Case report

Cervical cancer in women over 65: An analysis of screening

Yost S.[a], Hoekstra A.[b],*

[a] Western Michigan School of Medicine, Kalamazoo, MI, USA
[b] West Michigan Cancer Center, Kalamazoo, MI, USA

ABSTRACT

Objective: Evaluate the characteristics and screening history of patients diagnosed with cervical cancer over age 65.

Methods: A retrospective review of 34 patients who were diagnosed with cervical cancer after the age of 65 at a single community cancer center between 2006 and 2016 was performed. Data collected included screening history, method of detection, stage, and survival.

Results: Between 2006 and 2016, 346 women were diagnosed with cervical cancer at a single community cancer center, 34 (9.8%) of them were over 65 years old. 30 had known screening histories and could be evaluated. 15 women had adequate screening prior to being diagnosed with cervical cancer, indicating that 50% of women who developed cervical cancer after age 65 in this population followed screening guidelines and still developed disease.

Conclusions: Women over 65 make up a significant portion of women diagnosed with cervical cancer. As many as half of all cervical cancers over age 65 occur in women who get recommended screening, and some of these may be prevented or detected early if screening was extended beyond age 65.

1. Introduction

Cervical cancer is common worldwide, with 528,000 new cases and 266,000 deaths in 2012, 84% of which occur in developing countries without robust screening programs (UpToDate. Invasive Cervical Cancer: Epidemiology, n.d). The advent of cervical cytology screening was a major public health breakthrough, heralding a marked decline of cervical cancer in countries with resources to support widespread testing. New prevention and screening strategies have developed, based on increasing understanding of the role of HPV in the carcinogenesis of cervical cancer.

Current guidelines by the ACS, ACOG, and USPSTF support discontinuation of screening in many women over age 65 (Saslow et al., 2012; USPSTF. Screening for cervical cancer, 2012; ACOG Committee on Practice Bulletins-Gynecology, 2012). Based on SEER data from 2010 to 2014 the median age at diagnosis is 50 and the most common ages for new diagnosis are 35–54, yet about 20% of women diagnosed with cervical cancer are over 65 years old (SEER Cancer Stat Facts: Cervix uteri Cancer, n.d). The ACS notes the risk of cervical cancer doubles to 0.2 for women aged 70 and older compared to 0.1 for women aged 40–69 (Saslow et al., 2012). It has been suggested that greater risk may be incurred by non-adherence to screening recommendations at younger ages, while those with adequate prior screening are deemed a low risk population and released from screening at age 65 (Sawaya, 2016). In the United States, a woman turning age 65 today can expect to live until age 86.6 on average, more than 20 years without screening in a period of higher risk (Life tables for the United States Social Security Area 1900–2100, n.d).

There has been considerable debate in the literature regarding screening in women over age 65 (Sawaya, 2016; Elit, 2016). Observational case-control studies performed in the US, UK, Finland, Sweden, Italy, South Africa have shown reduced risk of cervical cancer in women over 65 screened with cytology, with the protective effect lasting from 1 to 5 years (Elit, 2016). However, Pap tests over 65 are asserted to carry high physical, emotional and financial costs. Among the more commonly cited concerns are the effectiveness of testing in older women, the burden of follow-up testing of positive results, and uncertain benefit of discovering lesions that may never have become clinically significant within the patient's lifetime (Sawaya, 2016).

We seek to assess what portion of women in our population were adequately screened according to guidelines and still developed cervical cancer after age 65. This is the population that was impacted by discontinuation of screening at age 65. With developing understanding of the natural history of HPV, prolonged survival times, changing sexual behaviors, and less frequent screening intervals with HPV co-testing, reassessment of screening this population may be warranted.

2. Methods

Approval was obtained from the West Michigan Cancer Center (WMCC) IRB to perform a retrospective review of patients with a diagnosis of invasive cervical cancer at age 65 and older treated at the WMCC from 2004 to 2016. Patient medical records were reviewed to identify characteristics of the patients, their screening history, disease characteristics, and outcomes. Patient demographics such as age at diagnosis were collected, as well as histologic subtype, stage, length of follow up, and disease status. Overall survival and progression free survival were evaluated. We defined overall survival (OS) as time from diagnosis to either death or last follow up. Progression free survival (PFS) is defined as time from diagnosis to discovery of recurrence or progression; for patients that never had radiographic evidence of recurrence or progression, the endpoint of either death or last follow up was used.

Treatment characteristics were also summarized. Pretreatment workup most often involved physical exam in the office, followed by pelvic MRI and PET/CT scan. Patients undergoing primary surgical management underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Primary radiation therapy included 45 Gy to the pelvis and 27.5 Gy delivered by HDR brachytherapy in the outpatient setting. When a boost was delivered, 5.4 Gy was given by either standard external beam or IMRT.

Each patient was categorized as adequately or inadequately screened based on current ACOG guidelines. Those patients who were categorized as adequately screened had at least 2 negative co-tests or 3 negative cytology tests in the previous 10 years, most recent test after age 60, and no high grade precancerous lesions within the last 20 years. All others were categorized as inadequately screened by current guidelines. Those patients whose screening history could not be ascertained from the record and could not be contacted were categorized as having unknown screening status and excluded from the analysis. Frequencies, proportions, means and standard deviations were obtained to compare the groups. Factors of interest were compared with the grouping variable using Fisher's exact test for categorical variables and Wilcoxon's rank sum test for quantitative variables. *P*-values were compared to a Bonferroni-adjusted significance level of $\alpha = (0.05/10) = 0.005$, to adjust for multiple comparisons.

3. Results

Between January 2004 and December 2016, 34 (9.8%) of 346 women treated for invasive cervical cancer at the West Michigan Cancer Center were over age 65. Four patients were excluded due to inability to obtain screening history. Of the 30 included patients, 15 were adequately screened by current ACOG guidelines ("screened" group) and therefore eligible to cease screening after age 65. The remaining 15 had inadequate screening ("unscreened" group).

Demographic and clinical characteristics of this patient cohort are shown in Table 1. In comparing screened vs. unscreened groups, we found significant differences in age at last screening (70 and 59 years, respectively), and time between screening and diagnosis (5 and 20 years, respectively). No other factors differed significantly between the screening groups.

The majority of patients (28/30) presented for evaluation of symptoms, primarily vaginal bleeding or pelvic pain. One patient in each group had a visible cervical lesion found on pelvic exam performed as part of a routine well-person physical; no cancers were identified by cytology or co-test performed for asymptomatic screening. The groups also did not differ on previous abnormal screening tests.

The pathologic characteristics did not differ between groups (Table 2). Most patients had cancer with squamous histology, with equal proportion of squamous and adenocarcinoma between groups. There was a trend toward higher stage at diagnosis among the inadequately screened, although the differences were not statistically

Table 1
Demographic and clinical characteristics of women diagnosed at age 65 or older.

Variable	Overall (n = 30)	Adequately Screened (n = 15)	Inadequately Screened (n = 15)	P Value
Age at Diagnosis [a]	75 (65–87)	77 (65–87)	72 (66–80)	0.0673
Age at Most Recent Screening [a]	66 (30–82)	70 (64–82)	59 (30–63)	0.0001
Interval between last screening and diagnosis (years) [a]	10 (1–46)	5 (1–16)	20 (10–46)	0.0010
Smoking status				0.2469
Never smoker	14(46.7%)	9(60.0%)	5(33.0%)	
Former smoker	8(26.7%)	4(26.7%)	4(26.7%)	
Current smoker	8(26.7%)	2(13.3%)	6(40.0%)	
Race				0.9999
White	28 (93%)	14 (93%)	14 (93%)	
Black	1 (3%)	1 (7%)	0	
Asian	1 (3%)	0	1 (7%)	
Method of detection				1.0000
Symptoms	28(93.3%)	14(93.3%)	14(93.3%)	
Screening	0	0	0	
Annual physical exam	2(6.7%)	1(6.7%)	1(6.7%)	
Previous abnormal screening	7 (23.3%)	4 (26.7%)	3 (20.0%)	1.0000

[a] Reported as median (range).

significant when analyzed by discrete stage or by stage grouping. Staging was performed by the treating provider based on FIGO clinical staging criteria, with stages grouped to correspond with data presented by SEER: Localized disease includes stage I; regional disease includes stages II and III; and distant disease includes stage IV (SEER Cancer Stat Facts: Cervix uteri Cancer, n.d).

Treatment approach was similar in both groups, with 24/30 women treated in a standard fashion with curative intent (Table 3). Eighteen received chemoradiation, and 6 were treated with primary surgery. Half of the patients treated with primary surgery received adjuvant radiation therapy. Of the 18 patients treated with chemoradiation, 3 were unable to complete brachytherapy due to medical or social comorbidities. Five patients received palliative WPRT, and 1 declined any treatment due to medical comorbidities and poor performance status. Of those with Stage IVB disease, one patient declined treatment and one patient was treated with chemoradiation.

No differences in mortality or survival found between groups reached statistical significance (Table 4). The mortality rate from cervical cancer in the inadequately screened group (5/15) was similar to that in the adequately screened group (6/15). At the time of data collection 9 patients were still alive, 7 with no evidence of disease; they were evenly distributed between groups, with 4 living patients in the screened group and 5 in the unscreened group. Patients in the screened group had higher OS (36.1 vs 23.5 months) and PFS (34.5 vs. 22.9 months). Among the 6 patients with early stage disease treated with primary surgery, OS and PFS were 49.0 and 48.4 months respectively, with 1 patient excluded as they were lost to follow up. Both OS and PFS were greatest for patients with local disease (38.9 and 36.6 months), lower with regional spread (30.3 and 29.5 months), and least for distant metastasis (16.9 and 16.8 months). One patient from the unscreened group was excluded from survival analysis as she was lost to follow up.

4. Discussion

This study characterizes the population of women who develop cervical cancer after age 65, half of whom in this study were adherent

Table 2
Histologic subtype and stage distribution.

Variable	Overall (n = 30)	Adequately Screened (n = 15)	Inadequately Screened (n = 15)	US Population *	P value
Histologic subtype					1.000
Squamous cell	24 (80.0%)	12 (80.0%)	12 (80.0%)		
Adenocarcinoma	6 (20.0%)	3 (20.0%)	3 (20.0%)		
Diagnostic stage					0.5572
IA1	0	0	0		
IA2	0	0	0		
IB1	5(16.7%)	4(26.7%)	1(6.7%)		
IB2	4 (13.3%)	3(20.0%)	1(6.7%)		
IIA	2(6.7%)	1(6.7%)	1(6.7%)		
IIB	8 (26.7%)	4(26.7%)	4(26.7%)		
IIIA	1 (3.3%)	0	1(6.7%)		
IIIB	6 (20.0%)	2(13.3%)	4(26.7%)		
IVA	2 (6.7%)	1(6.7%)	1(6.7%)		
IVB	2 (6.7%)	0	2(13.3%)		
Diagnostic stage grouping					0.1934
Localized	9 (30.0%)	7 (46.7%)	2 (13.3%)	46%	
Regional	17 (56.7%)	7 (46.7%)	10 (66.7%)	36%	
Distant	4 (13.3%)	1 (6.7%)	3 (20.0%)	14%	
Unknown				4%	

 * Based on SEER data (5).

Table 3
Treatment modality and intent.

Treatment*	Overall (n = 30)	Adequately screened (n = 15)	Inadequately screened (n = 15)
Chemoradiation	18	7	11
ChemoRT + Brachytherapy	15	6	9
ChemoRT+/− boost	3	1	2
Surgery	6	4	2
Surgery alone	3	2	1
Surgery + adjuvant WPRT	3	2	1
Palliative WPRT	5	3	2
No treatment	1	1	0

ChemoRT- Whole pelvic radiation with weekly cisplatin; WPRT- whole pelvic radiation therapy.
 * p = .4677.

to guidelines and likely would have continued screening. We report that whether women have followed guidelines or not, they are still at risk, as survival for women diagnosed after age 65 at this center was poor whether they had been appropriately screened or not. We found that the stage distribution and prognosis of women who were adequately screened was improved compared to those inadequately screened, but to a nonsignificant degree. Although it is possible that the differences in survival and stage at diagnosis between groups may represent a clinically significant difference, they were not found to be statistically detectable due to small sample size. A larger study with sample size analysis to detect a true difference is warranted. The trend toward increased survival may reflect improved overall preventive healthcare and a stronger relationship with the healthcare system, or continued protection from lifetime screening.

Screening tests are most effective at diagnosing disease in a premalignant or early, more treatable stage. A British study found that women with cytology in the 12 months prior to invasive cancer diagnosis had earlier stage disease than those without (Landy et al., 2015). When the stage distribution of the cohort with recent cytology was applied to the cohort without recent cytology, the case fatality rate was reduced by 17.3–26.4%. We believe it is reasonable to expect that a similar benefit could be seen by women over 65, although the specific prediction of the model was for a different population. Earlier stage cancers are more likely to be amenable to treatment with surgery rather than radiation and chemotherapy. This population is managing medical comorbidities which make it less likely they will tolerate radiation and chemotherapy related toxicities. Elderly women have been shown to be candidates for surgery, especially minimally invasive, with little added surgical risk compared to younger patients (Guy et al., 2016).

There was no comparison group in our study who had screening after age 65, but we know from international and historical data that screening effectively decreases the risk of developing or dying from

Table 4
Survival and mortality by screening history and diagnostic stage grouping.

	Screening group				Stage grouping			
	All patients (n = 30)	Adequately screened (n = 15)	Inadequately screened (n = 15)	P value	Local (n = 9)	Regional (n = 17)	Distant (n = 4)	P value
Overall survival (months)	30.8	36.1	23.5	0.2334	38.9	30.3	16.9	0.5358
Progression-free survival (months)	29.7	34.5	22.9	0.2677	36.6	29.5	16.8	0.4599
Alive without disease (# patients)	7	4	3					
Alive with disease (# patients)	2	0	2					
Died of disease (# patients)	11	6	5					
Died of other cause (# patients)	9	5	4					
Unknown mortality status (# patients)	1	0	1					

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cervical cancer at any age. A large case-control study using Surveillance Epidemiology End Results (SEER) data found a negative association between Pap testing and invasive cervical cancer in women aged 65–74 (OR = 0.39, 95% CI = 0.24–0.61) and a less strong but still significant negative association in women aged 75–84 (OR = 0.74, 95% CI = 0.58–0.93) (Rosenblatt et al., 2016). A Swedish case-control study that included women aged 20–99 found that the protective effect of screening remained strong in women over age 65 (OR 0.36, 95% CI = 0.24–0.53) (Andrae et al., 2008). A 2013 review could find no conclusive evidence to support optimal ages to begin or end screening for cervical cancer, suggesting that the selection of age 65 as a cut off for screening is at least somewhat arbitrary (Peirson et al., 2013).

Changes in our understanding of the role of HPV in cervical cancer carcinogenesis and screening require reevaluation of screening recommendations. We know HPV latency can be seen for years prior to positive HPV testing and development of dysplasia, with little relationship to sexual activity or the patient's last evidence of the infection or dysplasia. It is unclear how many years of normal Pap history is adequate to determine that a woman is "low risk" for development of dysplasia, especially when most women currently over 65 have had very little in the way of HPV testing in the past. HPV testing as part of screening led to a decrease in recommended frequency of screening. One frequently cited cost of cervical cancer screening is increased physical discomfort in older women. Screening at less frequent intervals means that this exam could be administered only 2–3 additional times in a woman's life and achieve 10–15 years of additional protection, while also reducing the additional cost. HPV only screening programs currently being evaluated may involve home collection of samples which would further ease the process of screening for mobility-challenged patients (Schiffman et al., 2018). Determining the cost-effectiveness of screening women over 65 is beyond the scope of this paper, but we do feel it is worth noting that an analysis of the New Mexico HPV Pap registry found that a co-testing strategy resulted in a reduction of cervical cancer incidence of 91.1% and mortality reduction of 93.5% at a with a cost of $59,440 per QALY gained; compared to similar protection at a cost of $1,185,990 per QALY gained for annual cytology (Kim et al., 2015). It is reasonable to expect that as primary HPV testing becomes more prominent, costs will fall further.

This study has several limitations, and is not intended to fully characterize this population of women. It is intended, however, to begin a conversation about this topic with the experience of one community cancer center. One limitation is the small sample size, which limits the ability to statistically detect possible real differences between adequately and inadequately screened patients. The retrospective study design, although necessary for practical purposes, limits how strongly the results can be interpreted. The population served by this community cancer center is ethnically homogenous, limiting applicability of this evaluation to other populations. The population does, however, represent many of the suburban and rural socioeconomically diverse communities found across this country. Larger multi-institutional study of this population is warranted as we strive to develop comprehensive cervical cancer prevention guidelines.

Conflicts of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

References

ACOG Committee on Practice Bulletins-Gynecology, 2012. ACOG practice bulletin no. 131: screening for cervical cancer. Obstet. Gynecol. 120 (5), 1222–1238. http://dx.doi.org/10.1097/AOG.0b013e318277c92a.

Andrae, B., Kemetli, L., Sparen, P., Silfverdal, L., Strander, B., Ryd, W., Dillner, J., Tornberg, S., 2008. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J. Natl. Cancer Inst. 100 (9), 622–629. http://dx.doi.org/10.1093/jnci/djn099.

Elit, L., 2016. Cervical cancer screening in women over 65. PRO: are we asking the right question? Gynecol. Oncol. 142, 381–382. http://dx.doi.org/10.1016/j.ygyno.2016.08.230.

Guy, M.S., Sheeder, J., Behbakht, K., Wright, J.D., Guntupalli, S.R., 2016. Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer. Am. J. Obstet. Gynecol. 214 (3), 350.e1–350.e10. http://dx.doi.org/10.1016/j.ajog.2015.09.085.

Kim, J.J., Campos, N.G., Sy, S., Burger, E.A., Cuzick, J., Castle, P.E., Hunt, W.C., Waxman, A., Wheeler, C.M., 2015. Inefficiencies and high-value improvements in U.S. cervical cancer screening practice: a cost-effectiveness analysis. Ann. Intern. Med. 163 (8), 589–597.

Landy, R., Castanon, A., Dudding, N., Lim, A.W.W., Hollingworth, A., Hamilton, W., Sasieni, P.D., 2015. Cervical cytology and the diagnosis of cervical cancer in older women. J. Med. Screen. 22 (4), 207–2012. http://dx.doi.org/10.1177/0969141315598174.

Life tables for the United States Social Security Area 1900–2100. https://www.ssa.gov/OACT/NOTES/as120/LifeTables_Body.html, Accessed date: 18 February 2018.

Peirson, L., Fitzpatrick-Lewis, D., Ciliska, D., Warren, R., 2013. Screening for cervical cancer: a systematic review and meta-analysis. Syst. Rev. 2, 35. http://dx.doi.org/10.1186/2046-4053-2-35.

Rosenblatt, K.A., Osterbur, E.F., Douglas, J.A., 2016. Case-control study of cervical cancer and gynecologic screening: a SEER-Medicare analysis. Gynecol. Oncol. 142, 395–400. http://dx.doi.org/10.1016/j.ygyno.2016.06.016.

Saslow, D., Solomon, D., Lawson, H.W., et al., 2012. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J. Clin. 62 (3), 147–172. http://dx.doi.org/10.3322/caac.21139.

Sawaya, G.F., 2016. Cervical cancer screening in women over 65. CON: reasons for uncertainty. Gynecol. Oncol. 142, 383–384. http://dx.doi.org/10.1016/j.ygyno.2016.08.229.

Schiffman, M., Kinney, W.K., Cheung, L.C., Gage, J.C., Fetterman, B., Poitras, N.E., Lorey, T.S., Wentzensen, N., Befano, B., Schussler, J., Katki, H.A., Castle, P.E., 2018. Relative performance of HPV and cytology components of contesting in cervical screening. J. Natl. Cancer Inst. 110 (5), djx225. http://dx.doi.org/10.1093/jnci/djx225.

SEER Cancer Stat Facts: Cervix uteri Cancer. National Cancer Institute. Bethesda, MD http://seer.cancer.gov/statfacts/html/cervix.html (accessed 02/18/2018).

UpToDate. Invasive Cervical Cancer: Epidemiology Risk Factors, Clinical Manifestations, and Diagnosis. https://www.uptodate.com/contents/invasive-cervical-cancer-epidemiology-risk-factors-clinical-manifestations-and-diagnosis?source=autocomplete&index=0~2&search=invasive%20cer, Accessed date: 6 February 2018.

USPSTF. Screening for cervical cancer, 2012. U.S. preventive services task force recommendation statement. Ann. Intern. Med. 156 (12), 880–891. http://dx.doi.org/10.7326/0003-4819-156-12-201206190-00424.