Multicenter Study Differentiated Thyroid Carcinoma (MSDS)

Diminished acceptance of adjuvant external beam radiotherapy

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Multizentrische Studie Differenziertes Schilddrüsenkarzinom (MSDS): verminderte Akzeptanz der adjuvanten perkutanen Strahlentherapie

Keywords
Thyroid carcinoma, radiotherapy, randomized trial, radioiodine, thyroidectomy

Summary
Aim: The Multicenter Study Differentiated Thyroid Carcinoma (MSDS) is an ongoing study in Germany, Austria, and Switzerland on the clinical benefit of adjuvant external beam radiotherapy (RTx) for locally invasive differentiated thyroid carcinoma (DTC) in TNM stages pT4 pN0/1/x M0/x (5th ed. 1997). **Methods:** MSDS was designed as a prospective randomized trial. Patients receive thyroidectomy, radioiodine therapy (RIT) to ablate the thyroid remnant, and TSH-suppressive L-thyroxine therapy with or without RTx after documented elimination of cervical iodine-131 uptake (http://msds-studie.uni-muenster.de). **Results:** 311 patients were enrolled between January 2000 and March 2003. 279 patients met the trial's inclusion criteria. 45 consented to randomization, of whom 17 were randomized into treatment arm A (RTx) and 18 into arm B (no RTx). Advised by the trial's independent Data Monitoring and Safety Committee, the MSDS steering committee decided to terminate randomization in April 2003 and continue MSDS as a prospective cohort study. 23 of the 234 patients in the observation arm of the trial were prescribed RTx by their physicians. Thus, 14% of the trial cohort were randomized or assigned to receive RTx (intention-to-treat analysis). In contrast, at least 44% of all patients with pT4 papillary DTC in Germany in the nationwide PCES study underwent RTx in 1996 ($p < 0.001$, χ^2-test). **Conclusions:** Acceptance of external beam RTx as a treatment modality for DTC has receded to a degree that accrual of a sufficient number of patients for a randomized trial has been impossible. Observation of the trial cohort is continued in order to assess clinical event rates with and without RTx and chronic RTx toxicity.

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Schlüsselwörter
Schilddrüsenkarzinom, Strahlentherapie, randomisierte Studie, Radioiod, Thyreoidektomie

Zusammenfassung
Ziel: Die Multizentrische Studie Differenziertes Schilddrüsenkarzinom (MSDS) ist eine laufende Studie in Deutschland, Österreich und der Schweiz zum klinischen Nutzen der adjuvanten perkutanen Strahlentherapie (RTx) bei lokal invasivem differenziertem Schilddrüsenkarzinom (DTC) in den TNM-Stadien pT4 pN0/1/x M0/x (5. Aufl.1997). **Methoden:** MSDS war als randomisierte Studie geplant. Die Therapie umfasst Thyreoidektomie, ablative Radioiodtherapie (RIT) und TSH-Suppressionstherapie mit oder ohne RTx nach dokumentierter Elimination des zervikalen Iod-131-Uptakes (http://msds-studie.uni-muenster.de). **Ergebnisse:** 311 Patienten wurden zwischen Januar 2002 und März 2003 gemeldet. 279 Patienten erfüllten die Einschlusskriterien. 45 stimmten der Randomisierung zu. 17 wurden in den Arm A (RTx) und 18 in Arm B (keine RTx) randomisiert. In Abstimmung mit dem unabhängigen Data Monitoring and Safety Committee beschloss das MSDS-Protokollkomitee im April 2003, die Randomisierung zu beenden. Von 234 Patienten im Beobachtungsarm wurden 23 dem RTx-Arm zugewiesen. Somit wurden 14% der MSDS-Kohorte per Randomisierung oder Zuweisung der RTx zugeteilt. Hingegen erhielten 1996 44% aller Patienten mit papillärem DTC pT4 in Deutschland RTx (PCES-Studie; $p < 0.001$, χ^2-Test). **Schlussfolgerung:** Die Akzeptanz der RTx zur Behandlung des DTC ist so weit zurückgegangen, dass die Rekrutierung einer ausreichenden Zahl von Patienten für eine randomisierte Studie nicht möglich ist. Die Beobachtung der MSDS-Kohorte wird fortgesetzt, um die Rezidivraten mit und ohne RTx und die chronische Toxizität nach RTx zu erfassen.

The Multicenter Study Differentiated Thyroid Carcinoma (MSDS) is an ongoing prospective study on the clinical benefit of adjuvant external beam radiotherapy (RTx) (23) for locally invasive differentiated thyroid carcinoma (DTC) without distant metastases, representing TNM stages pT4 pN0/1/x M0/x (35) until December 31, 2002 and pT3/4 pN0/1/x M0/x (34) from January 1, 2003. Since January 2000, 44 centers in Germany, Austria, and Switzerland enrolled a total of 339 patients, representing about half of the incident eligible patient population in Germany in the years of 2001 and 2002 (14). However, due to limited acceptance of RTx, randomization in the trial had to be stopped in April 2003. Even though MSDS continues as a prospective cohort study it is time to examine pertinent findings of the trial.

Methods

Study protocol

MSDS was designed as a comprehensive cohort trial with randomization and observation arms (25). The protocol was approved by the ethics review board at Münster University on June 16, 1997. Patients are enrolled at the time of the first ablative radioiodine therapy (RIT). Inclusion criteria were papillary or follicular

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DTC pT4 pN0/1/x M0/x (35), age between ≥18 and <70 years at the time of initial surgery, completion of primary surgical therapy with R0 (no tumour residues) or R1 (microscopic residues) resection, Karnofsky index ≥70%, freedom from distant metastases at the time of initial radioiodine therapy (RIT), and informed patient consent. Criteria for exclusion were secondary malignancy except basalioma, pregnancy, serious general disease, serious psychiatric disorder, inability to give informed consent, previous RTx and recurrence of previous DTC (21). From 2003, the first inclusion criterion was changed into DTC pT3/4 pN0/1/x M0/x (34) to reflect the 2002 revision of the TNM staging system.

The treatment protocol is in accordance with current guidelines (7-9, 29) and includes total thyroidectomy (TT) with central lymphadenectomy (LNA), RIT to ablate the thyroid remnant, and TSH suppressive therapy with L-thyroxine (TSH <0.1 mU/l) (15). RIT is administered under endogenous TSH stimulation after 4 weeks' cessation of L-thyroxine using standard activities of 1-4 and 1-2 GBq iodine-131 in patients with a 24 h iodine-131 uptake below 10% and 10-20%, resp., or individual dosimetry aiming for ≥300 Gy in the thyroid remnant (9). If scintigraphic iodine-131 uptake by the thyroid remnant persists at whole body scintigraphy (WBS; ≥200 MBq; ≥48 h) 3 months after RIT (8), a second fraction of RIT is given with 4-10 GBq.

Randomization

Patients who consented to randomization at centers actively taking part in randomization were randomized to treatment arms A (additional adjuvant RTx) and B (no RTx) 3 months after initial RIT (Fig. 1) after confirmation of the histological diagnosis by the reference pathologist and when distant metastases had been excluded by means of serum thyroglobulin (Tg), WBS (s. a.) and a native thoracic computed tomogram (TCT). Randomization was stratified according to histological type (papillary v. follicular), nodal status (pN0/1/x), and participating center, and performed by an operator-independent randomization routine embedded in the database (4). The remaining patients were assigned to arms A and B by the participating centers (25).

Radiotherapy

RTx is begun after documented elimination of cervical iodine-131 uptake in a iodine-131 WBS 3 months after the last fraction of ablative RIT (29). RTx includes the thyroid bed (in unilateral tumours only the affected side) with a dose of 59.4 Gy and 66.6 Gy after R0 and R1 resection, resp., and the regional lymph nodes of the neck and upper mediastinum including the posterior cervical chain from the mandible and mastoid process to the tracheal bifurcation with a dose of 50.4 Gy and 54.0 Gy in pN0 and pN1/x disease, resp. Fractionation is conventional (1.8 Gy/d, 5 days a week). 3-D or quasi 3-D planning according to IRCU 50 is mandatory (27).

Follow-up

Patient follow-up includes, as a minimum, outpatient appointments with cervical ultrasound and measurement of serum TSH, hTG (10, 12), anti-Tg antibodies (10) and a blood count 2 and 8 months after each RIT or WBS, and a WBS (≥200 MBq, ≥48 h) under endogenous TSH stimulation 3 and 12 months after ablative RIT (8, 16, 19) and then at 24-month intervals. FDG-PET (5) and other imaging modalities can be performed if needed. At each follow-up appointment, RTx toxicity is recorded according to RTOG (Radiation Therapy Oncology Group) criteria (28) and

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MSDS study participants (nuclear medicine; number of patients recruited until 15 Sept 2003 in parentheses): O. Schober, Christiane Franzius, M. Weckesser, Münster (41); H. Schicha, M. Dietlein, C. Kobe, Köln (39); H. Bihl, U. Dörr, Stuttgart (28); H. Lerch, H. Schlemmer, Wuppertal (24); Traute Mende, Jana Grimm, Halle (22); C. Kirsch, C. Alexander, U. Nestle, Homburg/Saar (16); C. Reiners, S. Ladner, Würzburg (14); R. Bauer, Semira Sepehr-Rezai, Nicole Bena-Boupda, Dagmar Steiner, Gießen (10); E. Moser, T. Zajic, Freiburg (9); A. Bockisch, Sandra Rosenbaum, R. Görges, Essen (8); M. Schwaiger, G. Meisetschläger, K. Scheidhauer, München (8); H. Otto, Peggy Fostitsch, R. Steinke, Magdeburg (8); W. Knapp, J. Müller, Daniela Paral, Eva Weckesser, Hannover (8); F. Maul, Cornelia Puskás, J. Peter, Karlsruhe (7); P. Lind, Gerhild Kumnig, Klagenfurt (7); H. Wieler, Elisabeth Ostwald-Lenz, Birthe Müller, Koblenz (7); B. Theophil, J. Borkopp, Gerlinde Thiemann, Dortmund (7); R. Dudczak, A. Becherer, Wien (7); P. Bartenstein, Waltraud Eichhorn, Mainz (7); B. Piotrowski, B. Hackmann, Hamm (6); C. Schümichen, P. Groth, Rostock (5); F. Gottschalk, Frankfurt/O. (5); T. Kuwert, E. Fiedler, A. Schwarz, Erlangen (4); G. von Schulthess, H. Steinert, Zürich (4); R. Schöneich, Gabriele Holl, Potsdam (4); W. Langsteger, Elfriede Rechberger, Linz (4); H. Müller-Gärtner, K. Kley, Düsseldorf (3); G. Klaushenke, Angelika Deutschmann, Oldenburg (3); P. Lindner, A. Glasow, Hildesheim (3); O. Sabri, P. Georgi, L. Otto, Leipzig (3); C. Eilles, A. Szikszai, Regensburg (3); J. Feldkamp, J. Herrmann, Nicole Mittemeyer, G. Frese, Bielefeld (3); M. Clausen, Vika Müller, Hamburg (3); M. Schmidt, R. Nastvogel, H. Philipp, Bamberg (2); R. Baum, M. Schmücking, Bad Berka (2); Ch. Dschietzig, Katrin Weigel, Cottbus (2); H. Biersack, K. von Mallek, Bonn (1); Wilhelmine Maschek, Elisabeth Dienstl, H. Huber, Linz (1); R. Aurisch, M. Tosch, Mönchengladbach (1); R. Thiele, Schwäbisch Hall (1); M. Bähre, E. Richter, Isabel Lauer, Lübeck (1); E. Bell, M. Fischer, Dernbach (1); K. Hering, H. I. Lux, H. Tonscheid, Dortmund (1); U. Haberkorn, J. Hoffend, S. Haufe, Heidelberg (1); K. Hahn, M. Hacker, P. Knesewitsch, München (1).

quality of life by the QLQ-C30 questionnaire (v. 3.0 German) of the EORTC (European Organization for Research and Treatment of Cancer).

Data management

The data management in the MSDS trial based on a central Oracle 8i database (Oracle Corp., Redwood Shores/CA) under Linux has been described in detail (4) and is illustrated in Fig. 2. Briefly, case report forms (CRF) in the Adobe® Portable Document Format (PDF) are downloaded from the MSDS website by the participating centers, and are mailed or faxed back to the study's data center. Data are entered into the study database. The database then automatically generates a status fax which confirms the incoming documentation, lists the patient's pertinent data such as each iodine-131 activity and the date of its application, hTg, TSH and blood count, and which contains a list of current documentation errors requiring correction. The surgical and histology reports are sent in for review by the study's reference surgeons and reference pathologists. The histological specimens are centrally reviewed and archived by the study's reference pathologists. RTx plans are reviewed by the study's reference radiotherapist before start of RTx. All reference centers including the clinical monitor have direct database access by means of a secure internet connection with 128-bit encryption. In compliance with Good Clinical Practice (GCP), the database maintains a complete audit trail for each entry of information (4).

Biometrics and safety management

The primary endpoints were locoregional recurrence or distant metastases and cancer related mortality. Secondary endpoints were acute and late RTx toxicity and quality of life. The required sample size was n = 250 randomized patients per treatment arm. The power calculation was based on Fisher's exact test ($p < 0.05$, two-tailed). The assumption was that the recurrence rate without RTx was 19% over a recruitment period of 5 years and a further 3 years follow-up and that a 50% reduction of the recurrence rate through RTx should be detected with 80% probability. Data were reviewed twice per year by an independent Data Monitoring and Safety Committee (DMSC) and immediately after each serious adverse event (SAE). The definition of SAE included all instances of acute, or chronic, grade 3 or higher toxicity (skin:

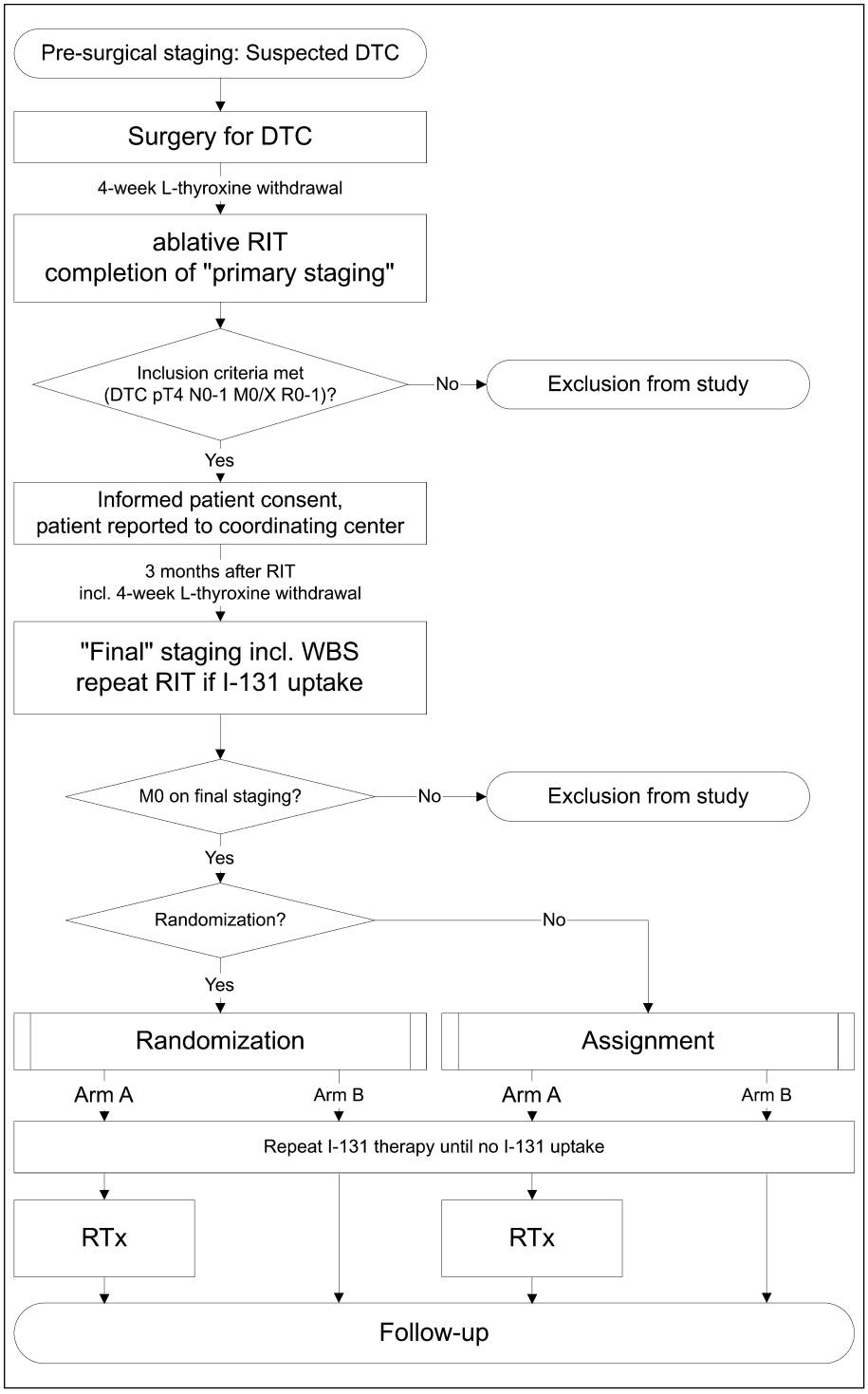

Fig. 1 MSDS design (RIT: radioiodine therapy, RTx: external beam radiotherapy, WBS: whole body scintigram).

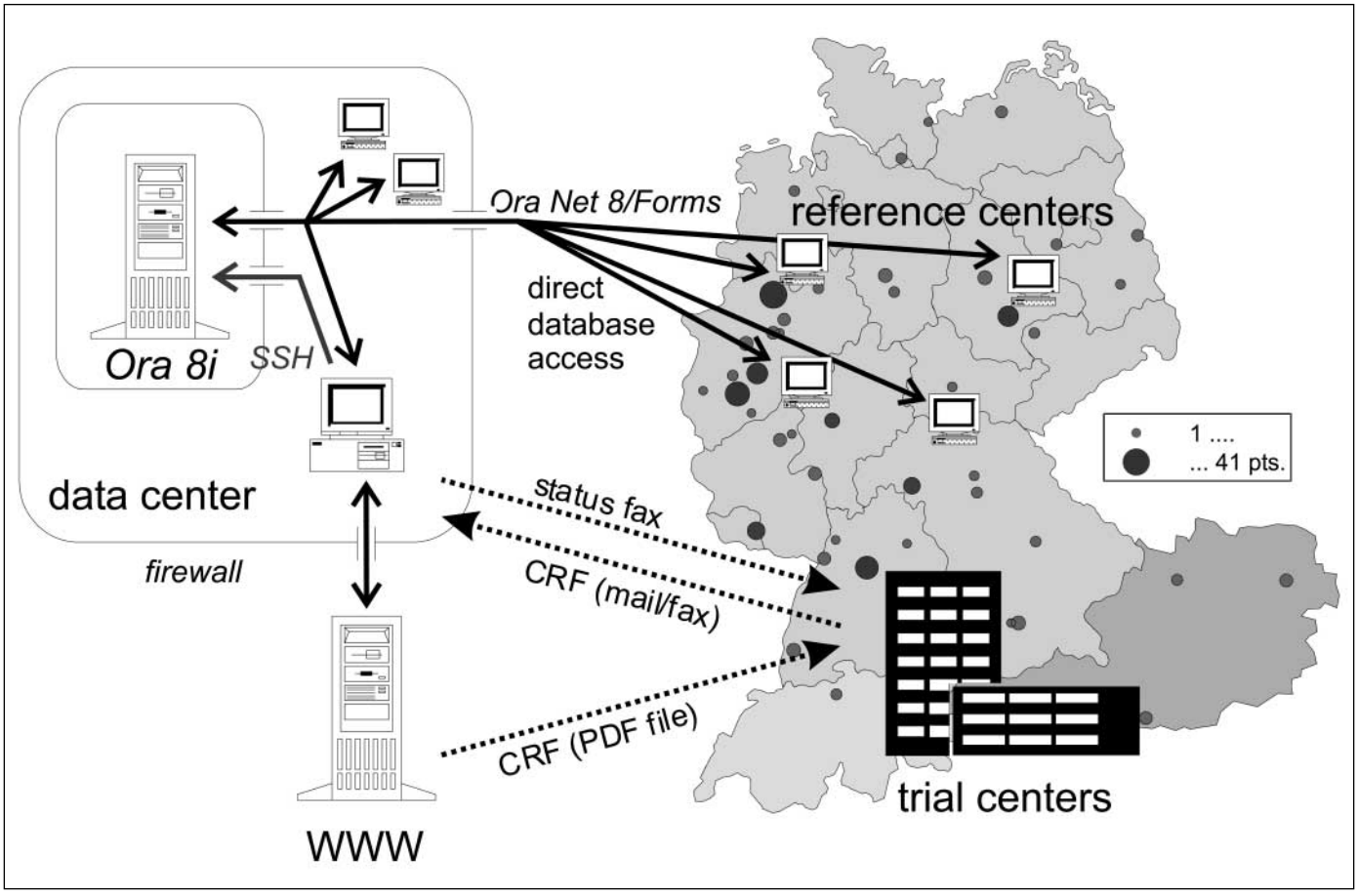

Fig. 2 MSDS: data management. Circles corresponding to the number of patients recruited until September 15, 2003 at each center.

grade 4) on the RTOG scale (28). The study protocol contained a step curve for premature termination of the trial (3 SAE for n ≤23 arm A patients, 4 SAE for 23 <n ≤45...) which was calculated by the sequential probability ratio test so as to account for sampling error ($\alpha = 0.1$, $\beta = 0.1$) and based on the requirement that 5% acute and 5% chronic serious toxicity should not be exceeded (21). Data were analyzed by SQL*-plus scripts under Oracle 8i, and statistical analysis performed under SAS 8.2 for Windows (SAS Institute, Inc.; Cary/NC).

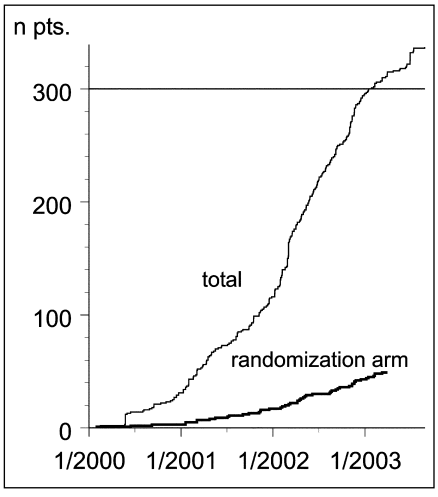

Fig. 3 Patient recruitment until September 15, 2003 (n = 339).

Results

Recruitment

From January until March 2000, n = 311 patients from 45 centers in Germany, Austria, and Switzerland were enrolled in the study (Fig. 3). Of the 45 centers, 28 had declared to actively take part in randomization, and 9 refused because they did not use RTx (n = 7) or only in specific circumstances (R1/2 resection, n = 1; age >40 years and infiltration of cervical viscera, n = 1). Of the 311 patients, 32 did not meet the inclusion criteria due to previous malignant disease (n = 8), age ≥70 years (n = 5), serious general disease (n = 5), low differentiation of the thyroid cancer (n = 4), withdrawn consent (n = 3), distant metastases at the time of initial RIT (n = 1), R2 resection (macroscopic tumour residues) (n = 1), previous RTx (n = 1) or other reasons (n = 6).

Of the 279 patients included, age at initial surgical therapy was 49 ± 12 (20-69) years (mean ± standard deviation, range). 73% of patients were women. Mean tumour diameter was 2.0 ± 1.4 (0.2-9.5) cm. Tumour diameter was ≤1 cm in 24%. DTC type was follicular in 5%.

Randomization

Of the 279 patients included in the study until March 31, 2003 at the time of the steering committee's decision to terminate the randomization, 45 were in the randomization arm. Of these, 36 patients underwent randomization, 17 into Arm A (RTx) and 18 into Arm B (no RTx). Another patient randomized into Arm B later withdrew consent and was therefore excluded from the trial (s. a.). Of the 17 patients randomized, and of 23 patients assigned, to receive RTx (Fig. 4), 4 and 1 patients refused to undergo RTx at the time of RTx, resp.

An in-depth report on RTx in the trial is about to be published (27). Preliminary results from other analyses of the trial data have been presented at international scientific meetings (2, 3, 22).

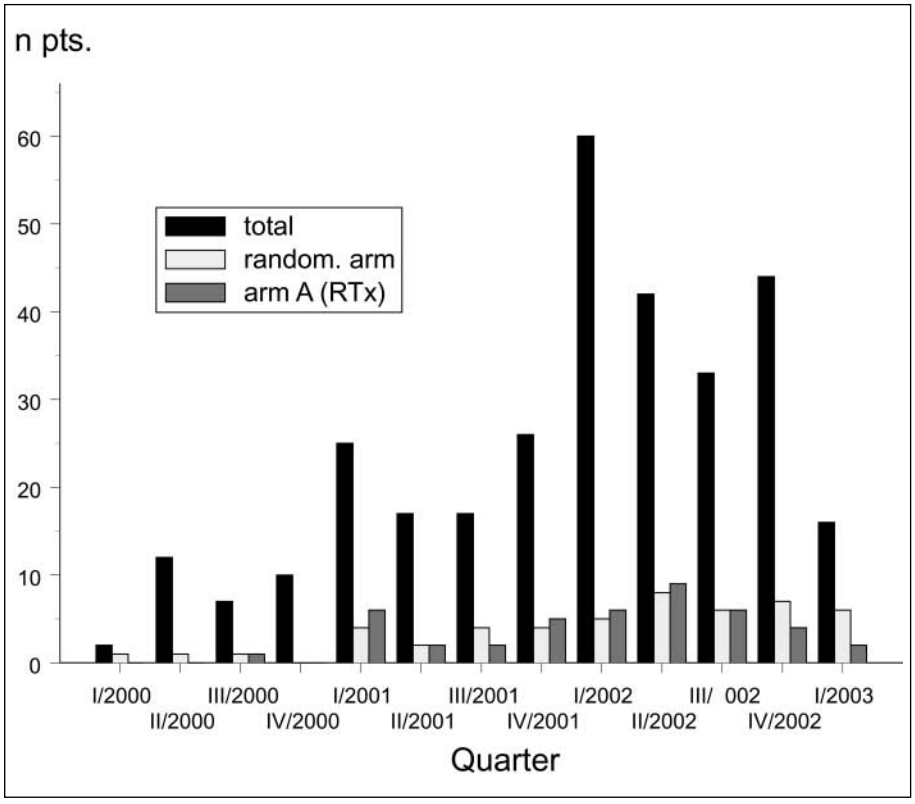

Fig. 4 Recruitment of patients per quarter until the decision to terminate randomization in April 2003: The decrease in recruitment in I/2003 coincides with the implementation of the 6th edition of the TNM classification encoding locally invasive DTC as pT4 *or* pT3 (34). (random.: randomization; Arm A (RTx): patients randomized or allocated for RTx).

Discussion

The main finding so far is that acceptance of external beam RTx as a treatment modality for DTC has receded to such a degree that recruitment of a sufficient number of randomized patients to answer the primary question of the trial has been impossible. In agreement with the trial's independent DMSC, the MSDS steering committee therefore decided to terminate randomization in April 2003.

At the time the trial was designed, RTx was a common mode of therapy for DTC. In the PCES survey, which included 80% of the incident patient population in Germany in the year of 1996, 142 out of 1685 patients with papillary DTC, and 43 out of 691 patients with follicular DTC received RTx (13). The former group included 29 patients with pT1-3 N0/1 M0 disease and 113 in higher disease stages. This amounts to at least 44% of the 258 pT4 M0 patients with papillary DTC in that cohort (14). In comparison, only 40 out of 279 (14%) of MSDS patients received RTx, 17 through randomization and 26 through assignment by their physicians, a number which includes 5 patient refusals. This indicates a significant change in the therapeutic approach to DTC (Fig. 5), particularly if the repeated campaigns by the study leadership to promote randomization in the trial are taken into account. A similar trial in North America under the auspices of the American College of Surgeons Oncology Group was not funded out of concerns that recruitment of the 400 patients required was not feasible

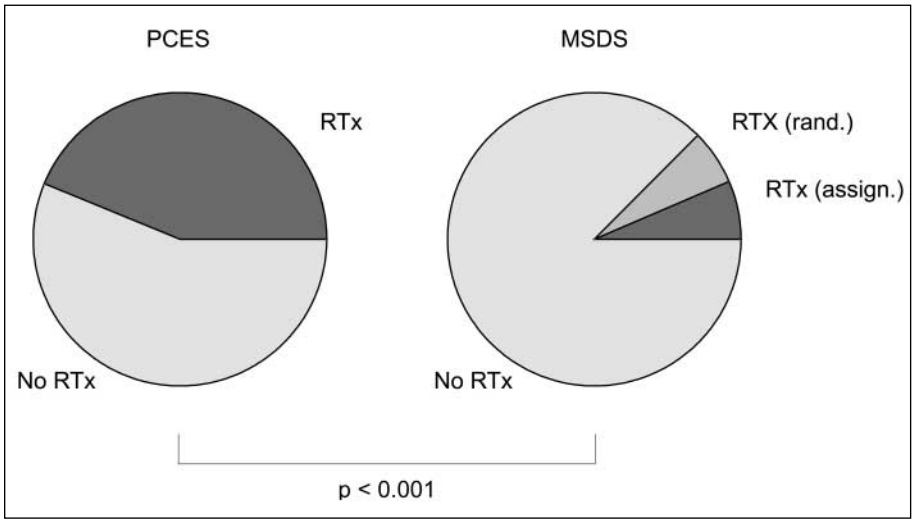

Fig. 5 External beam radiotherapy (RTx) in MSDS and PCES. 44% (113/258) versus 14% (40/279) of patients received RTx (rand.: randomization; assign.: assignment by physician) ($p < 0.001$; χ^2-test).

(Brierley JD; personal communication). Randomization in cancer trials can be a problem when the choice is between different therapeutic modalities, as exemplified by the German Breast Cancer Study Group trial of mastectomy versus breast preserving RTx in node negative tumours <2 cm: only 72 out of 1119 patients (6.5%) consented to randomization (31).

The trial's main question – the clinical benefit of external beam RTx – remains unanswered. The only studies to indicate a clear benefit of RTx were 3 retrospective single-institution surveys going back to the 1960s and 1970 (23, 26): in pT4 DTC in terms of survival (18) and freedom of recurrence (11) and in papillary DTC after R1 resection (32). Another trial reported improved locoregional control without a survival benefit (33). It has been a subject of intense debate whether these results still apply to present-day multimodal therapy with more radical surgery (2), more sensitive hTg assays and imaging methods including high-resolution cervical ultrasound. In the trial, RTx toxicity was lower than observed for the treatment of head and neck cancer (17), and did not conflict with the strict stopping rules of the study. So far, acute grade 3 toxicity has occurred in 2 out of 22 patients (9%; 95% confidence interval 1-29%). Both patients had dysphagia necessitating transient feeding via a nasogastric tube or parenteral nutrition (27). One patient with serious chronic toxicity has been reported so far. This patient with preexisting Reinke edema required tracheostomy due to larnygeal edema 9 months after the end of RTx.

An important open question will be the recurrence rate in Arm B patients treated by surgery, RIT and TSH suppression therapy alone. So far, the recurrence rate has been below the assumptions made in the power calculation on the basis of retrospective surveys even though local tissue invasion is a clear identifier for high risk of recurrence and mortality (1, 20). At present it is unclear whether improvements in therapy in the last decade, a higher level of competence in the participating centers (6) or a "healthy volunteer" effect contribute to better outcomes. These findings would however affect the risk-benefit ratio of adjuvant RTx, implying that at least 10 patients need to receive RTx in order for 1 to experience the benefit.

This underlies the decision of the trial's steering committee to continue MSDS as a prospective study. Many insights into the DTC treatment are to be expected. Not only is MSDS the second ever prospective multicenter study on DTC (30), but is also the second study with reference pathology (24) and the first multicenter study that will be able to correlate differences in surgical strategy (total thyroidectomy with or without lymph node dissection) with clinical outcomes.

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