

Migrations in Clinical and Pathological Stage of Prostatic Carcinoma in Patients Undergoing Radical Prostatectomy in the Period between 1993 and 2003

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ABSTRACT

The aim of this study based on an analysis of personal material was to establish stage migration in a relatively large number of patients who had undergone radical retropubic ascendant prostatectomy (RRP). Between 01.07.1993. and 31.06.2003. RRP was performed in 801 patients at the urology department of the Kliniken-Essen-Mitte. Data regarding diagnostic workup, treatment and postoperative course were collected prospectively into a database. An analysis was made regarding clinical and pathological stage and numbers of patients with positive lymph nodes. During the observation period the number of radical prostatectomies increased significantly from 8 in 1993 to 130 in 2002. The number of organ-confined tumors increased continuously between 1997 and 2003. In contrast to this, advanced and metastatic tumors showed a continuous decrease from 76% in 1997 to 66% in 2002. Between 1994 and 2003 the number of T1c tumors increased by 20%. Introduction of systematic 12-cylinder biopsy (S12C) increased the detection of prostatic carcinoma by 38% and the number of diagnosed tumors of a lower clinical stage increased. These facts confirm a trend towards clinical and pathological stage migration resulting from extensive use of prostate specific antigen (PSA) and S12C biopsy in the diagnosis of prostatic carcinoma.

Key words: prostatic carcinoma, clinical stage, pathological stage, changes

Introduction

More extensive use of prostate specific antigen (PSA), ultrasound-guided prostate biopsy and the introduction of anatomically oriented radical retropubic prostatectomy (RRP), have resulted in a considerable quantitative increase in diagnosed prostatic carcinoma and in the number of radical prostatectomies performed¹. Data from the USA, the Netherlands, Switzerland and Austria show that early detection of prostatic carcinoma through, PSA-screening is clearly associated with stage migration towards clinically nonmanifest tumor²⁻⁶.

Diagnosis of prostatic carcinoma is usually made by patients referring urologists, by means of laboratory and ultrasound studies and biopsy of the prostate.

In Germany treatment of non-metastatic, organ-confined prostatic carcinoma in patients of appropriate age is usually operative.

The aim of this study was to establish possible migration of clinical and pathological stage on the basis of an analysis of personal material on a relatively large number of patients who had undergone RRP during a ten-year period.

Subjects and Methods

Between July 1, 1993 and June 31, 2003, 801 patient underwent RRP at the urology department of the Kliniken Essen-Mitte. Demographic and descriptive data on

diagnostic workup, treatment and postoperative course were collected prospectively in database. In addition to demographic data, the following information was also collected: PSA values during the last 10 years, clinical stage, tumor grading, pathohistological stage and numbers of patients with positive lymph nodes. Apart from this, the preoperative workup included bone scintigraphy, CT and prostate biopsy. Parameters are presented as frequency, mean ± standard deviation or median, Q1, Q3 depending on scale. Time effects were tested for statistical significance by the Cochran-Mantel-Haenszel or U-test. All p-values are presented descriptively with no respect to multiple testing. Statistical analyses were performed by SAS®.

Results

The urology department of the *Kliniken Essen-Mitte* is one of four urology departments in the city of Essen, the seventh largest town in Germany and the second largest in the Ruhr region (5.5 million inhabitants). Between July 1, 1993 and June 31, 2003, 801 patients of the department underwent radical retropubic ascendent prostatectomy (RRP). The sharp increase in the number of patients treated between 1993 and 2003 is shown in Figure 1.

In 1993 operations were performed in 8 patients, in 2002 in 129 patients and in 2003 (up to June 30) in 75 patients. Most of these patients were in the age group 61–70, with almost equal numbers in the groups 51–60 and 71–80. Patients younger than 50 and older than 80 were the exception (Figure 2).

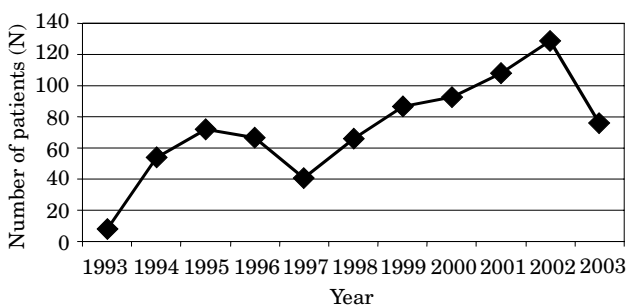


Fig. 1. Number of patients per year of operation (up to June 2003).

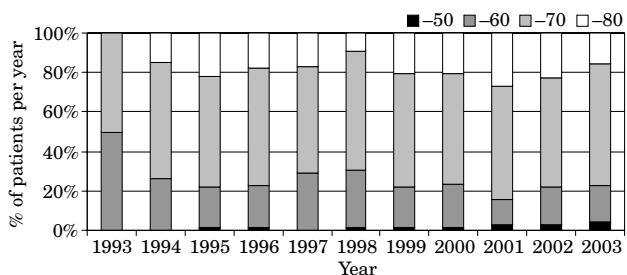


Fig. 2. Distribution of operated patients per patients age (1993–2003).

The lowest PSA value was 0.1 ng/ml and the highest 140 ng/ml. The mean PSA was 14.8 ng/ml, the median 9.2 ng/ml. In the years between 1993 and 1999 (except for 1997) a continuous decrease in the median PSA from 13.8 to 10 ng/ml was registered. From 2000 onwards the median PSA was about 8 ng/ml.

Although the Wilcoxon test on parallel PSA values does not show any differences, an increase in the number of patients with low PSA values was observed during the years. In 1996 the number of patients with PSA<10 ng/ml had increased by 15% and by 2002 it had increased by 20% (p<0.01) (Figure 3).

The clinical stages of patients operated on are shown in Figure 4 by year of diagnosis. A continuous increase in the number of cT3 tumors was registered between 1994 and 1998, after which a declining trend followed. A similar increase in the number of cT2 tumors was registered starting from 1994, reaching a maximum in 2002 and then falling again. The number of prostatic carcinomas diagnosed by transurethral resection (cT1a and c T1b) in the period from 1994–1999 changed from 1.5 to 11.1%. From 2000 onwards there was a continuous decrease in tumors detected in this way to 1%. On the other hand, from 1994 to 2003 an increase in T1c tumors from 22.2 to 43% was noted.

In the preoperative diagnostic workups CT was performed in 69–90% of patients between 1994 and 2000 and in 37–44.7% between 2001 and 2003. The figures for bone scintigraphy are similar. Up to 2001 more than 90% of patients had bone scintigraphy before radical prostatectomy, and from 2001–2003 the number amounted to between 77 and 94%.

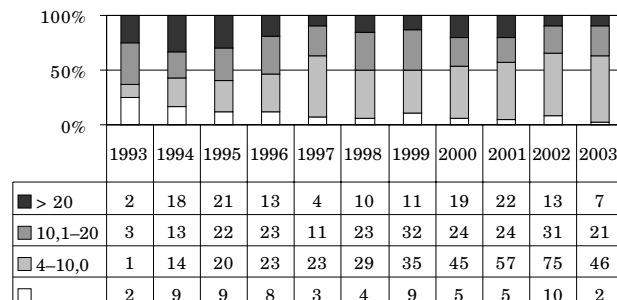


Fig. 3. Distribution of operated patients per pre-operative prostate specific antigen (PSA) values (1993–2003).

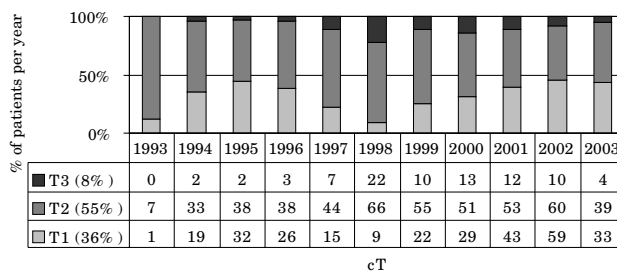


Fig. 4. Distribution of clinical stage (cT) of operated patients per year (1993–2003).

Before diagnosis patients had an average of two biopsies (range 1–3). Ultrasound-guided transrectal biopsy was performed in all cases.

Reliable information about the number of samples taken during biopsy exist since 1998.

At that time an average of 3 biopsy samples were taken (median-3, mean-3.5).

In the following years, precisely every second year, there was a statistically significant increase in the number of cylinders taken ($p < 0.01$). So, from 2001–2003 11 to 12 cylinders were taken from 75% of patients. When the department introduced a systematic ultrasound guided biopsy (S12C) the quantity of such operations increased here. Another result was a 38% better detection of prostatic carcinoma in relation to a traditional sextant (S6C) biopsy.

Migrations of tumor grading between 1993–1997 is shown in Figure 5. The increase in G1 is evident, with a peak of 30% in 1995, followed by a decrease.

Since the Gleason score was introduced in 1997, the changes from that time are shown in Figure 6. So, in 2000 one can observe a 50% increase in Gleason score 2–4, followed by a downward trend. Significant differences between years are also noticeable.

The distribution of pathohistologic stages by years is shown in Figure 7. Between 1993–1996 a large number of organ-limited tumors can be seen. While in 1997 the number of advanced tumors suddenly decreases by 80%, the following years show an increase in organ-confined tumors culminating in 65% in 2003.

Up to 1997 the number of patients with positive lymph nodes varied between 6% and 18.5%. In 1998 there was an inexplicable increase to 24% and in the first half of 2003 positive lymph nodes were only observed in 1.3% of patients. The frequency of diagnosing of affected lymph nodes in relation to preoperative PSA is shown in Table 1. Positive lymph nodes appeared only in 2 patients (3.0%) with PSA<4. On the other hand, in the group of patients with PSA between 4 and 10 ng/ml lymph nodes were affected in 20.7% in 1998 and in 1.3% in the first half of 2003.

The incidence of positive lymph nodes in PSA-groups 10.1–20 changed from 23% in 1994 to 0% in the first half

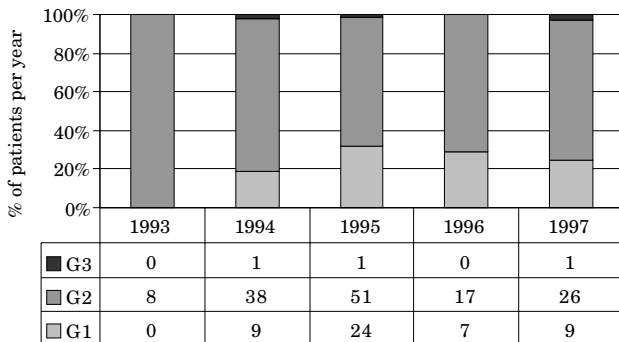
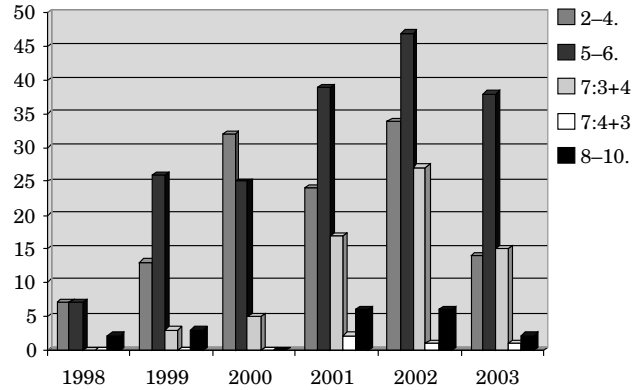


Fig. 5. Migration of tumor grading of operated patients per year (1993–2003).



Gleason score	1998	1999	2000	2001	2002	2003
2–4	7	13	32	24	34	14
5–6	7	26	25	39	47	38
7:3+4	0	3	5	17	27	15
7:4+3	0	0	0	2	1	1
8–10	2	3	0	6	6	2

Fig. 6. Migration of Gleason score of operated patients per year (1993–2003).

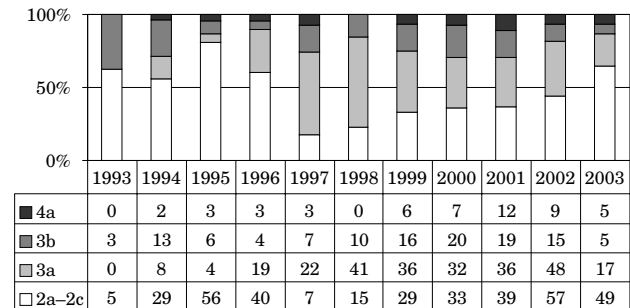


Fig. 7. Distribution of pathological stage of operated patients per year (1993–2003).

of 2003. Examination of lymph node specimens in patients with PSA > 20 ng/ml showed positive findings between 50% (1993) and 0% (first half of 2003).

Larger numbers of patients treated with hormonal therapy were noted in 1996, 1998 and 2003. This is a result of larger numbers of patients with clinically manifest and locally advanced tumors in these three years.

Patients who had received previous hormone treatment showed statistically significantly higher PSA values ($p = 0.04$, Table 2).

Discussion

Broader application of PSA, ultrasound-guided prostate biopsy and intensified public education of the population about the problem of prostatic carcinoma, has led to a significant increase in newly detected tumors dur-

TABLE 1
FREQUENCY OF DIAGNOSING OF AFFECTED LYMPH NODES RELATED TO PREOPERATIVE PSA VALUES

Op-Year	PSA (ng/ml)	Total	N+ (%)	Op-Year	PSA (ng/ml)	Total	N+(%)	
1993	< 4	2	0	1999	< 4	9	0 (0%)	
	4–10	1	0		4–10	35	3 (8.6%)	
	10.1–20	3	0		10.1–20	32	7 (21.9%)	
	> 20	2	1 (50%)		> 20	11	3 (27.3%)	
1994	< 4	9	0 (0%)	2000	< 4	5	0 (0%)	
	4–10	14	1 (7.1%)		4–10	45	2 (4.4%)	
	10.1–20	13	3 (23.1%)		10.1–20	24	2 (8.3%)	
1995	> 20	18	6 (33.3%)	2001	> 20	19	2 (10.5%)	
	< 4	9	0 (0%)		< 4	5	0 (0%)	
	4–10	20	3 (15.0%)		4–10	56	7 (12.5%)	
1996	10.1–20	22	1 (4.6%)	2002	10.1–20	24	2 (8.3%)	
	> 20	21	2 (9.5%)		> 20	22	8 (36.4%)	
	< 4	8	0 (0%)		< 4	10	1 (10.0%)	
1997	4–10	23	0 (0%)	2003	4–10	73	4 (5.5%)	
	10.1–20	23	1 (4.4%)		10.1–20	31	4 (12.9%)	
	> 20	13	3 (23.1%)		> 20	13	4 (30.8%)	
1998	< 4	3	0 (0%)	Total	< 4	66	2 (3.0%)	
	4–10	23	2(8.7%)		4–10	364	29 (8.0%)	
	10.1–20	11	1 (9.1%)		10.1–20	227	26 (11.5%)	
1998	> 20	4	1 (25.0%)		> 20	7	0 (0%)	
	< 4	4	1 (25.1%)					
	4–10	29	6 (20.7%)					
1998	10.1–20	23	5 (21.7%)					
	> 20	10	4 (40.0%)					

PSA – prostate specific antigen, Op-Year – year of operation, N+ – number of affected lymph nodes

TABLE 2
PSA VALUES OF PATIENTS WITH AND WITHOUT PREVIOUS HORMONAL THERAPY

	PSA (ng/ml)				
	N	Min	Max	X	SD
No hormonotherapy	714	0.1	140	14.2	16.2
Hormonotherapy	87	0.1	135	19.8	24.1

PSA – prostate specific antigen, Min – minimum, Max – maximum

ing the last 10 years⁷. These dramatic changes in the incidence of prostatic carcinoma have also resulted in migrations of clinical and pathological stage¹.

In our operative material most operations are on patients in the age group 60–70, and this does not differ from other European centres⁸. Unlike European studies, American studies show a lower age of operated patients (55–60 years)⁹.

In recent years there has been a considerable growth in the number of radical prostatectomies, both at other centers and here. A study from the USA shows a substantial increase in the number of radical prostatectomies in relation to other treatment options¹⁰, a study

from Hamburg, based on 1000 operated patients, shows an increase of 225% from 1992–1998^{11,12}. We also observed a significant increase, from 8 patients operated on in 1993 to 130 in 2002.

In the last few years, our patients do not have high PSA values so often, the median is the same, and PSA values <10 ng/ml have risen continuously since 1999. Similar results can be seen in a study by Winkler et al.¹³, where patients with PSA levels < 10 ng/ml increased from 30% (1988–94) to 63% (2001–2002) whereas patients with PSA values > 20 ng/ml decreased from 38% to 7% in the same period.

As for clinical stage, up to mid 1997 there were no substantial changes (p=0.7), and after that a significant increase in T1c stage can be seen (p<0.01). Other studies, too, mention an increase in T1c stage. Stamey and associates describe an increase in T1c stage from 10% in 1988 to 73% in 1996¹⁴. An increase in T1c from 35% (1988–1994) to 55% (1999–2000) is shown in a study from Great Britain¹³.

Reduced usage of CT and bone scintigraphy in prostatic carcinoma workup has resulted from the introduction of standards for preoperative diagnostics workup, drawn up by the German Urology Association. With

that, a trend of patients' treatment of lower tumor stage is shown.

The technique of prostate biopsy and the number of biopsy samples has changed in the course of time with an increase in both the number of samples taken and the number of early detected tumors. Similar results are described in other studies^{15,16}, too.

Analysis of the facts gathered from biopsy samples (especially tumor grading) shows two things:

- the number of patients who had a well differentiated tumor grading (G1) in the preoperative diagnostic workup changed from 17 to 50%,
- from 1998 an increase in the number of patients with low differentiated grading (G3) can be seen.

After introduction of the Gleason classification in 1997, the material in the database subsequently adapted to this classification. In our material, the changes in the Gleason score that appeared in the course of the years were statistically significant ($p < 0.01$).

Our study shows a continuous increase in organ-confined tumors from 1997 to 2003. On the other hand, advanced tumors continuously decrease, from 76% in 1997 to 66% in 2002.

In 1997 an unusually high percentage of advanced tumors can be observed, explicable by change of the pathologist and by the stricter pathological criteria created in that period. The high number of T3a tumors during the entire period is probably the result of a technical error, through which tumor-positive edges, so called »iatrogenic perforations of capsule«, were incorrectly interpreted as T3 tumors.

Other studies also describe migrations of pathological stage.

The National Cancer Data Base, for example, shows a growth of pT2 tumors by 20%, and a decline in pT1 and pT3 by 21% and 9%, in an investigation based on

350,000 cases from 1986^{17–19}. And a Hamburg study reports a 25% increase in pT2 and a considerable decrease in pT3 stages. The authors believe that the main reason for the 25% increase in the number of patients with pT2 stage was the too careful preoperative selection of patients with DRE, PSA, TRUS and prostate biopsy^{11,12}.

Similar results can be seen in a study of Hankey and associates, where diagnosis of organ-confined disease increased annually by 18.7% (1988–1992), followed by a decline.

On the other hand, the incidence of metastatic disease decreased annually by 1.3% (1988–1992), and during 1995 a decrease of 17.9% was registered. According to these findings, the percentage of patients with organ-confined disease who had a radical prostatectomy, increased from 7% in 1983 to 32% in 1992²⁰.

Stamey and associates also speak of an increase in the number of organ-confined tumors from 40 to 75% and of a decrease in the incidence of positive surgical margins from 65 to 62% per annum¹⁴.

In our series, inexplicably high oscillations of patients with positive lymph nodes can be noted in 1998 (24%) and in 2003 (1%).

Our study confirms migration of clinical and pathological stage of patients suffering from prostatic carcinoma in the period from 1993 to 2003 and confirms similar migrations described in the USA, Germany and other European countries. Stage migration is the result of application of stricter diagnostic criteria, and of selection of patients by their referring urologists who direct patients with different stages to different institutions. Another cause for stage migration is the introduction of S12C prostate biopsy at the end of 2001, which led to an increase in the number of patients with lower tumor stages.

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PROMJENE KLINIČKOG I PATOLOŠKOG STADIJA U PACIJENATA SA KARCINOMOM PROSTATE, KOD KOJIH JE UČINJENA RADIKALNA PROSTATEKTOMIJA U PERIODU IZMEĐU 1993. I 2003. GODINE

S A Ž E T A K

Cilj ovog rada je, da se na osnovi analize osobnog materijala relativno velikog broja pacijenata kojima je učinjena radikalna retropubična ascendentna prostatektomija (RRP) ustanovi promjena stadija. U periodu između 01.07.1993. i 31.06.2003. na Urološkoj klinici Kliniken-Essen-Mitte 801. pacijentu je učinjena RRP. Podaci o dijagnostici, liječenju i postoperativnom tijeku prikupljeni su prospektivno u jednu bazu podataka. Analiziran je klinički i patološki stadij te broj pacijenata sa pozitivnim limfnim čvorovima. Tijekom opservacijskog perioda došlo je do značajnog porasta broja radikalnih prostatektomija, od 8 u 1993. do 130 u 2002. g. Broj organ ograničenih tumora od 1997. do 2003. g je također u kontinuiranom porastu. Nasuprot tome, uznapredovali i metastatski tumori su u kontinuiranom padu od 76% u 1997. do 66% u 2002. g U periodu od 1994. do 2003. g. uočava se porast broja T1c tumora za 20%. Uvođenjem sistematske 12-cilindrične biopsije (S12C) detekcija karcinoma prostate se povećala za 38%, a također je došlo i do povećanja broja dijagnosticiranih tumora nižeg kliničkog stadija. Ovi podaci potvrđuju trend migracije kliničkog i patološkog stadija koji je nastao kao posljedica opsežnije uporabe PSA i S12C biopsije u dijagnostici karcinoma prostate.