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Age-specific differences in treatment and survival of patients with cervical cancer in the southeast of The Netherlands, 1986–1996[1]

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Abstract

Age at diagnosis has been proven to be an important determinant of the choice of initial treatment for several sites of cancer. Elderly patients are more likely to receive no treatment or less intensive treatment modalities. This study analysed the influence of age on treatment choice and survival in patients diagnosed with cervical cancer. This population-based study used data on 1176 new cases of invasive cervical cancer diagnosed in the period of 1986–1996 from three regional cancer registries in the Netherlands. All available information on treatment and survival (on 1 January 1998) was recorded. Relative survival rates were calculated according to the Hakulinen method. Relative risks (RR) for excess mortality due to the diagnosis of cervical cancer were calculated with a regression model for relative survival rates. Only 5% of the patients aged 70 years and older ($n=224$) were diagnosed with stage IA disease, compared with 11 and 30% of the patients aged 50–69 years and 49 years and younger, respectively. Almost 50% of the 70+ patients with stage IB-IIA were treated with radiotherapy as a single treatment modality, whereas 64% of the patients aged $\leqslant$49 years were treated with surgery alone. In all age groups, treatment for advanced stage disease (stage $\geqslant$IIB) was radiotherapy alone. No treatment was given to 10% of the patients aged 70 years and older, 5% of those aged 50–69 years and 1% of those aged 49 years and younger. Five-year relative survival was 69% (95% Confidence Interval (CI): 66–72%) and differed significantly ($P=0.001$) with age (70+ years: 49%; 50–69 years 58%; $\leqslant$49 years: 81%). Multivariate analyses on a subset of patients showed that age was not an independent prognostic factor, whereas stage and treatment modality were very important prognostic factors. Although elderly cancer patients were sometimes treated differently from younger patients, this was in accordance with the guidelines. Relative survival rates differed significantly by age. The multivariate analyses on the subset of patients also revealed that excess mortality increased with age. However, when adjustment was made for stage and treatment, this difference disappeared. The influence of treatment on survival is likely to be due to the selection of patients based on other characteristics, such as tumour volume, comorbidity and performance status.

Keywords: Cervical cancer; Elderly; Patterns of care; Survival; Treatment

1. Introduction

The prognostic significance of age in cervical cancer has been the subject of several studies since the early 1970s. The approach to studying age at diagnosis as a prognostic factor has not always been the same. Frequently, the question of whether young patients have a poorer prognosis than older patients was the central point of interest [1–5]. The assumption was that cancer is biologically more aggressive in younger patients. Other studies [6,7] have linked an older age with a poorer prognosis, assuming that elderly patients receive less aggressive, and hence inappropriate, treatment, thereby influencing their survival [8]. Several other survival studies on cervical cancer in general or evaluation studies on

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screening programmes [9–19] have included age as a prognostic factor in the survival analysis. Nevertheless, it is still not clear whether age is an independent prognostic factor in cervical cancer. To date, very few population-based studies have been published. One of the advantages of using population-based data from a cancer registry is that bias from referral policies is excluded. Studies on differences in patterns of care between older and younger cervical cancer patients are fairly scarce and the emphasis has mostly been on survival. The present population-based study is embedded in a regional project on cancer in the elderly [20–22]. The purpose of this study was two-fold: firstly, to study differences in treatment patterns for cervical cancer in elderly patients compared with younger patients and secondly, to study age-specific relative survival.

2. Patients and methods

The data for this study were obtained from three regional cancer registries: the Eindhoven Cancer Registry (eastern part) over the time period of 1986–1994, the Cancer Registry of the Comprehensive Cancer Centre East over the time period of 1989–1995 and the Maastricht Cancer Registry over the time period of 1986–1996. The total area represented a population of around 3 million in 1990. For a description of the regions and registration procedures, see Schouten and colleagues [23], Parkin and colleagues [24] and Van der Sanden and colleagues [25].

Data on patients with newly diagnosed invasive cervical cancer registered at one of the three registries were analysed. Patients who had a previous malignancy other than basaloid skin cancer, or had been diagnosed at autopsy, or had tumours with a rare histology (leiomyosarcoma ($n=10$), endometrial stromal sarcoma ($n=2$)) or tumours without a pathological diagnosis ($n=3$), were excluded, leaving 1176 patients. Information on the vital status up to 1 January 1998 was collected by means of an active follow-up.

Tumour stage was defined according to the 1989 International Federation of Gynecology and Obstetrics (FIGO) staging system [26], preferably based on pretreatment information. In 237 cases in whom pretreatment stage information could not be extracted from the medical files, postsurgical information was used. Patients with pathological stage IIB-IVA ($n=27$) were assumed to have clinical stage IB-IIA, as surgery is not the standard treatment for IIB-IVA tumours. Therefore, these patients were included in the analysis as IB-IIA cases [27]. Patients were categorised by stage, which resulted in five categories: IA, IB-IIA, IIB-IVA, IVB and unknown. These categories were chosen because treatment guidelines within these stages are uniform. During the study period, the treatment of first choice for stage IA and IB-IIA was surgery, especially in younger patients in order to preserve ovarian function, whereas radiotherapy was the treatment of first choice for locally advanced disease (i.e. stage IIB and higher) and in older patients and/or those at an increased operation risk [27].

In this study, treatment refers to the primary treatment modality applied during the first 3 months after diagnosis. It was classified as surgery, radiotherapy, surgery + radiotherapy and other/none (other treatment modalities such as chemotherapy/no initial treatment). Treatment is described according to age and FIGO stage.

2.1. Analyses

Survival was defined as the period between diagnosis and death, irrespective of the cause of death. As reliable information on the actual cause of death was lacking, correction for death from competing causes was achieved by computing relative survival according to the Hakulinen method, using the Finnish Cancer Registry survival software [28]. Relative survival is defined as the probability that a cancer patient will survive over a defined short period, divided by the probability that an age-matched individual will survive over the same period [29]. The latter figures were calculated from life tables (supplied by Statistics Netherlands) compiled according to sex and year of diagnosis in the regional population. Comparisons between groups were made by means of a likelihood-ratio test. A multiple regression procedure [30] analogous to the Cox model [31] was used to evaluate the simultaneous effect of several prognostic factors on relative survival in a selected group of patients (treated with surgery, radiotherapy or a combination of the two for stage IB-IVA squamous cell carcinoma and adeno(squamous)carcinoma). Cases with stage IA and IVB were excluded from these multiple regression models. The former because of a low number of events (death) and the latter because treatment was palliative and strongly individualised. Cases with unspecified histology and cases who did not receive surgery, radiotherapy or both were also excluded, because of low numbers and in order to create a fairly homogeneous group of patients. Age, stage and treatment factors were introduced in the models, as well as duration of follow-up (five levels, each of 1-year duration) and histological type (squamous cell carcinoma, adeno + adenosquamous carcinoma).

3. Results

Table 1 shows the characteristics of the entire patient population. The distribution of cases by age reflects the

Table 1
Patient characteristics

	Age (years)			
	⩽49	50–69	70+	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)
Total	612 (100)	340 (100)	224 (100)	1176 (100)
Stage (FIGO)				
IA	185 (30)	39 (11)	12 (5)	236 (20)
IB	278 (45)	98 (29)	51 (23)	427 (36)
IIA	46 (8)	54 (16)	34 (15)	134 (11)
IIB	50 (8)	48 (14)	42 (19)	140 (12)
IIIA	3 (<1)	6 (2)	9 (4)	18 (2)
IIIB	18 (3)	46 (14)	33 (15)	97 (8)
IVA	6 (1)	22 (6)	12 (5)	40 (3)
IVB	14 (2)	18 (5)	14 (6)	46 (4)
Unknown	12 (2)	9 (3)	17 (8)	38 (3)
Histology				
Squamous cell ca	454 (74)	267 (79)	169 (75)	890 (76)
Adenocarcinoma	108 (18)	54 (16)	44 (18)	206 (18)
Carcinoma NOS	50 (8)	19 (6)	11 (5)	80 (7)
Basis for diagnosis				
Cytological	2 (<1)	3 (1)	10 (4)	15 (1)
Histological	610 (100)	337 (99)	214 (96)	1161 (99)

ca, carcinoma; NOS, not otherwise specified.

rather young age at which this type of gynecological cancer occurs. 52% of the cases were aged ⩽49 years, 29% were 50–69 years and 19% were 70 years or older. Younger patients had more early stage tumours, while older patients had more advanced stage diseases. Histological types were equally distributed among the three age categories. The diagnosis had been histologically confirmed in more than 99% of the patients of younger than 70 years and in 96% of those aged 70+ years.

3.1. Treatment

- Stage IA. Most stage IA cases had been treated surgically (87%). For those aged 70 years and over, the number of cases with stage IA was small ($n=12$). These 70+ patients were treated with surgery (58%), radiotherapy (25%), or a combination of the two (8%). One of the elderly patients was not treated.
- Stage IB–IIA. In the age group of 70+ years, 50–69 years and ⩽49 years, radiotherapy was the single treatment modality in 48, 25 and 8% of the patients, respectively. For surgery, these proportions were 22, 40 and 64%, respectively. Surgery followed by radiotherapy was received by 27, 33 and 25% of the patients, respectively (Fig. 1).
- Stage IIB-IVA. Some of these patients did not receive curative treatment, especially in the 70+ age group (12.5%). This percentage was 6% in the 50–69 year age group, whereas all patients aged 49 years and younger received curative treatment. Most patients were treated with radiotherapy alone, i.e. 76% of the patients aged 70 years and older, 86% of the patients aged 50–69 years and 73% of the patients aged 49 years and younger.
- Stage IVB. Treatment for women with stage IVB cervical cancer ($n=46$) was palliative and strictly individualised (surgery, RT, chemotherapy and combinations of these). A total of 14 patients were not treated, of whom 3 patients were aged 49 years or younger, 7 were aged 50–69 years and 4 were aged 70+ years.

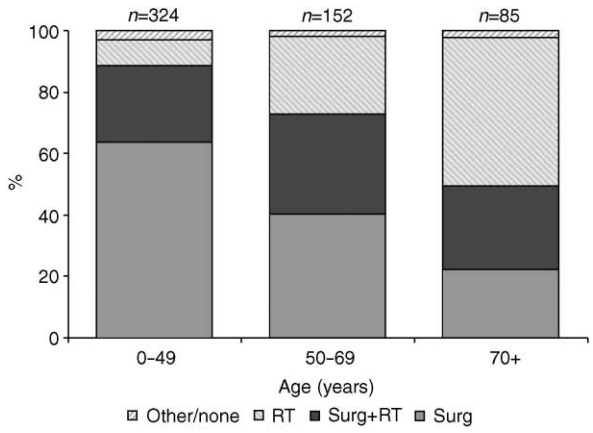

Fig. 1. Initial treatment for patients with cervical cancer stage IB-IIA, 1986–1996. RT, radiotherapy; Surg, surgery.

3.2. Survival

Overall relative 5 year survival was 69%. Cumulative relative survival rates at 1, 3 and 5 years after diagnosis, stratified by age and stage, are shown in Table 2. Older patients had a poorer prognosis (LR test: $P=0.001$) (Table 2; Fig. 2a and b). The survival difference between the three age groups was greatest in patients with stage IIB-IVA disease (LR test: $P=0.008$).

Table 3 shows 1-, 3- and 5-year relative survival rates stratified by histological type and age. In the oldest age category, patients with squamous cell carcinoma had a better 5-year survival than those with adenocarcinoma, i.e. 54 versus 37%, although this difference was not statistically significant (LR test: $P=0.4$).

Univariate and multivariate estimated relative risks of excess mortality are shown in Table 4. Relative risks for age 50–69 years and 70+ years, adjusted for stage and histology, were both significantly higher than the risks in the reference category ⩽49 years. When treatment was included in the model, the relative risks for the three age groups were no longer significant.

4. Discussion

This registry-based study addressed age-specific patterns of treatment and survival in patients with newly

Table 2
Number of cases (*n*) and cumulative relative survival at 1, 3 and 5 years after diagnosis; Confidence Intervals (CI) for the 5-year rates, stratified by stage and age

Stage	Age (years)	*n* at risk	Relative survival (%)			
			1 year	3 year	5 year	5-year 95% CI
IA	⩽49	185	100	99	97	93–99
	50–69	39	100	96	95	80–100
	70+	12	99	85	88	45–100
	All	236	100	98	97	92–99
IB-IIA	⩽49	324	95	85	81	76–86
	50–69	152	94	81	74	66–81
	70+	85	93	80	73	58–87
	All	561	95	83	78	74–82
IIB-IVA	⩽49	77	79	55	50	39–62
	50–69	122	74	46	34	25–43
	70+	96	56	34	30	19–43
	All	295	70	45	37	31–44
IVB	⩽49	14	29	20	20	7–48
	50–69	18	39	17	17	6–41
	70+	14	15	8	–	–
	All	46	29	14	14	7–29
Unknown	⩽49	12	100	92	92	65–99
	50–69	9	78	57	46	19–76
	70+	17	71	68	59	29–96
	All	38	82	73	68	48–85
All stages	⩽49	612	93	84	81	78–84
	50–69	340	84	66	58	52–64
	70+	224	71	55	49	41–59
	All	1176	87	74	69	66–72

diagnosed invasive cervical cancer. Age at diagnosis strongly influenced treatment choice, whereas stage of disease and treatment were the most strongly determining factors for survival.

In our study population, the older patients had more advanced disease than the younger patients. The same phenomenon has also been described in other studies and it is considered likely that in the older age group, this can be attributed to patient delay, fewer programmes that provide or promote screening and less compliance with recommended screening practices [7,12,32].

Table 3
Number of cases (*n*) and cumulative relative survival at 1, 3 and 5 years after diagnosis; 95% Confidence Intervals (CI) for the 5-year rates stratified by histological type and age

Histology	Age (years)	*n* at risk	Relative survival (%)			
			1 year	3 year	5 year	5-year 95% CI
Squamous cell carcinoma	⩽49	454	93	84	80	76–84
	50–69	267	86	67	58	52–65
	70+	169	72	60	54	44–65
	All	890	87	75	67	66–73
Adenocarcinoma	⩽49	108	96	87	83	75–90
	50–69	54	86	64	56	42–69
	70+	44	68	39	37	20–60
	All	206	88	72	69	61–76
Carcinoma NOS	⩽49	50	84	82	82	70–91
	50–69	19	64	59	60	38–80
	70+	11	66	31	23	6–61
	All	80	77	70	70	59–80

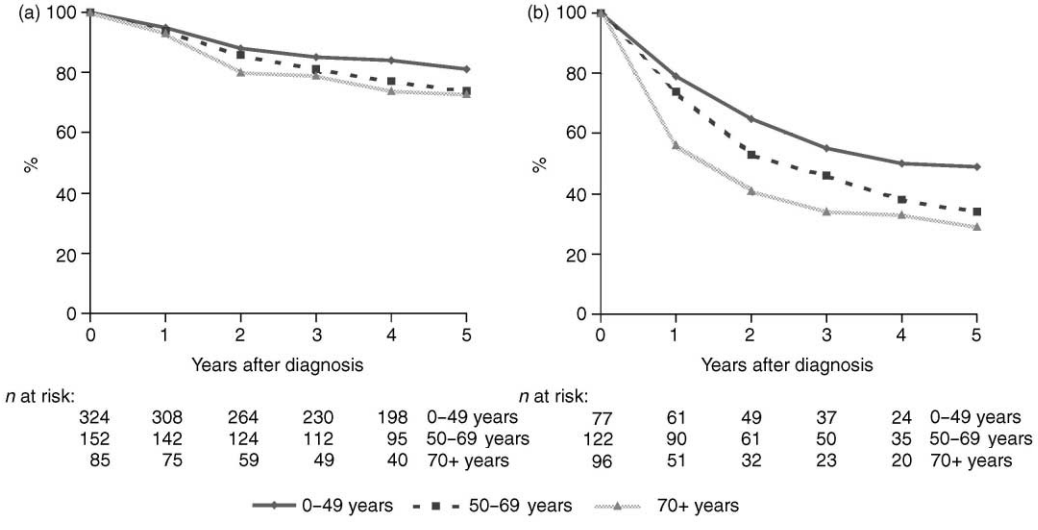

Fig. 2. (a) Cervical cancer: (a) stage IB-IIA, (b) stage IIB-IVA, 1986–1996. Relative survival rates by age.

Table 4
Results of univariate and multivariate analysis: estimated relative risks (RR) for excess mortality and associated 95% Confidence Intervals (CI) ($N=783$)[a]

	N	Univariate RR (95% CI)[b]	P value[c]	Multivariate[d]	P value	Multivariate + treatment[e] RR (95% CI)	P value
Age (years)							
⩽49	374	1 (reference)	0.001	1 (reference)	0.01	1 (reference)	0.42
50–69	254	2.1 (1.6–2.9)		1.5 (1.1–2.1)		1.2 (0.9–1.7)	
70+	155	2.5 (1.7–3.6)		1.7 (1.2–2.5)		1.2 (0.8–1.8)	
Stage							
IB-IIA	529	1 (reference)	0.001	1 (reference)	0.001	1 (reference)	0.001
IIB-IVA	254	4.5 (3.4–6.0)		3.7 (2.8–5.0)		2.1 (1.5–2.9)	
Histology							
Squamous cell	639	1 (reference)	0.74	1 (reference)	0.09	1 (reference)	0.06
Adenocarcinoma	144	1.1 (0.8–1.6)		1.3 (1.0–1.9)		1.4 (1.0–2.0)	

[a] Patients diagnosed with stage IA, IVB or stage unknown and patients who were not treated or in whom treatment was not known were excluded.
[b] RR: Relative Risk for excess mortality compared with reference category; 95% CI: Confidence Intervals.
[c] P values in univariate and multivariate analyses are from likelihood ratio tests.
[d] Multivariate analysis with adjustment for follow-up interval 1–5 years. In contrast to a standard Cox proportional hazards model, follow-up time is not taken as a continuous variable, but stratified into intervals.
[e] Multivariate analysis with adjustment for follow-up and for treatment (three categories: surgery, radiotherapy and surgery + radiotherapy).

In accordance with the guidelines, most patients received either radiotherapy (31%) or surgery (44%) as a single treatment modality. In almost 17% of the cases, surgery revealed indications for postoperative radiotherapy. In total, 4% of the patients did not receive any initial treatment (70+ years: 10%; 50–69 years: 5%; ⩽49 years: 1%).

The most commonly applied treatment in elderly patients with clinical stage IB-IIA disease was radiotherapy alone. Surgery as a single treatment was the most common in younger patients with stage IB-IIA disease, sometimes with adjuvant radiotherapy. These findings are in agreement with those of other recent studies [17,19]. In contrast with surgery alone and radiotherapy alone, the proportion of patients with stage IB-IIA who received radiotherapy after surgery was almost equal in the three age groups (Fig. 1). In this situation, however, RT after surgery will not always have been adjuvant RT. When positive lymph nodes were found during surgery, two scenarios were feasible: (1). surgery was only explorative and RT was given as the initial treatment; (2) radical surgery was carried out, followed by postoperative adjuvant RT. This implies that within this treatment group, there were cases with a pathologically proven worse prognosis that received RT as the initial treatment.

We found fairly large differences in treatment choice between patients with early stage disease, but this was not the case in patients with advanced stage disease (FIGO IIB-IVA), the majority of whom were treated with radiotherapy alone, irrespective of their age, which has also been reported by other authors [16,32].

We looked at survival differences by age. Five-year relative survival was 81% in women of 49 years or younger, 58% in women aged between 50 and 69 years and 49% in women of 70 years and older ($P=0.001$). These percentages are similar to those published in other large series of patients with cervical cancer [32,33]. The poor outcome in the oldest age group was partly related to their unfavourable stage distribution: 5-year survival in stage IB-IIA patients did not differ significantly between the age groups, but it did differ significantly in stage IIB-IVA patients.

To further analyse the effect of age, stage, morphology and treatment on survival, multiple regression analysis was used to estimate relative risks for excess mortality. The results in Table 4 illustrate very clearly the interdependency of age, stage and treatment. Age was an important prognostic factor in the model without treatment, but it did not have any significant influence on survival when treatment was included in the model. However, in observational studies, it is very hard to estimate any real differences in outcomes between groups that received different treatment, because prognostic characteristics will not be equally distributed over the groups [34]. There is general agreement that radical surgery is equally as effective as radical radiotherapy for the treatment of early stage invasive cervical cancer [32]. Therefore, the effect of treatment on survival is probably the result of patient selection on specific features/characteristics within the treatment and stage groups such as tumour volume, comorbid conditions and performance status. Unfortunately, we did not have any information about these items. It should be noted that when we calculated relative survival rates, all cases were included. In contrast, the multivariate analysis excluded cases who had not received treatment. Elderly patients especially were more represented within the latter category.

A population-based study in Sweden [14] revealed lower survival rates in older patients with cervical cancer than in younger patients (period 1960–1984, $n=17$ 377), but nothing was mentioned about the stage at diagnosis. Although the authors regarded a more advanced stage at diagnosis in older women to be a major cause of the difference in prognosis, they also suggested that a lower proportion of human papilloma virus-associated tumours in older patients, independent of stage, might explain the age-related differences in survival because those tumours carry a better prognosis than tumours without any identifiable human papilloma virus nucleic acids. However, the multivariate analyses in our study do not support this hypothesis, because they showed a very low influence of age on survival (besides stage and treatment). Another population-based Scandinavian study performed in Norway [13] reported on 7429 patients diagnosed with cervical cancer (period 1971–1990). Besides studying incidence and mortality trends, they conducted a multivariate analysis on relative survival rates, including stage, time and age. They found that there was a tendency towards a poorer prognosis in younger women, but age was not an important prognostic factor ($P=0.08$). In a patterns of care study in the US on cervical cancer patients diagnosed in the year 1984 ($n=5904$), an inverse relationship was found between survival and increasing age at diagnosis which was largely attributed to the unfavourable stage distribution in the elderly [32].

In our study, we also looked at survival stratified by histology and age. In contrast with most authors [13,17,35–37], but in concordance with others [16,38], we did not find significant differences in survival between squamous cell carcinoma and adenocarcinoma, either overall or in specific age groups.

We can conclude that the elderly cancer patients in our study were generally treated in accordance with the guidelines, although we did not have any detailed information about symptoms, radiotherapy doses or complications following treatment. Does survival in elderly cervical cancer patients give reasons for concern? We found that relative survival rates differed significantly by age. However, the multivariate analyses on a subset of patients showed that age *per se* did not have an independent prognostic effect on survival, but that stage and treatment were the explanatory factors. It is very likely that the effect of treatment was due to patient selection based on other characteristics, such as tumour volume, comorbidity and performance status.

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