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Late complications after radiotherapy for prostate cancer

An increasing number of patients survive cancer after having received radiation therapy. Therefore, the occurrence of late normal tissue complications among long-term survivors is of particular concern. Fortunately, radiation-induced late effects are observed rather infrequently following modern radiotherapeutic treatments. Since a relatively high number of events are required when studying the kinetics of the occurrence of late effects, data of earlier radiation treatments are of particular value for scientific evaluation.

The aim of the present study was to analyze in detail the time course of the incidence of late complications after radiation therapy (RT). For this purpose, unpublished data of patients irradiated at the department of radiotherapy at the University of Hamburg in the late 1980s were analyzed. At that time, several subgroups of patients were exposed to relatively high radiation doses applied to comparatively large tissue volumes. A considerable portion of these patients developed severe late complications. This led to litigation, which has been resolved in the meantime. The authors of this study were not involved in radiation treatment. In a previous study [5, 14], the occurrence of side effects in pelvic organs was studies for combining pre- and postoperative RT (the so-called sandwich method) in the treatment of rectal cancer. In the present report, the same pelvic organs were affected in patients irradiated for prostate cancer. Because of the relatively high incidence of late morbidity, a quantitative analysis of the time course appeared feasible.

It should be emphasized that the present study was not aimed at analyzing various treatment options with respect to clinical outcome.

Patients and methods

Patients

From 1986 to 1990, 180 consecutive patients received RT for prostate cancer at the radiotherapy department of the University Hospital of Hamburg. Two patients were excluded from analysis because of incomplete RT treatment, thus leaving 178 patients for evaluation. Data were obtained from patient records of the university hospital and from numerous other hospitals and private practices where most of the follow-up examinations had been performed. The collection of data was completed by the end of March 1997.

The median age of the patients was 66 years (range 41–88 years). All patients had a histological diagnosis of prostatic cancer (**Tab. 1**). Before referral to RT, 5 patients had a coronary bypass, 1 an ileal resection, 1 a sigmoid colon resection, 4 underwent urinary diversion, and 1 patient had a nephrectomy (**Tab. 1**,"other operations"). Seventy-two patients had a transurethral resection (TUR); 38 patients were subjected to previous radical prostatectomy (**Tab. 1**), 8 of them were operated on more than 3 months before the start of RT. Seven patients had both TUR and prostatectomy, 10 patients had prostatectomy and lymphadenectomy. Bilateral orchidectomy was performed on 128 patients and 93 were treated with antiandrogens (**Tab. 1**); 76 received both treatments, and 36 patients had no previous hormone manipulation. Seventeen patients had no surgery before RT treatment and 12 patients received no previous specific therapy for prostate cancer.

Irradiation

Irradiation was performed using 16 or 42 MV photons with 11 exceptions where part of the total dose was given by neutrons. The neutron dose was multiplied by a factor of 3 for conversion into a photon-equivalent dose. In the shrinking fields series, 3 patients were irradiated with neutrons in the first series to 6, 6, or 7.2 Gy (18 or 21.6 Gy photon equivalent); in the second series, 8 patients received neutron

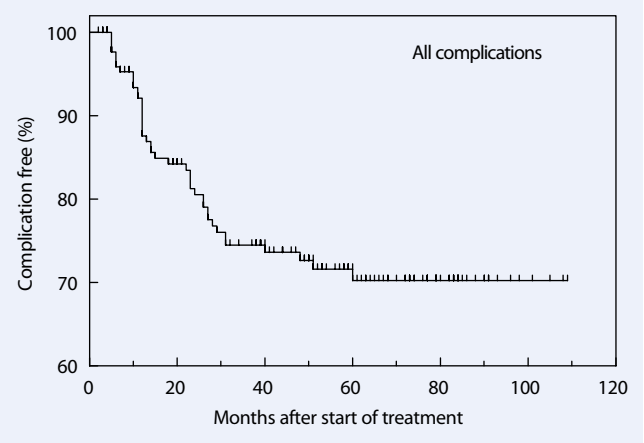

Fig. 1 ◀ Kaplan–Meier plot of the percentage of patients being free of any complications of grade 3 or higher after radiation therapy for prostate cancer

doses of 4 Gy (2 pt), 6 Gy (4 pt), 6.4, or 7 Gy (photon equivalent 12–21 Gy).

Multiple fixed or moving megavoltage field plans were used. Irradiation was targeted to a volume outlined by a 100% isodose, allowing up to 25% gradient within the treated volume. In ten exceptions, where the irradiation volume was defined by the 80% isodose, the distribution was recalculated for 100%. The ileum was not localized or protected. Irradiation was delivered in 2-Gy fractions per day with four exceptions: 2.5 Gy per fraction (total dose 40 Gy), 2.2 Gy (66 Gy), and 1.2 Gy twice a day (58 Gy and 60 Gy). Neutrons were applied at 0.8 Gy per fraction corresponding to 2.4-Gy photon equivalent.

Constant-volume RT

Sixty patients were treated with a constant volume. Of these patients, 20 were treated by a 1-field and 9 by a 2-field rotation plan. Three static fields were used in 5 patients, and in 26 patients a 4-field box technique was applied. The median of irradiated volume was 0.5 l (range 0.1–2.5 l; mean 0.63 l). The volume of 100% isodose was less than 0.5 l in 27, and between 0.5 and 1 l in 26 patients. The four largest volumes irradiated were 1.3, 1.5, 2.0, and 2.5 l in 1 patient each. There was a substantial dose variation over the treated volume. The maximum dose was between 120 and 125% in 37 patients and between 110 and 119% in 16 patients. The median overall treatment time was 52 days (range 28–75 days, mean 51.1 days).

Shrinking-field RT

In all, 118 patients were treated by two shrinking volumes. A large spectrum of dose combinations was used. The prescribed doses applied in the first and second series ranged from 8+58 Gy to 60+6 Gy, respectively. The most frequent combination was 50+14 Gy (in 15 patients) followed by 40+18 Gy, 40+24 Gy, or 50+16 Gy (8 patients each). In the first series, a median volume of 2.3 l (range 0.3–6.8 l, mean 2.1 l) was irradiated to a median nominal dose of 40 Gy (range 8–60 Gy, mean 42 Gy). Of these 118 patients, 111 were treated with a 4-field technique. The median of the maximum dose was 50 Gy (range 10–66.6 Gy, mean 51.2 Gy). In the second series, the median volume was reduced to 0.5 l (range 0.1–2.8 l, mean 0.62 l) exposed to a median prescribed dose of 18 Gy (range 6–58 Gy, mean 20.7 Gy). The maximum dose was 22.5 Gy (range 6.8–65 Gy, mean 25.8 Gy). Seventy-seven patients were treated with 4 fields and 31 with a rotation plan. Overall treatment time was 51 days (range 30–128, mean 51.2 days).

For *both treatment series* combined, the median prescribed dose was 64 Gy (range 40–76 Gy, mean 63.3 Gy), maximum dose was 77.5 Gy (range 56.3–95 Gy, mean 76.7 Gy), and overall treatment time was 51 days (range 28–128 days, mean 51.2 days).

Post-RT treatments

After the end of RT treatment, 56 patients had to undergo surgical treatments, and in several cases multiple operations were required. Eleven patients received RT, and another 13 patients had chemotherapy. Thirteen patients obtained medical treatments, in particular hormone treatments.

Classification of late damage

For this retrospective study, a modification of the EORTC and LENT-SOMA classifications of late complications was applied as described in an earlier paper [14]. Since systematic follow-up examinations had not been performed, the information collected from the medical files was often fragmentary, especially for assessing mild or moderate late effects (grade 1 or 2). Therefore, only complications of grade 3 or higher were scored for various organs. By definition, late effects are changes in the symptoms that appear or persist 3 months after the first RT session or later. Transient late effects were also included. Complications (late normal tissue effects grade ≥3) often require medical interventions such as hospitalization and intensive care (rehydration, transfusion) or surgery. Thus, severe late damage was less likely to be missed than moderate symptoms and signs. Therefore, the time point when symptoms of grade 3 or higher were diagnosed was used for analysis, as it could be taken from the records with much higher accuracy than would be possible for grade 1 or 2 symptoms. Late complications were scored in eight organs; the main classification criteria used are listed in ◘ **Tab. 2**.

Statistical analysis

Endpoints analyzed were late complications, overall and disease-free survival, local tumor control, and distant metastases. Data analysis was actuarial and the log-rank test was used to compare the various subgroups (SPSS 11.0). With the appearance of a local recurrence, the diagnosis of the late damage was censored.

A univariate analysis of the following prognostic parameters was performed: age, total prescribed dose, maximum dose (hot spot), overall treatment time, irradiation method (constant volume vs. shrinking fields), treatment plan (rotation plan vs. 4 fields), T stage (1+2 vs. 3+4), N stage (0 vs. 1+), histological grade (1+2 vs. 3+4), TUR, radical prostatectomy, bilateral orchidectomy, hormone treatment, and posttreatment surgery (0 vs. ≥1 operation). If not otherwise indicated, data were partitioned for analysis at the median.

Abstract · Zusammenfassung

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Late complications after radiotherapy for prostate cancer

Abstract

Background. The aim of the present study was to analyze in detail the time course of the incidence of radiation-induced late effects. For this purpose, unpublished data of patients treated by radiation therapy in Hamburg in the late 1980s were analyzed. Relatively large volumes were exposed to comparatively high doses, thus leading to a high rate of treatment-related side effects.

Patients and methods. A total of 180 consecutive patients received radiotherapy for prostate cancer. The median age was 66 years (range 41–88 years). The median of the maximum dose was 77.5 Gy (range 56.3–95 Gy) and overall treatment time was 51 days (range 28–128 days). Endpoints analyzed were late complications of grade 3 or higher, overall and disease-free survival, local tumor control, and distant metastases. Data analysis was actuarial and the log-rank test was used to compare the various subgroups.

Results. After 2 years, 80.5±3.2% of the patients were without any complications of grade 3 or higher, and after 5 years a constant level of 70.3±4.0% was approached. When multiple lesions occurred per patient, the later events were disregarded. A total of 66 complications occurred in 42 patients. The percentage of patients being free from late complications, plotted as a function of time after start of radiation therapy, was adequately described by an exponential function and a constant fraction. Complications approached a constant level of 70.3% at a rate of 5.3% per month. This means that patients who will develop a complication do so at exponential kinetics and at a relatively high rate, whereas about 70% of the patients will never experience a late effect even over long observation periods. After subdividing the maximum dose into three equal dose groups of 55 patients each (<73.3 Gy, 73.3–80 Gy, >80 Gy), the constant fraction decreased from 85.7 to 72.8% and 52.2%, whereas the incidence rate was 4.3%, 7.7%, and 5.6% per month and, thus, almost independent of radiation dose.

Conclusion. For a given group of patients, the rate of the incidence of late complications appears to be independent of radiation dose and (from analyzing data in the literature) independent of the grade of lesions, whereas the fraction of patients without late effects depends on both parameters.

Keywords

Late effects · Complications · Radiotherapy · Prostate cancer · Kinetics of late effects

Spätschäden nach Strahlentherapie bei Prostatakarzinom

Zusammenfassung

Hintergrund. Ziel der vorliegenden Untersuchung war, den zeitlichen Verlauf der Entwicklung von strahleninduzierten Spätschäden näher zu analysieren. Verwendet wurden bisher unveröffentlichte Daten von Patienten, die Ende der 1980er-Jahre in Hamburg strahlentherapeutisch behandelt worden waren. Damals wurden relativ große Volumina mit relativ hohen Dosen bestrahlt, was zu einer überdurchschnittlich hohen Rate an therapiebedingten Spätnebenwirkungen führte.

Patienten und Methoden. Insgesamt 180 konsekutive Patienten wurden wegen eines Prostatakarzinoms strahlentherapeutisch behandelt. Das Alter der Patienten lag bei 66 Jahren (Spanne: 41–88 Jahre). Der Median der maximalen Gesamtdosis betrug 77,5 Gy (56,3–95 Gy) und der Gesamtbehandlungszeit 51 Tage (28–128 Tage). Die untersuchten Endpunkte waren Spätkomplikationen Grad 3 oder höher, gesamtes und krankheitsfreies Überleben sowie Fernmetastasen. Die Daten der einzelnen Untergruppen wurden aktuarisch mit dem Log-Rank-Test analysiert.

Resultate. Nach 2 Jahren waren 80,5±3,2% der Patienten frei von Spätschäden Grad ≥3; nach 5 Jahren wurde ein konstantes Niveau von 70,3±4,0% erreicht. Bei Mehrfachnebenwirkungen pro Patient wurde jeweils nur das erste Ereignis berücksichtigt. Insgesamt traten 66 Komplikationen bei 42 Patienten auf. Der Prozentsatz komplikationsfreier Patienten wird adäquat durch eine Exponentialfunktion und einen konstanten Anteil als Funktion der Zeit nach Beginn der Strahlentherapie beschrieben. Die Spätschäden nähern sich mit einer Rate von 5,3% pro Monat an ein konstantes Niveau von 70,3% an. Das heißt, bei etwa 30% der Patienten, die eine Nebenwirkung erleiden, tritt diese relativ schnell auf, während etwa 70% der Patienten auch nach längeren Beobachtungszeiten keine Spätschäden entwickeln. Nach Unterteilung der Gesamtdosis in drei gleiche Gruppen mit jeweils 55 Patienten (<73,3 Gy, 73,3–80 Gy, >80 Gy) nahm der konstante Anteil beschwerdefreier Patienten von 85,7% über 72,8% auf 52,2% ab, während die Inzidenzrate 4,3%, 7,7% bzw. 5,6% pro Monat betrug und damit praktisch unabhängig von der Strahlendosis war.

Schussfolgerung. Innerhalb einer Gruppe bestrahlter Patienten scheint die Inzidenzrate von Spätnebenwirkungen unabhängig von der Strahlendosis und (nach Analyse von Daten aus der Literatur) unabhängig vom Grad des Spätschadens zu sein, während der Anteil der Patienten ohne Schäden von beiden genannten Parametern abhängt.

Schlüsselwörter

Spätnebenwirkungen · Komplikationen · Strahlentherapie · Prostatakarzinom · Kinetic von Spätschäden

Results

Complications and clinical outcome

Fig. 1 shows the percentage of patients without any complications of grade 3 or higher plotted as a function of time after the start of RT. After 2 years, 80.5±3.2% of patients were without any complications, and after 5 years a level of 70.3±4.0% was approached. In this type of plot, only the first complication occurring per patient is considered. When multiple lesions occur per patient, the later events are disregarded. In total, 42 patients experienced one or more complications.

Fig. 2 shows Kaplan–Meier plots of the incidence of complications in the seven organs affected. Altogether, 21 complications occurred in the anorectum, 29 in the bladder, eight in the ureters, three in bone, two in the ileum, two in the skin, and one in the lymphatic and soft tissue. In peripheral nerves, no complications were

Tab. 1 Patient and tumor characteristics

Parameter	Number of patients
Total cases	178
Age (years) at start of RT treatment	
40–49	4
50–59	43
60–69	69
70–79	56
80+	6
T stage	
T1	15
T2	40
T3	88
T4	24
Residuum	8
Unknown	3
N stage	
N0	112
N1	15
N2+	33
Unknown	3
M stage	
M0	160
M1	9
Unknown	9
Tumor grade	
Grade 1	20
Grade 2	82
Grade 3	66
Grade 4	2
Unknown	8
Pre-RT treatments	
Transurethral resection (TUR)	72
– 1 TUR	55
– 2 TUR	14
– 3 TUR	3
– Unknown	4
Radical prostatectomy	38
Lymphadenectomy	38
Bilateral orchidectomy	120
Hormone treatment	93
Unknown	5
Other operations	12
Single-series RT treatment (n=60)	
Treatment plan	
Rotation	29
2 fields	0
3 fields	5
4 fields	26
Irradiated volume (l)	
Up to 0.39	14
0.4	13
>0.4–0.6	13
>0.6–1	13
>1–2.5	7
Prescribed dose (Gy)	
Up to 59	5
60	8
62–64	5
66	29
68–70	13
Maximum dose (% of prescribed dose)	
100–109	6
110–124	22
125	31
Unknown	1
Maximum dose (Gy)	
56–59.9	3
60–69.9	11
70–74.9	9
75–79.9	11
80–84.9	13
85–88	12
Unknown	1
Overall treatment time (days)	
28–39	5
40–49	11
50–54	28
55–64	14
65–75	2
Shrinking fields RT treatment (n=118)	
Treatment plan—1st series	
Rotation	31
2 fields	3
3 fields	2
4 fields	111
Irradiated volume (l)	
Up to 1	11
1–1.5	16
1.8–2	30
2.3	21
2.5–2.8	21
3–4	15
5–6.8	2
Unknown	2
Prescribed dose (Gy)	
8–19	5
20–39	16
40	42
41–49	9
50	44
52–60	2
Maximum dose (% of prescribed dose)	
100–109	7
110–124	24
125	42
126–127	2
Unknown	9
Maximum dose (Gy)	
10–39	10
40–49	25
50	28
61–62	12
62.5	31
63–67	3
Unknown	9
Treatment plan—2nd series	
Rotation	31
2 fields	1
3 fields	8
4 fields	77
Unknown	1
Irradiated volume (l)	
Up to 0.3	27
0.4	22
0.5	19
0.6–0.7	22
0.8–1.5	19
1.8–2.8	6
Unknown	3
Prescribed dose (Gy)	
6–13	16
14–17	29
18–20	30
21–29	26
30–39	11
40–58	6
Maximum dose (% of prescribed dose)	
100–109	4
110–124	23
125	77
126	10
Unknown	10
Maximum dose (Gy)	
6–19	29
20–24	31
25–39	35
40–49	10
50–65	3
Unknown	10
Overall treatment time (days)	
30–39	8
40–49	41
50–54	35
55–64	28
65–128	3

Tab. 1 Patient and tumor characteristics (Continued)

Parameter	Number of patients
40–57	15
58–60	32
61–63	22
64–65	31
66	49
67–70	26
70–76	3
Maximum dose (Gy)	
56–59.9	4
60–69.9	28
70–74.9	27
75–79.9	36
80–84.9	45
85–89.9	23
90–95	2
Unknown	13
Overall treatment time (days)	
28–39	13
40–49	52
50–54	63
55–59	32
60–67	15
75–128	2
Unknown	1
Post-RT treatments	
Surgery	56
– 1 operation	31
– 2 operations	12
– 3–5 operations	10
– 6–10 operations	3
Radiotherapy	11
Chemotherapy	13
Medical (incl. hormones)	13

Tab. 2 Criteria for classification of late damage (grade ≥3)

Organ	Symptoms
Anorectum and colon	Hospitalization or surgery is required because of tenesmi, persistent bleeding, and low ileus
	Morphology: Ulceration or extensive erosion, and/or stricture to less than one third of the viscus
Bladder	Incontinence requiring the use of pads, bladder capacity less than 200 ml, hemorrhagic cystitis, fibrosed and thickened bladder wall
Bone	Pain and tenderness with mobility reduced to 80% or less
	Morphology: Bone necrosis or intensive sclerosis, fracture, sequestration, sinus
Ileum	Diarrhea more than 8 times a day, melena, abdominal pain, ileus. Therapy requires hospitalization or surgery (resection or anastomosis, colostomy)
	Morphology: X-rays show deformity of the terminal ileum, fluid levels, mucosal edema. Extensive adhesions
Lymphatic and soft tissue	Severely restricted mobility—need for crutches or a wheelchair
	Morphology: Moderate deformity or intensive edema due to the fibrotic hardening of soft tissues or contracture, or atrophy up to 50%
Nerves	Peripheral neuropathy causing pain and irritation—patient able to take only a few steps or requires a wheelchair. Functional loss 50% or more
Skin	Permanent pain, objectively deep erosion or ulceration or fistula or contracture
Ureters	Complete unilateral or partial bilateral obstruction with early signs of uremia requiring surgical diversion or stent

Tab. 3 Results (p values) from the explorative analysis of four endpoints in relation to 14 parameters

Parameter	All complications	Overall survival	Recurrences	Metastases
Age: ≤66 vs. >66 years	0.89	0.14	0.38	0.18
Prescribed dose: ≤64 vs. >64 Gy	0.011[a)]	0.35	0.44[i)]	0.061[a)]
Maximum dose: ≤77.5 vs. >77.5 Gy	0.030[a)]	0.99	0.090	0.043[a)]
Overall treatment time: ≤51 vs. >51 days	0.54	0.39	0.50	0.033[b)]
Method: one series vs. shrinking fields	0.028[c)]	0.42	0.73	0.37
Treatment plan: rotation vs. 4 fields	0.0019[d)]	0.38	0.27	0.55
T stage: 1+2 vs. 3+	0.49	0.018[e)]	0.39	0.0006[e)]
N stage: 0 vs. 1+	0.66	0.92	0.23	0.041[e)]
Grade: 1+2 vs. 3+4	0.37	0.16	0.15	0.0066[e)]
Transurethral resection	0.018[f) i)]	<0.0001[f)]	0.067	0.0006[f)]
Radical prostatectomy	0.39[i)]	0.0038[g)]	0.40	0.087
Bilateral orchidectomy	0.41	0.36	0.16	0.44
Hormone treatment	0.61	0.22	0.83	0.93[i)]
Posttreatment operations: 0 vs. ≥1	<0.0001[h)]	0.17	0.049[h) i)]	0.44

[a)]Higher dose: Shorter survival, fewer metastases, more complications[b)]Longer treatment time: fewer metastases[c)]Shrinking fields: fewer complications[d)]Four fields: fewer complications[e)]Higher T, N, grade: shorter survival, more metastases[f)]With TUR: shorter survival, more metastases, more complications[g)]With prostatectomy: more survival[h)]Patients with operations: more recurrences, more complications[i)]Already contained in **Fig. 4**
About three of the p values ≤0.05 might be due to chance results

observed. The total number of complications was 66. For example, the events in bone at 64 and 101 months and the event in the ileum at 35 months do not appear in **Fig. 1,** since these patients had earlier events in other organs and only these are considered in the Kaplan–Meier plot of all complications.

Fig. 3 shows the actuarial results for overall and disease-free survival, recurrent tumors, and distant metastases. By 2 years, the actuarial rates (± SE) for the four endpoints studied were 81.8±2.9%, 68.0±3.5%, 5.7±1.8%, and 22.8±3.2%, respectively. By 5 years, the corresponding figures were 58.1±3.8%, 49.4±3.9%, 8.4±2.4%, and 32.1±3.8%, respectively. By the end of the follow-up period, the rates were 37.1±6.5%, 18.5±13.6%, 13.3±4.2%, and 36.0±4.5%, respectively. During follow-up, 14 recurrences and 53 distant metastases were diagnosed.

Prognostic parameters

The collected data were analyzed for prognostic factors using univariate analysis (**Fig. 4**). As a first step, eight correlations were tested using parameters defined a priori. For all complications (42 events), total maximum dose (TD_{max}) and total prescribed dose (TD_{sum}) were subdivided into three approximately equal groups, whereas for recurrent tumors (14 events) TD_{sum} was partitioned at the median. Correspondingly, post-RT surgery was subdivided into three or two operation groups. The occurrence of compli-

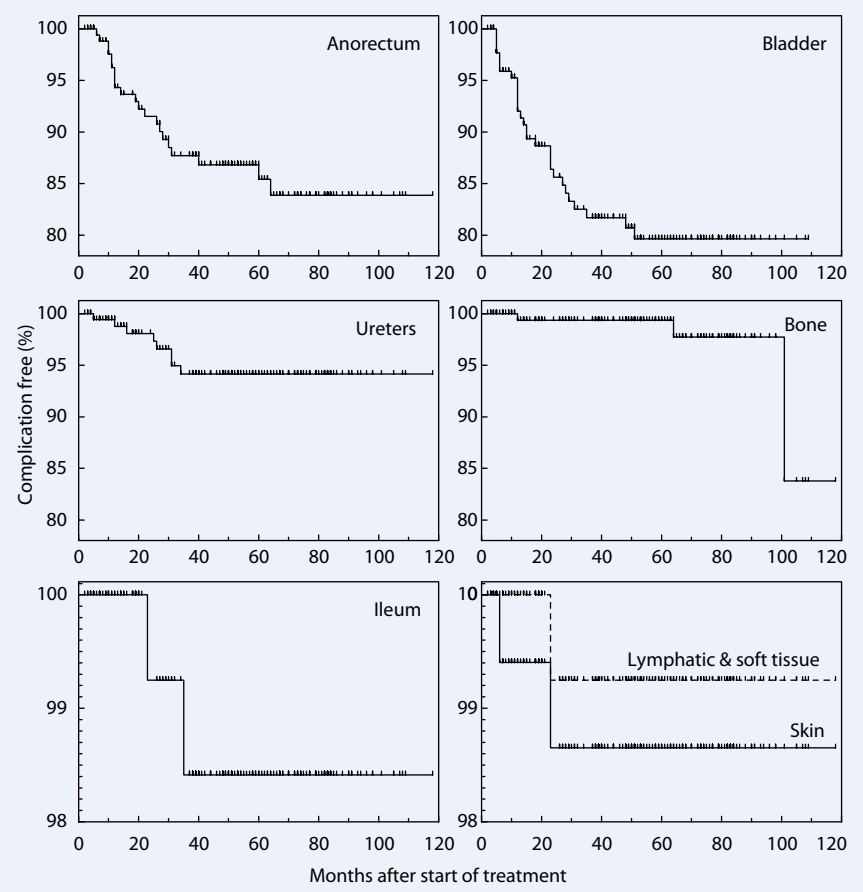

Fig. 2 ▲ Complications of grade 3 or higher occurring in the anorectum, bladder, ureters, bone, ileum, skin, and lymphatic and soft tissue

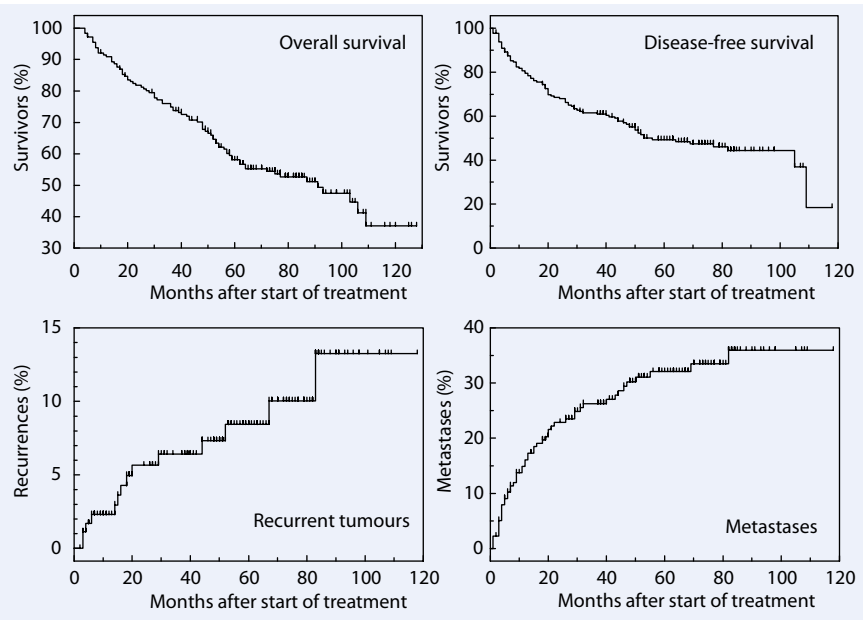

Fig. 3 ▲ Actuarial results for overall survival, disease-free survival, recurrent tumors, and distant metastases

cations was significantly associated with higher values of TD_{max} (p=0.0044) and TD_{sum} (p=0.037). Complications were significantly higher in patients with post-RT operations (p<0.0001); for recurrent tumors this association was of borderline significance (p=0.049). These results indicate that a major part of the surgical procedures were carried out in an attempt to repair late complications and, to a lesser extent, in the treatment for recurrent tumors. After TUR, patients showed a higher rate of complications (p=0.018).

After **Fig. 4** had been finalized, an explorative analysis of four endpoints in relation to 14 parameters was performed. The results obtained are presented in **Tab. 3**. Higher values of TD_{max} and TD_{sum} partitioned at the median were associated with a higher rate of complications (as was also shown for the three partitioned groups in **Fig. 4**). Treatments using shrinking fields were associated with a lower number of complications as compared to constant-volume treatments (p=0.028), and 4 fields appeared to cause fewer complications than found for rotation irradiation (p=0.0019). TUR was associated with a higher rate of complications (p=0.018; cf. **Fig. 4**) and metastases (p=0.0006), and a lower rate of survival (p<0.0001). Radical prostatectomy improved survival significantly (p=0.0038). Complications were associated highly significantly with post-RT surgery, independently of whether no surgery was compared with one or more operation (**Tab. 3**) or with one and with two or more operations (**Fig. 4**). In total, 56 associations were analyzed, and thus about three of the relationships that led to significant p values might be due to chance results.

Discussion

Discussion of results

In the actuarial plot of all complications shown in **Fig. 1**, 42 events are considered although a total of 66 complications were diagnosed. This indicates the shortcomings of Kaplan–Meier analysis when multiple late effects occur in one and the same patient. In fact, the curve for "all complications" represents only late effects

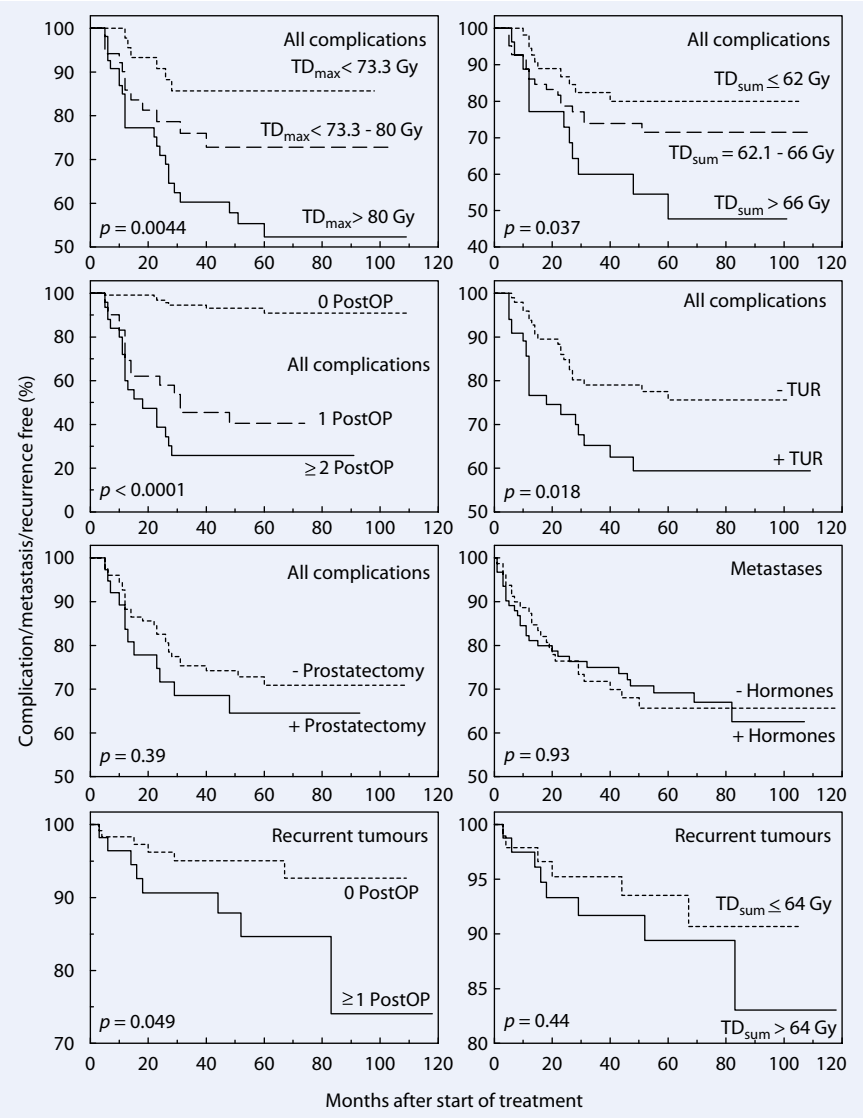

Fig. 4 ▲ Prognostic factors for various endpoints defined a priori

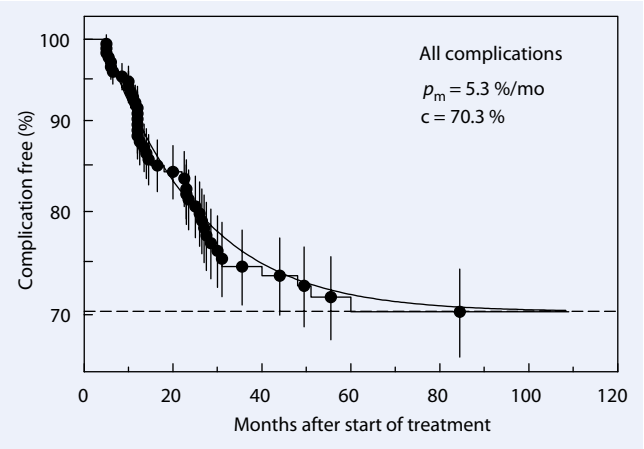

Fig. 5 ◀ Logarithmic Kaplan–Meier plot of all complications of grade 3 or higher occurring in a group of 178 patients treated with radiotherapy for prostate cancer (*staircase line*). *Error bars* indicate SE. The *solid line* drawn was obtained by fitting the data (*solid points*) to Eq. (1)

in the anorectum or bladder with one single exception (one event in the ureters at 26 months). All the other events in the ureters, bone, ileum, skin, or lymphatic and soft tissue (**Fig. 2**) are not included in the curve for all complications (**Fig. 1**) since the patients suffered from lesions in the anorectum or bladder before late effects occurred in the other organs mentioned. Thus, the curve for "all complications" refers to a relatively homogeneous group of lesions.

Curve fitting

The curve for all complications shown in **Fig. 1** approaches a constant level by 60 months after treatment. This indicates that patients who have not developed a complication within a follow-up period of 5 years will not experience any complication on further follow-up.

In a previous publication [5] we have shown that the incidence of late effects occurring after RT, in many instances, may be described by exponential kinetics. The data shown in **Fig. 1** were fitted by an exponential function and a constant fraction using the equation

(1)

$$P_{cf} = (100 - c) \cdot \exp\left[-k \cdot (t - t_{lag})\right] + c,$$

where P_{cf} is the percentage of actuarial freedom from complications, k is the slope coefficient of the curve, t is the time after treatment, t_{lag} is the lag time to the appearance of the first complications, and c is the percentage of patients who will never develop a complication, even after extended follow-up. The parameters k, t_{lag}, and c were calculated from the fit.

Fig. 5 shows the complication rate obtained after fitting the data from **Fig. 1** to Eq. (1). The parameters calculated were t_{lag}=5 months, k=0.053 per month, and c=70.3%. The percentage of patients at risk of developing a complication per month, termed p_m (= percentage per month), was 5.3%/month as obtained from the slope parameter k (p_m=100 · k). This may be explained by assuming that those patients who will develop a complication in the anorectum or bladder do

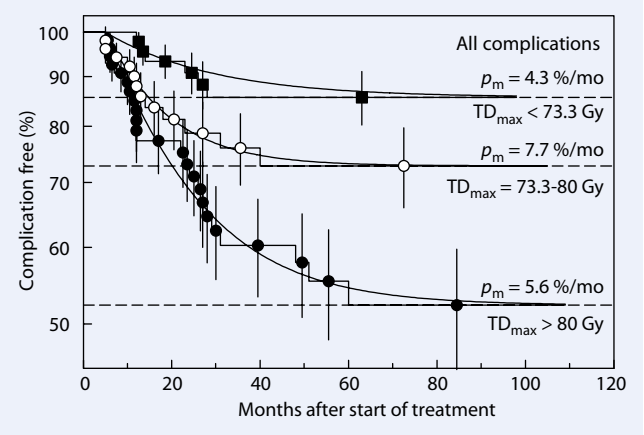

Fig. 6 ▲ Data for all complications (cf. ◘ **Fig. 5**) were subdivided into three equal dose groups of 55 patients each (TD_{max} <73.3 Gy, 73.3–80 Gy, or >80 Gy) and fitted separately to Eq. (1)

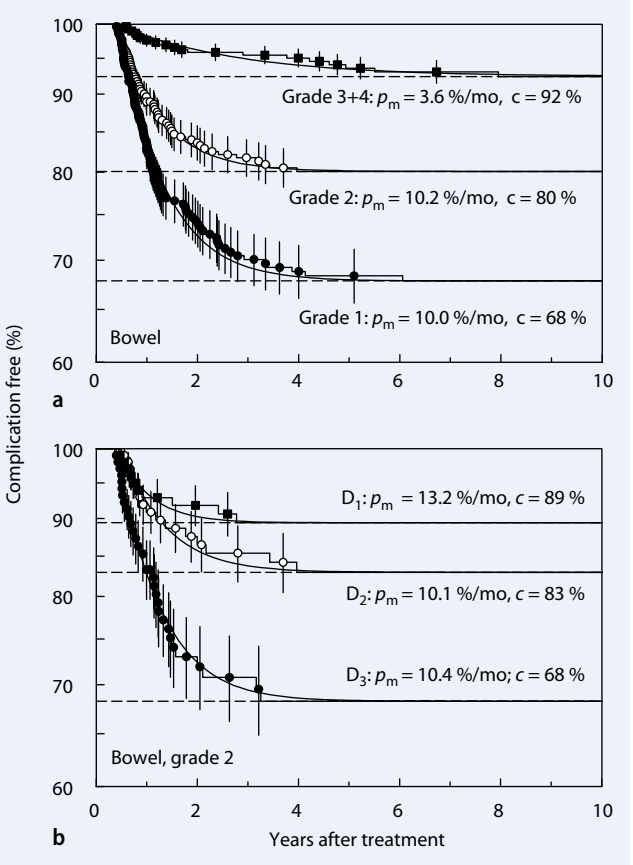

Fig. 7 ▶ Logarithmic Kaplan–Meier plot of late effects in the bowel occurring in a group of 317 patients irradiated for endometrial cancer (*staircase lines*) with a follow-up of 20 years (Note: All curves extent horizontally up to 20 years). Chart **a**: Grade 1, grade 2, and grade 3 and 4 lesions were analyzed separately. Chart **b**: Data on grade 2 lesions (57 events) were subdivided into three equal dose groups and analyzed separately. *Error bars* indicate SE. The *solid lines* drawn were obtained by fitting the data to Eq. (1). Original data provided by Jereczek-Fossa et al. [4]

so at exponential kinetics and at a rate of 5.3% per month, whereas 70.3% of the patients will never experience a late effect even for long observation periods.

◘ **Fig. 6** shows the data from ◘ **Fig. 5** (or ◘ **Fig. 1**) analyzed after subdividing into three equal dose groups of 55 patients each (TD_{max} was available for 165 patients, cf. ◘ **Tab. 1**). For TD_{max} <73.3 Gy, 73.3–80 Gy, or >80 Gy, the constant fraction of unaffected patients decreased from 85.7 to 72.8% and 52.2% (horizontal broken lines), whereas the incidence rate was 4.3%/month, 7.7%/month, and 5.6%/month and, thus, almost independent of radiation dose. In the three dose groups, 6, 12, or 23 complications occurred per 55 patients, respectively (for one event TD_{max} was unknown), showing a clear-cut dependence of dose, whereas the incidence rate per month was more or less the same.

Jereczek-Fossa et al. [4] published the data of 317 patients irradiated for endometrial cancer with a follow-up of up to 20 years. The original data were kindly provided to us for analysis. Not a single late effect was diagnosed between year 8 and year 20, thus supporting our hypothesis of a constant level for longer observation periods. The data for late effects in the bowel (93 grade 1, 57 grade 2, 20 grade 3+4) were analyzed in the same way as applied to our data (cf. ◘ **Fig. 6**) using Eq. (1). When analyzed separately for grade 1, grade 2, and grade 3+4, a clear-cut increase was observed for the constant fraction from 68 to 80% and 92%, whereas the incidence rate was about 10% per month (10.0%/month, 10.2%/month, and 3.6%/month, respectively; ◘ **Fig. 7,** top). When grade 2 lesions (57 events) were analyzed separately for three equal dose groups, the constant fraction decreased with increasing dose from 89 to 83% and 68%, whereas the incidence rate was about constant at 10% per month (13.2%/month, 10.1%/month, and 10.4%/month, respectively; ◘ **Fig. 7,** bottom).

Late effects in the rectosigmoideum recorded for a group of 442 patients irradiated for carcinoma of the cervix [10] are shown in ◘ **Fig. 8**. The dose distribution was relatively wide. The external dose ranged from 40 to 60 Gy, the intracavitary dose from 18 to 48 Gy. The constant fraction, *c*, (i.e., the percentage of patients remaining permanently unaffected by complications) increased with higher grades of the lesions. For grade 2, the constant fraction was 25%, for grade 3, 39%, for grade 4, 61%, and for grade 5, 90% (broken lines). The incidence rate was about constant at p_m=5–7% per month (6.9, 5.6, 4.9, and 4.9%/month, respectively). This is remarkably similar to the data shown in ◘ **Fig. 7** (top).

Discussion of possible mechanisms

The reasons for the occurrence of biphasic curves consisting of an exponential decline followed by a constant fraction are not known.

In the present study, the number of complications approached a constant level by about 5 years. This is in marked contrast to the results of our previous study on patients who received a combined pre- and postirradiation (sandwich) therapy for rectal cancer [14]. In this group, the incidence of late complications could be

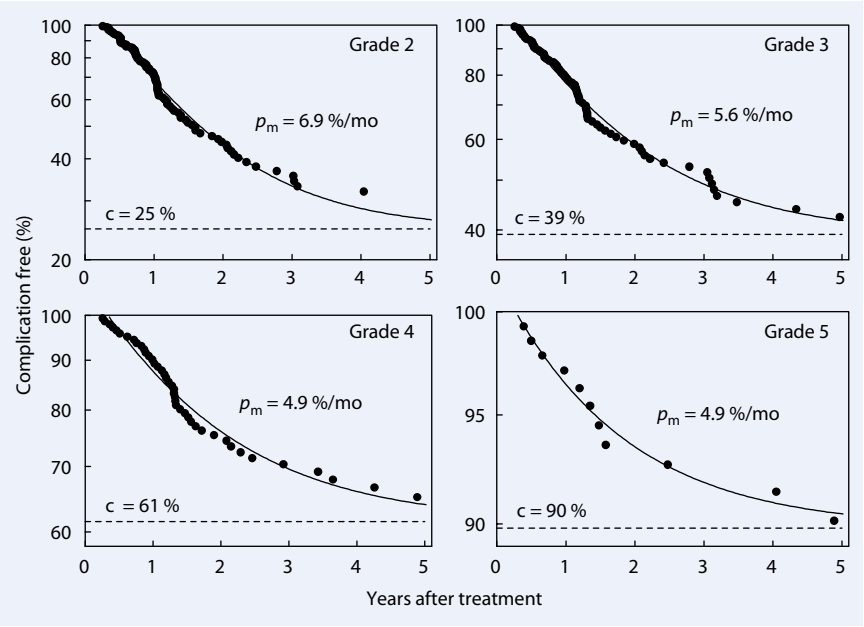

Fig. 8 ▲ Late effects in the sigmoideum occurring in a group of patients (stage FIGO IIIb) irradiated for carcinoma of the cervix. The data for lesions of grade 2, 3, 4, or 5 (*solid points*) were fitted separately to Eq. (1) resulting in the *solid lines* that approach exponentially a constant level (*broken lines*). Data from Pedersen et al. [10]

described by a single exponential function and the annual rate was about 10% per year, i.e., less than 1% per month [5]. In both studies, the same organs were considered and classification of damage was performed by one and the same individual (V.S.).

In a previous publication we showed 28 sets of data for "Type 1 kinetics" (**Fig. 3** in [5]). The late effects in various organs occurred at purely exponential kinetics and no constant level was observed for the entire follow-up period which ranged from 6 to 30 years in nine of the examples shown. The median of the incidence rates of late effects was 8%/year (range 0.9–66%/year) with 50% of the values ranging from 4.3 to 11%/year. The incidence rates obtained from the fit to the data shown in **Fig. 5, 6, 7, 8** are about 5–10% *per month*. Thus, the incidence rates for biphasic curves are roughly one order of magnitude larger than the values found for Type 1 kinetics.

It might be speculated that Type 1 kinetics originate from irradiating a whole organ to a dose somewhat exceeding the tolerance level of the tissue. By contrast, biphasic curves might be expected when an organ is exposed to a highly inhomogeneous dose distribution. One subgroup of patient exposed to a "hot spot" of dose might show a relatively rapid development of late effects, whereas in the other group of patients no late effects occur at all, even for long follow-up periods.

This hypothesis is supported by the observation that biphasic curves are often observed in three-dimensional conformal radiation therapy (3D-CRT) or brachytherapy treatments. For example, in 743 patient treated by 3D-CRT for prostate cancer, all of 75 lesions of grade 2 or higher late rectal toxicity occurred within the first 4 years of follow-up. This was followed by a constant level of 3.4% at 64.8 Gy, 7.8% at 70.2 Gy, 15.9% at 75 Gy, and 16.5% at 81 Gy [13].

In 339 patients receiving brachytherapy for cervical cancer, 85 out of 87 complications (35 out of 36 major complications) were diagnosed within the first 5 years of follow-up. In the following 10 years, the level of complications was about constant (except for the two events mentioned) and showed a clear dependence on dose: 15% (6% major complications) at 60 Gy, 23% (11%) at 65 Gy, 26% (11%) at 67.5 Gy, 40% (15%) at 70 Gy, and 55% (19%) at 75 Gy [11].

Similar results have been obtained in numerous studies on RT for prostate cancer, where virtually all of the complications occurred within 4 or 5 years after treatment followed by a dose-dependent constant level (cf. [2, 3, 9, 17]. This might possibly apply to small rather than to larger radiation doses (cf. [8, 15, 16]) or to gastrointestinal rather than to genitourinary toxicity (Ref. [1, 8]). Under certain conditions, some of the late effects become manifest at follow-up periods exceeding 5 years (cf. [6, 7, 12]).

Conclusion

In our group of patients, radiation-induced late effects occurred in about 30% of the individuals at exponential kinetics and relatively fast, whereas about 70% of patients did not suffer from late complications even over extended observation periods.

The rate of the incidence of radiation-induced late complications appears to be independent of radiation dose and (from analyzing data in the literature) also independent of the grade of the lesions, whereas the constant level of unaffected patients showed a clear-cut dependence on dose and grade.

In this study, TUR was highly significantly associated with a higher rate of complications and metastases, and a lower rate of survival.

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