Acute Toxicity of Adjuvant Radiotherapy in Locally Advanced Differentiated Thyroid Carcinoma

First Results of the Multicenter Study Differentiated Thyroid Carcinoma (MSDS)

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Background and Purpose: The indication for adjuvant postoperative radiotherapy in patients with differentiated thyroid carcinoma (DTC) extending beyond the thyroid capsule has been an issue of controversy during the past 2 decades. No randomized studies evaluating the benefit of radiotherapy have been published so far. In the Multicenter Study Differentiated Thyroid Carcinoma (MSDS), a randomization has been performed concerning external-beam radiotherapy in patients with DTC extending beyond the thyroid capsule (pT4 pN0/1/× cM0, TNM classification, 5th edition, 1997) following surgery and radioiodine therapy. Radiation-associated toxicity has been prospectively evaluated.

Patients and Methods: Radiotherapy was performed with 50.4 Gy (pN0) or 54.0 Gy (pN1/x) to the cervical, supraclavicular and upper mediastinal lymph nodes. A total dose of 59.4 Gy (R0 resection) or 66.6 Gy (R1) was used to treat the tumor bed. Conventional fractionation was used with 1.8 Gy/d. At the time of the analysis, 36 patients were randomized or allocated to treatment arm A (with external-beam radiotherapy). Of these, 22 were treated with radiotherapy, and documentation of acute toxicity was available. Toxicity was evaluated prospectively according to the RTOG/EORTC criteria.

Results: The maximal acute toxicity observed during radiotherapy was grade I in four patients, grade II in 16 patients, and grade III in two patients (9.1%; 95% confidence interval [95% CI] 1.1–29.2%). Toxicity was mainly observed at the pharynx, larynx, and skin. In 19 patients, residual toxicity within 100 days following radiotherapy was evaluated. No residual toxicity was observed in two patients. Maximal residual toxicity was grade I in 13 patients and grade II in four. No further grade III toxicity could be observed.

Conclusion: The majority of patients experience mild to moderate side effects from adjuvant external-beam radiotherapy. At the first follow-up examination, most side effects have subsided. Acute toxicity is tolerable in these patients.

Key Words: Differentiated thyroid carcinoma · Radiotherapy · Toxicity

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Akute Nebenwirkungen der adjuvanten Strahlentherapie beim lokal fortgeschrittenen differenzierten Schilddrüsenkarzinom. Erste Ergebnisse der Multizentrischen Studie Differenziertes Schilddrüsenkarzinom (MSDS)

Hintergrund und Ziel: Die Indikation zur postoperativen Radiotherapie bei Patienten mit differenziertem Schilddrüsenkarzinom (DTC) mit organkapselüberschreitendem Wachstum wurde in den letzten 20 Jahren kontrovers diskutiert. Bislang wurde keine prospektiv-randomisierte Studie zu dieser Fragestellung publiziert. In der Multizentrischen Studie Differenziertes Schilddrüsenkarzinom (MSDS) wurde eine Randomisierung der Radiotherapie bei Patienten mit lokalisiertem organkapselüberschreitendem DTC (pT4 pN0/1/× cM0, TNM-Klassifikation, 5. Auflage, 1997) nach abgeschlossener chirurgischer Therapie und ablativer Radiojodtherapie durchgeführt. Die Toxizität wurde prospektiv evaluiert.

Patienten und Methodik: Die Radiotherapie im Bereich der zervikalen, supraklavikulären und oberen mediastinalen Lymphabflussgebiete wurde mit 50,4 Gy (pN0) oder 54,0 Gy (pN1/x) durchgeführt. Das Tumorbett wurde mit 59,4 Gy (R0-Resektion) bzw. 66,6 Gy (R1) bestrahlt. Die Fraktionierung betrug 1,8 Gy/d. Zum Zeitpunkt der Analyse waren 36 Patienten in den Bestrahlungsarm der Studie randomisiert oder diesem zugewiesen. 22 dieser Patienten wurden bislang bestrahlt und bezüglich der Akutnebenwirkungen prospektiv nach den RTOG/EORTC-Kriterien evaluiert.

Ergebnisse: Während der Radiotherapie wurde bei vier Patienten maximal eine Nebenwirkung vom Schweregrad I beobachtet, 16 Patienten entwickelten maximale akute Nebenwirkungen Grad II und zwei Patienten Grad III (9.1%; 95%-Konfidenzinterval [KI] 1.1–29,2%) als. Die Nebenwirkungen traten hauptsächlich im Bereich des Pharynx, des Larynx und der Haut auf. Bei 19 Patien-

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ten wurden die Nebenwirkungen bei einer Folgeuntersuchung innerhalb von 100 Tagen nach Abschluss der Radiotherapie erneut evaluiert. Zwei Patienten zeigten dabei keine Nebenwirkungen mehr (Grad 0), 13 Patienten wiesen noch Grad-I- und vier Patienten Grad-II-Nebenwirkungen auf. Grad-III-Nebenwirkungen wurden nicht mehr beobachtet.

Schlussfolgerung: Die Mehrzahl der Patienten entwickelt unter der Strahlenbehandlung geringe bis mittelgradige Nebenwirkungen, die sich bei der ersten Nachsorgeuntersuchung bereits weitgehend zurückgebildet haben. Die Akutnebenwirkungen in diesem Patientenkollektiv sind somit gut vertretbar.

Schlüsselwörter: Differenziertes Schilddrüsenkarzinom · Radiotherapie · Toxizität

Introduction

Differentiated thyroid carcinoma (DTC) is a rare tumor with an incidence of 3/100,000 inhabitants in Germany [3]. It accounts for 1% of all cancers. There are two main histologic subtypes: papillary and follicular DTC. The standard treatment for locally advanced DTC is surgical resection, radioiodine therapy, and suppression of thyroid-stimulating hormone (TSH) [10, 15]. In some retrospective analyses, additional adjuvant radiotherapy was associated with improved local control or survival in these patients [7, 12, 27]. There has been no randomized trial so far that tested the use of radiotherapy in DTC. In 1999, the Multicenter Study Differentiated Thyroid Carcinoma (MSDS) was initiated. Patients with localized DTC extending beyond the thyroid capsule with or without lymph node metastases (pT4 tumors according to the UICC classification, 5th edition, 1997) were treated with surgery and radioiodine therapy. Patients were randomized to arm A with additional radiotherapy and to arm B with no further irradiation. Allocation to one treatment arm was performed when the center did not randomize patients or when the patient did not want to be randomized. As in other tumor entities, one of the major concerns of using adjuvant radiotherapy is increased toxicity [13, 19, 22]. We report on acute radiation-associated toxicity during radiotherapy and toxicity at the first control following radiotherapy in these patients. To our knowledge, this is the first report on a prospective evaluation of acute radiogenic side effects in the adjuvant treatment of DTC.

Patients and Methods

Study Design

The study design is shown in Figure 1. Patients with stage pT4 pN0/1/x M0 DTC (according to the UICC classification, 5th edition, 1997) with completion of surgical therapy with R0/R1 resection were enrolled at the time of initial radioiodine therapy for ablation of the thyroid remnant, 4 weeks after surgery. Patients had to be 18–69 years old and had to have a Karnofsky index ≥ 70% at the time of surgery. Patients with recurrent disease of DTC, secondary carcinoma (except basalioma), pregnancy, and serious medical disease were excluded from the trial. All patients had to give informed consent. The trial was approved by the institutional review boards of the contributing centers.

Iodine-131 (^{131}I) therapy for ablation of the thyroid remnant was conducted according to the guidelines of the "Deutsche Krebsgesellschaft" (German Cancer Society) [10].

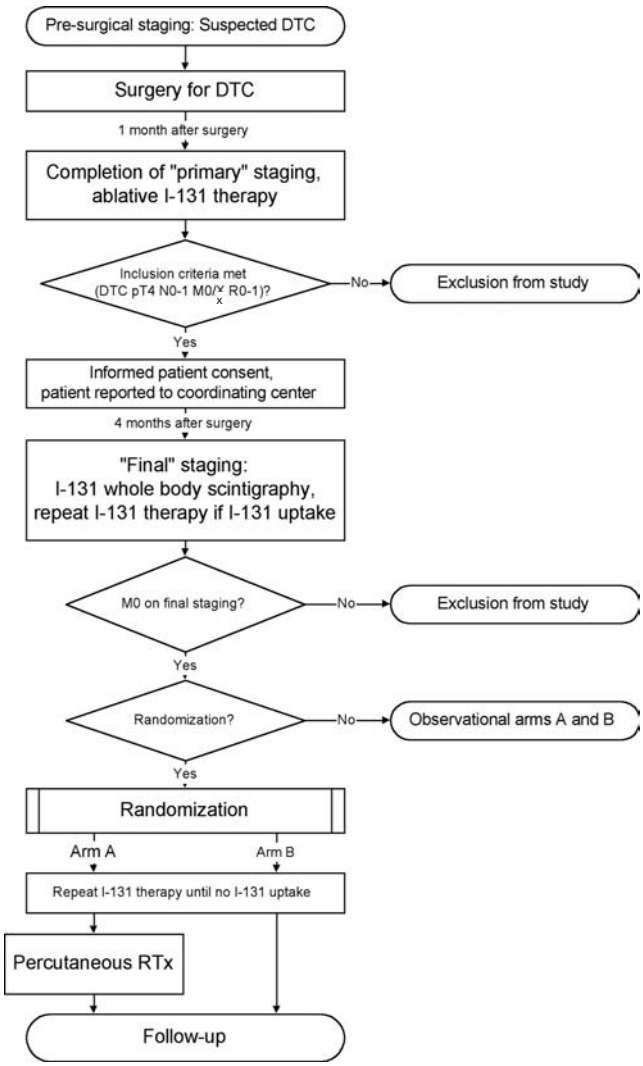

Figure 1. Flow sheet of the trial. DTC: differentiated thyroid carcinoma; RTx: radiotherapy.

Abbildung 1. Design der Multizentrischen Studie Differenziertes Schilddrüsenkarzinom (MSDS). DTC: differenziertes Schilddrüsenkarzinom; RTx: Radiotherapie.

Following completion of surgery, L-thyroxine was withdrawn for 4 weeks to ensure adequate endogenous TSH stimulation. To assess the size of the thyroid remnant, the 24-h ^{131}I uptake was determined after oral application of a test capsule (≤ 100 MBq). Thyroid ablation was then performed with 3–4 GBq ^{131}I if the uptake was < 10% or with 1–2 GBq ^{131}I if the uptake was between 10–20%. If the uptake was > 20%, reoperation was to be considered before ablative radiotherapy. A posttherapeutic whole body scan was obligatory.

Patients were restaged 3 months after initial ablative radioiodine therapy. This included determination of human thyroglobulin (hTG) after endogenous TSH stimulation following 4 weeks withdrawal of L-thyroxine and the following imaging modalities: ^{131}I whole body scan, ultrasound imaging of the neck and abdomen, chest X-ray in two planes, and one thoracic CT scan without contrast agents any time between the time of surgery and the restaging. Patients who were free of distant metastases at the time of "final" staging were eligible for randomization.

Randomization was stratified according to histologic type (papillary vs. follicular), nodal status (pN0 vs. pN1/x), and participating center. In arm A, external-beam radiotherapy was part of the treatment, whereas in arm B, it was omitted. Nonrandomized patients were allocated to therapy arms A and B by the participating centers.

Radiotherapy

Patients randomized or allocated to therapy arm A (external-beam radiotherapy) received external-beam radiotherapy in addition to surgery, ablative radioiodine therapy, and TSH-suppressive L-thyroxine therapy (TSH < 0.1 μU/ml). In accordance with the current guidelines of the German Society of Radiation Oncology (DEGRO) [24], external-beam radiotherapy was initiated after completion of ablative radioiodine therapy with complete elimination of cervical ^{131}I uptake. The following clinical target volumes were defined:

- first order: thyroid (tumor) region. In case of clearly unilateral involvement according to the surgeon's and the pathologist's report, the first-order target volume was limited to the affected side. In case of bilateral or uncertain involvements, the first-order target volume included the entire thyroid bed.
- second order: thyroid bed, cervical lymph node regions including the central cervical compartment, the parajugular and submandibular lymph nodes, infra- and supraclavicular lymph nodes, and upper mediastinum. Field margins were the mandible and mastoid process (cranial), tracheal bifurcation (caudal), and posterior cervical lymph nodes (posterior).

The radiation doses are shown in Table 1. Three-dimensional (3-D) or quasi-3-D planning according to ICRU 50 (International Commission of Radiation Units and Measurements) was mandatory. The patient was usually treated with retroflex neck in order to spare the parotid gland [8]. To ensure uniform standards of radiation therapy, treatment planning was verified by the reference radiotherapist prior to radiotherapy.

Table 1. Radiation doses in the Multicenter Study Differentiated Thyroid Carcinoma (MSDS). Patients were classified as pNx when less than two lymph nodes were found in the surgical specimen and when those were without tumor.

Tabelle 1. Bestrahlungsdosen in der Multizentrischen Studie Differenziertes Schilddrüsenkarzinom (MSDS). Die Patienten wurden als pNx klassifiziert, wenn weniger als zwei Lymphknoten im Resektionspräparat gefunden wurden und diese nicht befallen waren.

Tumor stage	First-order target volume (Gy)	Second-order target volume (Gy)
pT4 pN0 M0 R0	59.4/1.8	50.4/1.8
pT4 pN1/x M0 R0	59.4/1.8	54.0/1.8
pT4 pN0 M0 R1	66.6/1.8	50.4/1.8
pT4 pN1/x M0 R1	66.6/1.8	54.0/1.8

Toxicity

Radiation-associated toxicity has been evaluated prospectively according to the RTOG/EORTC criteria [23] for bone marrow, skin, mucosa, salivary glands, pharynx and esophagus, larynx, lung, upper gastrointestinal tract, and spinal cord. These are shown in Table 2. The evaluation of toxicity is performed by the treating radiation oncologist at the end of external-beam radiotherapy and at the first follow-up visit of the patient which is scheduled 2 months after the end of radiotherapy. The documented toxicity during radiotherapy refers to the observed maximal grade of toxicity for any organ at risk. Further annual toxicity-orientated follow-up examinations by the radiation oncologist are scheduled at 1-year intervals. Furthermore, a toxicity evaluation is performed at each follow-up visit at the Department of Nuclear Medicine.

Toxicity data are collected from the participating centers on case report forms (CRF), which are held available as files in the portable document format (PDF) on the study's webserver. Data reported on the CRF are entered into the GCP-compliant central study database under Oracle 8i/SuSe Linux [5]. After each entry of documentation, a status fax that includes all entered radiotherapeutic and toxicity data is automatically generated and faxed to the participating center for verification. In two patients, toxicity at the first follow-up examination was reported in medical documents only. These data were coded by the reference radiotherapist and entered into the study database.

Based on a maximum rate of 5% serious acute and of 5% serious chronic toxicity and a 10% chance of type 1 and type 2 error, a step function was calculated in advance for the maximum number of serious adverse events (SAE) at a given number of completed radiotherapies, and incorporated into the

Table 2. Definitions for acute toxicity according to RTOG/EORTC.

Tabelle 2. Definition der akuten Nebenwirkungen nach RTOG/EORTC.

	0	I	II	III	IV
Skin	No change	Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating	Tender or bright erythema; patchy moist desquamation; moderate edema	Confluent, moist desquamation other than skin folds; pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	No change	Injection, may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinous discharge; may experience moderate pain requiring analgesic	Confluent fibrous mucositis may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis
Salivary gland	No change	Mild mouth dryness; slightly thickened saliva; may have slightly altered taste such as metallic taste; these changes are not reflected in base-line feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness; thick, sticky saliva; markedly altered taste	(Complete dryness; no taste)	Acute salivary gland necrosis
Pharynx and esophagus	No change	Mild dysphagia or odynophagia; may require topical anesthetic or nonnarcotic analgesics; may require soft diet	Moderate dysphagia or odynophagia; may require narcotic analgesics; may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss (> 15% from pretreatment base line) requiring NG tube, i.v. fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	No change	Mild or intermittent hoarseness; cough not requiring antitussive; erythema of mucosa	Persistent hoarseness but able to vocalize; referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic; cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic; confluent fibrinous exudate; marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
Lung	No change	Mild symptoms or dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents; dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agents or dyspnea at rest; clinical or radiologic evidence of acute pneumonitis; intermittent oxygen or steroids may be required	Severe respiratory insufficiency; continuous oxygen or assisted ventilation
Spinal cord	No change	Mild Lhermitte's sign	Severe Lhermitte's sign	Paresthesia, paresis	Mono-, para-, quadriplegia
Bone marrow	Normal	Leucos (n/µl): < 4,000–3,000	< 3,000–2,000	< 2,000–1,000	< 1,000
		Thrombos (n/µl): < 100,000–75,000	< 75,000–50,000	< 50,000–25,000	< 25,000
		Hb (g/dl): < 11–10	< 10–8	< 8–6.5	< 6.5

study protocol. If the precalculated limits are met, the feasibility of the study design must be discussed with the independent Safety Monitoring Committee. For the first 23 patients, the calculated critical number of patients experiencing serious acute or chronic toxicity is three cases. 95% confidence intervals (CI) for toxicity rates were calculated using standard SAS software.

Patients

From January 1999 to December 2002, 289 patients were included in the trial. There were 43 patients in the randomization arm and 246 patients who were allocated to a treatment arm. 36 patients were in arm A (radiotherapy). In six of these patients, radiotherapy was not performed because of withdrawal of consent to radiotherapy, wrong allocation, or due to persistent disease after radioiodine therapy. Eight patients just received or were to receive radiotherapy at the time of the analysis. In the remaining 22 patients, acute toxicity during radiotherapy was evaluated, and in 19 of these patients, at least one follow-up examination after the completion of radiotherapy was performed. According to the protocol, this first follow-up examination was scheduled 2 months after radiothera-

py was completed. It was performed within 100 days following radiotherapy in all 19 evaluable patients. The date of the analysis is December 15, 2002.

The second-order target volume was treated with 45 Gy in one patient, 50 Gy in twelve, 54 Gy in six, and 60 Gy in two patients. One patient discontinued radiotherapy after 30 Gy and received treatment for a depressive psychosis. The patient felt that she had difficulties in swallowing, and she was offered a percutaneous enterogastrostomy. Yet, only very moderate objective side effects were evident. After contacting the local radiotherapy department, the Safety Monitoring Committee decided that this patient did not experience grade III side effects.

The irradiation of the second-order target volume included the cervical, supraclavicular and upper mediastinal lymph nodes in all evaluable patients.

The first-order target volume was irradiated with 30 Gy in the aforementioned patient. One further patient received 54 Gy. 60 Gy were given in 14 patients and 66 Gy in six.

Results

Acute side effects were absent (grade 0) or observed at grade I levels in the skin in ten of 22 patients (45.5%), at the mucosa in eleven of 21 patients (52.4%), at the salivary glands in 14 of 21 patients (66.7%), at the pharynx in nine of 22 patients (40.9%), and at the larynx in eleven of 21 patients (52.4%). Grade III toxicity at the mucosa was observed in one patient and at the larynx and pharynx in two patients.

At the first follow-up examination within 100 days after radiotherapy, there were no grade III toxicities. Grade II side effects at the skin were not observed, but were seen at the mucosa in two of 19 patients (10.5%), at the salivary glands in two of 19 patients (10.5%), at the pharynx in one of 19 patients (5.3%), and at the larynx in two of 18 patients (11.1%). Maximal acute toxicity for skin, mucosa, salivary glands, pharynx, and larynx during radiotherapy and toxicity at the first follow-up visit after radiotherapy within 100 days after completion of treatment are shown in Figures 2a to 2e.

There was no bone marrow, lung, and spinal cord toxicity > grade I.

In four patients, grade I was the maximal acute toxicity observed (18.2%; 95% CI 5.2–40.3%); 16 patients experienced grade II acute toxicity (72.7%; 95% CI 49.8–89.3%) and two patients grade III reactions (9.1%; 95% CI 1.1–29.2%).

In the two patients who experienced grade III toxicities, a follow-up evaluation within 100 days after radiotherapy was performed and, at the time of this examination, no or only grade I toxicities were evident. In 19 patients, residual toxicity at the first follow-up examination within 100 days following radiotherapy was evaluated. No residual toxicity was observed in two patients (10.5%; 95% CI 1.3–33.1%). Maximal toxicity was grade I in 13 patients (68.4%; 95% CI 43.5–87.4%) and grade II in four (21.1%; 95% CI 6.1–45.6%). No grade III toxicity could be observed.

Treatment was stopped in one patient (see above). In two patients, radiotherapy was delayed for 3 and 9 days because of acute side effects. In all other patients, there was no toxicity-related delay during radiotherapy.

The critical value of grade III and IV acute and chronic side effects as defined in the trial was not observed in the radiation arm.

The median Karnofsky index during radiotherapy was 90% (range 50–100%). The median Karnofsky index at the first follow-up examination was also 90% (range 50–100%).

Discussion

In patients with localized DTC extending beyond the organ capsule, radiotherapy may have a potential benefit. These tumors were classified as pT4 in the 5th edition of the UICC classification from 1997. In 2003, a new classification was introduced by the UICC: tumors with minimal penetration in the surrounding soft tissues are now classified as pT3, tumors which show an infiltration of adjacent organs or structures are classified as pT4. For DTC extending beyond the thyroid capsule, a positive influence on local control and survival has been shown in several retrospective analyses [7, 12, 27]. The DEGRO recommends radiotherapy for patients who present with pT4 tumors according to the UICC classification (5th edition, 1997) and considers radiotherapy a treatment option in patients with pT3 tumors and extensive lymph node involvement. On the other hand, excellent treatment results could be achieved in these situations without additional radiotherapy [11, 14–16, 21]. Whether radiotherapy was applied or not, has, so far, depended on each center's policy in Germany and Austria [20]. In the MSDS trial, a randomization was performed in order to evaluate the role of radiotherapy in patients with tumors extending beyond the organ capsule. The timing of radiotherapy, the doses, and the target volume were defined according to the guidelines of the DEGRO [24]. Depending on nodal involvement, the cervical and upper mediastinal lymph node sites were irradiated with 50.4 or 54.0 Gy, and the primary tumor site was irradiated with 59.4 or 66.6 Gy depending on the resection margins. One of the main arguments against the use of radiotherapy is the associated additional toxicity.

In the published series about postoperative radiotherapy in DTC, there has been no systematic evaluation of radiation-associated toxicity so far. Therefore, as in head and neck tumors, toxicity may have been underreported in the retrospective analyses [4].

Simpson et al. reported on 10% erythema, lymphedema and pharyngitis in 144 patients irradiated for advanced DTC. One patient developed necrosis of an infected tracheostoma [25].

Tsang et al. reported acute tracheitis and esophagitis requiring hospitalization in 13 of 185 patients (7%). 3% of the

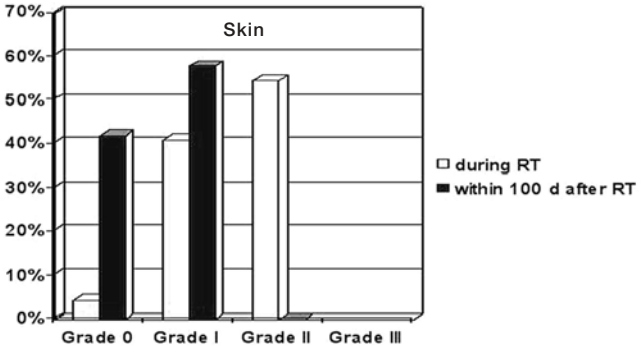

Figure 2a – Abbildung 2a

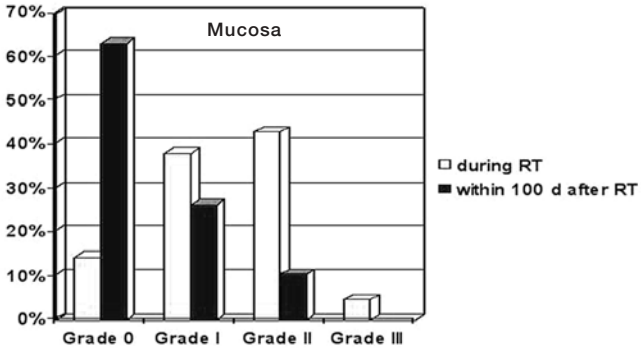

Figure 2b – Abbildung 2b

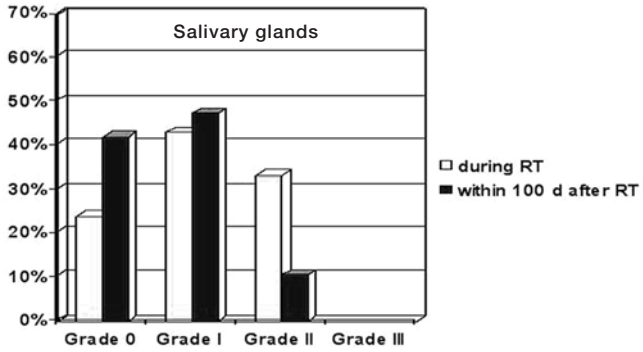

Figure 2c – Abbildung 2c

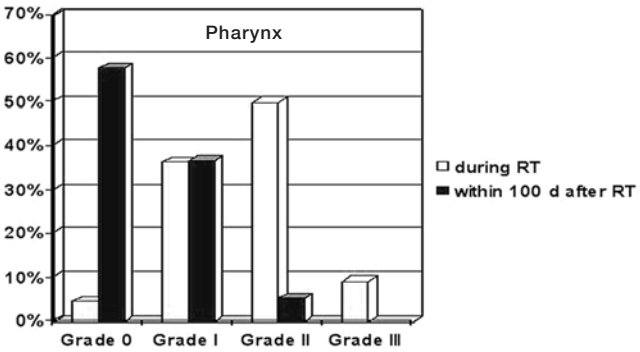

Figure 2d – Abbildung 2d

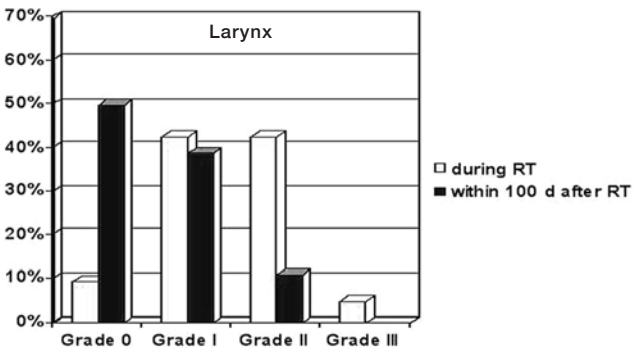

Figure 2e – Abbildung 2e

Figures 2a to 2e. Toxicity at the skin (a), mucosa (b), salivary glands (c), pharynx (d), and larynx (e) during and within 100 days after radiotherapy (RT).

Abbildungen 2a bis 2e. Nebenwirkungen an der Haut (a), der Schleimhaut (b), den Speicheldrüsen (c), am Pharynx (d) und am Larynx (e) während und innerhalb von 100 Tagen nach Abschluss der Radiotherapie (RT).

patients developed subcutaneous fibrosis, and one patient developed spinal cord necrosis after repeated irradiation to the spinal cord [27]. In both trials, most patients received irradiation to the thyroid bed only. The radiation doses ranged between 35 and 65 Gy.

Farahati et al. reported on erythema, lymphedema and pharyngitis in 33% of 99 irradiated patients. No chronic toxicity was observed [7]. The radiation field included the cervical and upper mediastinal lymph nodes. 50–60 Gy were given in this series. Treatment was performed with megavoltage photon beams.

Phlips et al. observed one case of grade III dysphagia requiring treatment interruption in 38 patients receiving radiotherapy for DTC. There was one case of severe skin fibrosis. The radiation fields included the cervical and upper mediastinal lymph nodes, and 55 Gy were given [18].

In the MSDS trial, the compliance with randomization has been limited. At the time of the analysis, 43 of 289 patients were in the randomization arm. Furthermore, only a few patients were allocated to the radiotherapy arm. 36 patients have been randomized or allocated to arm A (with external-beam radiotherapy). In 22 patients, radiotherapy has been completed, and data of acute toxicity is evaluable. The maximal toxicity observed during the course of radiotherapy, toxicity within 2 months after radiotherapy, and toxicity at the annual follow-up at the treating radiation oncologist have been recorded.

Furthermore, toxicity has been documented at each follow-up visit at the Department of Nuclear Medicine. The RTOG/EORTC score was chosen because it evaluates radiation-associated acute and chronic side effects and is easier to handle in a multicenter study than the LENT-SOMA score. The maximal toxicity observed during radiotherapy was grade II in 16 of 22 patients and grade III in two patients. In 19 patients, toxicity at the first follow-up within 100 days following radiotherapy is available. Of these, no residual toxicity was observed in two patients. Maximal toxicity was grade I in 13 patients and grade II in four. No further grade III toxicity could be observed.

There was no bone marrow, lung, and spinal cord toxicity > grade I. Organ-specific toxicity during radiotherapy and at the first follow-up visit after radiotherapy for other organs at risk is shown in Figures 2a to 2e. There was marked acute toxicity in a number of patients with radiotherapy, especially at the skin, the pharynx, and the larynx. Soon after the end of treatment, these side effects had decreased or were no more observed. So far, there is no sufficient follow-up data available to evaluate chronic radiation side effects. The salivary function also changed during the observed period of time: even though the number of patients with grade II toxicity is reduced at the follow-up visit, > 50% of the patients experience some sort of salivary impairment. Radioiodine therapy has a negative effect on salivary function [1]. The only salivary glands involved in the radiation field are the submandibular glands. The MSDS trial will show how much radiotherapy contributes to chronic salivary dysfunction.

In head and neck cancers, the acute and chronic toxicities of conventional radiotherapy have been defined in the past. Using the RTOG score, the rates of acute grade III and IV toxicities have been generally < 25% in RTOG studies. However, some groups have reported up to 50% acute grade III toxicities using RTOG or similar descriptive criteria [6, 9, 17, 26]. Although radiation doses are similar, radiation fields differ considerably between patients with head and neck cancers and patients with DTC. In particular, marked toxicity of the mucosa of the mouth and impairment of salivary function are frequent in patients with oropharyngeal tumors [2]. This may account for the fact that the observed toxicities in the present study of radiotherapy in DTC are somewhat lower than the experiences from head and neck series.

Conclusion

In summary, the main acute toxicity in the patients of this study who received postoperative radiotherapy for locally advanced DTC was pharyngitis, esophagitis, laryngitis, and skin reactions. These reactions quickly improved after radiotherapy had been completed. Salivary function is mildly or moderately impaired in most patients. Radioiodine therapy and radiotherapy may contribute to this effect. Postoperative radiotherapy is a feasible treatment for patients with locally advanced DTC. A longer follow-up is necessary to prospectively evaluate the late effects of the treatment.

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