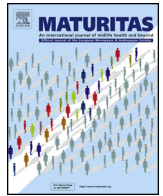




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Review

Cervical cancer in the older woman

Q1 Laurie Elit*

Department of Obstetrics and Gynecology, McMaster University, 699 Concession Street, Hamilton, ON, Canada L8V 5C2

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ABSTRACT

Objectives: (1) To understand whether women who are older when diagnosed with cervical cancer have a poorer survival compared to those younger, and if so, to determine the relative importance of patient, tumor and treatment factors. (2) To review whether older women are candidates for aggressive curative treatment for their cervical cancer and the age related effectiveness and toxicity.

Methods: A review of the published English literature from 1990 to 2014 using search terms related to cervical cancer and older age was conducted.

Results: A number of confounders may influence whether advanced age impacts survival such as patient comorbidities, stage, histology, grade, no or incomplete treatment, less radical surgery, palliative rather than curative treatment, lack of adjuvant radiation after surgery, lower rates of chemotherapy and others. When older women are treated as aggressively as their younger counterparts, survival is the same; however, especially where radiation or chemotherapy is used, toxicities may occur at the same or slightly higher rate.

Conclusions: The more recent population based studies have larger sample sizes and minimize the biases seen in single center studies. They have also corrected for confounders giving a more accurate answer concerning the outcomes of older women treated for cervical cancer. Performance status (or "frailty") and not chronologic age should define the optimal treatment strategy for older women with cervical cancer. Treatment related toxicities can be managed with treatment breaks or dose reductions. For those who receive curative treatment, the outcomes appear similar regardless of age.

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* Tel.: +1 905 389 5688; fax: +1 905 575 6343.
E-mail address: laurie.elit@jcc.hhsc.ca

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47 **1. Introduction**

48 Globally, cervical cancer is the third most common cancer with
49 528,000 estimated new cases in 2012. It is the fourth leading cause
50 of death for women worldwide with an estimated 266,000 deaths
51 in the same year [1]. We know that the age distribution of new cer-
52 vical cancer cases is bimodal with peaks around 30-39 and 60-69
53 years of age [2] (Fig. 1). This is important because in the USA, there
54 is a growing proportion of the population in the 65 years and older
55 age range from 6.95% in 2001 to 7.85% in 2011 and by 2021, it is
56 predicted to be 9.77% [3,4]. There are reports that cervical cancer
57 mortality rates also increase with age [5,6]. Wright [5] reported
58 that women 65 years old and older die from cervical cancer at a
59 rate of 7.6 per 100,000 compared to 2.1 per 100,000 for those that
60 are younger. Thus, the prevention and management of cervical cancer
61 especially in the woman 65 years old and older should take on
62 increasing importance.

63 The definition of "old" is not clear. The United Nations has
64 agreed to a cutoff of 60 years and older [7]. Some countries
65 use a specific event to define old like the age a person is pen-
66 sionable. An underlying principal in the concept of 'old' is that
67 chronologic age is different than biologic age. "Old" can represent
68 varying degrees of comorbidities, organ dysfunction, functional sta-
69 tus, nutritional status, polypharmacy, smoking history, cognitive
70 function (i.e., dementia), depression and social supports (i.e., avail-
71 ability of transportation) [8-11]. All of these can adversely affect
72 a person's tolerance to stresses like surgery. Recently, "frailty" has
73 been defined as "a medical syndrome with multiple causes and con-
74 tributors that is characterized by diminished strength, endurance
75 and reduced physiologic function that increases an individual's vul-
76 nerability for developing increased dependency and/or death" [12]
77 especially when exposed to a stressor like cancer. The current tools
78 used to document frailty have not been prospectively included in
79 the studies of treatment outcome in women of advanced age with
80 cervical cancer.

81 The objectives of this paper are: (1) to understand whether
82 women who are older when diagnosed with cervical cancer have a
83 poorer survival compared to those younger, and if so, to determine
84 the relative importance of patient, tumor and treatment factors;
85 and (2) to review whether older women are candidates for aggres-
86 sive curative treatment for their cervical cancer and the age related
87 effectiveness and toxicity.

88 **2. Literature review**

89 A literature review was conducted using PubMed from 1990 to
90 2014. The search terms included were cervical cancer (i.e., cervi-
91 cal neoplasms, cancer) and older age (i.e., elderly, postmenopause,
92 older, aged). The abstracts were reviewed to ensure the manuscript
93 was in English, involved a review of at least one centre's data, and
94 reported outcomes of treatment for cervical cancer in women 60
95 years and older. The references of the manuscripts of interest were

96 also reviewed for pertinent articles. In this paper we will highlight
97 the findings from the publications since 2000 but we will allude to
98 themes identified in the literature prior to this time.

99 **3. Question 1. Do women have a poorer survival if cervical**
100 **cancer is diagnosed when they are older?**

101 There are two groups of studies that provide diametrically
102 opposed answers to this question. There are studies that suggest
103 older age is associated with poorer survival [5,13-21]. However,
104 there are equally as many studies that suggest advanced age is not
105 associated with poorer survival [14,24-31] (Table 1). Why this lack
106 of congruence? In part, the problem is based on the quality of
107 the research. Age can be a proxy for poor prognostic factors like
108 comorbidities or stage. When the research accounts for these con-
109 founders, age may no longer be related to survival [27]. For example,
110 univariate analysis shows which variables impact survival; how-
111 ever, multivariate analysis can provide information on the relative
112 contribution a specific prognostic factor has in relation to others.
113 In addition, retrospective data from single center studies may be
114 biased due to referral policies or treatment recommendations (i.e.,
115 physicians may offer older women palliative treatment when a
116 similar presentation in a younger patient would be managed with
117 curative intent [14]). Population based studies are considered to be
118 of superior quality because they minimize such biases.

119 We will review the various patient, disease and treatment fac-
120 tors that may be confounding the association of advanced age with
121 survival in women with cervical cancer.

122 **3.1. Patient factors**

123 **3.1.1. Comorbidities**

124 It is well known that an individual with more comorbidities has a
125 poorer survival [32]. As people age, the number of comorbidities per
126 person increases [33]. Women with cervical cancer are no different
127 [15,18,23,33,35,36]. Van der Aa [18] showed in 775 women with
128 cervical cancer that 76% of women 70 years and older had a comor-
129 bidity compared to only 23% in those under 70 years ($p < 0.001$).
130 Their multivariate analysis showed that those with at least 1 comor-
131 bidity had worse overall survival compared to no comorbidities (HR
132 2.0, 95%CI 1.3-3.0, $p = 0.006$).

133 **3.2. Disease factors**

134 **3.2.1. Stage**

135 In the USA, 54% of women with cervical cancer have local
136 disease, 35% have regional disease and 11% have distant disease
137 [37]. A woman's survival with cervical cancer is related to stage.
138 For example, the 5 year survival for those with localized disease
139 is 91.2%, 57.8% for regional disease and 17% for metastatic (dis-
140 tant) disease [38]. A statistically significant relationship of more
141 advanced stage of disease with older age has been described

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