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Changes in Prognostic and Therapeutic Parameters in Prostate Cancer from an Epidemiological View over 20 Years

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Keywords

Prostate cancer · Survival · Cancer registry · Time trend

Summary

Background: The study objective was to examine changes in prognosis and treatment of prostate cancer patients over 20 years and to evaluate their impact on survival. **Patients and Methods:** 38,861 prostate cancer patients diagnosed between 1990 and 2010 and living in the catchment area of the Munich Cancer Registry were analysed. **Results:** Pre-therapeutic prostate-specific antigen (PSA) testing increased substantially in the early 1990s. A shift from capsule-exceeding tumours to capsule-limited tumours also took place especially in the 1990s. The proportion of radical prostatectomy increased continuously over the last 20 years from 20% to almost 50% whereas hormone therapy decreased from 55% to 18%. Radiation therapy and transurethral resection of the prostate increased slightly from about 5% to 10%. The 5- and 10-year relative survival rates increased from 92% to 97% and from 86% to 92%, respectively. **Conclusions:** 2 reasons may account for the rise in survival rates over 20 years: First, the establishment of widely used PSA testing resulted in a shift towards more favourable T categories due to the detection of many additional small tumours as well as the noticeable change in initial treatment strategy towards more radical prostatectomies. The second factor that likely increased survival was improvements in the therapies themselves.

Introduction

Population-based data supplied by cancer registries have increasingly attracted attention, provided that valid information on clinical and pathological findings, therapies, follow-up and long-term results are available. With these data, regional cancer care can be presented with total transparency. This transparency ranges from knowledge about the variability of initial examination findings to the variability of treatments and the question whether therapies are applied in agreement with guidelines that in general represent the best-proved evidence. It should be pointed out explicitly that cancer registries with their collection of prospectively surveyed cohorts can reach level 2 of evidence, close behind randomised clinical trials (RCTs) [1].

Therefore results of cancer registry studies can be meaningful and pose innovative questions in cases of treatment options when level 1 evidence (RCTs) does not exist for specific groups of patients. Furthermore, health care providers should regularly be given feedback about the actuality and variability of their treatment in comparison to a wider environment, e.g. the total catchment area of the cancer registry. Significant deviations can be revealed and communicated. In addition, cancer registry data can show to what extent results of RCTs can be realised in the general population and which subgroups may not benefit from treatment improvements. Comparisons with national and international data contribute to valid ascertainment [2]. Results over time are interesting with regard to quality assurance and can give incentives for clinical science [2]. Transparency of regional health care results can be offered contemporarily on the Internet [3–5]. Prostate cancer as the most common cancer of men in the USA [3] and in Germany [4] and the second most common cancer of men after lung cancer in the world [5] exemplifies the value of registry data for understanding progress in the detection and treatment of cancer over decades.

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Patients and Methods

Data Collection

The Munich Cancer Registry (MCR) is the population-based clinical cancer registry of Upper Bavaria and parts of Lower Bavaria (Southern Germany). Its catchment area has been enlarged stepwise from 2.3 million to 4.6 million inhabitants in 2007 [6, 7]. Pathologic reports of solid tumours are available from all pathology laboratories in this area. From these reports, the number of prostate cancer patients in the region is systematically obtained. In addition, data about disease characteristics as histology, tumour/node/metastasis (TNM) stage, prostate-specific antigen (PSA), Gleason score and therapy are prospectively collected from MCR-affiliated hospitals. Life status is systematically maintained by both information from the clinicians and death certificates. Thus, active follow-up data are available for about 95% of cases.

Patients

A total of 46,797 patients diagnosed with malignant tumours of the prostate and living within the catchment area were registered prospectively over 2 decades from 1990 to 2010. Patients with evidence of lymphoma or sarcoma, those with registration by death certificate only (DCO) and patients with previous or synchronous malignant tumours were excluded. Thus, time-trend analyses were performed on the epidemiological cohort of 38,861 patients with prostate cancer as the first malignant tumour. All survival analyses are based on 36,530 patients with an active follow-up (fig. 1).

Statistical Analysis

The MCR organises data in an Oracle database. Statistical analyses were run in SAS (Statistical Analysis System v. 9.2). The percentages of the presented subcategories are related to the sum of each item with available data; missing values are not taken into account. Overall survival (OS) was estimated by the Kaplan-Meier method. Differences in subgroups were tested by the log-rank test. Relative survival (RS) was computed by the ratio of the observed survival rate to the expected survival rate. The expected survival time of age-matched male individuals was calculated from life tables of the general German population. The significance level in all analyses was set at 5%. The study period was divided into 4 intervals (1990–1994, 1995–1999, 2000–2004, 2005–2010) to describe trends in patient characteristics and survival.

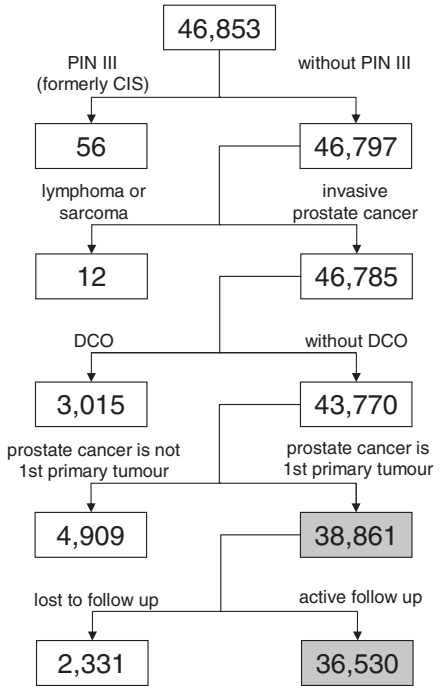

Fig. 1. Flow chart of the patient cohort 1990–2010. PIN = Prostatic intraepithelial neoplasia, CIS = carcinoma in situ, DCO = death certificate only.

Results

Incidence

In the first 3 years of the study period (1990–1992) a crude incidence rate (CIR) of 55.0 per 100,000 is measured. Converted into the European (ASR(EU)) or the world age-standardised rate (ASR(W)) according to Segi, an incidence rate of 55.2 or 35.9, respectively, is observed per 100,000. In the last 3 years (2008–2010), the CIR is 106.0 per 100,000 (ASR(EU): 78.6, ASR(W): 53.8). Thus, the incidence rates increased noticeably during the selected study period, regardless of the applied standard.

The patient characteristics and prognostic parameters by period are presented in table 1.

Age at Diagnosis

The age distribution stays stable over 2 decades. The median age is about 69 years. The 25% and 75% percentiles are 64 and 75 years and the 10% and 90% percentiles are 58 and 80 years. At initial diagnosis, every 10th man is older than 80 years.

T Category

Figure 2A presents the distribution of the T category over time. T is a combination of pT and cT, if pT is not available. The proportion of T1 rises from 14% in the year 2001 to 32% in 2010. The proportion of T2 tumours more than doubles from 25% in 1992 to 61% in 1998. Stable for 5 years since 2004, it decreases inversely to the development of T1. The proportions of T3 and T4 tumours develop inversely compared to T2. The T3 proportion decreases from 50% in 1992 to 15% in 2006, now again increasing to 22% in 2010. In contrast, the proportion of T4 decreases from 12% in 1990 to 2% in 2010.

Prostate-Specific Antigen

Figure 2B shows the distribution of the PSA values available since 1994. The lowest category (< 4 ng/ml) remains stable between 11 and 15%. The proportion of PSA values of 4 to < 10 ng/ml increases from a rate of 29% up to 52%. The 2 highest categories decrease simultaneously from about 30% to 20%. Overall, a shift towards lower PSA values has taken place.

Gleason Score

This marker presented in figure 2C is well documented since 1998. In the time-trend analysis, the decrease of the proportions of the 2 lowest categories is most noticeable. Score 2–4 decreases from 10% to 1% and score 5–6 is reduced from 46% to 32%. Inversely score 7 doubles in proportion from 21% to 43%. The highest score (8–10) fluctuates around a rate of 22%. Thus, the distribution of the Gleason score has shifted towards higher scores.

Initial Treatment

As presented in figure 2D, the proportion of radical prostatectomies increases from initially 20% to nearly 50% over 2 decades. The

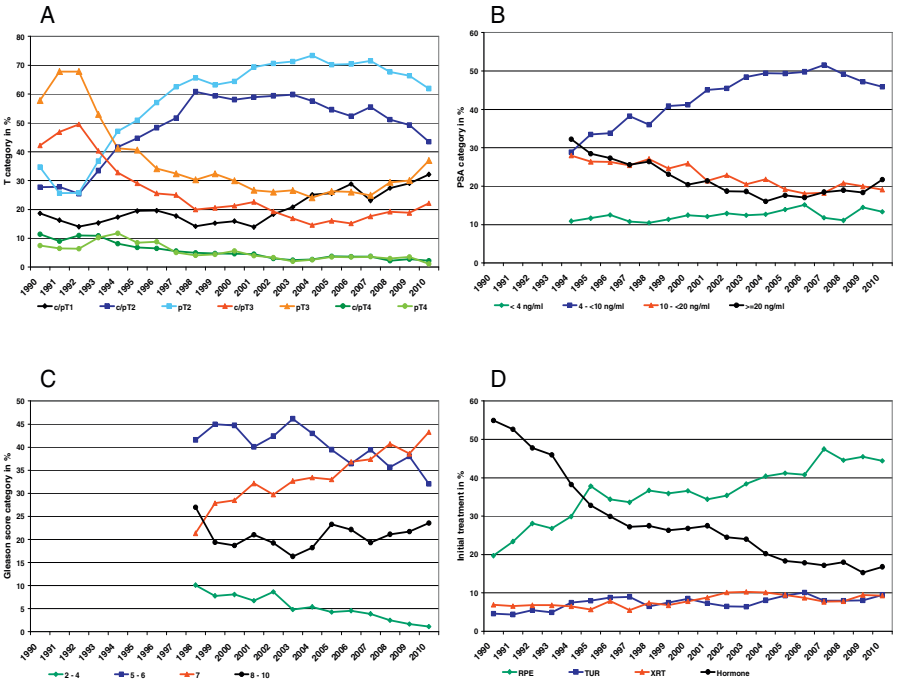

Fig. 2. Changes over time in (**A**) c/pT and pT category, (**B**) PSA category, (**C**) Gleason score, (**D**) initial treatment. RPE = Radical prostatectomy, TUR = transurethral resection, XRT = radiation therapy, Hormone = hormone therapy.

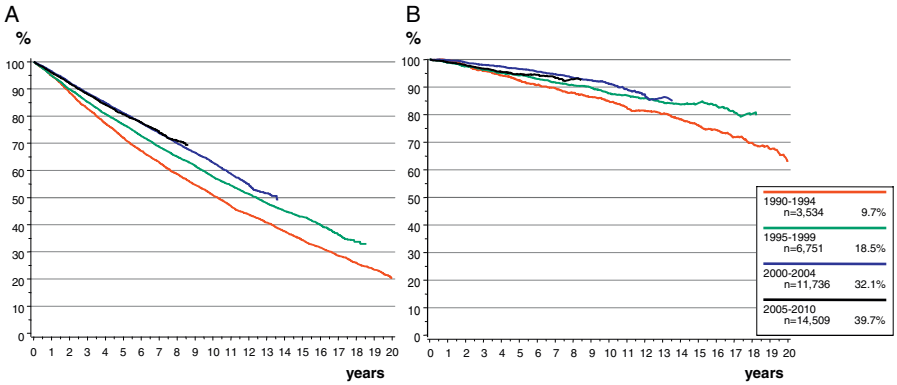

Fig. 3. Survival by year of initial diagnosis (n = 36,530). (**A**) Overall ($p < 0.0001$), (**B**) relative.

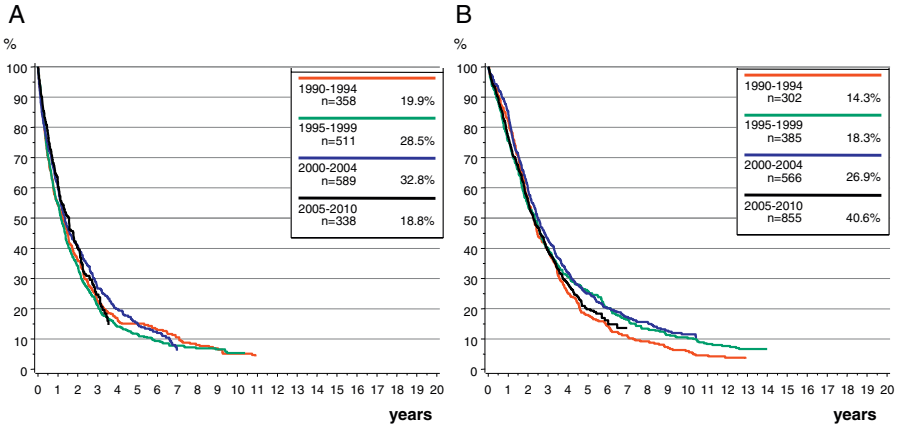

Fig. 4. PPS from distant metastasis by year of diagnosis of metastasis for (**A**) primary M0 (n = 1,796, p = 0.2240), (**B**) primary M1 (n = 2,108, p = 0.1170).

use of radical prostatectomy as an initial treatment is highly correlated with the number of capsule-remaining tumours (Pearson's r = 0.88). The use of hormone therapy experienced a major decline. Starting at a rate of 55% in 1990, it accounts for 17% in 2010. Both transurethral resection of the prostate and radiotherapy showed a slight increase up to 10% in 2010.

Table 1. Prognostic parameters by year of diagnosis

	Year of diagnosis									
	1990–1994		1995–1999		2000–2004		2005–2010		All	
	N	%	N	%	N	%	N	%	N	%
All	3,725	100.0	7,154	100.0	12,527	100.0	15,455	100.0	38,861	100.0
Age										
Median, years	69.8		68.5		68.0		68.9		68.6	
< 50	38	1.0	72	1.0	137	1.1	226	1.5	473	1.2
50–54	156	4.2	260	3.6	427	3.4	522	3.4	1,365	3.5
55–59	339	9.1	874	12.2	1,279	10.2	1,298	8.4	3,790	9.8
60–64	554	14.9	1,264	17.7	2,650	21.2	2,450	15.9	6,918	17.8
65–69	801	21.5	1,596	22.3	2,832	22.6	4,187	27.1	9,416	24.2
70–74	752	20.2	1,431	20.0	2,447	19.5	3,382	21.9	8,012	20.6
≥ 74	1,085	29.1	1,657	23.2	2,755	22.0	3,390	21.9	8,887	22.9
c/pT category[a]										
T1	501	16.4	942	17.0	1,894	19.4	3,356	27.5	6,693	21.9
T2	988	32.3	2,981	53.8	5,751	58.8	6,280	51.4	16,000	52.3
T3	1,270	41.5	1,309	23.6	1,812	18.5	2,204	18.0	6,595	21.5
T4	304	9.9	313	5.6	320	3.3	379	3.1	1,316	4.3
Missing[b]	662	17.8	1,609	22.5	2,750	22.0	3,236	20.9	8,257	21.2
cT category										
T1	545	19.5	1,057	21.2	2,130	27.0	3,694	49.2	7,426	32.0
T2	863	30.8	2,617	52.5	4,300	54.5	2,873	38.2	10,653	45.9
T3	1,125	40.2	1,059	21.3	1,194	15.1	704	9.4	4,082	17.6
T4	268	9.6	250	5.0	264	3.3	242	3.2	1,024	4.4
Missing[b]	924	24.8	2,171	30.3	4,639	37.0	7,942	51.4	15,676	40.3
pT category										
T2	711	35.8	2,255	60.3	4,581	70.3	6,075	68.3	13,622	64.5
T3	1,095	55.2	1,264	33.8	1,719	26.4	2,537	28.5	6,615	31.3
T4	179	9.0	223	6.0	212	3.3	277	3.1	891	4.2
Missing[b]	1,740	46.7	3,412	47.7	6,015	48.0	6,566	42.5	17,733	45.6
Metastasis status										
M0	3,412	91.6	6,752	94.4	11,926	95.2	14,549	94.1	36,639	94.3
M1	313	8.4	402	5.6	601	4.8	906	5.9	2,222	5.7
Missing[b]	621	16.7	1,734	24.2	3,363	26.8	4,022	26.0	9,740	25.1
Lymph node status										
N+	202	5.4	198	2.8	326	2.6	722	4.7	1,448	3.7
N0	1,515	40.7	2,583	36.1	5,233	41.8	7,426	48.0	16,757	43.1
NX	1,387	37.2	2,639	36.9	3,605	28.8	3,285	21.3	10,916	28.1
PSA value										
Median, ng/ml	14.0		10.2		8.4		7.8		8.5	
≤ 4	222	16.1	587	12.3	1,142	13.2	1,608	13.9	3,559	13.5
> 4–10	325	23.5	1,785	37.4	4,017	46.5	5,676	49.2	11,803	44.8
> 10–20	330	23.9	1,194	25.0	1,889	21.9	2,165	18.8	5,578	21.2
> 20	505	36.5	1,212	25.4	1,589	18.4	2,089	18.1	5,395	20.5
Missing[b]	2,343	62.9	2,376	33.2	3,890	31.1	3,917	25.3	12,526	32.2
Gleason score										
2–4	5	16.1	76	8.6	752	6.6	459	3.1	1,292	4.8
5–6	4	12.9	367	41.8	4,961	43.4	5,440	37.0	10,772	39.8
7	4	12.9	228	25.9	3,604	31.5	5,600	38.1	9,436	34.9
8–10	18	58.1	208	23.7	2,115	18.5	3,204	21.8	5,545	20.5
Missing[b]	3,694	99.2	6,275	87.7	1,095	8.7	752	4.9	11,816	30.4

PSA = Prostate-specific antigen.

[a]c/pT category = a combination of pT and cT; if pT is not available (e.g. no surgery), cT is inserted.

[b]The percentage of the subcategories is related to the sum of each item with available data; missing values are not taken into account.

Table 2. Therapeutic parameters by year of diagnosis

	Year of diagnosis									
	1990–1994		1995–1999		2000–2004		2005–2010		All	
	n	%	n	%	n	%	n	%	n	%
All	3,725	100.0	7,154	100.0	12,527	100.0	15,455	100.0	38,861	100.0
Initial treatment										
RPE	976	30.4	2,556	43.7	4,664	44.9	6,799	53.5	14,995	46.6
TUR	210	6.5	561	9.6	913	8.8	1,363	10.7	3,047	9.5
HIFU			107	1.8	251	2.4	154	1.2	512	1.6
XRT	250	7.8	483	8.3	1,202	11.6	1,347	10.6	3,282	10.2
Hormone	1,739	54.1	2,037	34.8	3,040	29.3	2,674	21.0	9,490	29.5
Chemo	16	0.5	27	0.5	64	0.6	65	0.5	172	0.5
Drug					3	0.0	11	0.1	14	0.0
AS and WW	22	0.7	76	1.3	245	2.4	292	2.3	635	2.0
Missing[a]	512	13.7	1,307	18.3	2,145	17.1	2,750	17.8	6,714	17.3

RPE = Radical prostatectomy, TUR = transurethral resection of the prostate, HIFU = high-intensity focused ultrasound, XRT = radiation therapy, Hormone = hormone therapy, Chemo = chemotherapy, Drug = medical treatment, AS = active surveillance, WW = watchful waiting.

[a]The percentage of the subcategories is related to the sum of each item with available data; missing values are not taken into account.

Survival

Figure 3A, B presents OS and RS curves stratified by time periods. In 1990–1994, the 5- and 10-year OS and RS rates were 72.0% and 50.9% and 92.5% and 84.9%, respectively. Survival improves continuously with 5-year OS and RS rates of 80.7% and 94.7%, respectively, in 2005–2010 and 10-year OS and RS rates of 62.9% and 91.3%, respectively, in 2000–2004.

Post-progression survival (PPS) from diagnosis of distant metastasis is presented in Figure 4A, B for primary M0 and M1 patients. In both subgroups, no essential improvement can be seen within the last 20 years. Primary M0 patients have a median PPS of about 1.3 years, primary M1 patients of about 2.4 years.

Discussion

This German study population shows a lower incidence level of prostate cancer compared to Germany in general and other industrialised countries [4, 5], probably due to underreporting in outpatient care. The rise in the incidence rate over time, however, is comparable. A detailed view on the incidence rate reveals that the rise affects T1 and, most notably, T2 tumours in the 1990s (c/pT and pT), while the incidence of advanced capsule-penetrating tumours stays low and stable over time. Similar differences are seen between the screening and non-screening cohorts in the European Randomized Study of Screening for Prostate Cancer (ERSPC) [8]. Compendiously, the numbers of detected tumours correlate moderately with the numbers of PSA tests [9]. Altogether, this supports the assumption that the broad use of PSA tests starting in the 1990s in Europe has led to the augmented additional detection of many small tumours [10–12]. Presumably, this may be the main reason for the observed stage shift from capsule-penetrating to capsule-remaining tumours. It is most unlikely that this stage shift is caused purely by today's early detection of formerly advanced tumours.

The shift of the PSA distribution towards lower values may also be caused by the increased use of PSA tests [9, 10].

The changes of the Gleason score distribution may reproduce newly made modifications and recommendations in the grading system. Nowadays, a Gleason score of 2 is categorised as adenosis (atypical adenomatous hyperplasia) rather than adenocarcinoma. A score of 2–4 should not be assigned to a definite grade by needle biopsy only, due to problems of reproducibility and the danger of underestimating the dignity of the tumour [13, 14]. The category shift from Gleason score 5–6 to 7 can be the result of modifications in the grading system in 2005 when some cell structures were categorised into higher Gleason grades. Additionally, a different derivation of the Gleason score on biopsies – adding the most common and the highest Gleason pattern instead of adding the most common and the second most common pattern – can also lead to the observed changes [15]. Further changes in the Gleason score distribution may be expected due to the update in 2010 when again some cell structures were assigned to higher Gleason grades [16].

Thus, the contradictive behaviour of the PSA distribution (drifting towards lower values) and the Gleason score distribution (drifting towards higher scores) may be plausible.

The use of radical prostatectomy as an initial treatment is highly correlated with the number of capsule-remaining tumours. This might indicate that the observed change of treatment to more surgical therapy depends less on improvements in practice but more on the increased number of PSA-detected localised tumours with the option of curative radical prostatectomy [13, 14]. Overall, changes in prognostic parameters are accompanied by changes in therapeutic parameters (table 2).

The improvement in the 5- and 10-year RS by about 6 percent units can also be seen in other German population cohorts [17].

These authors also conclude that the survival improvement might be attributable to the shift to more localised tumours due to the increased use of PSA screening. Also treatment improvements may have an influence on better survival. Analyses stratified by time period and T category show an improvement in cancer-specific survival in stages T1 and T2, and also in stages T3 and T4 after prostatectomy. A 3-percentage point better tumour-specific 12-year survival was found in a study that compared radical prostatectomy and observation in 1994–2002: 95.6% versus 92.6% [18]. In cases of such good prognosis, this 3-percentage point improvement seems small, but relatively it amounts to about 40%. Such stage-specific improvements can be a hint at partial treatment improvements [19–21].

The prostate cancer survival in the MCR catchment area is comparable or even slightly better than in other German and European regions, as recently published by the European Cancer Registry (EUROCARE)-5 study [22]. The MCR 5-year RS rate is 95.9% (95% confidence interval (CI): 95.2–96.6%) compared to the Germany mean of 89.4% (95% CI: 88.8–89.9%) and the European mean of 83.4% (95% CI: 83.1–83.6%).

There may be a good chance that the observed stagnation in the PPS may be overcome in the near future when newly developed and approved agents keep their promises in metastatic castration-resistant prostate cancer [23].

In summary, 2 reasons may account for the rise in survival rates over the last 20 years: First, the establishment of widely used PSA testing resulted in a shift towards more favourable T categories due to the detection of many additional small tumours, and a noticeable change in initial treatment strategy towards more radical prostatectomies, which by itself may partially be the result of the T category shift. The second reason may be improvements in the applied therapies themselves.

Disclosure Statement

The authors declare that they have no conflict of interest.

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