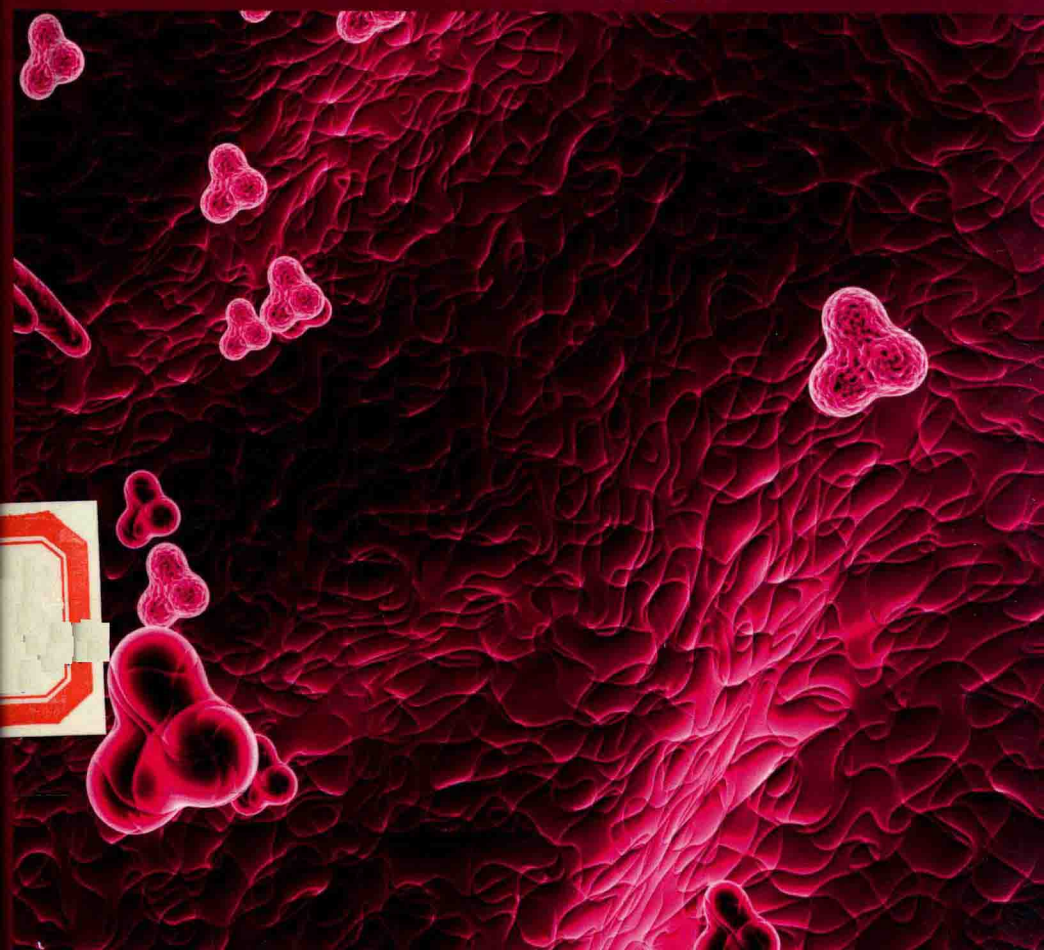
Recent Advances in **Prostate Cancer Research**

Karl Meloni



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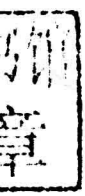

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Preface

This book has been a concerted effort by a group of academicians, researchers and scientists, who have contributed their research works for the realization of the book. This book has materialized in the wake of emerging advancements and innovations in this field. Therefore, the need of the hour was to compile all the required researches and disseminate the knowledge to a broad spectrum of people comprising of students, researchers and specialists of the field.

Prostate cancer is one of the most widespread types of cancer in men and its cure was limited to surgery for confined state and androgen ablation for advanced disease until new alternatives became accessible. This book talks about a broad spectrum of novel facets of the epidemiology of prostate cancer, the diagnosis, cure and patient care, radiation therapy and various other available medical treatments.

At the end of the preface, I would like to thank the authors for their brilliant chapters and the publisher for guiding us all-through the making of the book till its final stage. Also, I would like to thank my family for providing the support and encouragement throughout my academic career and research projects.

Editor

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Chapter 1

Epidemiology of Prostate Cancer

Martin Dörr, Anne Schlesinger-Raab and Jutta Engel

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1. Introduction

This chapter presents the current state of prostate cancer epidemiology and compares data from different regions. The data are taken from several sources:

Globocan 2008 [1] gives a glance on the worldwide situation in cancer epidemiology and permits the comparison of more and less developed regions in every continent.

The "Surveillance, Epidemiology and End Results" Program (SEER) [2] in the USA and the Robert Koch Institute (RKI) [3] in Germany present epidemiologic data of highly industrialized nations with maximally developed medical systems.

The Munich Cancer Registry (MCR) [4], a population-based clinical cancer registry of Upper Bavaria, an area of 4.5 million inhabitants in the South of Germany, presents detailed analyses of clinical data, distributions of prognostic factors and therapy, and survival analyses. Data of the MCR have also contributed to the publication "Cancer Incidence in Five Continents, Volume IX" [5].

2. Incidence and mortality

In Table 1 absolute numbers and age-standardized rates of incidence and mortality are presented for selected regions and countries [1]. In 2008 it was estimated that nearly every seventh case of male malignoma was prostate cancer (899 thousand new cases, 13.6% of the total). Therefore, in men prostate cancer was the second most diagnosed cancer after lung cancer. Approximately three quarters of these cases were diagnosed in more developed countries. The highest incidence rates were measured in Australia, New Zealand, Northern and Western Europe and Northern America. Moderate incidence rates were found in South

America and Eastern Europe. The lowest incidence rates were reported from South-Central Asia.

Region	Incidence absolute	Incidence ASR (W)	Mortality absolute	Mortality ASR (W)
World	899	27.9	258	7.4
More developed regions	644	61.7	136	10.5
Less developed regions	255	11.9	121	5.6
Asia	133.2	7.2	59.6	3.2
North America	213.7	85.7	32.6	9.9
Central America	20.5	34.8	8.1	12.6
South America	84.1	50.2	29.2	16.2
Australia and New Zealand	21.0	104.2	4.0	15.4
Central and Eastern Europe	58.4	29.1	23.1	10.9
Northern Europe	64.9	73.1	17.4	15.4
Southern Europe	79.5	50.0	20.4	10.4
Western Europe	167.9	93.1	28.7	12.4
Germany	70.8	82.7	12.2	11.7
Japan	38.7	22.7	10.0	5.0
USA	186.3	83.8	28.6	9.7
Brazil	41.6	50.3	14.4	16.3
China	33.8	4.3	14.3	1.8
India	14.6	3.7	10.4	2.5
Russian Federation	22.1	26.1	9.5	10.8
SouthAfricanRepublic	7.5	59.7	2.5	20.8

Absolute numbers in thousands; ASR (W): age standardised rate per 100,000 by world standard

Table 1. Absolute numbers and age-standardised rates of incidence and mortality for selected regions and countries [1]

Despite its high proportion of cancer diagnoses, prostate cancer is the cause of cancer specific death in only every 16th case (258 thousand deaths, 6.1% of the total). This places prostate cancer on the sixth position of cancer-specific causes of death, topped by lung, liver, stomach, colorectal and oesophageal cancer. These deaths occur almost equally in both, more developed and less developed regions, thus leading to a twofold higher mortality rate in the more developed regions.

2.1. Incidence and mortality trends

Table 2 shows the current incidence and mortality of the USA [2], Germany [7, 8] and the Munich Cancer Registry [4]. These rates have changed considerably over time. Time series of more developed countries show that the incidence rates experience a drastic rise from 1985 to 1995 and remain at this high level. In the USA incidence (by world standard per 100,000) increases slowly from 1975 until 1985 (from 50 to 65). Then it rises rapidly reaching a peak of 135 in 1992. Then it decreased, since 1995 more slowly, but it remains on a higher level than before the peak (around 110). In Germany incidence is rising continuously since 1988 (from 30 to 75). The main explanation for these trends is the broad use of prostate specific antigen (PSA) testing as a screening method and performing biopsies, which started in the mid-1980s in the USA and in the early 1990s in Germany.

	USA (SEER, NCHS) [2, 6]	Germany (RKI) [7, 8]	MCR [4]
Absolute incidence	241.7	70.8	2.9
Crude incidence		157.7	145.1
Incidence ASR (W)	106.1	82.7	76.4
Mortality ASR (W)	10.2	11.7	13.3*
Lifetime risk(%)	16.2	13.0	
Median age at diagnosis(years)	67.0	69.5	67.2
Median age at death(years)	80.0		76.7
5-year overall survival(%)		77.0	79.2
5-year relative survival(%)	99.2	92.0	93.4
10-year overall survival(%)			58.2
10-year relative survival(%)	98.3		87.8

Absolute numbers in thousands

ASR (W): age standardised rate per 100,000 by world standard

Incidence and mortality from cohorts of 2008 (all regions)

Absolute incidence numbers of the USA are estimates of SEER data from 2012

* Mortality ASR (W) for singular prostate cancers is 9.9

median ages from cohorts of 2005-2009 (all regions)

5-year survival from cohorts of 2002-2008 (SEER and MCR)

10-year survival from cohorts of 1998-2008 (SEER and MCR)

Table 2. Epidemiologic basic numbers

In the USA, mortality initially increases slightly from 1975 and since 1992 it is decreasing more rapidly (from 14 over 17 to 10). In Germany the mortality rate (by world standard per 100,000) stays stable at 13.

2.2. Age distribution and age-specific incidence and mortality rate

Nearly all patients (≈ 99%) who are diagnosed with prostate cancer have reached an age of fifty or higher. The age distribution at diagnosis describes a positively skewed unimodal distribution with its modus at the age group 65-69. This age group contributes to nearly 25% of all prostate cancer cases. The risk of getting prostate cancer increases nearly exponentially with increasing age. This makes prostate cancer one of the most distinctive cancers in aging populations (Figure 1) with a ASIR of 800-1000 per 100,000 in the elderly of 70 years and older.

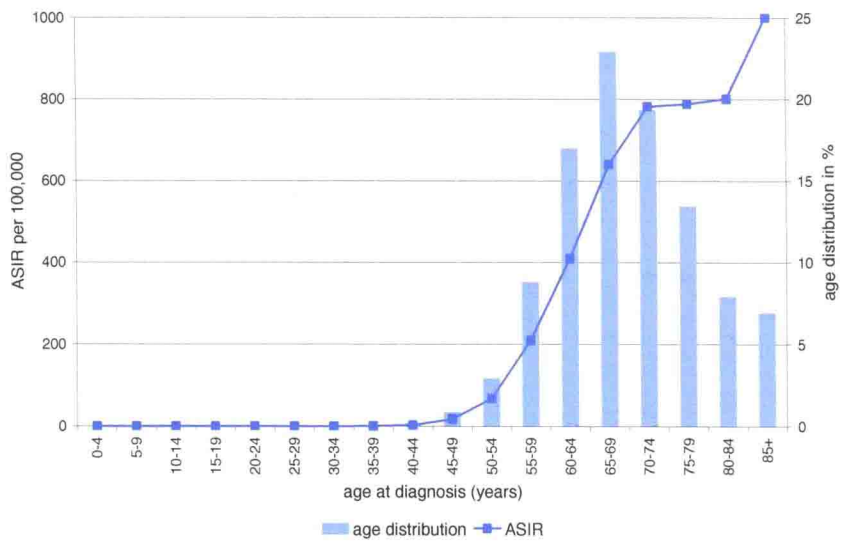

Figure 1. Age distribution at diagnosis and age-specific incidence rate (ASIR) of prostate cancer (1998-2008) [4]

Nearly all patients who died of prostate cancer (singular initial malignoma) have reached an age of fifty-five or higher. The distribution of age at death describes a negatively skewed unimodal distribution with its modus at the highest age group 85+. Here the age-specific mortality rates (ASMR) can perfectly be described by an exponential function. The risk of dying by prostate cancer increases accelerated with increasing age (Figure 2). The ASMR reaches 450 per 100,000 for men with an age of 80-84 and already 600 per 100,000 for men older than 84.

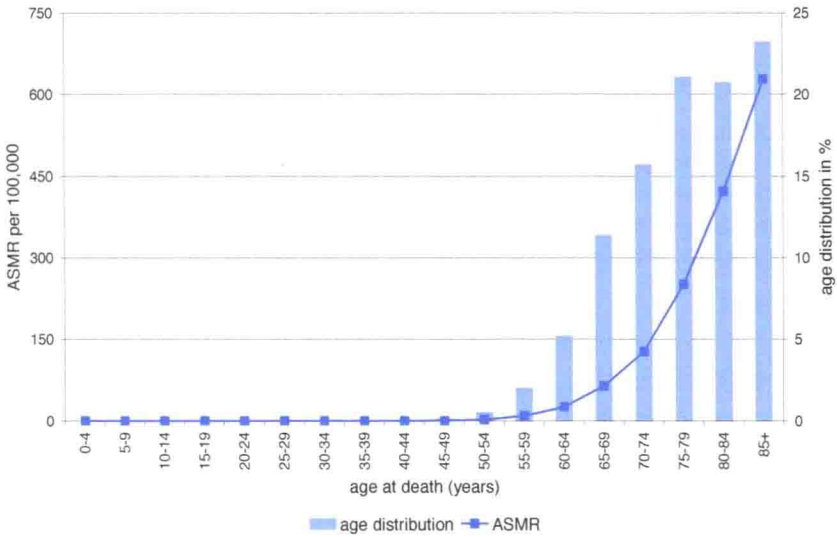

Figure 2. Age distribution at death and age-specific mortality rate (ASMR) of prostate cancer (1998-2009) [4]

3. Prognostic factors

According to Table 3 the conditional age distributions of the combined T categories 2 until 4 have the same shape and the modus at the age group of 65 until 69. These distributions are shifted slightly towards higher ages with the increasing T category. This simply reflects that it takes time to develop an advanced tumour. However, in those patients diagnosed with T1 category (clinically) the age distribution appears to be totally different. Here 80% of the men are older than 64 (about 60% within the other T categories) and every third man is older than 74.

Lymph node category (N), distant primary metastases (M), Gleason Score, initial PSA value and Gleason Score are positively correlated with the combined T category: the higher the T category, the higher the PSA value, the higher the Gleason Score and the higher the porportion of regional or distant metastases.

A positive lymph node status is mostly diagnosed when the tumour has spread through the prostatic capsule. Nearly 20% of those men with T3 and almost 50% with T4 tumours therefore are diagnosed with lymph node metastasis.

	T category				
	T1 % (n=1826 13.3%)	T2 % (n=8219 59.9%)	T3 % (n=3164 23.0%)	T4 % (n=503 3.7%)	All % (n=13712 100%)
Age (years)					
<50	0.5	2.3	1.4	1.8	1.8
50 - 54	1.5	4.5	3.5	3.0	3.8
55 - 59	3.0	11.0	10.2	11.1	9.8
60 - 64	9.7	20.2	18.2	15.1	18.2
65 - 69	20.9	31.4	32.8	26.4	30.1
70 - 74	26.1	20.2	23.1	19.7	21.7
≥75	38.3	10.4	10.8	22.9	14.7
Lymph node status					
N+	2.5	1.6	18.4	45.1	7.3
N0	40.6	85.2	73.5	33.6	76.2
NX	56.9	13.2	8.1	21.2	16.5
Metastasis status					
M0	97.4	98.8	95.4	72.6	96.9
M1	2.6	1.2	4.6	27.4	3.1
PSA value (ng/ml)					
< 4	25.8	13.2	7.8	3.7	13.2
4 - <10	42.0	60.7	41.5	18.9	52.4
10 - <20	17.5	18.3	24.9	15.7	19.7
≥20	14.7	7.8	25.7	61.8	14.8
Gleason Score					
2 - 4	14.3	1.6	0.2	0.2	2.9
5 - 6	54.8	48.1	12.3	4.2	39.1
7	19.1	40.5	49.4	26.6	39.3
8 - 10	11.8	9.8	38.2	68.9	18.7

Presented numbers are column-wise percentages.

T category is a combination of cT and pT.

The disease cohort is limited to 2005-2009 to provide best current estimators.

Table 3. Prognostic factors by T category [4]

Although, only 2.4% of all prostate cancer cases have primary distant metastases, already 25% of the T4 patients are diagnosed with metastases.

About 50% of the men with prostate cancer have a PSA value of 4 to 10 ng/ml at initial diagnosis.

According to Figure 3aa shift from capsule exceeding tumours to capsule limited tumours took place in the 1990s. In the late 1980s about 15% of the diagnosed tumours were staged T4, some 45% T3 and nearly 25% T2. In the 2000s only some 5% of the diagnosed tumours were staged T4, good 20% T3 and about 60% T2. The T1 category was unaffected and oscillated around 12% during the whole time period. It seems that PSA-Screening has considerably lowered the proportion of locally advanced tumours.

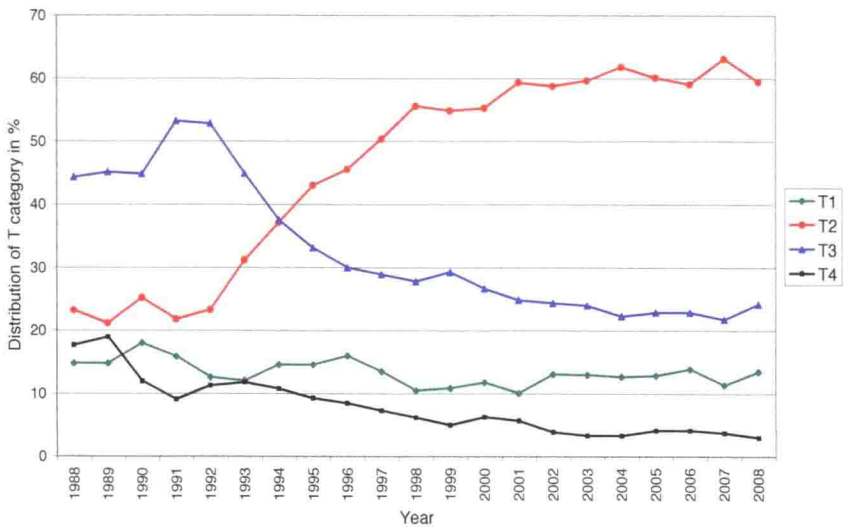

Figure 3. Distribution of T category over time (n = 35544) [4]. T category is a combination of cT and pT.

4. Therapy

Table 4 presents in detail the effects of combined T category on the choice of therapy. Guidelines [9] note that radical prostatectomy, radiation therapy and hormone therapy in combination with radiation therapy are the main primary treatment options when the tumour remains within the prostate capsule (T2) or does not invade nearby structures other than the seminal vesicles or the bladder neck (T3). A spreading prostate cancer should be treated with a hormone therapy. Active surveillance (AS) and watchful waiting (WW) are only note-

worthy initial therapy strategies for tumours detected in an early stage. Although these are accepted treatment options in localised prostate cancer, they are seldom chosen compared to radical prostatectomy and hormone therapy. Transurethral resection of the prostate is not an appropriate surgical treatment option in prostate cancer but its proportion in T1 category (46.7%) indicates a greater proportion of incidentally found prostate cancers during a treatment of benign hyperplasia. Without further surgical or hormone therapy, one could classify these cases into the AS or WW groups.

	T category				
	T1 % (n=1826 13.3%)	T2 % (n=8219 59.9%)	T3 % (n=3164 23.0%)	T4 % (n=503 3.7%)	All % (n=13712 100%)
Initial therapy					
RPE		74.9	65.9	31.3	61.8
TUR	47.2	3.2	2.5	11.4	9.0
HIFU	4.5	3.4	0.8	0.2	2.8
XRT	16.6	6.1	9.8	12.7	8.5
Hormone	23.7	11.6	20.3	44.2	16.4
AS and WW	8.0	0.8	0.7	0.2	1.6

Presented numbers are column-wise percentages.

T category is a combination of cT and pT.

The disease cohort is limited to 2005-2009 to provide best current estimators.

RPE: radical prostatectomy, TUR: transurethral resection of the prostate, HIFU: high-intensity focused ultrasound, XRT: radiation therapy, Hormone: hormone therapy, AS: active surveillance, WW: watchful waiting

Table 4. Initial therapy by T category [4]

As Figure 4 shows impressively, initial therapy strategies have changed noticeably over the last 20 years. In the late 1980's radical prostatectomy was the initial therapy in about 25% of all treatments. Its rate increased continuously and finally reaches almost 60%, making this the most selected initial therapy per year since 1995. The curve of hormone therapy developed oppositely. To be more precise: hormone therapy was the most selected treatment till 1994. From 65% in 1989 it continuously decreased to now 20%. Radiation therapy (XRT) slightly increased to 10% as initial therapy. Finally, within the whole time span transurethral resection of the prostate (TUR) remains stable at a proportion of nearly 10%.

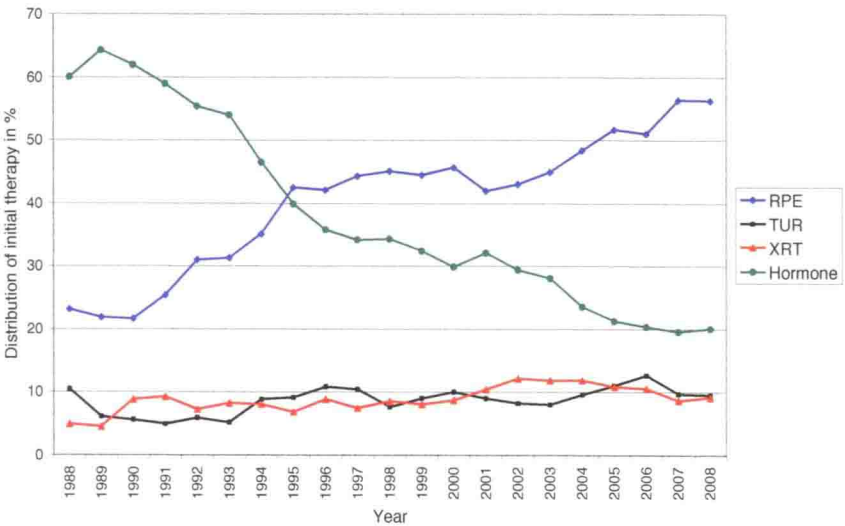

Figure 4. Distribution of initial therapy strategies over time (n = 35544) [4]. RPE: radical prostatectomy, XRT: radiation therapy, Hormone: hormone therapy, TUR: transurethral resection of the prostate

5. Survival

The following figures mainly present the relative survival (RS) curves, an estimator for the cancer specific survival. This is calculated by dividing the overall survival (OS) of the observed cohort by the expected survival of a normal population with the same distribution regarding birth-date and sex.

When looking at the influence of the year of diagnosis on the overall survival (Figure 5) or relative survival (Figure 6) only the curve of patients with a diagnosis in the years 1998 until 1992 noticeably differs from the other ones. Here the 5- and 10-year relative survival was 85.0% and 74.3%, respectively. In the group of patients diagnosed between 1993 and 1997 the 5- and 10-year relative survival was 94.9% and 88.6% in the group of 1998-2002 the 5- and 10-year relative survival was 94.0% and 84.1% and in the recent group of 2003-2008 the 5-year relative survival was 92.1%. Therefore, the following survival analyses are presented for patients with a diagnosis between 1998 - 2008.