Chapter 5

AGE AND CO-MORBIDITY IN CANCER PATIENTS: A POPULATION-BASED APPROACH

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The mean age of patients diagnosed with cancer is increasing in western countries due to rising incidence rates of most cancers with age and ageing of the population. In most European countries more than 40% of all new patients with cancer are over the age of 70, which implies that they increasingly suffer from one or more other serious (chronic) diseases and from interactions with and side effects from their treatment. Besides affecting the life expectancy co-morbid conditions and their treatment may complicate the clinical management of cancer patients, especially when they are frail. Since they are often excluded from clinical trials, little is known about treatment outcome, such as complications, quality of life and survival. Choice of curative treatment of cancer for older patients may be influenced by the physical condition of the patient (co-morbidity, reduced functional reserves, interaction between medications, performance status), the psychological condition (depression, dementia) and social parameters (informal care, mobility)[1-3].

This chapter focuses on the role of age and co-morbidity in cancer patients. The value of studying co-morbidity is demonstrated by data of the

population-based Eindhoven Cancer Registry [4]. We were looking for answers on questions on guideline adherence from local clinicians who increasingly experienced problems with an increasing number of elderly patients. The clinical context is one of community hospitals only, within the framework of the Comprehensive Cancer Centre [5]. We give insight in the prevalence of co-morbidity in unselected cancer patients, and the effects of co-morbidity on treatment and prognosis.

1. METHODS

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with now 2.3 million inhabitants and only general hospitals. Since 1993 serious co-morbidity with prognostic impact has been recorded for all patients. The Charlson Co-morbidity Index is most widely used for recording co-morbidity and was validated in various studies [6]. We used a slightly adapted version of this index for recording co-morbidity (Table 1). Co-morbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis and/or received some treatment or surveillance.

Table 1. Classification of co-morbidity, according to an adapted version of the list of Charlson et al. (1987)

Chronic Obstructive Pulmonary Diseases (COPD)
Cardiovascular disease: myocardial infarction, cardiac insufficiency, angina pectoris, CABG (coronary artery bypass graft)
Peripheral arterial disease: intermittent claudication, abdominal aneurysm, surgical intervention
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell skin carcinoma)
Hypertension
Diabetes mellitus
Other:
- autoimmune diseases: sarcoidosis, Wegener's disease, SLE (systemic lupus erythematosis)
- rheumatoid arthritis (only severe)
- kidney diseases: glomerulonephritis, pyelonephritis
- gastrointestinal: stomach ulcer & resection, colitis
- liver diseases: cirrhosis, hepatitis
- dementia
- chronic infection

The data were extracted from the medical records between 6 and 18 months after diagnosis, when the trained registry personnel does its routine view. Previous admissions, letters from and to general practitioners (every patient has his GP in the Netherlands) and other specialists, the medical history and preoperative screening were used as sources. On average, it takes about 5 minutes per patient to record co-morbidity. The medical record is generally regarded as the most complete source of information on the patient's past and current health status[7].

Patients with cancer of the esophagus, stomach, colon or rectum, pancreas, lung, breast, cervix uteri, corpus uteri, ovary, prostate, bladder, kidney, and non-Hodgkin's lymphoma, newly diagnosed between 1995 and 2001 (N=48,030), were included for this overview. Patients with cancer diagnosed at autopsy (N=447 or 1%) were excluded. Treatment was classified as surgery (resection), radiotherapy, chemotherapy, hormonal therapy (or combinations) and 'other or none'. Surgery did not comprise diagnostic operations.

Survival analyses were restricted to patients with cancer of the colon or rectum, lung, breast, prostate or non-Hodgkin's lymphoma diagnosed between 1995 and 1999 (N=21,984). Vital status was available up to 1 April 2002. In addition to passive follow-up via the hospitals, this information was also obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Central Bureau for Genealogy. The latter is an institution that collects data on all deceased Dutch citizens via the civil municipal registries. In this way, information on patients who moved outside the registry area was also obtained. Patients who died outside the Netherlands were lost-to follow-up. The estimated proportion of these patients was less than 1%.

Survival time was defined as the time from diagnosis to death or the end of the study. Survival generally decreases with age, because other causes-of-death also take their share. The prevalence of co-morbidity increases with age. Therefore, we calculated relative survival rates which are an estimation of disease-specific survival. Survival of cancer patients is adjusted for mortality from all causes of death in the background population with the same age structure. Relative survival is calculated as the ratio of the observed to the expected rates [8]. Expected survival rates were estimated from life tables for regional male and female populations.

2. RESULTS

2.1 Prevalence

The prevalence of co-morbidity usually increased with age (Table 2), but remained stable or decreased above age 80 for some tumours. About 60% of all new cancer patients older than 65 also suffered from at least one other serious disease. The most frequent concomitant diseases were previous cancers, heart disease, hypertension, COPD, and diabetes mellitus, with prevalence rates up to 20%, 23%, 26%, 17%, and 16%, respectively. The prevalence of co-morbidity was highest for patients with lung cancer (over 70% for men aged 65 or older) and lowest for patients with breast cancer (about 55% for women aged 65 or older) (Table 3). The prevalence of cardiovascular diseases was higher among men compared to women, and was up to 35% of male and 28% of female patients with cancer of the digestive tract, lung, and kidney, and non-Hodgkin's lymphoma (Table 4). The prevalence of COPD was relatively high among older patients with lung cancer (31% of males and 24% of females), and also among men with esophageal and bladder cancer (20%). The prevalence of hypertension was highest among women with gynaecological tumors (38%) or adenocarcinoma of the kidney (up to 45%). High prevalence rates of diabetes in older patients were observed for cancer of the pancreas (up to 27%), cervix uteri (32%), corpus uteri (25%) and kidney (22%). The prevalence of diabetes in women with cervical cancer was twice as high among those with squamous cell than with adenocarcinoma, being 16% and 7% respectively (not shown).

The higher prevalence rates of digestive tract conditions among males compared to females were largely due to concomitant stomach ulcers (3.5% versus almost 2%) and previous gastrectomy (2.7% versus 0.6%), whereas the prevalence of colitis was about similar with 0.3%.

2.2 Treatment (see overview in Table 5)

Patients with colon cancer underwent surgery regardless of age or the number of co-morbid conditions: more than 95% with Dukes A-C did so and about 75% of patients with Dukes D. However, patients with Dukes C received less adjuvant chemotherapy with the rise of age: from 65% of patients at middle age to 33% of patients aged 65 or older (data 1997-2001). The proportion of patients with Dukes D receiving adjuvant chemotherapy decreased from 56% at middle age to 20% of patients aged 65 or older. The proportion receiving adjuvant chemotherapy also decreased from 27% of patients without co-morbidity to 17% of those with co-morbidity. The proportion of rectal cancer patients receiving adjuvant radiotherapy

decreased from 53% of patients younger than 65 to 37% of patients aged 65 or older, and also decreased with co-morbidity from 51% of patients without co-morbidity to 39% in case of co-morbidity.

Table 2. Age-specific prevalence (%) of serious concomitant diseases among newly diagnosed cancer patients in southeastern Netherlands, 1995-2001.

	MEN			WOMEN		
	Age (years)			Age (years)		
Concomitant disease	50-64 (n = 8294)	65-79 (n = 14,593)	80+ (n = 3362)	50-64 (n = 8210)	65-79 (n = 9621)	80+ (n = 3623)
Other cancers[a]	8.2	15	20	8.3	13	16
Heart disease	11	22	23	3.6	12	19
Peripheral vascular disease	4.4	8.8	7.4	1.4	3.1	3.2
COPD	9.5	17.1	17	5.7	8.4	7.1
Hypertension	12	16.2	12	14	26	24
Diabetes mellitus	5.7	9.3	11	5.2	14	16
Cerebrovascular disease	2.3	5.7	6.7	1.2	4.3	7.1
Autoimmune	0.7	1.0	0.9	0.9	1.6	1.8
Chronic infection	1.3	2.3	1.7	1.0	2.1	1.9
Central nervous system	0.1	0.5	2.5	-	0.8	4.1
Liver disease	0.9	0.7	0.5	0.5	0.5	0.3
Urinary	0.5	0.5	0.5	0.3	0.4	0.4
Gastro-intestinal	4.7	6.4	6.0	1.8	2.5	3.9
Connective tissue	0.3	0.1	-	0.3	0.2	0.3
Together[b]	**43**	**63**	**64**	**34**	**56**	**63**

Source: Eindhoven Cancer Registry; [a] also in same organ (but not metastasis of primary tumor), excluding basal cell skin Carcinoma; [b] more conditions per patient

Table 3. Age-specific prevalence (%) of the number of serious concomitant diseases among newly diagnosed patients with 13 major cancers in southeastern Netherlands, 1995-2001 Source: Eindhoven Cancer Registry.

				number of co-morbid conditions			
		age		None	1	≥2	unknown
tumor site	sex	(years)	N	%	%	%	%
All cancers	Men	50-64	8294	42	28	15	15
		65-79	14593	25	33	30	12
		80+	3362	20	32	33	16
	Women	50-64	8170	52	25	9	14
		65-79	9587	33	31	24	11
		80+	3618	23	31	32	14
Esophagus	Men	50-64	200	42	28	23	8
		65-79	216	24	33	39	4
		80+	57	21	35	37	7
	Women	50-64	73	48	30	11	11
		65-79	100	40	30	24	6
		80+	50	18	42	34	6
Stomach	Men	50-64	356	41	30	18	11
		65-79	619	26	32	34	7
		80+	171	18	32	40	10
	Women	50-64	132	51	27	16	7
		65-79	284	35	29	27	9
		80+	196	24	29	39	7
Colon/rectum	Men	50-64	1254	50	26	14	11
		65-79	2029	28	33	31	7
		80+	522	22	33	37	8
	Women	50-64	916	53	27	10	10
		65-79	1733	35	32	24	9
		80+	773	25	30	35	10
Pancreas	Men	50-64	156	35	32	18	15
		65-79	274	27	30	35	8
		80+	45	27	31	33	9
	Women	50-64	105	47	28	12	13
		65-79	255	29	34	27	9
		80+	85	24	31	34	12

Table 3 continued

Lung	Men	50-64	1945	39	32	21	8
		65-79	3478	22	35	38	5
		80+	518	21	31	40	8
	Women	50-64	673	45	32	15	8
		65-79	741	27	33	33	8
		80+	94	32	27	33	9
Breast	Women	50-64	3247	60	21	7	12
		65-79	2655	37	31	22	10
		80+	824	25	33	33	9
Cervix uteri	Women	50-64	125	57	26	9	8
		65-79	87	44	32	18	6
		80+	37	27	30	32	11
Corpus uteri	Women	50-64	507	54	27	10	9
		65-79	490	31	34	28	7
		80+	126	19	34	42	5
Ovary	Women	50-64	380	57	26	8	9
		65-79	386	36	33	24	7
		80+	102	29	36	25	9
Prostate	Men	50-64	1158	45	27	11	18
		65-79	3316	30	33	22	15
		80+	784	27	32	25	16
Bladder	Men	50-64	350	39	30	16	16
		65-79	804	22	38	31	9
		80+	248	18	35	38	9
	Women	50-64	87	30	38	14	18
		65-79	186	32	30	31	8
		80+	109	22	31	29	17
Kidney	Men	50-64	263	42	32	16	10
		65-79	315	22	34	34	10
		80+	50	8	34	44	14
	Women	50-64	157	42	31	13	13
		65-79	241	23	35	32	10
		80+	58	17	31	43	9
NHL	Men	50-64	268	50	24	15	11
		65-79	335	29	36	31	5
		80+	63	14	41	33	11
	Women	50-64	201	54	24	10	12
		65-79	280	36	33	26	6
		80+	98	32	30	36	3

Table 4. Age-specific prevalence (%) of the most common serious concomitant diseases among newly diagnosed patients with 13 major cancers, 1995-2001. Source: Eindhoven Cancer Registry.

		other cancers			heart /vascular disease			COPD			hypertension			diabetes		
age (yrs)		50-64	65-79	80+	50-64	65-79	80+	50-64	65-79	80+	50-64	65-79	80+	50-64	65-79	80+
tumor	Sex	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Esophagus	M	7	19	26	15	35	32	12	16	23	15	20	9	5	11	16
	W	11	16	16	4	16	16	14	9	8	10	17	24	4	13	14
Stomach	M	6	12	20	19	33	26	7	14	16	15	15	19	6	9	12
	W	10	13	15	8	15	25	4	9	7	14	26	29	7	14	20
Colon/rectum	M	7	15	22	13	28	31	6	15	16	16	20	15	7	10	12
	W	10	14	16	5	14	24	5	8	9	15	25	25	6	14	16
Pancreas	M	6	13	13	22	26	33	5	17	16	12	18	18	13	20	22
	W	8	9	7	8	15	27	3	9	6	15	27	28	11	27	25
Lung	M	9	16	17	18	33	31	20	29	31	10	15	10	6	10	11
	W	9	15	14	11	21	21	21	24	14	12	22	18	5	12	10
Breast	W	6	10	14	4	12	21	4	6	7	13	29	26	5	13	16
Cervix uteri	W	5	8	11	6	16	22	5	6	3	13	21	27	9	15	32
Corpus uteri	W	8	10	19	3	12	23	4	6	12	23	38	33	8	22	25
Ovary	W	12	13	15	4	15	16	5	7	5	13	26	26	4	12	12
Prostate	M	6	9	14	12	23	27	6	12	14	13	17	11	5	8	9
Bladder	M	19	24	30	16	28	28	8	15	21	9	16	13	4	11	11
	W	24	23	17	8	13	24	9	7	8	11	31	18	7	17	15
Kidney	M	12	16	28	15	32	34	6	15	16	16	25	18	8	10	20
	W	7	18	17	6	18	28	8	6	3	27	32	45	9	18	22
NHL	M	5	13	17	14	28	35	4	15	10	12	18	11	5	10	11
	W	6	15	15	6	11	24	2	8	4	15	25	21	7	11	13

Table 5. Influence of age and co-morbidity on primary treatment, according to tumor type and/or stage

Tumor	**Stage**	**Influence of rising age (> 60 yrs)**	**Influence of co-morbidity**
Colon	Dukes A/B	None	None
	Dukes C/D	Less adjuvant CT, none >80yrs	Age 65-79: less adjuvant CT
Rectum	Dukes B/C	Less adjuvant RT	Less adjuvant RT
NSCLC*	I/II	Less surgery, more RT alone	Age 60-79: less surgery
	III/IV	Less CT	None
SCLC**	Limited	Less CT+RT, more CT alone	Age 70-79: less CT+RT
	Extensive	Less CT, more abstinence	None
Breast		Less surgery, more endocrine	Less adjuvant RT, more endocrine
Prostate		Less prostatectomy, more endocrine	Age 60-79: less prostatectomy, more endocrine
NHL***	Indolent	Less CT, more RT and wait & see	None
	Aggressive	Less CT, more abstinence	Age 70+: less CT

* Non-small cell lung cancer

** Small cell lung cancer

*** Non-Hodgkin's lymphoma

CT=chemotherapy

RT=radiotherapy

Source: Eindhoven Cancer Registry

The proportion of patients with localized non-small cell lung cancer who underwent surgery with or without radiotherapy was only 9% of those aged 80 or older versus 92%, 79% and 61% of the age groups <60, 60-69 and 70-79, respectively. Patients aged 60-69 and 70-79 received less surgery in the presence of co-morbidity. Most patients with non-localized non-small cell lung cancer received only radiotherapy. The proportion receiving chemotherapy (with or without radiotherapy) was considerably higher among patients younger than 60 (24%) than among those aged 80 or older (2%). Older patients more often did not receive oncological treatment. The number of co-morbid conditions had no substantial influence on treatment chosen for patients with non-localized disease. Elderly patients with limited small cell lung cancer received less adjuvant radiotherapy and more chemotherapy alone. Among patients aged 70-79 with limited small cell lung cancer the proportion receiving adjuvant radiotherapy also decreased in the presence of co-morbidity.

Among patients with breast cancer younger than 80 years over 90% underwent surgery, compared with only 74% of those aged 80 or older. The proportion receiving systemic treatment (mostly chemotherapy for those below 50 years and endocrine treatment for those aged 50 or older) increased from about 40% of those younger than 80 to 57% of patients aged 80 or older. In the presence of co-morbidity less patients received adjuvant radiotherapy (50% of patients with co-morbidity compared to 65% of those without co-morbidity) and more older women received endocrine treatment only.

The number of prostate cancer patients undergoing prostatectomy decreased with increasing age, from 42% of patients younger than 60 to 1% of patients aged 80 or older. The proportion of patients receiving curative radiotherapy also decreased from 17% among those at middle age to 4% of those aged 80 or older. With the rise of age prostate cancer patients received more often hormonal therapy: from 19% of patients below 60 to 59% of patients aged 80 or older. Among patients aged 60-69, the proportion who underwent prostatectomy decreased significantly with co-morbidity from 31% of patients without co-morbidity to 18% of patients with two or more comorbid conditions. In those aged 70-79, these percentages were 8% and 3% respectively. The proportion of patients aged 60-69 receiving hormonal therapy increased from 22% of patients without co-morbidity to 27% of those with two or more co-morbid conditions. In those aged 70-79, these proportions were 36% and 41%, respectively. In the other age groups (< 60 years and 80+ years) there was no significant influence of co-morbidity on treatment choice.

Among patients with non-Hodgkin's lymphoma the proportion receiving chemotherapy decreased with age. For patients with indolent disease the proportion receiving chemotherapy decreased from 60% of patients younger

than 70 to 40% of those aged 70 or older. For patients with aggressive disease the proportion receiving chemotherapy decreased from about 80% to about 60%. Among patients with aggressive disease aged 70 or older the proportion receiving chemotherapy also decreased with co-morbidity.

2.3 Prognosis (see Table 6)

Five-year relative survival rates for colon cancer patients aged 70 or older without co-morbidity exceeded those of patients younger than 70: 75% versus 61%. Relative survival decreased in the presence of co-morbidity, especially for patients aged 70 or older and in case of COPD. Rectal cancer patients younger than 70 exhibited a 5-year survival rate of 65%, which amounted to 62% for patients aged 70 or older. For the latter, the presence of diabetes and cardiovascular diseases lowered 5-survival to 34%. One-year relative survival rates of patients with localized non-small cell lung cancer (NSCLC) were clearly lower for older patients: a 1-year survival rate of 81% for patients younger than 70 and 62% for patients aged 70 or older. The presence of COPD and diabetes affected survival negatively. Survival of non-localised NSCLC was mostly affected by the presence of diabetes. Although survival of small cell lung cancer was strongly related to age at diagnosis, co-morbidity did not seem to have a clear prognostic impact. Breast cancer patients without co-morbidity exhibited 5-year relative survival rates of 86% (when younger than 70) and even 90% (aged 70 or older). But the presence of diabetes and cardiovascular diseases lowered 5-year survival rates of patients aged 70 or older substantially: 56% and 58%, respectively. Prostate cancer patients without co-morbidity had a 5-year survival rate of 88% (no difference between younger and older patients), whereas diabetes and COPD had a negative impact on survival of patients aged 70 or older. Indolent non-Hodgkin's lymphoma patients younger than 70 without co-morbidity had a 1-year survival rate of 94%, versus 80% of patients aged 70 or older. One-year survival of aggressive non-Hodgkin's lymphoma without concomitant diseases at diagnosis was 80% for patients younger than 70 and 73% for patients aged 70 or older. The presence of cardiovascular diseases lowered 1-year survival to 51% for patients younger than 70 and to 43% for patients aged 70 or older.

		Relative survival (SE)			
		<70 years		>70 years	
Tumor type	**Co-morbidity**	1-year	5-year	1-year	5-year
Colon	**None**	**0.82 (1)**	**0.59 (2)**	**0.82 (2)**	**0.75 (4)**
	Diabetes	**0.77 (4)**	**0.51 (6)**	**0.67 (3)**	**0.50 (5)**
	COPD	**0.73 (4)**	**0.47 (6)**	**0.68 (4)**	**0.41 (6)**
	Cardiovascula	**0.74 (4)**	**0.54 (5)**	**0.68 (3)**	**0.45 (4)**
Rectum	**None**	**0.89 (1)**	**0.65 (2)**	**0.80 (3)**	**0.62 (5)**
	Diabetes	**0.78 (5)**	**0.46 (8)**	**0.73 (5)**	**0.34 (7)**
	COPD	**0.87 (4)**	**0.53 (8)**	**0.68 (5)**	**0.40 (7)**
	Cardiovascula	**0.80 (4)**	**0.55 (6)**	**0.72 (4)**	**0.34 (6)**
NSCLC* localised	**None**	**0.81 (3)**	***0.68 (3)***	**0.62 (6)**	***0.46 (6)***
	Diabetes	**0.75 (6)**	***0.59 (7)***	**0.57 (7)**	***0.29 (7)***
	COPD	**0.77 (3)**	***0.60 (4)***	**0.53 (4)**	***0.29 (4)***
	Cardiovascula	**0.76 (4)**	***0.65 (4)***	**0.59 (5)**	***0.39 (5)***
NSCLC* non-local	**None**	**0.29 (2)**	***0.13 (1)***	**0.21 (3)**	***0.10 (2)***
	Diabetes	**0.29 (5)**	***0.16 (4)***	**0.11 (4)**	***0.03 (2)***
	COPD	**0.26 (3)**	***0.10 (2)***	**0.22 (3)**	***0.09 (2)***
	Cardiovascula	**0.26 (3)**	***0.11 (2)***	**0.21 (3)**	***0.07 (2)***
SCLC**	**None**	**0.41 (3)**	***0.10 (2)***	**0.15 (4)**	***0.05 (2)***
	Diabetes	**0.28 (6)**	***0.06 (3)***	**0.15 (7)**	***0.04 (4)***
	COPD	**0.33 (4)**	***0.17 (4)***	**0.19 (4)**	***0.06 (2)***
	Cardiovascula	**0.31 (4)**	***0.10 (3)***	**0.18 (4)**	***0.09 (3)***
Breast	**None**	**0.99 (0)**	**0.86 (1)**	**0.98 (0)**	**00.. (3)**
	Diabetes	**0.95 (2)**	**0.82 (4)**	**0.88 (2)**	**0.56 (5)**
	COPD	**0.97 (2)**	**0.82 (4**	**0.92 (3)**	**0.71 (8)**
	Cardiovascula	**0.93 (2)**	**0.76 (4)**	**0.91 (2)**	**0.58 (5)**
Prostate	**None**	**0.99 (1)**	**0.88 (2)**	**0.99 (1)**	**0.89 (4)**
	Diabetes	**0.92 (3)**	**0.74 (7)**	**0.93 (3)**	**0.64 (7)**
	COPD	**0.92 (30**	**0.81 (5)**	**0.86 (3)**	**0.63 (5)**
	Cardiovascula	**0.95 (2)**	**0.78 (4)**	**0.90 (2)**	**0.70 (4)**
NHL*** indolent	**None**	**0.94 (2)**	***0.90 (3)***	**0.80 (9)**	***0.78 (10)***
	Diabetes	**0.88 (11)**	***0.77 (16)***	**0.73 (17)**	***0.79 (19)***
	COPD	**0.92 (9)**	***0.84 (12)***	**0.86 (19)**	***0.46 (25)***
	Cardiovascula	**0.95 (6)**	***0.71 (12)***	**0.79 (12)**	***0.78 (14)***
NHL*** aggressive	**None**	**0.80 (3)**	***0.68 (3)***	**0.73 (7)**	***0.61 (8)***
	Diabetes	**0.64 (11)**	***0.65 (11)***	**0.70 (11)**	***0.58 (13)***
	COPD	**0.80 (11)**	***0.81 (11)***	**0.56 (12)**	***0.38 (12)***
	Cardiovascula	**0.51 (9)**	***0.41 (9)***	**0.43 (8)**	***0.42 (8)***

Table 6. Relative 1- and 5-year survival rates, according to age and co-morbidity. Source: Eindhoven Cancer Registry. SE= standard error. * Non-small cell lung cancer. ** Small cell lung cancer. *** Non-Hodgkin's lymphoma. *# 2-year survival*

3. DISCUSSION

3.1 Validity of Data

Co-morbidity is a multidimensional variable with a variation in severity. Diseases that influence mortality may not be the same as those influencing function or tolerance to treatment. Although there is general agreement about the importance of co-morbidity for cancer management and prognosis, there is no consensus about the types of diseases that should be included, nor about the weighing of the conditions. There are several methods for determining the total score of diseases. The most global measure is the sum of the number of conditions present. Secondly, a severity score can be assigned to each condition and the total score is the summation of all the severity scores present in a patient at a certain moment. A third method is to assign a severity score to each condition and the total severity is based on the most severe condition present in a patient. When a patient has more than one disease, there may also be a multiplicative or synergistic effect on outcomes, and grading severity according to only the sum of diseases or scores or to only the single most severe condition may miss the burden that multiple chronic diseases can place on an individual. Several systems have been proposed, each with its own classification and scoring system. The choice of the classification system is dependent on the aim of the study, the clinical problem to be explored. The five most widely used systems are: the indexes of Kaplan-Feinstein [9], Charlson [6], and of the National Institute of Ageing/National Cancer Institute (NIA/NCI) [10], the Cumulative Illness Rating Scale-Geriatric (CIRS-G) [11], and the Index of Co-Existent Diseases (ICED) [12]. In the Eindhoven Cancer Registry an adapted version of the Charlson co-morbidity index was chosen for the following reasons: it was the most widely used validated classification system at the time and it is relatively easy to use [4, 13]. We wanted to avoid the plethora of minor conditions, each with their classification problems and changes in the natural history. Scoring needed to be done by cancer registry personnel trained in oncological diagnoses who could only spend a limited amount of time on this.

For the assessment of co-morbidity several sources can be used. Although the medical record is generally regarded as the most complete source of information on the patient's past and current health status, there may be some limitations in using medical records, such as differences in information in the records between hospitals or specialists, or possible selection bias due to differences in the number of physician visits. Data on co-morbidity can also be gathered from administrative medical record databases or discharge data. In a comparison between the Charlson co-morbidity index derived from medical records with that derived from databases of administrative medical

records, the data derived from the medical records had a better predictive value than the administrative disease data[7].

Between 2001 and 2003 the completeness and accuracy of our data on co-morbidity in the Eindhoven Cancer registry were validated in a random sample of 2607 patients with colorectal, lung, breast and prostate cancer and non-Hodgkin's lymphoma aged 40 and older and diagnosed between 1995 and 1999. Co-morbidity scored by the registry team was compared with that scored by a team of a surgeon and an epidemiologist. Recording of co-morbidity proved to be entirely correct for almost 70% (ranging from 59% to 72%) of patients. Some under-registration occurred especially of cardiovascular conditions (Internal report, 2002). This appeared to be mainly due to the use of unknown terminology, unknown abbreviations or illegible handwriting of the specialist. Although the unregistered conditions were at the time not very severe, this would imply that the real effects of co-morbidity on treatment and survival are probably stronger than those presented in this chapter and in our publications.

3.2 Prevalence

The higher prevalence of co-morbidity among older patients was expected, because the prevalence of chronic diseases generally increases with age. The prevalence of co-morbidity among older patients may even be underestimated due to ascertainment bias. Younger patients underwent surgery more often and received chemotherapy more often. The prevalence of co-morbidity reported by the treating physician might then be more elevated among younger patients, due to the required screening examinations before treatment.

The high risk of cardiovascular diseases and chronic obstructive pulmonary diseases for patients with cancer of the esophagus, stomach, lung, bladder and kidney can be explained by the high proportion of smokers among these patients, especially men [14, 15]. That diabetes mellitus occurred in a high proportion of patients with cancer of the pancreas is not surprising [16, 17]. A history of diabetes has been consistently associated with a two-fold increased risk for endometrial cancer [18], probably because both are related with obesity. The increased prevalence of diabetes among patients with cervical cancer was more strongly related to squamous cell carcinoma than to adenocarcinoma. Kidney cancer has been associated with hypertension, although it is unknown whether this results from the hypertension itself or from the anti-hypertensives [19]. Previously, we also found an association of hypertension with the incidence of gliomas [20]. The risk of renal cancer is also elevated among patients with diabetes[21].

The prevalence of cardiovascular diseases and pulmonary diseases was higher among men compared to women, which can be largely explained by a

higher prevalence of smoking among men in the past. By contrast, the prevalence of hypertension (a less serious condition) and diabetes was higher among women.

3.3 Treatment

If alternative treatment strategies were available, older patients were often treated less aggressively than younger patients. After stratification for age, the influence of age and co-morbidity on treatment choice differed, according to tumor type.

When surgery is inevitable like in patients with colorectal cancer, higher age or the prevalence of co-morbidity did not have any influence on the resection rate. On the other hand, older patients with non-small cell lung cancer (with serious co-morbidity) more often received radiotherapy instead of surgery [22]. Surgical mortality increases markedly with age and is especially high for pneumonectomy [23, 24]. The resection rate also declined with co-morbidity, probably because of the expected higher incidence of postoperative complications and mortality [25]. However, in everyday practice the resectability is not determined primarily by co-morbid conditions, but by its effects on lung function and cardiac function. The resection rate for prostate cancer also decreased with co-morbidity, whereas the proportion receiving hormonal treatment increased[26].

Administration of adjuvant chemotherapy markedly decreased with rising age and co-morbidity for patients with Dukes C or D colon cancer [27], probably because of the higher rate of hematological complications [28,29,30]. Administration of primary chemotherapy also decreased with age and co-morbidity in patients with non-Hodgkin's lymphoma[31].

Administration of adjuvant radiotherapy decreased with age and co-morbidity in patients with rectal cancer, limited small cell lung cancer or breast cancer [13, 27, 32]. However, we did not find that the rate of expected complications of radiotherapy was higher for older patients with co-morbidity. Therefore, the reluctance of offering adjuvant radiotherapy might be related to practical reasons like the distance to a radiotherapy institute or the burden of the 20 to 30 visits to the radiotherapy institute.

Several authors also found less aggressive treatment of patients with co-morbidity in case of breast cancer, colorectal cancer, or prostate cancer[33,34, 26, 35, 36].

Age seemed to have more influence on treatment chosen than co-morbidity. Apparently, co-morbidity alone does not entirely explain why elderly non-small cell lung cancer patients and prostate cancer patients underwent surgery less often and why those with colon cancer, rectal cancer, small cell lung cancer and breast cancer received less (adjuvant) chemotherapy or adjuvant radiotherapy. Performance status, the psychological condition of

the patient, social factors and patient's decision, families decision or doctor's decision may also play a role [33, 2]. The lower proportion of elderly patients undergoing surgery or receiving chemotherapy also appeared in another area of the Netherlands[37].

3.4 Survival

For most tumor types relative survival for those without co-morbidity did not decrease with age, except for patients with lung cancer or non-Hodgkin's lymphoma. The outcome of patients without co-morbidity could be comparable to the outcome of patients in clinical trials, because those with co-morbidity are often excluded from clinical trials.

For patients with lung cancer co-morbidity had no independent prognostic effect [22]. This contradicts some other studies [38-41], but they were not population-based. They also used other scales for measuring co-morbidity: the Kaplan-Feinstein Index [9] and the Cumulative Illness Rating Scale-Geriatric (CIRS-G) [11]. In one of the studies, co-morbidity affected overall survival in surgically resected stage I NSCLC patients, when co-morbidity was rated according to CIRS-G, but not according to the Charlson scale [39]. In another American study co-morbidity count and the Charlson index were significant predictors for lung cancer survival, but only explained 2.5% and 2.0% of the survival variation, respectively [42]. Probably the influence of co-morbidity on survival is of less importance in the case of a lethal disease such as lung cancer. Most of these patients die from lung cancer, before they become at risk of dying from the co-morbid condition.

For the other tumors, co-morbidity had an independent prognostic effect. This negative influence of co-morbidity on survival of cancer patients might be due to several mechanisms: the increased risk of death due to the co-morbid condition itself, more contra-indications for anti-cancer treatment, more indications for dose reduction and a higher rate of treatment-related complications such as infections and cardiovascular events. In several of our recent studies the adverse effects of co-morbidity on survival appeared to be independent of treatment, so less aggressive treatment could not (fully) account for the observed differences in survival between patients with and without co-morbidity [22, 27, 32, 31]. The minor effects of cardiovascular conditions on relative survival of lung or colon cancer may be explained by earlier detection of the cancer through surveillance (X-thorax) or early bleeding of polyps by thrombolytic therapy. Some studies have shown that performance status and co-morbidity are both independent prognostic factors [1, 2], which therefore may need to be included in future prognostic studies, supplemented by the psychological or mental condition of the patient, and the patient's and/or family decision or even doctor's decision should be included.

4. CONCLUSIONS

There is now clear evidence that the prevalence of co-morbidity among older cancer patients is high and that older patients (with co-morbidity) are often treated less aggressively, which seems to have a negative influence on survival. However, would outcomes really improve if more patients were treated, according to the guidelines that were developed on the basis of results in groups of younger patients without co-morbidity? Would more complications occur in older patients with co-morbidity? If that is the case, is it possible to develop special treatment regimens for older cancer patients with co-morbidity and adapt the guidelines? It remains relevant to study the influence of age and co-morbidity on toxicity from treatment, quality of life and prognosis in unselected groups of patients.

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