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Factors influencing treatment decision and guideline conformity in high grade endometrial cancer patients- a population-based study

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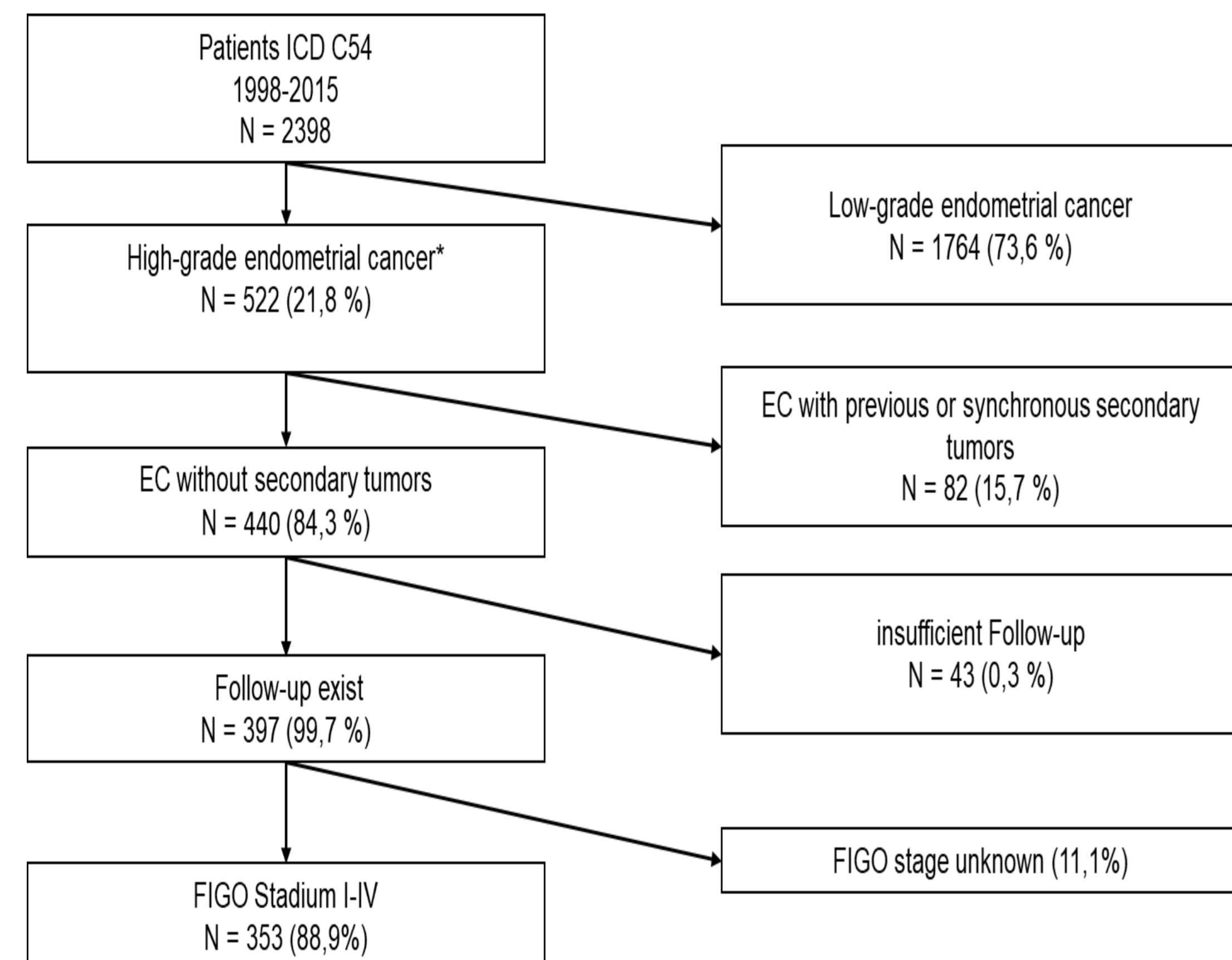
Purpose

National and international cancer guidelines have been established to aid physicians and patients in treatment decisions. Treatment according to guidelines has been demonstrated to improve survival in a number of different cancer entities. In a National Cancer Database study on 57,472 patients with non-endometrioid endometrial cancer, the odds of survival were roughly 15% lower for patients not treated in accordance with NCCN guidelines. Nevertheless, only 43.8% received guideline-concordant therapy (GCT). Deviations from guidelines depend on several factors, including the patient's preferences, age and comorbidities. The aim of this study was to assess the adherence to guideline recommendations concerning surgical and adjuvant treatment in endometrial cancer. Furthermore, we sought to evaluate the reasons for non-adherence to guidelines by further examining the influence of comorbidities and age.

Fig. 1 Flow-chart showing inclusion and exclusion criteria

Methods

The influence of age, comorbidities, tumor stage and histological subtype on guideline adherence was evaluated by multivariable logistic regression in a cohort of 353 high grade endometrial cancer patients. High grade endometrial cancer was defined as carcinosarcoma, Type II (serous, clear cell, mixed cell carcinoma) and Type I G3 histology.
As guideline recommendations were not very specific for FIGO stage IVB tumors, we carried out a second analysis including only stages IA-IVA (n=293).

Guideline conformity was measured according to the current German guideline at the time of diagnosis (DGGG Guideline available for 1998, 1999, 2004, 2006, 2008) and S2k guideline (published 2010) .

Overall survival (OS) was calculated from the date of cancer diagnosis to the date of death from any cause. Risk-adjustment was performed in multivariable Cox regression analyses to adjust for confounding factors: age at diagnosis, year of diagnosis, comorbidity, obesity, LNE, lymph vessel invasion, blood vessel invasion, oophorectomy, radiotherapy and chemotherapy. Comorbidity was adjusted using Charlson Comorbidity Index CCI (Charlson et al 1987). For multivariable binary logistic regression analysis, target variables were converted into a binary system (i.e. age ≥70/<70; CCI≥1/=0).

Table 1: General patients characteristics in complete cohort and according to Charlson Index Score (CCI)

		Charlson Index									Chi-square p
		0		1		>1		total			
		n	%	n	%	n	%	n	%		
Age at date of diagnosis	< 60	61	21.0%	4	4.9%	1	4.2%	66	16.6%		0.003
	60 - 69	97	33.3%	29	35.4%	5	20.8%	131	33.0%		
	70 - 79	106	36.4%	38	46.3%	15	62.5%	159	40.1%		
	80+	27	9.3%	11	13.4%	3	12.5%	41	10.3%		
Menopausal status	premenopausal	11	3.8%			1	4.2%	12	3.0%		0.009*
	perimenopausal	6	2.1%					6	1.5%		
	postmenopausal	187	64.3%	71	86.6%	18	75.0%	276	69.5%		
	unknown	87	29.9%	11	13.4%	5	20.8%	103	25.9%		
Year of diagnosis	1998-2003	77	26.5%	13	15.9%	6	25.0%	96	24.2%		0.292
	2004-2009	96	33.0%	32	39.0%	6	25.0%	134	33.8%		
	2010-2015	118	40.5%	37	45.1%	12	50.0%	167	42.1%		
Histologic type	Type 1	188	64.6%	57	69.5%	14	58.3%	259	65.2%		0.270
	Carcinosarkoma	35	12.0%	13	15.9%	2	8.3%	50	12.6%		
	Typ 2	68	23.4%	12	14.6%	8	33.3%	88	22.2%		
T	T1	161	55.3%	45	54.9%	5	20.8%	211	53.1%		0.049*
	T2	39	13.4%	7	8.5%	5	20.8%	51	12.8%		
	T3	66	22.7%	21	25.6%	8	33.3%	95	23.9%		
	T4	6	2.1%	3	3.7%	1	4.2%	10	2.5%		
	TX/kA	19	6.5%	6	7.3%	5	20.8%	30	7.6%		
N	N0	178	61.2%	54	65.9%	8	33.3%	240	60.5%		0.046*
	N1	55	18.9%	14	17.1%	6	25.0%	75	18.9%		
	NX/unknown	58	19.9%	14	17.1%	10	41.7%	82	20.7%		
	Gesamt	291	100.0%	82	100.0%	24	100.0%	397	100.0%		
M	M0	194	66.7%	59	72.0%	14	58.3%	267	67.3%		0.043*
	M1	39	13.4%	13	15.9%	8	33.3%	60	15.1%		
	MX/unknown	58	19.9%	10	12.2%	2	8.3%	70	17.6%		
FIGO stadium	I	129	44.3%	38	46.3%	5	20.8%	172	43.3%		0.132*
	II	24	8.2%	3	3.7%	2	8.3%	29	7.3%		
	III	63	21.6%	19	23.2%	5	20.8%	87	21.9%		
	IV	41	14.1%	16	19.5%	8	33.3%	65	16.4%		
	unknown	34	11.7%	6	7.3%	4	16.7%	44	11.1%		
	Gesamt	291	100.0%	82	100.0%	24	100.0%	397	100.0%		

Results

Guideline adherence
FIGO stage I-IVB (n=353)
The rate of GCT in the complete cohort was 34.3%. The extent in which patients were treated according to guideline recommendations significantly correlated positively with patients younger age (p<0.001) and higher tumour stage (p<0.001) (Table 3). While 42.3% of patients age <70 years received a guideline conform therapy, only 25.7% of patients ≥ 70 years were treated accordingly. The rate of patients treated in accordance with guideline recommendations was highest in the age group ≤60 years with 49.2% and lowest in the group of patients ≥ 80 years with only 13.3%. Comorbidities and CCI did not significantly influence guideline conformity (p=0.563 and p=0.543, respectively). The rate of patients treated according to guidelines in the group of CCI≥1and CCI=0 was 37.5% and 33.1%, respectively. In a multivariable model, age (p<0.001) and tumour stage (p<0.001) remained significant.
FIGO stage I-IVA (n=293)
The rate of GCT was 22.5%. GCT correlated positively with patients younger age (p<0.001), and higher tumor stage (p=0.020) (Table 4). Comorbidities and CCI did not significantly influence guideline conformity (p=0.877 and p=0.935, respectively). In a multivariable model, age (p<0.001) and tumor stage (p=0.021) remained significant.

Overall Survival
Kaplan-Meier analysis
CCI≥1 was associated with a significantly reduced OS (p<0.001), as was age≥70 (p<0.001) (Figure 2). Other factors associated with worse OS were higher FIGO stage (p<0.001), obesity (p<0.001), year of diagnosis (p=0.036), blood vessel invasion (p=0.016), lymph vessel invasion (p<0.001), and histological subtype (p<0.001). Surgery (p<0.001), systematic LNE (p<0.001) and radiotherapy (p<0.001) improved OS. When considering FIGO stages separately, CCI≥1 was only significant in FIGO stage I tumours (p<0.001) and unknown tumor stage (p<0.001). Age ≥ 70 years, on the other hand, was significant in stages I (p<0.001), III (p=0.030 and IV (p=0.022). In stage II tumours it trended towards significance (p=0.077). CCI≥1 was significantly associated with inferior OS in patients age 60-69 (p<0.001). In the other age groups, there was no statistically significant correlation between CCI≥1 and OS (<60 years p=0.121; 70-79 years p=0.123 and ≥80 years p=0.728). CCI≥1 was significantly associated with OS in patients not treated according to guidelines (p=0.042) and in patients treated in conformity to guidelines (p=0.039).
Cox-Regression Analysis
In a multivariable model, age (p<0.001), FIGO stage (p<0.001) and histologic subtype (p<0.001), surgery (p<0.001), chemotherapy (p<0.001), obesity (p=0.011) and systematic LNE (p=0.011) remained significant factors on OS. CCI≥1 (p=0.541), year of diagnosis (p=0.060), lymph vessel invasion (p= 0.103), blood vessel invasion (p=0.522) and radiotherapy (p=0.555) were not significantly associated with OS.
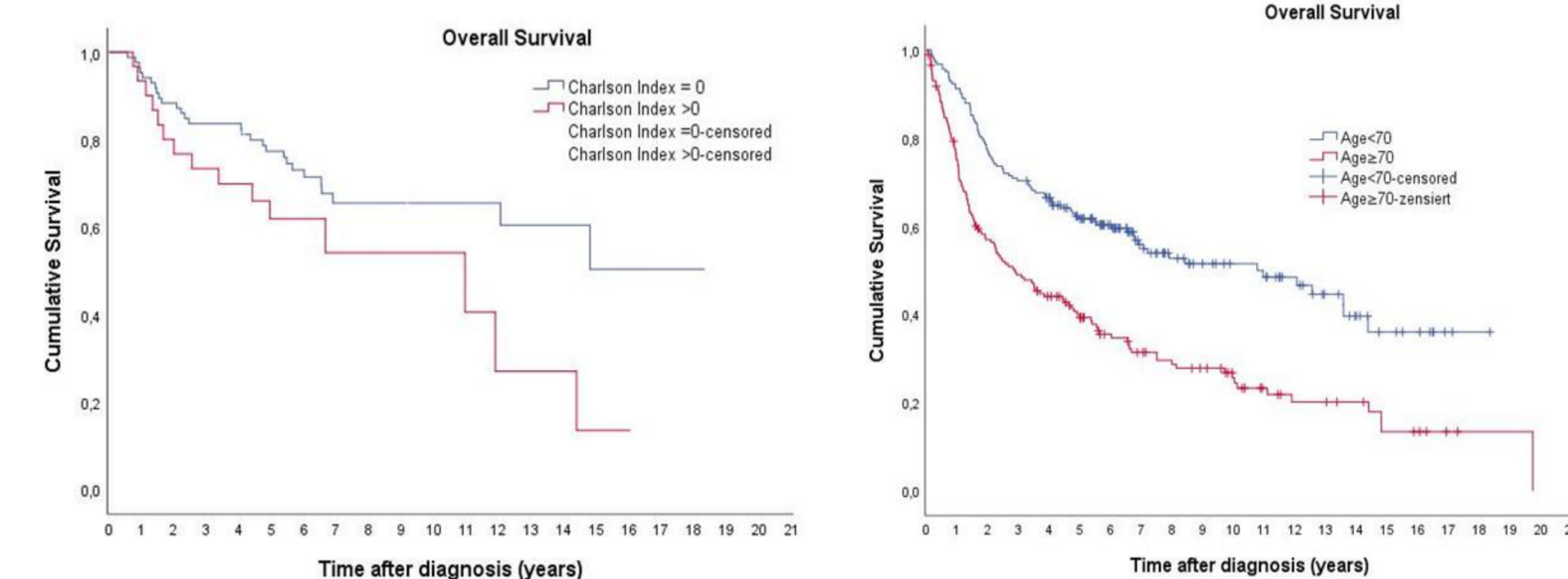

Figure 2: Kaplan–Meier curves comparing overall survival depending on CCI and age.

Conclusions

Age seems to be the strongest independent factor leading to guideline deviation. Comorbidities were associated with less aggressive treatment, but not with deviations from guidelines.

References

Dholakia J, Llamocca E, Quick A, Salani R, Felix AS (2020) Guideline-concordant treatment is associated with improved survival among women with non-endometrioid endometrial cancer. Gynecologic Oncology. https://doi.org/10.1016/j.ygyno.2020.03.016

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