Second Primary Tumors after Radiotherapy for Malignancies

Treatment-Related Parameters

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Purpose: The aim of the present analysis was to identify radiotherapy-related parameters that influence the development of second malignancies.
Patients and Methods: Between 1969 and 1989, about 31,000 patients were treated in Dresden with low voltage (≤ 180 kV X-rays) or telecobalt radiotherapy or a combination of both. Of these 203 were readmitted after earlier radiotherapy, for radiotherapy of a newly developed malignancy. Based on definitive diagnosis of a secondary tumor and completeness of documentation 53 patients were selected for further analysis. This included the spatial relation between the new tumor and the primary treatment fields, and the incidence in relation to the dose at the site of origin. The material does not allow for risk estimation
Results: Primary malignancies comprised breast and gynecological tumors in female, and tumors of prostate, head and neck and lymphomas in male patients. Second tumors developed mainly in corpus uteri, respiratory, gastrointestinal and urinary tract. The high incidence of 9.9% second primary corpus/cervix uteri tumors in patients with primary breast cancers suggests a common etiology. The majority of second tumors was observed within the margin of the planning target volume (PTV), which was defined as the volume 2.5 cm inside to 5 cm outside the field margin proper. Inside the PTV developed < 10%, outside 11% of the second tumors. With regard to dose the majority of second tumors was observed in the region receiving < 6 Gy.
Conclusions: A significant number of second primary tumors is found in the volume receiving ≤ 6 Gy, i.e. at the margins of the PTV. This should be considered for multiple field radiotherapy and IMRT, where the relevant volumes may be substantially increased.

Key Words: Tumor induction · Second primary tumors · Radiotherapy · Dose dependence · Localization

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Entstehung von Zweittumoren nach Strahlentherapie von Malignomen: behandlungsbezogene Einflussfaktoren

Hintergrund: Ziel der vorliegenden Untersuchung war die Identifikation von Faktoren der Strahlentherapie maligner Erkrankungen, die möglicherweise die Entwicklung von Sekundärtumoren beeinflussen.
Patienten und Methoden: Im Zeitraum zwischen 1969 und 1989 wurden in Dresden etwa 31 000 Patienten mit weicher Röntgenstrahlung (≤ 180 kV), ^{60}Co-γ-Strahlung oder einer Kombination aus beiden behandelt. Von diesen wurden 203 zur erneuten Strahlentherapie aufgrund eines neu entstandenen Tumors vorgestellt. Ausgehend von der sicheren Diagnose eines Sekundärtumors und der Vollständigkeit der Dokumentation der initialen Strahlenbehandlung wurden 53 Patienten zur Analyse ausgewählt. Diese beinhaltete die räumliche Beziehung zwischen dem Entstehungsort des neuen Tumors und den ursprünglichen Bestrahlungsfeldern und die Tumorinzidenz in Abhängigkeit von der Dosis am Entstehungsort. Eine Risikoabschätzung ist aus dem vorhandenen Material nicht möglich.
Ergebnisse: Die Primärtumoren umfassten im Wesentlichen Mamma- und gynäkologische Tumoren bei Frauen sowie Prostata- und Kopf-Hals-Tumoren bei Männern. Sekundärtumoren wurden hauptsächlich in Corpus uteri, Atemwegen, Gastrointestinal- und Harnorganen beobachtet. Die mit 9,9% hohe Inzidenz von Sekundärtumoren von Corpus/Cervix uteri bei Patientinnen mit primären Mammatumoren deutet auf eine gemeinsame Ätiologie hin. Der Hauptteil der Sekundärtumoren wurde an den Rändern des ursprünglichen Planungszielvolumens (PTV) gefunden, welche als das Volumen von 2,5 cm innerhalb bis 5 cm außerhalb des eigentlichen Feldrandes definiert wurden. Innerhalb des PTV fanden sich < 10%, außerhalb des Randbereiches 11% der Sekundärtumoren (Abbildung 1). In Bezug auf die Dosis am Entstehungsort wurde der Hauptteil der Sekundärtumoren in der mit < 6 Gy belasteten Region beobachtet (Abbildung 2).
Schlussfolgerung: Eine signifikante Anzahl an Sekundärtumoren findet sich in dem mit ≤ 6 Gy belasteten Volumen, d.h. an den Rändern des PTV. Dies sollte bei Mehrfelder- und intensitätsmodulierter Strahlentherapie in Betracht gezogen werden, da hier die relevanten Volumina deutlich ausgeweitet sein können.

Schlüsselwörter: Tumorinduktion · Zweittumoren · Strahlentherapie · Dosisabhängigkeit · Lokalisation

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Introduction

Of all patients with malignant diseases about 70% are treated by radiotherapy exclusively or in combination with other modalities [1]. During the recent years, major advances have been made in the physical aspects of treatment planning and administration, like 3-D planning techniques or conformal irradiation through multiple fields. Also, inclusion of novel biological knowledge resulted in modern unconventional therapy schedules, such as hyperfractionated or accelerated protocols or a combination of both. These developments are yielding increasing rates of tumor cures and survival. As direct consequence, the risk for the manifestation of late radiation sequelae will increase. This does not solely include non-stochastic deterministic effects in the normal tissues irradiated but also stochastic effects, i.e. induction of tumors in the tissues exposed.

Although ionizing radiation in general is considered a weak carcinogen, the number of patients receiving radiotherapy and the increased survival times may cause a progressive increase in the numbers of patients suffering from second primary malignancies, induced by the therapy of the first primary tumor.

The present study was initiated in order to identify therapy-related parameters, such as dose distribution and spatial relation between the original treatment fields and the site of second tumor development, in a population of patients readmitted for tumor radiotherapy at the Department for Radiotherapy, Dresden, after a first course of radiotherapy for malignant disease.

Patients and Methods

Patients and Treatment Characteristics

Between 1969 and 1989, about 31,000 patients were treated at the Department of Radiotherapy of the University Hospital (former Medical Academy) Dresden. Among these were 203 patients, i.e. about 0.65%, which were readmitted for radiotherapy because of a newly developed tumor after initial radiotherapy between 1950 and 1986. Primary radiotherapy was performed because of a tumor in 148 patients and because of a combination of malignant and benign diseases in 24 patients. 31 patients who had initially been irradiated for benign diseases, are not included in this analysis. Out of this population of 172 patients, 53 patients were selected for further analysis.

Basis for the selection was that metastases and late recurrences could be excluded. The widely used criteria for the definition of secondary tumors, according to Tassile et al [21], were: 1. malignant character of both tumors, 2. different histological characteristics, 3. exclusion of metastases (autochthonous histological character), and 4. in cases of similar organ localization (e.g. colon tumors, where 2. did not apply) sufficient distance from first manifestation.

This selection was also based on completeness of documentation of the first treatment, particularly with regard to treatment fields and dose distribution, and to definition of the site of origin of the second tumors.

The primary treatment was performed because of a malignant tumor in 53 patients. However, additional radiotherapy for benign disease was administered in 15 patients with breast cancer who received irradiation of the ovaries for induction of menopause. One patient received three courses of radiotherapy because of a first, second and third primary tumor; the first and second treatment series were regarded as independent, and hence a total of 54 malignancies were found after tumor radiotherapy. The median age at first treatment was 55.3 years (range 4–85) in male patients, and 50.7 years (range 18–82) in female patients, respectively.

The most frequent types of secondary solid tumors and their primary tumors are summarized in Table 1. Treatment was performed with low voltage (≤ 180 kV) X-rays in 32 cases, with ^{60}Co-γ-rays in 16 cases, and with a combination of both in six patients, respectively.

Reconstructive Dosimetry

Detailed reconstructive dosimetry was performed in order to define the dose at the localization where the second malignancy developed. This was done in relation to radiation quality, filter, size of the cone, and distance from central beam and field margin.

A RANDO® phantom, simulating a male body with a height of 173 cm and a weight of 73.5 kg, in which various materials represent the various tissues [7, 17, 18] was applied. The treatment documents were used to reconstruct localization of the disease and application of individual treatment fields. A channel in slices of polyacrylate allowed for positioning of the ionization chamber. A M2300 dosemeter (Robotron, Dresden, Germany) was used. Each measurement was preceded by calibration of the system according to the instructions of the manufacturer.

The radiation devices used were T250 (TUR Dresden, Germany) for low voltage X-irradiation and Philips Universal (Philips, Germany) for ^{60}Co-γ treatment.

For further analysis, doses at the site of origin of the second tumor were grouped into 1-Gy groups for doses < 30 Gy, and into 5-Gy groups for higher doses.

Definition of Distances

In relation to the margin of the initial treatment field (planning target volume, PTV), the following distances for the origin of the second malignancies were defined, as illustrated in Figure 1, as in-field (central beam to -2.5 cm from margin), margin region (-2.5 to +5 cm), adjacent area (5–20 cm from the field margin) and distant area (> 20 cm). Within the margin region, the margin proper was defined within the first 2.5 cm outside the field.

Results

Second Primary Malignancies

A variety of second tumors was observed, as illustrated in Table 1. A total of twelve second tumors were observed in the

Table 1. Entities of second primary tumors, in descending frequency, and first primary tumors which had been treated by radiotherapy (ALL: acute lymphatic leukemia; CLL: chronic lymphatic leukemia; MH: Morbus Hodgkin; NHL: non-Hodgkin lymphoma; sa.: sarcoma).

Tabelle 1. Sekundärtumorentitäten in absteigender Häufigkeit und bestrahlte Ersttumoren.

Second tumor	Number	First tumors
Corpus uteri	8	Mamma (4), cervix, ovary, inguin. fibrosa., sa. thigh
Vagina/vulva	5	Cervix (3), corpus, vulva
Anus	4	Cervix, bladder, mamma, vulva
Bronchial tree	4	Axill. melanoblastoma, MH, NHL (2)
Cervix uteri	4	MH, mamma (3)
Rectum	4	Cervix (2) MH, mamma
NHL	3	MH, seminoma, cervix
Ovary	3	Mamma (3)
Urinary bladder	3	Cervix, mamma, kidney
MH	2	Cervix (2)
Stomach	2	Corpus (2)
Left kidney	2	Mamma (2)
CLL	1	Cervix
Gland. submandibularis	1	NHL
Brain	1	NHL/ALL
Testis	1	NHL
Left mamma	1	Right mamma
Esophagus	1	Mamma
Thigh sa.	1	Cervix
Thyroidea	1	MH
Vocal cord	1	Larynx
Tonsil	1	MH

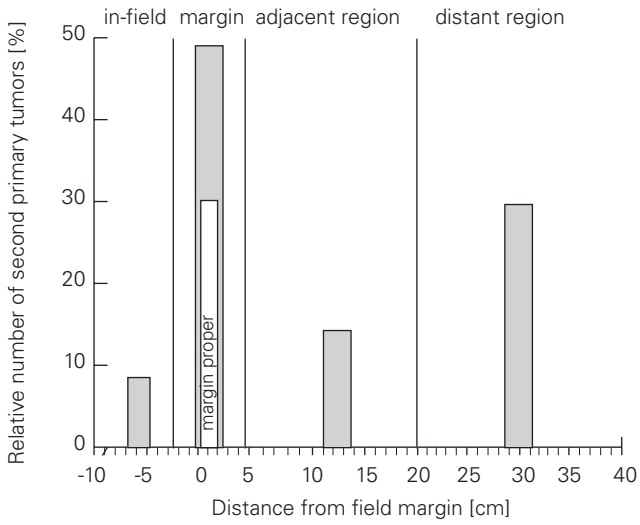

Figure 1. Tumor incidence in relation to the initial treatment field. For the present analyses, volumes were defined relative to the margin of the initial treatment field (planning target volume). These include the margin region, with a margin proper, the adjacent region, and the distant region. The incidence of second primary tumors was assessed in each of the volumes. Tumors in the margin region are clearly overrepresented in comparison to those in other regions.

Abbildung 1. Tumorinzidenz in Beziehung zum Bestrahlungsfeld. Für die vorliegende Analyse wurden Volumina relativ zum Rand der initialen Behandlungsfelder (Planungszielvolumen) definiert. Diese beinhalten die Randregion mit dem eigentlichen Rand, angrenzende und feldferne Bereiche. Die Inzidenz der Sekundärtumoren wurde in jedem der Teilvolumina bestimmt. Tumoren im Randbereich sind im Vergleich zu den anderen Regionen deutlich überrepräsentiert.

uterus; seven of these patients were initially irradiated for breast cancer, and in all seven the tumor treatment was combined with irradiation of the ovaries (4–6 Gy) for induction of menopause. Similarly, three ovary tumors, two tumors in the left kidney and one carcinoma of the rectum were found after menopause induction in addition to mammary carcinoma treatment.

Localization of Second Tumors in Relation to the Initial Treatment Volume

In order to analyze the relation between the initial treatment volume and the site of origin of the second primary tumors, the distances from the initial field margin were defined as shown in Figure 1. The relative frequency of second tumors observed in the individual regions is illustrated in Figure 1. The vast majority, almost 50%, of second tumors was observed in the margin region of the initial treatment volume, while < 10% were seen within the field and a comparable number (> 10%) in the adjacent region.

About 30% (16) of the second tumors were found in a distance of more than 20 cm from the initial field margin (distant region). This includes 13 patients who had initially been treated for mammary carcinoma, which defined the distance from the initial field. However, the site of the second tumors was in the PTV of the ovarial field (for menopause induction) or its margins in 13/16 cases. This suggests that the proper rate of second primary tumors at ≥ 20 cm distance from the primary field is 1/54, i.e. < 2%.

Development of Second Tumors in Relation to Dose at the Site of Origin

Detailed retrospective dosimetry of the initial treatment for the first primary tumor allowed for analysis of radiotherapy dose at the site of origin of second primary tumors. The results, i.e. number of second tumors in relation to dose, is shown in Figure 2. 23 of the tumors, i.e. 43%, developed within a volume which received a local dose of < 6 Gy at first treatment. In contrast, 18 tumors developed at doses between 10 and 30 Gy, and few tumors at higher doses resulting in an average incidence of about one tumor in each dose group of 1 Gy. Therefore, a clear increase in tumor frequency was observed within the low dose volumes.

Latent Time between Radiotherapy and Diagnosis of Second Tumors

Latent time analysis was performed separately for each radiation quality. Patients with second tumors after radiotherapy with low energy X-rays were readmitted after a mean latency of 18.4 ± 1.6 years (n = 32), independently of dose (p = 0.53). Irradiation with γ-rays or a combination of both qualities resulted in shorter latencies of 8.2 ± 1.9 and 6.3 ± 1.3 years, respectively, which were also independent of dose.

Discussion

Radiation treatment has considerably improved during the last few decades. These improvements, in consequence, lead to increased local tumor control and survival rates. Moreover, severe late side effects of radiotherapy which may shorten the survival of the patients, have become rare events. However, with a larger number of patients surviving for longer times after treatment, the incidence but also the pattern of late effects observed after radiotherapy have changed. Moderate changes in organ function may occur after latent times which clearly exceed the usual routine follow-up of 5 years in radiation oncology. Similarly, an increased incidence of second primary tumors is found. For obvious reasons, this was initially observed in young patients with good prognosis, i.e. after treatment for Hodgkin's disease [2, 9, 10, 22] or testicular cancer [19, 20]. In recent years, it has also been reported for other entities of primary tumors [2, 16].

One of the major problems in most analyses of the factors influencing the development of second primary tumors is that in the vast majority of studies chemotherapy had been included in the treatment protocol compromising detailed analysis of the effect of radiotherapy parameters. The latter include the relation of the site of origin of the second tumor to the initial radiotherapy volume or radiation dose at the site of origin.

The present study included second tumors observed in a population of 31,000 patients treated between 1969 and 1989 at the Department of Radiotherapy in Dresden. Of these, about 85% were treated for malignancies. Chemotherapy was rare in these patients, due to entity, histological characteristics of the first tumor, and clinical routine at the time of treatment.

Of 172 patients who had initially been treated for malignant disease, 53 were selected for further analysis. Excluded were patients in which metastases or late recurrences could not be excluded on the basis of widely used criteria [21]. Selection was also based on the comprehensiveness of documentation of the initial treatment, which had to allow for precise dose reconstruction. Moreover, patients could only be included if the site of origin of the secondary tumor could unequivocally be identified in order to facilitate analysis of a correlation to dose and position of the initial treatment volume. Induction of secondary tumors, however, should be independent of the parameters applied in this selection process with regard to dose at the site of origin and relation to the initially irradiated volume. Hence the conclusions of the present study are independent of the patient selection.

The analysis only included patients who were readmitted for radiotherapy, and excluded all those who were admitted to other radiotherapy departments. This, however, was a rare event due to limited migration in Germany. The analyses also excluded those patients admitted to medical oncology departments, e.g. for treatment of secondary leukemia. Therefore, estimates of the risk for second primary tumors cannot be made from the present data set.

A number of analyses after treatment for Hodgkin's disease, recently reviewed by Slanina et al [18], resulted in an incidence between 2.5% at 5 years and 16% at 20 years. The incidence of solid tumors was around 3–4% [8, 9]. After radiotherapy for prostate carcinoma, Neugut et al [14] reported a relative risk for bladder carcinoma of 1.5 at 8 years, but not for rectal tumors or leukemia. This analysis was based on data from the US NCI Surveillance, Epidemiology and End Results Program (SEER). In a more recent analysis of SEER data, Brenner et al [4] reported a relative tumor risk of 6% after radiotherapy relative to surgery, which increased to 34% in patients who survived 10 years or more. In absolute terms, this translated into one secondary tumor in 290 of all patients, and in one second malignancy in 70 of long-term survivors. The most frequent tumors were found in bladder, rectum and lung,

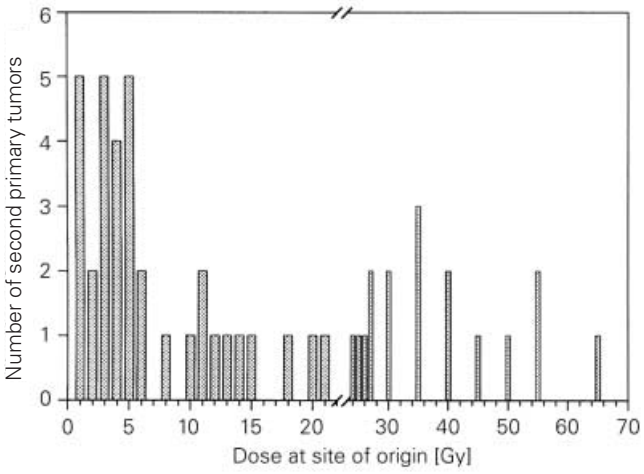

Figure 2. Tumor incidence in relation to dose at the site of origin. Dose groups at the site of origin of second primary tumors were defined in 1-Gy steps at doses < 30 Gy, and in 5-Gy steps at higher doses. At doses > 6 Gy, an average of about one tumor per dose group was observed. In contrast, a significantly higher number of tumors was found at doses < 6 Gy. This was independent of the radiation quality used for the initial treatment.

Abbildung 2. Tumorinzidenz in Abhängigkeit zur Dosis am Entstehungsort. Die Dosisgruppen am Entstehungsort der Sekundärtumoren wurden für Dosen < 30 Gy in 1-Gy-Schritten, für höhere Dosen in 5-Gy-Schritten festgelegt. Bei Dosen > 6 Gy wird im Durchschnitt ein Tumor pro Dosisgruppe gefunden. Im Gegensatz dazu trat bei Dosen < 6 Gy eine deutlich höhere Anzahl an Tumoren auf. Dies ist unabhängig von der verwendeten Strahlenqualität.

and in-field sarcomas. Again, no increase in the risk for leukemia was seen.

The lower frequency of secondary tumors of 0.65% in the present series may be due to absence of chemotherapy, to loss of patients or, most likely, to different treatment fields and doses. Moreover, 15% of the patients had initially been treated for benign disease, but no data are available for the tumor incidence after this treatment. Recently, a risk factor between 0.3% and 0.7% has been calculated for young patients [5], which is lower than for tumor therapy. Radiobiological modeling of the risk for radiation-induction of second primary tumors, however, is compromised by lacking knowledge of radiation sensitivity of patients and cell types within the exposed volume [13].

The majority of second primary tumors was observed in the volume adjacent to the initial treatment field (see Figure 1). With regard to dose, about one tumor was observed per dose group at doses > 6 Gy. In contrast, a significantly higher number of tumors was seen at radiation doses of the first treatment in the range of ≤ 6 Gy, i.e. in the penumbra of the initial radiotherapy volume.

In patients with cervix cancer, Boice et al [3] found the risk for leukemia other than chronic lymphocytic leukemia increased by a factor of 2. In this study, the maximum relative risk was found at a dose to the active bone marrow of about 4 Gy, in good accordance with the results from the present study. The latter are also supported by the higher incidence of second primary tumors in organs in proximity to the treatment volume in cervix cancer [4, 14].

There is no true data basis to separate between spontaneously arising secondary tumors, secondary tumors based on common etiological factors or proper treatment-induced tumors. The average tumor incidence over all regions can be considered the average rate of tumor development independent of prior radiation treatment. However, the increased incidence in the region of the initial radiation field argues for radiation at least as a component of tumorigenesis, which may or may not be accompanied by genetic susceptibility [16] or other factors of the patient. The latter has been suggested by studies of secondary tumors after radiotherapy for hereditary vs non-hereditary retinoblastoma [11]. In patients with brain tumors, an increased risk for CNS and non-CNS tumors was described [15] with a standardized incidence ratio (SIR) of 1.2. This was moderately increased after surgery (SIR 2.0) and substantially increased after radiotherapy (SIR 5.1). However, there is no convincing evidence, apart from some rare syndromes, that genomic instability contribute to tumor induction by radiotherapy, as reviewed by Hendry [8].

In the present study, the latent time to clinical manifestation of second primary tumors was 18 years for low energy X-rays and 6 years for γ-rays. The latent time for low voltage X-rays is in the range reported from other studies [6, 22]. It has to be noted that X-rays were used predominantly before 1985, while γ-irradiation was applied preferentially during the later period. Therefore, more second primary tumors might be expected in further follow-up investigations. If the latent times after both types of radiation are similar, the overall rate after a mean follow-up period of 20 years may well increase to 1–2%.

It has to be taken into consideration for modern multifield radiotherapy plans that the low-dose volume is significantly larger than with simple opposing-field techniques. For example, with a two-field technique, a dose per fraction within the planning target volume (PTV) of 2 Gy corresponds to a dose of > 1 Gy in the beam channel. In contrast, the same PTV dose given in a five-field technique results in only ~0.2 Gy within each beam channel. However, low voltage X-ray or telecobalt beams are associated with a substantially smaller fall-off in dose, and hence a larger low-dose volume at the beam margins than a linear accelerator beam.

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