DOI: 10.1093/jnci/djq525
Advance Access publication on January 6, 2011

ARTICLE

Randomized Trials in 2466 Patients With Stage I Seminoma: Patterns of Relapse and Follow-up

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Manuscript received April 15, 2010; revised November 23, 2010; accepted November 24, 2010.

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Background From July 1, 1989, through March 31, 2001, 2466 patients with stage I seminoma were evaluated in three randomized noninferiority trials: the TE10, TE18, and TE19 trials. We analyzed mature results of these studies.

Methods The TE10 trial randomly assigned 478 patients to para-aortic and ipsilateral iliac lymph node (dogleg field) or para-aortic only radiation therapy (total dose = 30 Gy). The TE18 trial randomly assigned 1094 patients to a total dose of 30 or 20 Gy of radiation therapy, predominantly to a para-aortic field. The TE19 trial randomly assigned 1477 patients to radiation therapy or a single injection of carboplatin at a dose of seven times the area under the curve. Time to relapse was determined from Kaplan–Meier curves, and such data were compared by use of Cox regression models. Noninferiority in TE18 and TE19 required the upper limit of the 90% confidence intervals (CIs) (reflecting the one-sided test for noninferiority at a 5% statistical significance level) to exclude a hazard ratio (HR) of greater than 2.0 and a doubling of the 5-year relapse rates observed in the control arm. The TE10 trial was not powered to exclude clinically relevant differences in overall relapse rates but was assessed against the same criteria.

Results Median follow-up times were 6.4–12 years in the three trials. We identified the noninferiority of the following treatments: 20 Gy of radiation therapy in the TE18 trial (HR of relapse = 0.63, 90% CI = 0.38 to 1.04) and carboplatin in the TE19 trial (HR of relapse = 1.25, 90% CI = 0.83 to 1.89). Para-aortic radiation therapy in the TE10 trial was associated with a hazard ratio of relapse of 1.15 (90% CI = 0.54 to 2.44). Relapse occurred after 3 years in only four (0.2%) of all 2466 patients. Computed tomography scans had little impact on the detection of relapse after radiation therapy; seven of the 904 patients allocated radiation therapy in TE19 had a relapse detected by this method.

Conclusion This large and mature dataset from three randomized trials has provided support for the use of either radiation therapy or carboplatin therapy as adjuvant treatment for stage I seminoma.

J Natl Cancer Inst 2011;103:241–249

The most commonly diagnosed germ cell cancer is stage I seminoma (ie, 40%–45% of all patients with germ cell cancers) (1). In surveillance studies (1), disease will relapse in 15%–20% of these patients. Almost all patients are curable regardless of management approach. The three management options that have been developed for this group are surveillance (1), adjuvant radiation therapy (2,3), and adjuvant chemotherapy, usually with carboplatin (4). The latter two options have been the subject of large randomized trials from the Medical Research Council (MRC). From July 1, 1989, through March 31, 2001, 2466 patients with stage I seminoma were entered into one of the only three randomized noninferiority trials ever conducted in this disease. These three trials were the TE10 (International Standard Randomized Controlled Trial Number [ISRCTN] 54221666), TE18 (European Organisation for Research and Treatment of Cancer [EORTC] 30942, ISRCTN18525328), and TE19 (EORTC 30982, ISRCTN27163214) trials. The TE10 trial aimed to assess whether or not the radiation field could be reduced from the standard "dogleg" field (ie, the para-aortic plus ipsilateral iliac lymph nodes) to a para-aortic field only. The first publication (2) showed that there was an increased rate of pelvic relapse but similar overall relapse rates with the reduced field. The TE18 trial compared a standard radiation dose of 30 Gy in 15 fractions to a reduced dose of 20 Gy in 10 fractions and showed (3) that the relapse-free rates were noninferior after 20 Gy. Finally, the TE19 trial compared radiation therapy with a single dose of carboplatin and showed (4) that carboplatin was noninferior with respect to relapse at a median follow-up of 4 years. We analyzed the mature results of these three randomized noninferiority trials.

Patients and Methods

From July 1, 1989, through March 31, 2001, three randomized noninferiority trials (2–4) were conducted in a total of 2466 patients with stage I seminoma. Each trial was approved by the

CONTEXT AND CAVEATS

Prior knowledge

Seminoma is the most commonly diagnosed germ cell cancer. Three randomized noninferiority trials (the TE10, TE18, and TE19 trials) that compared several radiation therapy regimens and carboplatin chemotherapy in patients with stage I seminoma had been conducted in the period 1989–2001.

Study design

Mature data were analyzed for time to relapse after median follow-up of 6.4–12 years in the three noninferiority trials.

Contribution

Noninferiority of the following therapies was identified: 20 Gy of radiation therapy (vs 30 Gy) in the TE18 trial and carboplatin (vs radiation therapy) in the TE19 trial. Relapse after 3 years occurred in very few patients. Computed tomography scans had little impact on the detection of relapse after radiation therapy.

Implications

Results of these trials support the use of radiation therapy or carboplatin therapy as adjuvant treatment for stage I seminoma.

Limitations

The randomized comparison in the TE10 trial was not powered to exclude modest differences in overall relapse rates. Despite median follow-up times of 6–12 years, the possibility that further late relapses may occur cannot be excluded.

From the Editors

appropriate Research Ethics Committee, and patients gave written informed consent to participate. After orchidectomy, we confirmed that all patients had received a normal physical examination and had normal levels of α-fetoprotein and human chorionic gonadotrophin; α-fetoprotein levels before orchidectomy were also required to be normal. In the TE10 trial (2), either bipedal lymphography or an abdominal and pelvis computed tomography (CT) scan were required to be normal. In the TE18 (3) and TE19 (4) trials, a normal whole-body CT scan was a requirement.

The TE10 Trial

The TE10 trial (2) was conducted from July 1, 1989, through May 31, 1993. Eligible patients had stage T1–T3 seminoma with no history of ipsilateral inguinoscrotal surgery. Patients were randomly assigned to radiation therapy with a para-aortic field or a dogleg field (para-aortic plus ipsilateral iliac lymph nodes) and were treated with radiation therapy to a midplane dose of 30 Gy given in 15 fractions during a 3-week period to opposing anterior and posterior fields. The trial was designed to exclude, with 90% power at a 5% statistical significance level (one-sided test for noninferiority), an increase in the 3-year pelvic relapse rate of 3% in the para-aortic field treatment arm. This power calculation required 400 patients to be randomly assigned to treatment, and 478 patients were randomly assigned.

The TE18 Trial

The TE18 trial (3) was conducted from May 1, 1995, through January 15, 1998. Eligible patients had stage T1–T3 seminoma. The patients were randomly assigned to receive radiation therapy to a total dose of 30 Gy in 15 fractions or to a total dose of 20 Gy in 10 fractions. Radiation therapy was given to a para-aortic field in most cases; however, in this trial, patients with previous inguinoscrotal surgery were eligible for trial entry but were treated with a dogleg field.

The trial was originally designed as a noninferiority study to exclude, with 90% power at a 5% statistical significance level (one-sided test for noninferiority), a difference of 4% in 2-year relapse rates. This power calculation required entry of 600 patients, and 625 patients were randomly assigned. When the TE19 trial, which was designed to compare radiation therapy with carboplatin therapy, commenced before the results of TE18 were known, the opportunity was taken to offer continuing randomization of radiation therapy dose as in the TE18 trial to provide the chance to exclude a 3% difference in 2-year relapse rates. In total across the two trials, 1094 patients were randomly assigned to receive radiation therapy at 30 or 20 Gy.

The TE19 Trial

The TE19 trial (4) was conducted from September 1, 1996, through March 31, 2001. Eligibility criteria were identical to those for the TE18 trial. Patients were randomly assigned, in a 5:3 ratio, to radiation therapy or to carboplatin therapy. Carboplatin therapy was given intravenously as a single injection at a dose of seven times the area under the curve (AUC7). Centers could choose to randomly assign patients to radiation therapy to a total dose of 20 or 30 Gy, as an extension of the TE18 trial (see above) or to treat patients to a total dose of radiation therapy of between 20 and 30 Gy, according to their standard practice. Para-aortic radiation therapy was the standard treatment, with dogleg radiation therapy recommended for patients with previous inguinoscrotal surgery. If a 2-year relapse-free rate of 96%–97% was assumed after radiation therapy, then 1200 patients were required to exclude a doubling of the 2-year relapse rates (ie, a hazard ratio [HR] > 2.0) with 90% power at a 5% statistical significance level (one-sided test for non inferiority). In total, 1477 patients were randomly assigned to treatment.

The frequency of follow-up visits was uniform across all three trials. Patients were examined at 3-month intervals for year 1 after treatment and then at 4-month intervals for year 2, 6-month intervals for year 3, and then one visit per year thereafter. At each visit, blood was collected to assess serum levels of α-fetoprotein and human chorionic gonadotrophin. Chest x-rays were obtained at the 6-, 12-, 20-, 30-, and 36-month visits. Chest, abdominal, and pelvic CT scans were obtained at years 1, 2, and 3 (although the chest CT scan was optional in the TE10 trial).

Patients were restaged at relapse and generally treated with platinum-containing chemotherapy, although radiation therapy was used for selected patients. In the TE19 trial, detailed information was obtained about relapse detection by retrospective chart review.

Statistical Methods

Randomization in all three trials used minimization to allocate patients to treatment while ensuring that patient characteristics were balanced across the treatment groups. Treatment and unique

identifiers were allocated through a telephone call to the MRC Clinical Trials Unit (TE10, TE18, and TE19 trials) or to the EORTC Data Center (the TE19 trial only), at which a separate minimization process that used the same factors was implemented. For all trials, follow-up data including dates of first recurrence if not previously notified, dates of any new primary malignancies, and survival status were requested from the participating sites. In this analysis, for patients whose most recent data provided only survival status, without definite information on relapse status (eg, data from the UK Office of National Statistics), the date of last clinic visit was used to calculate relapse-free survival. For the TE10 trial, the minimum follow-up period specified in the protocol was 5 years, although many sites routinely followed patients for longer. For the TE18 and TE19 trials, the protocol specified a 10-year follow-up period. The most recent requests for data took place in 2006 for the TE10 and TE18 trials and in 2007 for the TE19 trial.

Relapse-free rates were calculated from the date of randomization to the date of relapse or the date last known to be alive and relapse free. Relapse-free rates were presented by use of Kaplan–Meier event-free curves. For comparisons of the primary randomized treatments, treatment hazard ratios for relapse and 90% confidence intervals (CIs) were calculated from the Cox proportional hazards regression model. Formal tests of the proportional hazards assumption by use of time-dependent covariates did not indicate statistically significant deviation from proportionality in any of the three trials. However, confidence intervals for the differences in 5-year relapse-free rates were calculated from the hazard ratio and its 90% confidence interval and also by direct comparison of the 5-year rates because the estimates and confidence intervals may differ as a result of nonproportional hazards or later events. TE18 and TE19 were originally powered to exclude a doubling of the 2-year relapse rate. Therefore, to indicate non inferiority with respect to long-term results, we required the upper 90% confidence limit for the difference in relapse-free rates at 5 years to exclude a doubling of the rate in the control arm, and the upper 90% confidence limit for the hazard ratio to exclude values greater than 2.0. One-sided tests for the primary treatment comparisons were preplanned, as recommended in the International Conference on Harmonization guideline E9, Statistical Principles for Clinical Trials, because all three trials were noninferiority studies. Hence, the hazard ratios and comparisons of relapse rates at 5 years in the randomized arms were presented with 90% confidence intervals to reflect the one-sided 5% statistical significance level that was used in the design of all three trials. The upper limits of these confidence intervals were emphasized because these values reflect the maximum adverse effect of the experimental arm that can be reliably excluded at the 5% statistical significance level. Additionally, 95% confidence intervals for the hazard ratios are reported and all other comparisons used two-sided statistical tests and, with estimates of event rates at specific time points, were presented with 95% confidence intervals.

Results

Details of all three trials are summarized in Table 1 and Figure 1. Median age, the only characteristic that was reported in all three

Table 1. Summary details of the TE10, TE18/19, and TE19 randomized trials by allocated treatment*

	TE10		TE18/19 (EORTC 30942)		TE19 (EORTC 30982)	
	Allocated treatment		Allocated treatment		Allocated treatment	
Detail	Dogleg	PA	30-Gy radiation therapy	20-Gy radiation therapy	Radiation therapy†	Carboplatin
No. of patients	242	236	550	544	904	573
Median follow-up, y	10.7	12.0	7	7	6.4	6.5
% followed for >5 y	81	79	84	85	80	76
Relapses, No. of patients (mo after treatment)						
Total	9	10	27	17	37	29
<3 y from entry	9	9	26	17	35	28
≥3 y from entry	0	1 (91)	1 (64)	0	2 (61, 64‡)	1 (50)
5-y RFR, % (95% CI)	96 (93 to 98)	96 (93 to 98)	95 (93 to 97)	97 (95 to 98)	96 (95 to 97)	95 (93 to 96)
No. of deaths from seminoma	0	1	2	1	1§	0
HR (90% CI)	1.15 (0.54 to 2.44)		0.63 (0.38 to 1.04)		1.25 (0.83 to 1.89)	

* CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; PA = para-aortic strip; RFR = relapse-free rate .

† Note: some of these patients also contribute to the radiation therapy comparison between 30 and 20 Gy.

‡ This patient (relapse at 64 months) was also reported under the TE18/19 trial.

§ This patient was also reported under the TE18/19 trial.

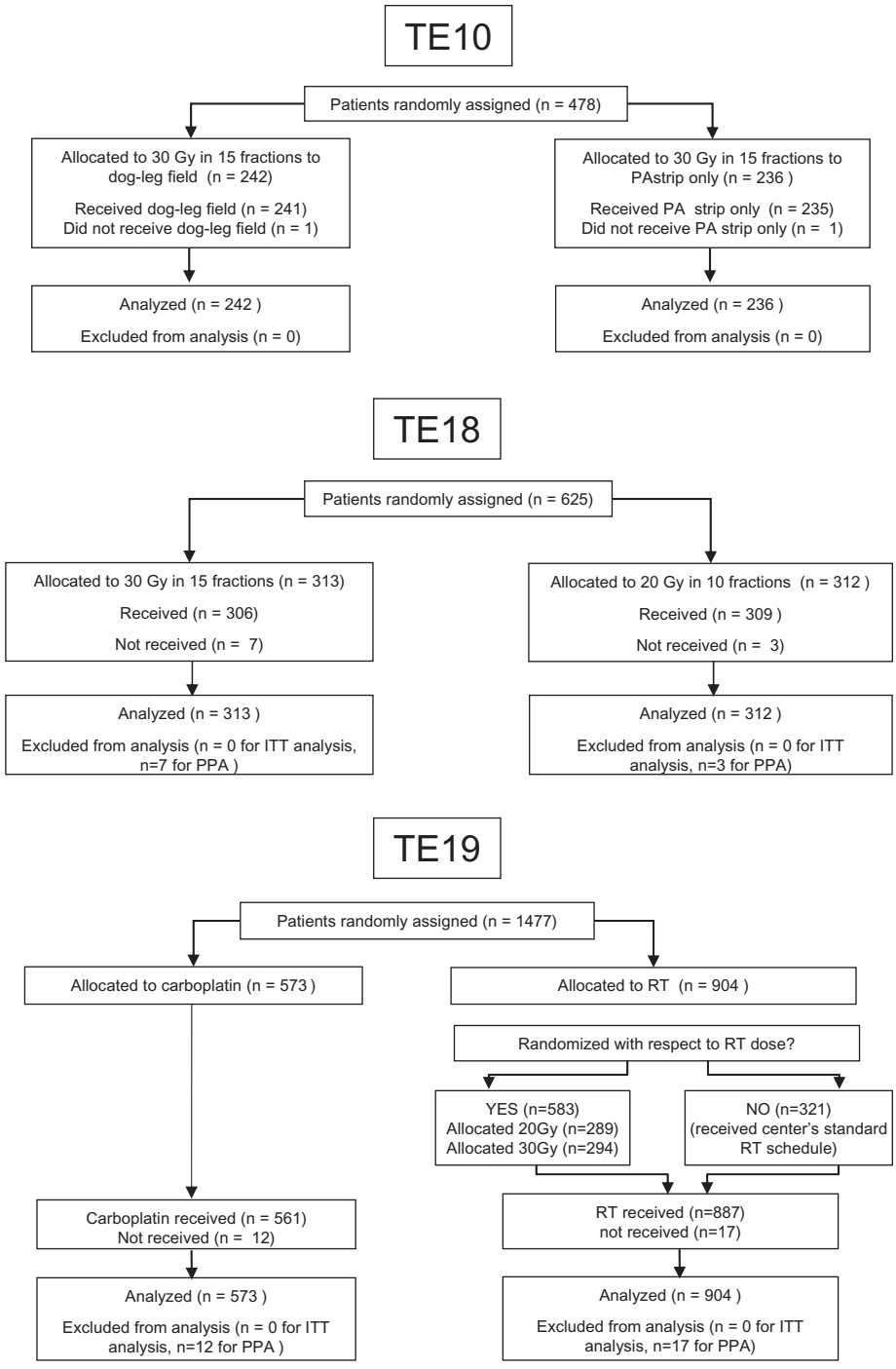

Figure 1. CONSORT diagrams for the TE10 (2), TE18/19 (3), and TE19 (4) randomized trials. ITT = intention to treat; PA = para-aortic; PPA = per protocol analysis; RT = radiation therapy.

trials, was similar in all three trials and was balanced across the treatment arms. The median age was 37 years in TE10 and TE19 and 38 years in TE18, with an age range across all trials of 18–80 years. The results for the individual trials are described below.

The TE10 Trial

Four hundred seventy-eight patients were randomly assigned to either para-aortic strip (n = 236) or dogleg field (n = 242) radiation therapy in the TE10 trial (2). In the dogleg arm, median follow-up was 10.7 years (interquartile range [IQR] = 5.2–14.1 years), and the proportion of patients with data available at 5 years was 80.6%. In the para-aortic arm, median follow-up was 12.0 years (IQR = 5.5–14.2 years), and the proportion of patients with data available at 5 years was 78.8%. Five-year relapse-free rates were 96.1% (95% CI = 92.6% to 97.9%) in the para-aortic strip arm and 96.2% (95% CI = 92.7% to 98.0%) in the dogleg arm (difference in 5-year relapse rates = 0.1%, 90% CI = −3.2% to 3.3% by direct comparison of proportions and 90% CI = −1.7% to 5.2% by use of the HR and its 90% CI; overall HR of relapse = 1.15, 90% CI = 0.54 to 2.44, and 95% CI = 0.47 to 2.82) (Figure 2, A).

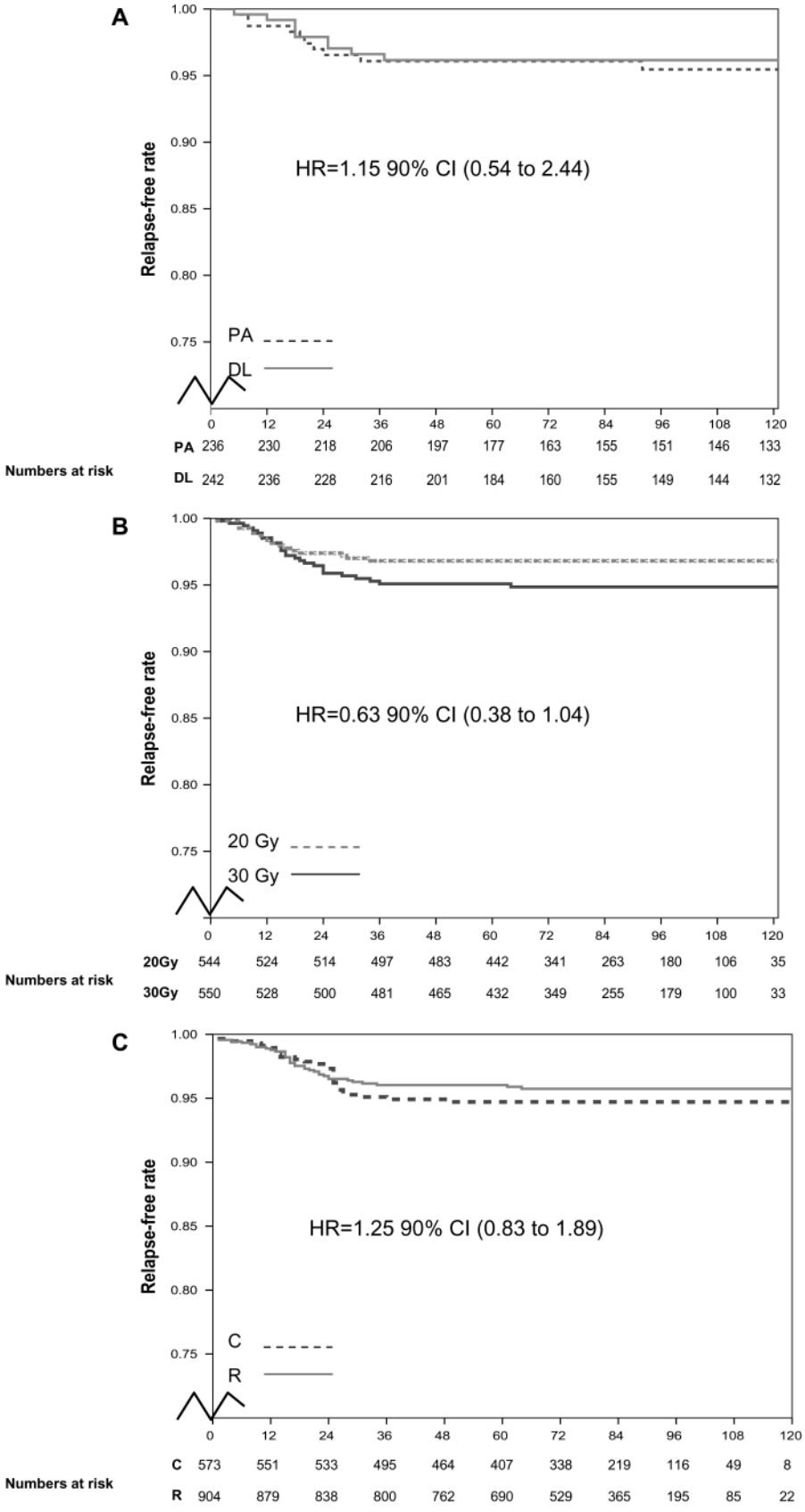

Figure 2. Relapse-free rate analyses for the TE10, TE18/19, and TE19 randomized trials shown with truncated Y axis. **A**) TE10 Trial. Relapse-free rates are presented by allocated radiotherapy field (hazard ratio [HR] = 1.15, 90% confidence interval [CI] = 0.54 to 2.44). **B**) TE18/19 Trial. Relapse-free rates are presented by allocated radiotherapy dose (HR = 0.63, 90% CI = 0.38 to 1.04). **C**) TE19 Trial. Relapse-free rates are presented by allocated treatment (HR = 1.25, 90% CI = 0.83 to 1.89). C = carboplatin; DL = dogleg; PA = para-aortic; R = radiation therapy.

Disease relapsed in a total of 19 patients (nine in the dogleg arm and 10 in the para-aortic arm); only one of these 10 relapses occurred later than 3 years after study entry (that relapse was in the para-aortic arm at 91 months). Although no pelvic relapses were reported in the dogleg arm, four pelvic relapses were recorded in the para-aortic arm, all were reported in the initial publication (2),

in two patients the pelvic lymph nodes were the only site of relapse and, in the other two patients, disease relapsed in the pelvis and chest or abdomen. A single death from progressive seminoma related to the original cancer was recorded in a patient in the para-aortic arm.

The TE18 Trial

Six hundred twenty-five patients had been originally randomly assigned to treatment in the TE18 trial (3). The last 114 of these 625 patients and another 469 patients were randomly assigned to receive a radiation therapy dose of 30 or 20 Gy, having been randomly assigned to radiation therapy in the TE19 trial, for a total of 1094 patients. Data from all 1094 patients were included in this analysis. Briefly, a total of 550 patients were randomly assigned to receive a total radiation therapy dose of 30 Gy and 544 were randomly assigned to receive a total radiation therapy dose of 20 Gy. The median follow-up time in both arms was 7 years (IQR = 5.3 to 8.5 years), with follow-up data at 5 years available for 83.3% of patients in the 30-Gy arm and 84.2% in the 20-Gy arm.

Relapse-free rates at 5 years were 95.1% (95% CI = 93.1% to 97.1%) in the 30-Gy arm and 96.8% (95% CI = 95.2% to 98.4%) in the 20-Gy arm (difference in 5-year relapse-free rates = −1.7%, 90% CI = −3.8% to 0.4% by direct comparison of proportions, or 90% CI = −3.0% to 0.2% by use of the HR and its 90% CI; overall HR of relapse = 0.63, 90% CI = 0.38 to 1.04, 95% CI = 0.34 to 1.15) (Figure 2, B). Forty-four relapses occurred, all but one of which occurred within 3 years. The patient who experienced relapse beyond 3 years (also was randomly assigned to treatment in the TE19 trial) was in the 30-Gy arm and relapsed at 64 months. There were two deaths in the 30-Gy arms (one in the TE18 trial and one in the TE19 trial) and one death in the 20-Gy arm of the TE18 trial.

The TE19 Trial

One thousand four hundred seventy-seven patients were randomly assigned to treatment in the TE19 trial (4), with 904 in the radiation therapy arm and 573 in the carboplatin arm (ie, a single injection of carboplatin at AUC7). Median follow-up times were 6.4 years (IQR = 5.1–7.9 years) for the radiation therapy arm and 6.5 years (IQR = 5.0–7.9 years) for the carboplatin arm; 79.7% of patients in the radiation therapy arm and 75.8% in the carboplatin arm were followed for 5 years. Sixty-six patients relapsed, for a 5-year relapse-free rate of 96.0% (95% CI = 94.5% to 97.1%) for the radiation therapy arm and 94.7% (95% CI = 92.5% to 96.3%) for the carboplatin arm (difference in 5-year relapse-free rates = 1.34%, 90% CI = −0.7% to 3.5% by direct comparison of proportions, and 90% CI = −0.7% to 3.4% by use of the HR and its 90% CI; overall HR of relapse = 1.25, 90% CI = 0.83 to 1.89, 95% CI = 0.77 to 2.03) (Figure 2, C).

There were only three relapses that occurred more than 3 years after study entry (one of these patients was described above in the TE18 trial). Of the two remaining relapses, one occurred at 61 months in the radiation therapy arm and the other occurred at 50 months in the carboplatin arm. There were no additional deaths (except for the one that was described above in the TE18 trial) in the radiation therapy arm and no deaths in the carboplatin arm.

Overall Relapses, Survival, and Patterns of Relapse

Among the 2466 patients randomly assigned to treatment in the three trials, the original cancer relapsed after the start of treatment in 98. The relapse occurred more than 3 years after treatment in only four (0.2%) of the 2466 patients at 61, 64, and 91 months in the radiation therapy arm and at 50 months in the carboplatin arm. Four patients died as a result of metastatic relapse from their original germ cell cancer (crude cancer-specific survival = 99.8%, 95% CI = 99.6% to 99.9%).

Relapse sites were analyzed by treatment modality and irradiation field rather than by trial (Figure 3). Striking differences in relapse sites were observed. Among the 17 patients who were treated with dogleg radiation therapy, the relapse site for 11 (64.7%) was the lymph nodes in the mediastinum and neck. Among the 27 patients who were treated with carboplatin, the relapse site for 18 (66.7%) was the retroperitoneum. Among the 54 patients who were treated predominantly with para-aortic irradiation, the relapse site for 20 (37.0%) was the pelvis and for 14 (25.9%) was the mediastinum or neck. An abdominal site of relapse was rare in patients treated with para-aortic or dogleg radiation therapy and a pelvic site of relapse rare in patients treated with dogleg radiation therapy or carboplatin. Relapse identified by elevated markers (α-fetoprotein or human chorionic gonadotrophin) only was observed in only two patients, and relapse at sites that included multiple lymph nodes plus multiple visceral sites was observed in similar numbers of patients in each treatment group (ie, dogleg field radiation, para-aortic field radiation, and carboplatin).

The temporal pattern of relapse was analyzed by treatment modality and radiation therapy field (Figure 4). Diagnoses of relapses were clustered around the annual CT scan dates, with relapses among those treated with radiation therapy predominantly detected at the 1-year scan and relapses among those treated with carboplatin predominantly detected at the 2-year abdominal scan, at which nine of the 14 relapses among those treated with carboplatin were identified. Relapse after 3 years was rare, as mentioned above.

A more detailed description of the first indication of relapse in 57 of the 60 patients in the TE19 trial whose disease relapsed after starting treatment is presented in Table 2 (data were not available for three patients). In the radiation therapy arm, relapse was most commonly detected by symptoms or clinical examination, reflecting the predominant relapse sites in the neck, mediastinum, and pelvis. In seven of 904 patients overall or seven (22.6%) of 31 patients with information on relapse detection, the relapse was detected by a routine CT scan. By contrast, relapses of 15 (57.7%) of the 26 patients with relapse in the carboplatin arm were detected by a routine abdominal CT scan. Relapse was detected in only one patient by a routine chest CT scan.

Discussion

This large patient cohort, which was assembled from three randomized trials, has provided the best data available on long-term outcomes among patients with stage I seminoma who were treated with either adjuvant radiation therapy or carboplatin. Overall cancer-specific survival at 99.8% (95% CI = 99.6% to 99.9%) was remarkably good.

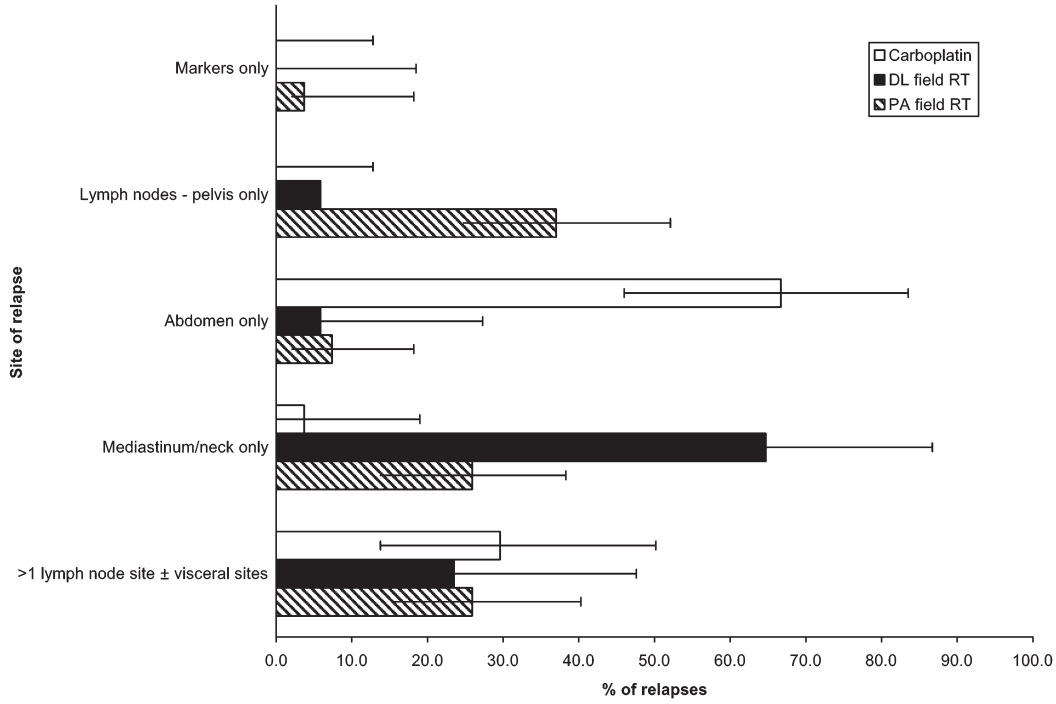

Figure 3. Sites of relapse by treatment type (n = 98 relapses). "Markers only" = raised α-fetoprotein or human chorionic gonadotropin as the only indication of relapse. DL = dogleg; PA = para-aortic; RT = radiation therapy. All error bars indicate 95% confidence intervals.

Mature results of the three randomized trials confirmed, as shown previously (3,4), the noninferiority of radiation therapy at 20 Gy compared with that at 30 Gy and the noninferiority of carboplatin compared with radiation therapy with respect to the relapse-free rate, with the 90% confidence limits excluding a doubling in the 5-year relapse rates. A noninferiority bound (ie, the maximum acceptable increase in relapse rate) with respect to overall relapse rates was not predefined for the comparison, para-aortic vs dogleg field radiation therapy (TE10) because this study was powered with respect to pelvic relapse rates; however, in this trial, the smallest of the three trials, we could exclude an absolute increase in the 5-year relapse rate of more 3.3% by a direct comparison of proportions and an increase of more than 5.2% by using the hazard ratio method. The data also provided helpful information about relapse sites, timing, and detection to guide clinicians in the follow-up of these patients.

This study had several limitations. As noted above, the randomized comparison in the TE10 trial was not powered to exclude

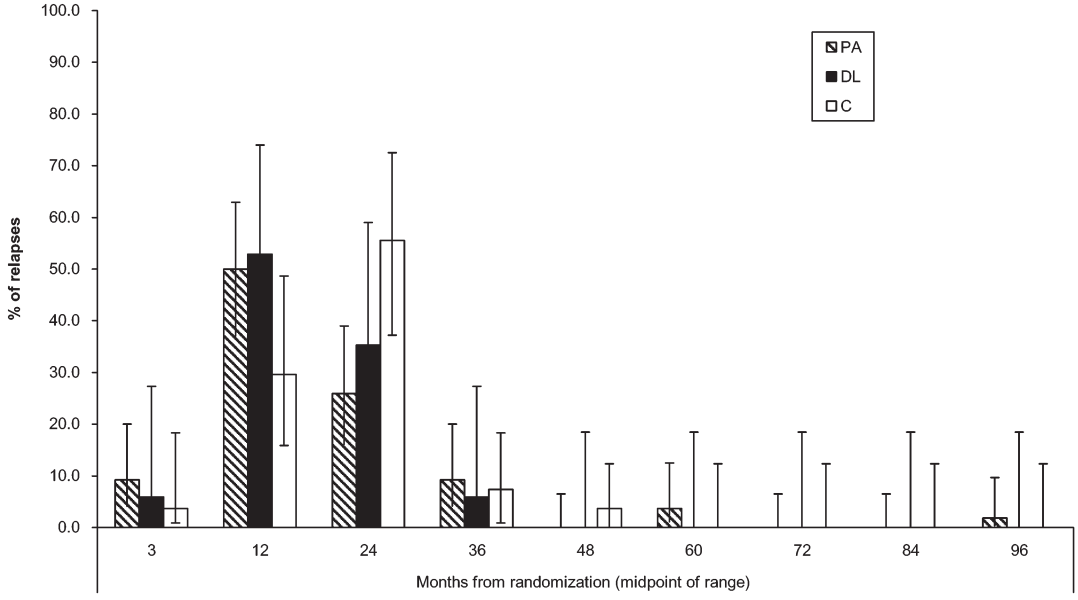

Figure 4. Time of relapse by treatment type (n = 98 relapses). All error bars indicate 95% confidence intervals. C = carboplatin; DL = dogleg; PA = para-aortic.

Table 2. The TE19 randomized trial: first indicator of relapse by treatment arm*

	Radiotherapy arm (n = 904)			Carboplatin arm (n = 573)		
First indicator of relapse	**No. relapses**	**% of relapses**	**% of patients**	**No. relapses**	**% of relapses**	**% of patients**
Symptoms/examination	18	58.1	2.0	7	26.9	1.2
Markers (AFP, HCG)	6	19.4	0.7	3	11.5	0.5
Abdominal CT	4	12.9	0.4	15	57.7	2.6
Chest CT	2	6.5	0.2	1	3.8	0.2
Pelvic CT	1	3.2	0.1	0	—	—
Chest x-ray	0	—	—	0	—	—
Not yet known	2	—	—	1	—	—
Total relapses	33	100	3.7	27	100	4.7

* AFP = α-fetoprotein; CT = computed tomography; HCG = human chorionic gonadotrophin.

clinically relevant differences in overall relapse rates. In addition, our recommendations with respect to follow-up were based on nonrandomized data from the three trials but were strengthened by the consistency of follow-up policies they used. Finally, despite median follow-up times of between 6 and 12 years, we cannot exclude the possibility that further late relapses may occur.

Results from surveillance studies [as reviewed (1)] indicate that 15%–20% of patients with stage I seminoma have low-volume metastatic disease that becomes apparent on follow-up. That study (1) and other studies (2–4) also indicate that cure should be almost universally possible for these patients, and management decisions, therefore, rest predominantly on the likely morbidity and convenience of different management approaches. Particular concern has been expressed about the treatment of this young patient population with adjuvant radiation therapy, which is associated with a marked increase in second malignancies after prolonged follow-up (5–7) and is thereby in rapid decline in the United Kingdom and the United States (8).

Surveillance is an entirely rational management approach because it avoids treatment-related morbidity for patients whose disease was cured by orchidectomy. This approach can be restricted to lower-risk patients, so that adjuvant treatment can be reserved for the remaining patients (9,10). There are, however, problems with surveillance. Unlike patients with nonseminoma, many patients with stage I seminoma relapse without elevation of serum marker levels α-fetoprotein and/or human chorionic gonadotrophin, which emphasizes the importance of CT scanning during follow-up. Relapses can also occur late, with 6.6% occurring after 5 years, as described previously (1). In addition, follow-up schedules have not been standardized, although an evidence-based proposal has recently been published (11), and many centers perform multiple follow-up CT scans for many years after diagnosis. Increasing concern has been expressed about the radiation exposure from CT scans (12), particularly among younger patients (13). Tarin et al. (12) reported that a single CT scan to the chest, abdomen, and pelvis delivers an organ-specific dose of 19 mSv to the stomach and 20 mSv to the bladder and lung and that from their calculations the lifetime attributable risk of secondary malignancy associated with a pretreatment CT scan followed by three more annual CT scans for an 18-year-old man, as used in the TE19 trial for example, would be approximately 0.64%. This estimate is approximately 25% of the risk associated with the National Comprehensive Cancer Network surveillance protocol, which includes 16 scans, as reported previously (12). Such issues motivated an MRC randomized trial (14) in patients with stage I non seminoma that sought to reduce radiation exposure by reducing the number of CT scans during surveillance and found that that a limited CT schedule was entirely effective at detecting relapse at an early stage. Although results for seminoma are yet not available, the ongoing MRC TE24 Trial of Imaging and Schedule in Seminoma Testis (TRISST) (15) was designed to identify the optimum surveillance strategy for stage I seminoma by examining scan frequency and comparing results of magnetic resonance imaging scans of the retroperitoneum with those of CT scans. Results of this trial have the potential of showing that this patient group can be screened by magnetic resonance imaging and so avoid exposure to x-rays from CT scans.

Adjuvant carboplatin therapy is a well-tolerated single treatment that has been shown to produce outcomes that are similar to those from radiation therapy, with the additional advantage of a marked reduction in the incidence of contralateral testicular cancer (4). Concerns have been expressed about the potential for long-term treatment-related morbidity in these patients, as described previously in patients who were treated with combination chemotherapy (7,16,17). However, the almost complete lack of toxicity associated with adjuvant carboplatin therapy, apart from short-term myelosuppression, and the lack of nephrotoxicity argue against this possibility, as confirmed in a recent retrospective review (18).

Adjuvant treatment with radiation therapy or carboplatin therapy has changed the natural history of seminoma, reducing the risk of relapse by approximately two-thirds. The relapse of only four (0.2%) of the 2466 patients in these studies occurred more than 3 years after treatment, indicating that screening with CT scans can be omitted after 3 years and also that routine follow-up may be unnecessary. Furthermore, close examination of relapse sites and the first symptoms or signs of relapse in patients in the TE19 trial (4) strongly indicates that follow-up with CT scanning may be unnecessary in patients treated with radiation therapy and can be limited to only two abdominal CT scans in patients treated with carboplatin therapy at years 1 and 2 after treatment. When discussions take place about management options for stage I seminoma, these proposals for a markedly reduced follow-up and the marked reduction in incidence of contralateral testicular cancer that was associated with this treatment—as described previously (4) and as confirmed in a recent update to the original article (19)—may have appeal for patients.

In summary, results of the three randomized trials that were described in this article provide data, which may be regarded as definitive, for the management and follow-up of patients with stage I seminoma who are treated with adjuvant radiation therapy or with carboplatin therapy. Results of this study confirm that cure rates need not be an issue when patients make management decisions after diagnosis for stage I seminoma. More important aspects of care were short-term treatment-related morbidity, long-term potential morbidity, follow-up schedules, and the duration of follow-up. We also have provided evidence that carboplatin therapy has changed the natural history of this disease, allowing short follow-up with minimal x-ray exposure and excellent long-term survival rates.

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Funding

Medical Research Council through its core funding of the MRC Clinical Trials Unit.

Notes

The authors had full responsibility for the design of the study; the collection, the analysis; and interpretation of the data; the decision to submit the article for publication; and the writing of the article.

We thank all the patients who consented to take part in these three trials, and all the investigators and research staff at the participating institutions for continuing to provide follow-up data on patients.

The Chief Investigator for TE10 was Professor S. D. Fossa (Norwegian Radium Hospital), for TE18 Dr Bill Jones (Cookridge Hospital, Leeds, UK [retired]), and for TE19 Professor Tim Oliver (St Barts and the London Hospitals [retired]) and Professor Malcolm Mason (Velindre Hospital, Cardiff, UK); Professor Hans von der Maase was Chief Investigator for the EORTC. All trials were coordinated by the Medical Research Council Clinical Trials Unit, London, UK, overseen by S. P. Stenning (senior statistician) with further statistical support from Sarah Kirk, Patrick Fogarty, and Rhian Gabe. The trial manager responsible for long-term follow-up was P. Pollock, and the data managers were James Pickering and Hassan Khan. TE18 and TE19 were supported by the EORTC, and independent oversight of the trials is provided by the Independent Trial Steering Committee (Chair Dr David Guthrie, other members Professor John Schofield and Dr Richard Cowan).

American Society for Clinical Oncology Annual Meeting, Chicago, June 2008; Clinical Trials Showcase, National Cancer Research Institute Annual Conference, Birmingham UK, October 2008.

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