Comorbidity and age affect treatment policy for cervical cancer: a population-based study in the south of the Netherlands, 1995-2004

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Summary

Objective. The aim of this study was to estimate the effects of age and comorbidity on the choice of treatment modalities and prognosis for patients with cervical cancer. *Methods.* All patients with cervical cancer newly diagnosed between 1995 and 2004 (n = 775) were selected from the population-based Eindhoven Cancer Registry. Time trends in treatment modalities and differences in treatment between older and younger patients, and those with and without comorbidity were evaluated. *Results.* Older patients with FIGO Stages IB-IIA, elderly and those with comorbidity underwent less surgery. In multivariate survival analysis, age had independent prognostic value. For patients with FIGO Stages IB2, IIB-IVA, age affected the choice of chemoradiation significantly. According to multivariate survival analysis, comorbidity and FIGO stage were independent prognostic factors. *Conclusion.* Older patients with cervical cancer and those with comorbidity were treated less aggressively. Because of the ever-increasing role of comorbidity in clinical decision-making for increasingly older patients in the near future, development of age-specific guidelines incorporating levels and management of specific comorbidity seems warranted.

Key words: Cervical cancer; Comorbidity; Radical hysterectomy; Radiotherapy; Chemoradiation.

Introduction

As in most northwestern European populations, the incidence of and mortality from cervical cancer have been decreasing in the Netherlands [1]. The main risk factor for cervical cancer, Human Papillomavirus (HPV), is found in almost all patients with cervical cancer, being strongly related to sexual behaviour, especially with multiple partners and early age at first intercourse [2]. Smoking markedly affects risk while a large number of live births and oral contraceptive use are also risk indicators [3, 4].

According to the national recommendations in 1990 for FIGO Stage IB and IIA cervical cancer, primary surgery and radiotherapy were equal therapeutic options, the choice depending mainly on patient characteristics such as age and comorbidity. Radiotherapy was the treatment of first choice for FIGO Stages IIB-IVA [5]. In 1999 the American National Cancer Institute (NCI) announced that adding chemotherapy to radiation therapy was highly recommended. This statement was based on five clinical trials which demonstrated the superiority of combined platinum-based chemoradiation over radiotherapy alone for patients with high risk and/or locally advanced cervical cancer [6-10]. A Dutch trial combining radiotherapy with hyperthermia also resulted in a significant improvement in the 3-year overall survival for patients with FIGO Stages IIB-IVA [11]. Therefore, from 2004 on the revised national guideline recommends primary chemoradiation or radiotherapy combined with hyperthermia for patients with FIGO Stage IB2, IIB and higher [12].

In general, treatment guidelines are based on the results of clinical trials from which patients with comorbidity and/or older age are often excluded. However, treatment of individual patients will be affected by age and comorbidity [13]. Therefore, we studied the influence of age and comorbidity on the treatment modalities chosen and the ultimate survival of unselected patients with cervical cancer.

Materials and Methods

Data collection

All patients with cervical cancer diagnosed between 1 January 1995 and 31 December 2004 (n = 775) were selected from the Eindhoven Cancer Registry, where data is recorded on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants that is served by the Comprehensive Cancer Centre South (IKZ). It consists of ten community hospitals at 16 sites and two large radiotherapy institutes in Tilburg and Eindhoven.

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Table 1. — *Classification of comorbidity, according to an adapted list of Charlson et al. [14].*

Previous malignancies (except basal cell skin carcinoma and cervix carcinoma in situ)
Chronic obstructive pulmonary diseases
Cardiovascular diseases – Myocardial infarction – Heart failure – Angina pectoris – Intermittent claudication – Abdominal aneurysm – Cardiomyopathy – Valve prothesis (aorta or mitralis)
Cerebrovascular diseases – Cerebrovascular accident – Hemiplegia
Hypertension
Digestive tract diseases – Ulcerative disease (only registered since 1997) – Patients who underwent major surgery for ulcerative disease (Billroth I or II) – Chronic inflammatory diseases (Crohn's disease, ulcerative colitis except polyposis coli)
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other – Urinary tract diseases – Connective tissue diseases – Dementia – Chronic infections

After notification from the pathological laboratories, trained registration clerks collect information from the medical records on diagnosis, tumour stage and treatment. To explore the increasing complexity of oncological care in an older population, serious comorbidity with prognostic impact at the time of cancer diagnosis has been recorded for all patients since 1993, according to a slightly modified version of the Charlson index (Table 1) [14]. Information on comorbidity is obtained from reports on previous admissions, letters from and to other specialists, the medical history, and preoperative screening. In the absence of information on comorbidity in the patient files, the registrars have to code this as 'unknown'. Patients for whom comorbidity was unknown were excluded from the survival analyses (n = 37 with FIGO Stage IB-IIA and n = 37 with FIGO Stage IB2, IIB-IVA).

Tumour stage was defined according to the FIGO staging system, based on preoperative clinical information. Only patients with FIGO Stage IB-IVA were included for further analysis of treatment and survival. Because of the different treatment recommendations, the patients were divided into two groups: FIGO Stages IB (excluding IB2)-IIA and FIGO Stages IB2, IIB-IVA. FIGO Stage IB2 was included in the Stage group IIB-IVA because treatment of FIGO IB2 is considered to be chemoradiation since the publication of the National Cancer Institute in 1999 [10]. Although FIGO Stage IB was divided into Stages IB1 and IB2 in 1997, this modification has been included in the cancer registry only since 1999 [15].

Treatment of patients with FIGO Stages IB-IIA was classified as surgery (± radiotherapy, ± chemotherapy), radiotherapy (± chemotherapy) and other/none (palliative, lymph node dissection only, chemotherapy only, metastasectomy and unknown therapy). Treatment for FIGO Stages IB2, IIB-IVA was classified as radiotherapy, chemoradiation (including radiotherapy combined with hyperthermia, n = 2), surgery (± radiotherapy, ± chemotherapy) and other/none (palliative, lymph node dissection only, chemotherapy only, metastasectomy and unknown therapy).

Socioeconomic status (SES) was considered to be a possible confounder. The SES of each patient was defined at the neighbourhood level (based on postal code of residence, 17 households on average) combining mean household income and mean value of the house, derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to three SES categories: low (1st-3rd decile), intermediate (4th-7th decile) and high (8th-10th decile). Postal codes of institutions, such as nursing homes, were assigned to a separate category and excluded from the analyses of SES (n = 39).

Vital status was available up to January 1, 2006. In addition to passive follow-up via the hospitals, this information was also obtained through the National Genealogical Office and the Municipality Administration Database, where all deceased and emigrated persons in the Netherlands are registered via the civil municipal registries.

Statistical analysis

The prevalence of comorbidity was analysed according to age, dividing younger patients and the elderly (< 70 and ≥ 70 years). Time trends in treatment modalities and differences in treatment between patients with and without comorbidity were assessed by Chi-square analysis overall, and by age group.

Crude 5-year survival rates were computed, survival time being the time from diagnosis to death or January 1, 2006. The log-rank test was performed to evaluate significant differences between survival curves in univariate analyses. A multivariate Cox regression model was constructed for evaluation of the independent prognostic effects of age and comorbidity on survival. The independent prognostic effects of age and comorbidity were first estimated using a model without treatment modality. Then treatment was included in the model in order to investigate whether the prognostic effects of age and comorbidity could be fully explained by the treatment modality chosen. The prognostic effect of the number of comorbid conditions was also evaluated. The prognostic impact of specific diseases and combinations of diseases could not be evaluated because the number of patients in each subgroup was too small. Hazard ratios (HR) and 90% confidence intervals (CI) were calculated. Due to the small number of patients in each subcategory, p-values of 0.10 were considered significant. The period of diagnosis, SES and FIGO stage were divided into categories and entered into the model as dummy variables using a stepwise approach. Variables were considered confounders and included in the model when the regression coefficient of the variable of interest (treatment) changed by more than 10%. Separate analyses were performed for survival of those with Stages IB-IIA and Stages IB2, IIB-IVA. Furthermore, relative survival was calculated to estimate differences between the two age groups as a measure of disease-specific survival using the Ederer II method in STATA version 9.2 [16]. Relative survival is the ratio between crude and expected survival and approaches disease-specific survival. Relative survival was used only to estimate differences between age groups since overcorrection would occur if patients without comorbidity were compared with the general population.

Results

General

All patients with cervical cancer diagnosed between 1 January 1995 and 31 December 2004 (n = 775) were included in this study. The median age of the patients in this study was 48 years (range 15-100), 81% being younger than 70 years at diagnosis. Most patients presented with FIGO Stage IB (excluding IB2)-IIA (37%, n = 288), followed by 28% of patients with FIGO IA (n = 200) and 26% of patients with FIGO Stages IB2, IIB-IVA (n = 214). Six percent of the patients presented with metastatic disease (n = 46). FIGO stage was unknown in 3% of cases (n = 27). The proportion of patients with one or more comorbid conditions at the time of diagnosis was 18% for patients aged < 70 and 59% for patients aged ≥ 70 (p < 0.001). The most frequent comorbidity in both age categories was hypertension. Cardiovascular diseases and diabetes were also very common among those aged ≥ 70 (Table 2).

Table 2. — *Number and type of comorbid conditions present in newly diagnosed patients with cervical cancer in south-eastern Netherlands, 1995-2004, according to age group.*

	< 70 yrs n (%)*	≥ 70 yrs n (%)*	Total n (%)*
Number of comorbid conditions			
0	408 (65)	43 (29)	451(58)
1	84 (13)	49 (33)	133 (17)
2 or more	27 (4)	40 (27)	67 (9)
Unknown	106 (17)	18 (12)	124 (16)
Type of comorbid condition			
Previous cancer	20 (3)	15 (10)	35 (5)
Cardiovascular disease	22 (4)	38 (25)	60 (8)
Hypertension	36 (6)	42 (28)	78 (10)
COPD	23 (4)	9 (6)	32 (4)
Diabetes mellitus	24 (4)	28 (19)	52 (7)
Cerebrovascular	4 (1)	10 (7)	14 (2)
Dementia	0 (0)	3 (2)	3 (0.4)
Digestive tract	7 (1)	1 (1)	8 (1)
Other	14 (2)	6 (4)	20 (3)

* One patient may have more than one comorbid condition, so the total of all comorbid conditions can be more than 100% (i.e., more than the number of patients in the study).

FIGO IB (excluding IB2)-IIA

Median age of patients with FIGO Stages IB-IIA was 47 years (range 24-88 years). Patients aged ≥ 70 exhibited comorbidity more frequently than patients aged < 70 (76% vs 23%, p < 0.001). Both age and presence of comorbidity had a significant influence on the choice of treatment modality. Eighty-three percent of patients aged < 70 underwent surgery as the primary treatment, i.e., 92% of those without comorbidity and 69% with at least one comorbid condition (p < 0.001). In contrast, only 46% of patients aged ≥ 70 years underwent primary surgery: 73% of those without comorbidity and 41% with at least one comorbid condition (p = 0.006) (Table 3).

Five-year relative survival for patients aged ≥ 70 was 61% versus 81% for patients aged < 70 years (p = 0.005).

Table 3. — *Treatment of cervical cancer in south-eastern Netherlands according to FIGO stage, age and comorbidity, 1995-2004.*

Age	Comorbid conditions	FIGO IB-IIA			FIGO IB2, IIB-IVA			
		Surgery n (%)	RT* n (%)	Other/none n (%)	RT* n (%)	CHEMRT* n (%)	Surgery n (%)	Other/none n (%)
< 70	0	145 (92)	8 (5)	5 (3)	42 (44)	29 (30)	15 (16)	10 (10)
	1+	33 (69)	13 (27)	2 (4)	13 (50)	10 (38)	1 (4)	2 (8)
	Unknown	21 (62)	3 (9)	10 (29)	10 (37)	3 (11)	2 (7)	12 (44)
≥ 70	0	8 (73)	3 (27)	0 (0)	13 (65)	1 (5)	3 (15)	3 (15)
	1+	14 (41)	18 (53)	2 (6)	29 (83)	0 (0)	1 (3)	5 (14)
	unknown	1 (33)	0 (0)	2 (67)	2 (20)	1 (10)	1 (10)	6 (60)

*RT = radiotherapy, CHEMRT = chemoradiation (including 2 patients who received radiotherapy + hyperthermia).

Crude five-year survival rates were significantly worse for patients aged ≥ 70 (50% vs 80%, respectively), for patients with FIGO Stage IIA (65% versus 78% for FIGO IB and 79% for FIGO IB1, respectively), and for patients with comorbidity (83% without, 66% with one, and 48% with two or more comorbid conditions) (Table 4). Survival for patients with FIGO Stage IB-IIA receiving primary radiotherapy was 47% versus 81% for those who underwent primary surgery. No effect on survival was found for period of diagnosis or SES. According to multivariate survival analyses, age was the only independent prognostic indicator (Table 4). The risk of dying increased by 2% with every additional year in age. The hazard ratios for age and comorbidity did not change when primary treatment was introduced into the model.

FIGO IB2, IIB-IVA

Median age of patients with FIGO Stages IB2, IIB-IVA was 57 years (range 28-94 years). Patients aged ≥ 70 suffered comorbidity more frequently than patients aged < 70 (64% vs 21%, p < 0.001). Especially age had a significant influence on the choice of treatment: 28% of patients aged < 70 received chemoradiation, 30% of those without comorbidity and 38% of those with at least one comorbid condition. Only 3% of patients aged ≥ 70 received chemoradiation, 5% of those without comorbidity and none of those with at least one comorbid condition (p < 0.001) (Table 3). Differences in the use of chemoradiation according to the presence of comorbidity, within both age categories, were not significant. A small group of patients with FIGO Stages IB2, IIB-IVA without comorbidity underwent surgery more often than patients with one or more comorbid conditions (n = 18 vs n = 2, p < 0.001). The use of chemoradiation increased from 9% in the period 1995-1997 to 32% in the period 2001-2004 (p = 0.01), i.e., 41% of patients aged < 70 and 5% of patients aged ≥ 70 (p = 0.02) in the latter period. Analysing the time trend per year revealed that the use of chemoradiation had already started to increase from 1999, the year of the clinical alerts of the NCI (p = 0.02). The number of patients who received radiotherapy combined with hyperthermia was too small (n = 2) to reveal a time trend.

Table 4. — *Overall survival of cervical cancer patients diagnosed in south-eastern Netherlands, 1995-2004.*

			Univariate			Multivariate		
			N	5 year (%)	p	HR	90% CI	p
FIGO IB-IIA	Age							
	FIGO	IB	167	78				
		IB1	64	76				
		IIA	57	65	0.09			
	Period of diagnosis	1995-1997	89	78				
		1998-2000	88	74				
		2001-2004	111	73	0.9			
	Comorbidity	0	169	83		1	reference	reference
		1	48	66		1.2	0.6-2.3	0.60
		2+	34	48	< 0.001	1.5	0.7-3.0	0.37
	Treatment	Surgery	222	81		1	reference	reference
		Radiotherapy	45	47		1.7	0.9-3.2	0.14
		Other/none	21	64	< 0.001	5.4	1.9-15.1	0.007
FIGO IB2, IIB-IVA	Age		214	–		1.0	0.9-1.0	0.9
	FIGO	IIB	91	55		1	reference	reference
		IIIA	21	33		2.0	1.1-3.6	0.05
		IIIB	38	23		3.5	2.2-5.5	< 0.001
		IVA	31	16		7.7	4.7-12.7	< 0.001
		IB2	13	54	< 0.001	1.2	0.5-2.9	0.68
	Period of diagnosis	1995-1997	67	39				
		1998-2000	63	38				
		2001-2004	84	48	0.9			
	Comorbidity	0	116	42		1	reference	reference
		1	42	24		2.0	1.3-3.0	0.006
		2+	19	40	0.03	1.6	0.8-2.9	0.25
	Treatment	Radiotherapy	109	38		1	reference	reference
		Chemoradiation*	23	49		0.8	0.5-1.3	0.44
		Surgery	44	57		–	–	–
		Other/none	38	29	0.004	2.2	1.3-3.7	0.009

HR = Hazard Rate for death; 90% CI = 90% Confidence Interval; * (including 2 patients who received radiotherapy + hyperthermia).

Five-year relative survival for patients aged ≥ 70 was worse compared to patients aged < 70 (32% vs 51%, p = 0.05). According to univariate analysis, five-year crude survival was significantly worse for patients aged ≥ 70 (24%, compared to 48% for patients aged < 70), those with one comorbid condition (24%, compared to 42% without comorbidity), for patients with FIGO IIIA (33%), IIIB (23%) and IVA (16%) compared to patients with FIGO IB2 or IIB (54% and 55%, respectively) and for those receiving radiotherapy (38% compared to 49% for patients receiving chemoradiation and 57% for surgery) (Table 4). No effect was found for period of diagnosis and SES. According to multivariate survival analysis, comorbidity and FIGO were independent prognostic factors (Table 4). The risk of dying for patients with one comorbid condition was twice as high as that for patients without comorbidity. Furthermore, the risks of death of patients diagnosed with FIGO IIIA, IIIB, and IVA were 2.0, 3.5 and 7.7 times higher respectively, compared to patients diagnosed with FIGO IIB. The hazard ratios for age and comorbidity did not change when treatment was introduced into the model.

Discussion

Substantial variations were found in the treatment of women with cervical cancer in this retrospective population-based study. In previous studies concerning patients with FIGO Stage IB (excluding IB2)-IIA cervical cancer, primary surgery and radiotherapy were shown to be equal therapeutic options, resulting in similar outcomes [17, 18]. However, the present study showed that for elderly patients, especially in the presence of comorbidity, radiotherapy remained the treatment of first choice. For patients with FIGO Stages IB2, IIB-IVA cervical cancer, age especially influenced the therapy of choice: radiotherapy or chemoradiation. Only 5% of patients aged 70 years or older received chemoradiation versus 41% of patients younger than 70 years in the period 2001-2004. As a matter of fact, chemoradiation was proposed as a superior alternative to radiotherapy alone in 1999 but was only incorporated in the guidelines in 2004.

It is known that the elderly are less likely to be included in clinical trials and to receive aggressive therapy because of considerations concerning patient safety [19, 20]. In addition, older women are more likely than their younger counterparts to refuse aggressive treatment [21, 22]. We found that older patients and patients with comorbidity were indeed treated differently compared to younger

patients and patients without comorbidity with both lower and higher FIGO stages. Both the patient's and the doctor's preference might play a major role in the explanation of this phenomenon. We had no further information on this topic.

Relative survival (adjusting for survival in the general population of the same age) for patients with FIGO Stage IB (excluding IB2)-IIA older than 70 years was worse than that for their younger counterparts, which may be explained by the higher proportion of FIGO IIA tumours in older patients ($p < 0.001$). However, also according to a multivariate analysis age was the only independent prognostic indicator after adjustment for other prognostic factors as comorbidity and treatment, which has also been confirmed in another recent study [23]. In FIGO Stages IB2, IIB-IVA, prognosis was determined by the number of comorbid conditions and FIGO stage. Patients with one comorbid condition exhibited worse survival compared to patients without comorbidity. In contrast, the increased risk of death for the rather small group of patients with multiple comorbid conditions did not reach statistical significance. Furthermore, no change was seen in the hazard ratio for age when treatment was included in the model. Treatment was not an independent prognostic factor for either stage group, which could indicate that the right treatment modality was in general offered to the right patient. Nevertheless, worse survival was found for patients who received 'other therapies' or no therapy and most of these patients were elderly patients.

As cervical cancer is assigned a FIGO stage based on specified clinical tests, it is not uncommon for the physician to have other non-specified tests at their disposal (CT scan, MRI). Often it is known that the patient has metastatic disease but the FIGO stage can not officially be upstaged based on these findings. However, the treatment choice certainly is affected. This bias is present and may be a major confounder for any analysis of stage-adjusted outcome based on treatment modality.

Although this population-based study has the advantage of avoiding selection bias, detailed and uniform information on the performance status of the patient, adherence to protocol (dose reduction, treatment delay) for radio- and/or chemotherapy and treatment-related complications were not available. These and other factors which determine frailty, for example cognitive disorders, might also affect the choice of treatment and prognosis of the patients.

Although severity of comorbidity was not recorded, misclassification of comorbidity seems to be limited because the concomitant conditions are recorded routinely by trained registry personnel directly from the medical records of the patients, thereby using a variety of sources. A validation study of breast cancer patients showed some under-registration, mainly for less severe cardiovascular conditions [24]. Furthermore, not all cases of non insulin-dependent diabetes are subclinical, implying that the prognosis of patients without diabetes might therefore be underestimated. The true effects of comorbidity on treatment choice and survival may thus be stronger than described here.

In conclusion, in cervical cancer, treatment modalities chosen but also prognosis differed between younger and older patients and between patients with and without comorbidity. Attention should be directed toward treatment in relation to ageing and comorbidity. In an increasingly older population (on the basis of recent numbers of population growth it is estimated that the number of women over 65 years will increase by 23% [25]), comorbidity and other factors that determine frailty - such as performance status - will probably play an increasing role in clinical decision-making and outcome. Development of age-specific guidelines, which incorporate levels of comorbidity and for example performance score, may therefore be warranted. Furthermore, this may lead to an increased awareness of comorbidity among physicians.

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