age of 75 and 84 were less likely to receive surgery, radiotherapy and chemotherapy than women under the age of 55 for high-grade endometrial cancer [18]. Similar findings were found from an analysis of three GOG studies which showed that only 64% of patients over the age of 70 who were offered adjuvant radiotherapy actually went on to receive treatment [19].

Although there have been international efforts to increase the recruitment of older patients into clinical studies, women over the age of 65 remain underrepresented in practice-changing studies [20–22] and yet form a significant proportion of patients being treated in daily clinical practice. For example, among 28,766 patients enrolled into 55 registration studies in the US across a number of malignancies including ovarian cancer, 35% of the study population were over the age of 65 compared with 60% in the US

population in clinical practice [20]. The discrepancy increases with age; with the exception of hormonal therapy trials in breast cancer, only 4% of patients over the age of 75 entered clinical trials. For example, in the pivotal GOG-158 phase trial which contributed to the establishment of carboplatin in combination with paclitaxel as standard care for first-line treatment in ovarian cancer, 11% of the patients enrolled were over the age of 71 and only 1% over the age of 81 [49]. There is a lack of prospective clinical studies focusing on older, less fit patients with gynaecological malignancies.

Finally, it has been recognised that there is a need for an alternative assessment method to guide treatment decisions in the older population. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is the accepted standard for evaluation of a patient's functional status both in clinical studies and in routine clinical practice. It is widely accepted that this is a limited tool for assessment of older patients and does not accurately represent limitations in functional or cognitive capability [23–25].

In the remainder of this review, the evidence for treatment of gynaecological cancers in older women, methods of assessing older patients for cancer therapy and potential steps towards improving outcomes are discussed.

Endometrial and cervical cancer

Studies addressing the management of older patients with endometrial and cervical cancer are limited and largely consist of retrospective cohort analyses. The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 trial showed that women over the age of 60 were threefold more likely to have a locoregional recurrence following radical surgery compared to younger patients (HR 3.90 $p = 0.0017$) [26]. Following 15-year follow-up, the local recurrence rate in the overall study population was reduced from 15.5% to 6.0% with the addition of post-operative external beam radiotherapy (EBRT). However, in older patients who may have co-morbidities and/or functional limitations, the potential treatment toxicities (primarily bladder and bowel) as well as the need for a daily treatment over 5 weeks needs to be considered. The PORTEC-2 trial in which almost half of the patients were over the age of 70, high-dose rate (HDR) brachytherapy was shown to be equivalent to EBRT for local control in intermediate-high risk disease with a more tolerable toxicity profile in terms of gastrointestinal side effects [27].

A retrospective case series of 113 women over 70 years old (median age 76) who received brachytherapy for stage I–IV cervical cancer reported grade III/IV rectal, small bowel and urinary tract toxicities rates in 1.8%, 0.9% and 2.7% of patients respectively. The 3-year disease-specific survival was 81% [28]. A retrospective study from Japan evaluated outcomes according to age. 132 of the 727 women whom received radical radiotherapy were over 75 years old. In this case series, there was no significant difference in late radiation bladder toxicity between patients aged ≤ 64 , 65–74 and ≥ 75 years old. There appeared to be lower rectal toxicity in the over 75 year old patients group but this may be a reflection of the lower radiation dose delivered in this group (median dose 45 Gy compared to 53 Gy in those under the age of 64). The 5 and 10-year disease-specific survival rates were not significantly different between the three groups [29].

To date, there have been no prospective studies focusing on treatment tolerance and outcomes in older women with endometrial cancer or cervical cancer. Prospective studies including geriatric assessment to evaluate treatment outcomes and tolerability of chemotherapy and radical treatment options such as external beam radiotherapy, brachytherapy and radical hysterectomy specifically in older patients are required.

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