abstract

The diagnosis and management of cervical cancer in the older patient presents important challenges to the geriatrician and oncologist. Cervical cancer almost never occurs in older patients who have followed screening guidelines and have had a history of normal Pap smears prior to age 70. Early stage disease is best managed by radical surgery. While radical pelvic surgery has been proven safe in selected older patients, the current management of early cervical cancer depends upon the resources available to the geographical location. For locally advanced cervical cancer and early stage patients who are not surgical candidates, radiation therapy with concurrent platinum-based chemotherapy is the standard of care. Radiation therapy and chemotherapy can be safely administered to older patients once allowances are made for age-related physiologic changes. Advanced age should not be used as justification to alter the standard of care for the management of cervical cancer.

Key words: cervical cancer, older adults, chemotherapy, radiation therapy, radical pelvic surgery

Cervical Cancer in the Older Patient: Diagnosis and Management

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Introduction

Age has been shown to have a major impact on the survival of cancer patients. Among women, the poorer survival associated with increasing age represents a global public health problem affecting patients with cancers of the lung, breast, colon, pancreas, stomach, blood, uterus, and ovary.[1] Results from the most recent reporting period (1996 to 2000) from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program demonstrated 57% of new cancer cases and 71% of cancer deaths in the United States occurred in patients 65 years and older. Aging individuals (generally defined as 65 years and older) account for just under 13% of the United States population; however, current projections estimate this proportion will rise to as high as 20% by the year 2030.[1] Consistent with North American statistics, the Canadian Institutes of Health Research (www.cihr-irsc.gc.ca) reports that 38% of Canadian women and 41% of Canadian men will develop cancer during their lifetime.

Although this may sound disconcerting to the older reader, cervical cancer occurs less commonly in the older population than in the younger population with a median age for incidence of 48.[2] Similarly, information provided from Health Canada (www.hc-sc.gc.ca) demonstrates the highest incidence of cervical cancer occurs in women between 40 and 59 years old with approximately 1,400 new cases of cervical cancer and 410 deaths due to this disease in Canada in 2002. Partly due to the decreased incidence in the older population, our understanding of the impact of age on cervical cancer has lagged behind our understanding of other cancers afflicting the female population. Therefore, the diagnosis and management of cervical cancer in the older patient present important challenges to the geriatric clinician.

Screening and Diagnosis

Early detection of cervical disease has been one of the greatest success stories in medicine. Cervical cancer mortality in the United States has decreased by over 70% in the past five decades largely due to the introduction of cervical cytological evaluation (the Pap smear).[3] Cervical cancer screening recommendations continue to change with emerging data and technology (e.g., liquid-based cytology and human papillomavirus testing) and are beyond the scope of this article; however, the interested reader is referred to the American Cancer Society and the FDA websites at www.cancer.org and www.fda.gov, respectively. The above notwithstanding, the diagnosis of cervical cancer in older women is almost completely limited to the unscreened and underscreened population, and therefore routine testing in patients over 70 years of age with a history of normal Pap smears is not warranted.[3] Specifically, the choice of age 70 as a screening cut-off is based on expert opinion, taking into account mathematical modeling (balancing benefits and risks of screening) as well as significant data

demonstrating that the majority of cervical cancers in older women occur in patients who were not previously screened or who did not have three consecutive normal cytology results.[3–6] For example, one study reported declining rates of high-grade intraepithelial lesions in women aged 60 to 69 with increasing number of prior normal Pap smears.[4] Similarly, lower rates of squamous intraepithelial lesions have been reported in women 65 years and older with at least one previous normal cytology result within the previous three years.[5] With regard to diagnosis, once an abnormal Pap smear is detected, colposcopy with directed cervical biopsies and endocervical curettage are used to confirm or disprove the presence of cervical cancer.[7]

Staging

Management of cervical cancer in older women is similar to management of cervical cancer in the younger population and largely depends upon the extent of disease. In general, older patients are more likely to present with more advanced stage cancers.[8] However, the reader should be aware that cervical cancer is staged clinically using the International Federation of Gynecology and Obstetrics (FIGO) nomenclature (Table 1), and therefore a patient's stage may not reflect her true extent of disease.[8] In fact, one study demonstrated only a 52% correlation between clinical stage and surgical findings.[9] Despite this, clinical staging is the standard worldwide as cervical cancer remains a leading cause of death in women in developing countries, where limited health care resources do not allow for surgical evaluation.[10]

Management of Early Cervical Cancer

Management of early cervical cancer (stages IA2, IB, and IIA) depends upon the resources available to the geographical location. In North America and most developed countries, where surgical expertise in radical pelvic surgery is widely accessible, management of early lesions can be generally divided into lesions amenable to primary surgical treatment (radical hysterectomy and bilateral pelvic lymphadenectomy) and those deferred to primary radiation treatment with concurrent chemotherapy.[8–11] In this context, radiation therapy is generally reserved for

Table 1: Carcinoma of the Cervix Uteri Clinical Staging: International Federation of Gynecology and Obstetrics (FIGO) Nomenclature (Montreal, 1994)

Stage 0	Carcinoma *in situ*, cervical intraepithelial neoplasia 3 (CIN 3)
Stage I	Carcinoma confined to the cervix (extension to corpus disregarded) – IA Invasive carcinoma diagnosed by microscopy only. All visible lesions are allotted to stage IB carcinomas. Invasion is limited to maximum depth of 5mm and horizontal extension ≤ 7mm into stroma • IA1 Stromal invasion of < 3mm in depth and extension of ≤ 7 mm • IA2 Stromal invasion of > 3mm and < 5mm in depth and • extension of < 7mm – IB Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA • IB1 Clinically visible lesions < 4cm • IB2 Clinically visible lesions > 4cm
Stage II	Cervical carcinoma invades beyond the uterus, but not to pelvic wall or lower third of vagina – IIA No obvious parametrial involvement – IIB Obvious parametrial involvement
Stage III	Carcinoma extends to the pelvic wall. On rectal examination there is no cancer-free space between the tumour and the pelvic wall. The tumour invades the lower third of the vagina. All cases of hydronephrosis and nonfunctioning kidney are included, unless they are known to be due to another cause. – IIIA Tumour involves lower one third of the vagina, with no extension to the pelvic wall – IIIB Extension to the pelvic wall or hydronephrosis or nonfunctioning kidney
Stage IV	Carcinoma extends beyond the true pelvis, or involves (biopsy-proven) the mucosa of the bladder or rectum. Bullous edema, as such, does not permit a case to be allotted to stage IV. – IVA Spread of the growth to adjacent organs – IVB Spread to distant organs

Source: Adapted from Hacker NF, 2000.[8]

patients who are considered poor surgical candidates.[11]

Radical Surgery

Importantly, radical pelvic surgery has been proven to be safe in the older population.[12–14] Specifically, one study performed a retrospective evaluation of 62 patients over the age of 65 undergoing radical hysterectomy and pelvic lymphadenectomy in a gynecologic oncology practice.[14] The authors found that while patients 65 years and older had significantly more comorbidites than their younger counterparts, there were no differences in operative morbidity or mortality between the two groups. Similarly, a retrospective analysis of radical pelvic surgery in 226 consecutive patients at a single institution found age to be a poor determinant of surgical risk even though women over 70 years old had a significantly worse presurgical performance status and increased comorbidities.[13] Intuitively, the older patient with associated comorbidities may be at a higher risk for surgery than their younger counterparts. However, research on surgical procedures involving a variety of solid tumours has now shown that, with careful management of comorbidities during the preoperative, intraoperative, and postoperative period, major surgery can be safely performed in the older patient.[15]

Management of Locally Advanced Cervical Cancer

Patients with locally advanced cervical cancer confined to the pelvis (including bulky stage IB, and IIB to IVA disease) should receive concurrent platinum-based chemotherapy and radiation therapy. On February 23, 1999, the National Cancer Institute issued a clinical announcement stating that "strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer." This statement was based on the results of five randomized trials[11,16–19] that demonstrated a 30–50% improvement in survival among patients receiving cisplatin-based chemotherapy concurrently with radiation therapy.[20] Only three of the five studies stratified patient age into categories.[16–18] Based on these three studies, patients 61 years and older represented approximately 8–18% of cervical cancer patients studied. Although radiation therapy is generally well tolerated in the older patient, the adverse effects of treatment in the above studies were not separated based on age of the patient. Therefore, we cannot make any definitive conclusions regarding older patients and their ability to tolerate concurrent cisplatin-based chemotherapy and radiotherapy. However, chemotherapy in the aged patient has been well studied, and age-related changes in physiologic function with subsequent alterations in pharmacokinetic and pharmacodynamic parameters have been described.[21] Importantly, cisplatin can be safely administered in older adults, with retrospective studies showing no significant increase in renal toxicity.[21] In addition, cisplatin therapy does not significantly reduce creatinine clearance in the older patient when compared to the younger counterpart.[22] Although not as extensively studied in the treatment of cervical cancer, carboplatin has a mechanism of action similar to cisplatin while possessing a more favourable non-hematologic toxicity profile.[23] While carboplatin is not routinely used interchangeably with cisplatin, the chemosensitizing effects of carboplatin have been studied in a variety of tumours.[16] Therefore, carboplatin may be an attractive alternative chemotherapeutic agent in the older patient who may not otherwise be able to tolerate cisplatin-based chemotherapy during her radiation treatment. As chemotherapy with different agents becomes more common in the older patient, dosing and choice of agents should be individually tailored, taking into account age-related limitations of drug absorption, distribution, metabolism, and excretion, as well as patient compliance and dose modifications for end organ dysfunction.[21,24]

Adjuvant Therapy

Finally, postoperative adjuvant therapy is appropriate in selected patients. Women with clinical stage IA2, IB, and IIA carcinoma of the cervix initially treated with radical hysterectomy and pelvic lymphadenectomy that are found to have positive risk factors for recurrence (positive pelvic lymph nodes, positive margins, and microscopic parametrial involvement) should receive postoperative concurrent chemotherapy with pelvic radiation therapy.[11] In this population of patients, a statistically significant improvement in progression-free and overall survival was demonstrated in patients receiving concurrent cisplatin-based chemotherapy compared to patients receiving pelvic radiation alone.[11] Postoperative adjuvant pelvic radiation therapy has also been shown to reduce cancer recurrences in patients with stage IB disease with the intermediate risk factors of significant stromal invasion, capillary lymphatic space involvement, and large clinical tumour diameter.[25] Although chemotherapy was not used in this particular study, most authorities agree that platinum-based chemotherapy should be given concurrently with radiation therapy whenever treating patients with cervical cancer based on the findings as described previously.

Conclusion

In summary, the diagnosis and management of cervical cancer in the older woman provides unique challenges to the practising geriatrician and oncologist. Overall, cervical cancer treatment modalities are well tolerated by older patients. Therefore, age alone should not be used as criterion to alter the standard of care for the management of cervical cancer in the older patient. u

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