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ORIGINAL REPORT

Randomized Trial of 30 Versus 20 Gy in the Adjuvant Treatment of Stage I Testicular Seminoma: A Report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328)

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To assess the possibility of reducing radiotherapy doses without compromising efficacy in the management of patients with stage I seminoma.

Patients and Methods
Patients were randomly assigned 20 Gy/10 fractions over 2 weeks or 30 Gy/15 fractions during 3 weeks after orchidectomy. They completed a symptom diary card during treatment and quality-of-life forms pre- and post-treatment. The trial was powered to exclude absolute differences in 2-year relapse rates of 3% to 4% ($\alpha = .05$ [one sided]; 90% power).

Results
From 1995 to 1998, 625 patients were randomly assigned to treatment. Four weeks after starting radiotherapy, significantly more patients receiving 30 Gy reported moderate or severe lethargy (20% *v* 5%) and an inability to carry out their normal work (46% *v* 28%). However, by 12 weeks, levels in both groups were similar. With a median follow-up of 61 months, 10 and 11 relapses, respectively, have been reported in the 30- and 20-Gy groups (hazard ratio, 1.11; 90% CI, 0.54 to 2.28). The absolute difference in 2-year relapse rates is 0.7%; the lower 90% confidence limit is 2.9%. Only one patient has died from seminoma (allocated to the 20-Gy treatment group).

Conclusion
Treatment with 20 Gy in 10 fractions is unlikely to produce relapse rates more than 3% higher than for standard 30 Gy radiation therapy, and data on an additional 469 patients randomly assigned in a subsequent trial support and strengthen these results. Reductions in morbidity enable patients to return to work more rapidly. Prolonged follow-up is required before any inference can be made about any impact of allocated treatment on new primary cancer diagnoses.

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INTRODUCTION

Approximately 75% of all seminoma patients present with clinical stage I disease. Of these, approximately 15% to 20% have subclinical metastatic disease, usually in the para-aortic lymph nodes, but reliable identification of these patients is not currently possible. Therefore, 80% to 85% of patients with stage I disease undergo unnecessary treatment in an attempt to achieve nearly 100% cure of the whole group. This gives impetus to initiatives to minimize or even omit adjuvant therapy postorchidectomy.

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Studies of surveillance in stage I seminoma[1,2] have confirmed the pattern of relapse, with the majority occurring in the retroperitoneal lymph nodes. The traditional treatment is therefore adjuvant radiotherapy to the retroperitoneum (para-aortic strip [PAS]), sometimes with the inclusion of the ipsilateral iliac nodes (dog-leg field [DL]). Such treatment is highly effective[3,4] and the great majority of patients experiencing relapse can be cured with additional radiotherapy or chemotherapy.

The acute side effects of abdominal irradiation include reversible nausea, occasional vomiting, and decreased performance status during and after treatment.[5] Later adverse effects can include reduced fertility and peptic ulceration.[6] The risk of developing new primary cancers after irradiation for seminoma is low, but significantly higher than in the normal population.[7] Many, if not all of these sequelae are likely to be radiation field and/or dose related. The Medical Research Council (MRC) randomized trial, TE10,[8] compared PAS only with DL irradiation of 30 Gy in 478 patients. There were nine relapses in each group (including four *v* zero pelvic relapses in the PAS and DL groups, respectively) and acute toxicity benefits with PAS. PAS irradiation is generally now considered standard treatment, with DL irradiation reserved for patients with prior ipsilateral inguinopelvic or scrotal surgery.

Although 30 Gy in 15 fractions is a widely used schedule, some centers have, apparently successfully, used doses as low as 20 Gy.[9,10] In addition to the potential patient benefits, reducing the radiotherapy dose could also reduce financial costs and save hospital radiotherapy resources if such a reduction were not associated with an increase in relapse rates.

This trial (MRC TE18/European Organisation for Research and Treatment of Cancer [EORTC] 30942) was therefore designed to compare the efficacy and the acute and long-term morbidity of standard radiotherapy with 30 Gy in 15 fractions versus 20 Gy in 10 fractions. Our subsequent trial TE19 (EORTC 30982), comparing radiotherapy with single-agent carboplatin, began recruiting before the results of TE18 were available. Optionally, patients allocated radiotherapy within TE19 could be randomly assigned between 20 and 30 Gy, with the intention that these patients could also contribute to the question addressed by TE18 at a later date. The main body of this report concerns only the patients entered onto TE18/30942, but early data on the additional TE19 patients are included at the end of Results.

PATIENTS AND METHODS

Eligibility

Patients had histologically confirmed seminomatous germ cell tumor of the testis, with stage I disease based on clinical and radiologic examination, and normal postorchidectomy alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG). Increased serum AFP (but not HCG) preorchidectomy rendered a patient ineligible. Patients with pT1-3 tumors were eligible but not those with involvement of the cut end of the spermatic cord (pT4).[11] Patients had no coexistent or previously treated malignant disease or other condition or factor preventing adherence to the study schedule and follow-up, and gave written informed consent for entry into the study before they were randomly assigned to treatment. Local ethical committee approval had to be obtained by each participating center.

Randomization

Patients were randomly assigned to treatment within 8 weeks of orchidectomy by telephoning the Cancer Division of the MRC Clinical Trials Unit (London [formerly Cambridge], United Kingdom). Treatment was allocated using minimization, with stratification for center and intended radiotherapy field (DL/PAS), and was to start within 2 weeks of random assignment.

Treatment

Treatment planning. Radiotherapy was planned with the aid of an intravenous urogram to define the position of the kidneys. For the rectangular para-aortic field, margins were drawn to represent the 50% isodose line as follows: upper border, D10-11 disk space; lower border, L5-S1 disk space; ipsilateral margin, out to the renal hilum; contralateral margin, to include the transverse processes in the para-aortic area. For the DL field (to be used for patients with prior inguinopelvic or scrotal surgery) the treating center's usual technique was used, with scrotal shielding applied in patients wishing to preserve fertility.

Patients were treated only on linear accelerators. Treatment was given by anterior and posterior equally weighted fields; both fields were treated daily, 5 days/wk.

Dose and fractionation. Treatment comprised 30 Gy (midplane dose) given in 15 daily (Monday through Friday) fractions of 2 Gy, or 20 Gy in 10 daily fractions of 2 Gy. Patients who missed a fraction for any reason were treated to the same dose and with the same fraction size, extending the overall treatment time slightly. A weekly CBC was required, plus any other investigation directed by the clinical situation.

Follow-Up Investigations and Management of Relapse

Follow-up assessments took place every 3 months in year 1, every 4 months in year 2, every 6 months in year 3, and annually until year 10. Clinical examination and serum tumors markers were required at each visit; chest x-rays were required at the 6-, 12-, 20-, 30-, and 36-month visits; and computed tomography scans of chest, abdomen, and pelvis were required at the 12-, 24-, and 36-month visits. On suspicion of recurrence, thorough investigation to document the site and extent of disease was required. Current standard chemotherapy regimens for metastatic seminoma were generally recommended, but relapses that were well localized outside the previously irradiated volume could be managed with radiotherapy at the treating clinician's discretion.

Outcome Measures

The primary outcome measure was the relapse-free rate, with relapse defined as the development of new masses (detected clinically or radiologically), or increasing tumor-specific markers (AFP, HCG). All deaths and causes of death, and all second malignancies were also recorded.

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A secondary objective was to determine the impact of dose on acute morbidity and quality of life. Patients therefore completed a diary card of symptoms (lethargy, work status, nausea or vomiting, diarrhea, and medication for symptoms) daily for 4 weeks from the start of treatment and then weekly for the next 8 weeks. Symptoms were recorded as none, mild, moderate, or severe, with the number of vomits and bowel openings also recorded. The diary card was not developed with specific psychometric testing, but was based on those used extensively in MRC trials of radiotherapy in lung cancer. Clinicians also reported the maximum WHO grade for nausea or vomiting and hematologic toxicity recorded during treatment.

Patients were also asked to complete the EORTC core quality-of-life questionnaire[12] and testis cancer module[13] before random assignment to treatment, and then at 3, 6, 12, and 24 months after random assignment. These data will be examined in a subsequent article.

Statistical Considerations

Sample size. A 2-year relapse-free rate of 3% to 4% was anticipated. The trial was designed as a noninferiority trial, aiming to exclude clinically relevant differences in relapse rate through the use of the lower radiotherapy dose. Clinicians were asked to define what absolute difference in relapse rates (in favor of 30 Gy) would lead them to use 20 and 30 Gy routinely; the points in between defined their ranges of equivalence. The typical range of equivalence was from 2% to 4%. It was therefore essential that, under the assumption of underlying equivalence, the trial could exclude a 4% deficit and it was desirable to exclude smaller differences. To exclude a difference of 4% required 600 patients (probability of erroneously concluding noninferiority, 5%; probability of correctly concluding noninferiority, 90%); to exclude a 3% (2%) difference would require 1,100 (2,500) patients with the same error rates. A target of 600 patients was set for this trial, with additional patients (bringing the total to approximately 1,100) to be contributed from the subsequent TE19/30982 trial in which patients were randomly assigned between carboplatin and radiotherapy, with an optional random assignment with respect to radiotherapy dose as in TE18. An independent Data Monitoring Committee reviewed data from both trials before recommending publication of the TE18 results.

We estimated that 15% to 20% of patients would report moderate to severe lethargy (which influenced their work status) during treatment with 30 Gy, with the peak effect occurring during and immediately after the final week of treatment. A total of 600 patients was sufficient to detect a 50% relative reduction in the proportion of patients suffering moderate or severe lethargy or limitation of their ability to work, at 4 weeks and also 3 months from the start of treatment ($>$ 90% power; 5% significance level, two-sided).

Analysis. Relapse-free rates were calculated using the Kaplan-Meier method and compared using the log-rank test; hazard ratios (HRs) and 90% CIs were computed using Cox's proportional hazards regression model (HR $>$ 1 favors 30 Gy). The absolute differences in relapse rates at specific time points and their 90% CIs were first computed using direct comparison of proportions. Given that event rates at specific time points are not necessarily good estimates of the overall pattern of differences, these results were confirmed by applying the HR (based on the entire event-free curves) and its 90% CI to the control group event-free rate at the time points of interest. This makes use of the relation HR = $\ln P_2/\ln P_1$ under the proportional hazards assumption. Comparisons of categoric data used χ^2 tests or χ^2 tests for trend as appropriate. For the primary outcome measure, both intent-to-treat and per-protocol analyses were carried out, the latter being more conservative for equivalence and noninferiority trials,[14] in which compliance is poor.

RESULTS

Between May 1995 and January 1998, 625 patients were randomly assigned by 80 clinicians from 45 hospitals in the United Kingdom, the Netherlands, Italy, Norway, Belgium, Australia, and New Zealand. Median patient age was 38 years in each treatment group (range, 20 to 80 years).

Treatment

The median time from orchidectomy to the start of treatment was approximately 7 weeks, comprising a median of 37 days from orchidectomy to random assignment and 10 days from random assignment to the start of radiotherapy. Exact treatment compliance, as shown in Table 1, was more than 98% in both arms.

Acute Morbidity

Physician-reported toxicities noted during treatment are shown in Table 2; 19.7% of patients allocated 30 Gy and 18.4% of patients allocated 20 Gy had grade 3 to 4 nausea and vomiting, and overall there was a slight trend toward higher grades in the 30-Gy group (χ^2 test for trend, $P = .06$). It should be noted that 5-hydroxytryptamine-3 serotonin antagonist antiemetics became available during the time period in which the study was performed, and were available to patients in both study arms. Leukopenia was also more pronounced in the 30-Gy group (χ^2 test for trend, $P = .02$). However there was no grade 4 toxicity and only two patients with grade 3 toxicity were reported (both in

Table 1. Treatment Allocated and Received

Treatment	Allocated Treatment: 30 Gy (n = 313) No. of Patients	30 Gy (n = 313) %	20 Gy (n = 312) No. of Patients	20 Gy (n = 312) %
Dose received				
30 Gy in 15 fractions	306	98.1	2	0.6*
28 Gy in 14 fractions	2‡			
26 Gy in 13 fractions	1‡			
20 Gy in 10 fractions	2	0.6†	309	99.0
None	1§		1§	
Dose missing	1		0	
% Having para-aortic strip irradiation		88.1		88.7
% Using scrotal shielding		9.4		10.0

*One in error, one by patient request post-randomization.
†One in error, one patient refused last five fractions.
‡All three patients refused final fraction(s) due to gastrointestinal toxicity.
§Patient withdrew.

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Table 2. Maximum Toxicity During Radiotherapy (physician recorded)

	Allocated Treatment			
	30 Gy, 15 Fractions		20 Gy, 10 Fractions	
Toxicity (grade)	Count	%	Count	%
Nausea or vomiting*				
0	68	22.0	95	30.6
1	133	43.0	127	41.0
2	47	15.2	31	10.0
3	60	19.4	56	18.1
4	1	0.3	1	0.3
Not known	4		2	
Leucopenia†				
0	241	81.7	244	85.9
1	34	11.5	35	12.3
2	18	6.1	5	1.8
3	2	0.7	0	0.0
Not known	18		28	
Thrombocytopenia‡				
0	292	99.0	285	100
1	2	0.7	0	0.0
3	1	0.3	0	0.0
Not known	18		27	
Total	313		312	

*χ^2 (trend) $P = .06$.
†χ^2 (trend) $P = .02$.
‡χ^2 (trend) $P = .12$.

patients allocated 30 Gy). Twenty percent of the patients receiving 30 Gy and 16.7% of the patients receiving 20 Gy reported dyspepsia during radiotherapy ($P = .30$).

Seventy-two percent of patients completed at least part of the diary cards. Approximately 15% of patients in each treatment group stopped completing the diary cards immediately after completing treatment. However, the dropout rate was equal in the two treatment groups at 4 weeks after starting treatment, and there was no evidence that dropout was related to the previous morbidity pattern. The data are therefore assumed to be missing completely at random, and Figures 1 and 2 (which show the proportion of patients reporting moderate or severe lethargy and inability to carry out normal work, respectively) include all data available at each time point and not just those patients completing the entire diary card. Both the proportion with moderate to severe lethargy (20% *v* 5%) and the proportion unable to work (46% *v* 28%) were significantly higher in the group receiving 30 Gy at 4 weeks ($P < .001$), but levels in both groups returned to baseline by 12 weeks.

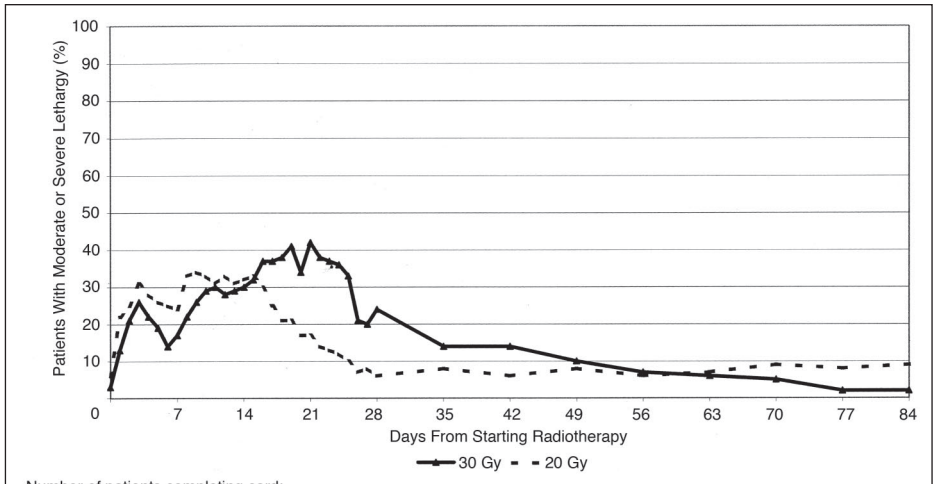
Follow-Up

Median patient follow-up is now 61 months in each group; 95% of patients have been observed for at least 2 years and 70% for at least 5 years.

Relapse, Survival, and Second Malignancies

A total of 21 relapses have been reported; 10 in the 30-Gy group and 11 in the 20-Gy group. Details of initial treatment received and the site, timing, and treatment of relapse are shown in Table 3; the Kaplan-Meier relapse-free curves are shown in Figure 3.

Of patients allocated to receive 30 Gy, the site of relapse was in the pelvic lymph nodes only in six patients, abdominal lymph nodes in three patients, and mediastinum in one patient. The majority of patients received bleomycin, etoposide, and cisplatin chemotherapy for relapse, although one patient received etoposide and cisplatin. One patient was managed by surgery alone when a 1.5-cm abdominal node, which appeared 20 months after starting radiotherapy, was found to contain teratoma differentiated only. All



Number of patients completing card:

	Weeks From Start of Treatment											
	1	2	3	4	5	6	7	8	9	10	11	12
30 GY	210	223	225	206	141	138	136	135	130	125	116	106
20 Gy	221	228	209	165	144	139	136	130	123	115	112	105

Fig 1. Patient diary card: percentage of patients with moderate or severe lethargy.

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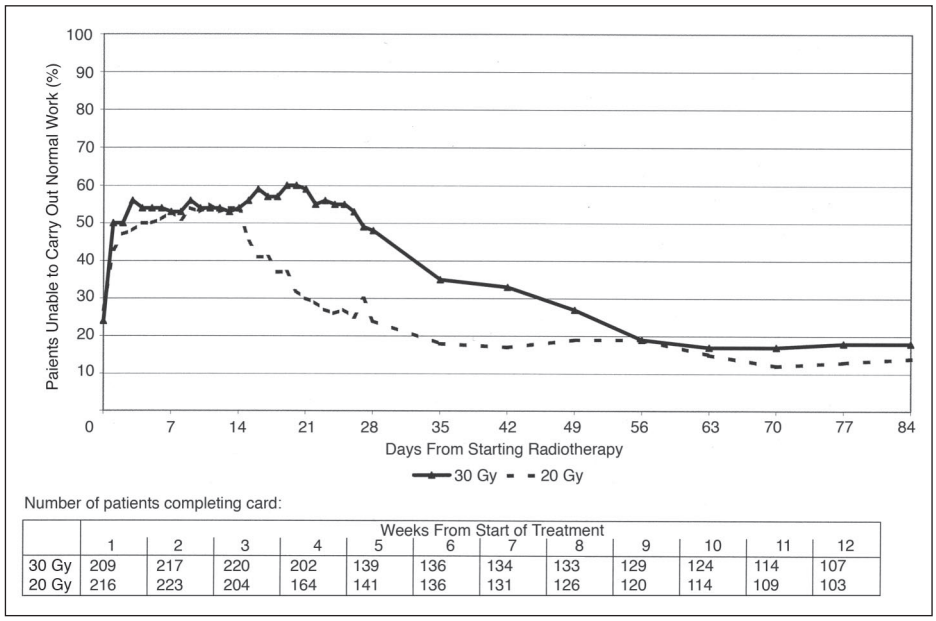

Number of patients completing card:

	Weeks From Start of Treatment											
	1	2	3	4	5	6	7	8	9	10	11	12
30 Gy	209	217	220	202	139	136	134	133	129	124	114	107
20 Gy	216	223	204	164	141	136	131	126	120	114	109	103

Fig 2. Patient diary card: percentage of patients unable to carry out normal work.

but two patients remain alive and free of active disease after treatment for relapse; one patient is alive with disease at multiple sites and another died as a result of suicide 32 months after his relapse was successfully treated. One additional (relapse free) patient died in a car accident 12 months after random assignment to treatment.

Of those allocated to receive 20 Gy, the sites of relapse were pelvic lymph nodes only in three patients, elevated

Table 3. Relapse Details

Patient No.	Received Treatment	Time to Relapse (months)	Site of Relapse	Maximum Diameter (cm)	Treatment	Current Status	Follow-Up Time Since Relapse (months)
Relapses in patients allocated 30 Gy in 15 fractions							
1	30 Gy/15# PAS	7	Pelvic nodes	2.3	BEP	Disease free	12
2	30 Gy/15# DL	10	Pelvic nodes	6	BEP	Disease free	60
3	30 Gy/15# PAS	11	Pelvic nodes	6	BEP	Inactive LN disease	21
4	30 Gy/15# PAS	13	Pelvic nodes	4	BEP/EP	Disease free	70
5	30 Gy/15# PAS	13	Mediastinal nodes	3	BEP	Disease free	38
6	30 Gy/15# PAS	18	Pelvic nodes	3	BEP	Dead, suicide	32
7	30 Gy/15# PAS	20	Abdominal nodes	1.5	Surgery	Disease free	49
8	30 Gy/15# PAS	24	Mass behind bladder	6	BEP	Active disease, multiple sites	37
9	30 Gy/15# PAS	36	Pelvic nodes	4	BEP	Disease free	24
10	30 Gy/15# PAS	64	Abdominal nodes, HCG	1.7	EP	Disease free	9
Relapses in patients allocated 20 Gy in 10 fractions							
1	20 Gy/10# PAS	6	Left pelvis/Iliac nodes	3	BEP	Disease free	21
2	20 Gy/10# PAS	6	Abdominal nodes, lung	Not given	EP	Dead, recurrent seminoma	24
3	20 Gy/10# DL	9	Bone, pleura	—	DXT C-BOP/BEP	Disease free	44
4	20 Gy/10# PAS	11	Right pelvis	10	BEP	Disease free	75
5	20 Gy/10# PAS	10	Marker only, HCG	—	BEP	Disease free	10
6	20 Gy/10# DL	12	Mediastinal nodes	2.7	BEP	Disease free	18
			Supraclavicular nodes	6			
7	20 Gy/10# DL	14	Abdominal, HCG	7	EP	Residual mass on surveillance	6
8	20 Gy/10# DL	16	Mediastinal nodes	3	DXT; EP	Disease free	51
9	20 Gy/10# PAS	19	Right pelvis	8	BEP	Disease free	53
10	20 Gy/10# PAS	28	Mediastinal	8	BEP	Disease free	12
11	20 Gy/10# PAS	34	Mediastinal	Not given	BEP	Disease free	23

NOTE. # symbol indicates number of fractions.
Abbreviations: DL, dog-leg field; PAS, para-aortic strip; BEP, bleomycin, etoposide, cisplatin; EP, etoposide-cisplatin; DXT, radiotherapy; C-BOP, carboplatin, bleomycin, vincristine, cisplatin; HCG, human chorionic gonadotropin.

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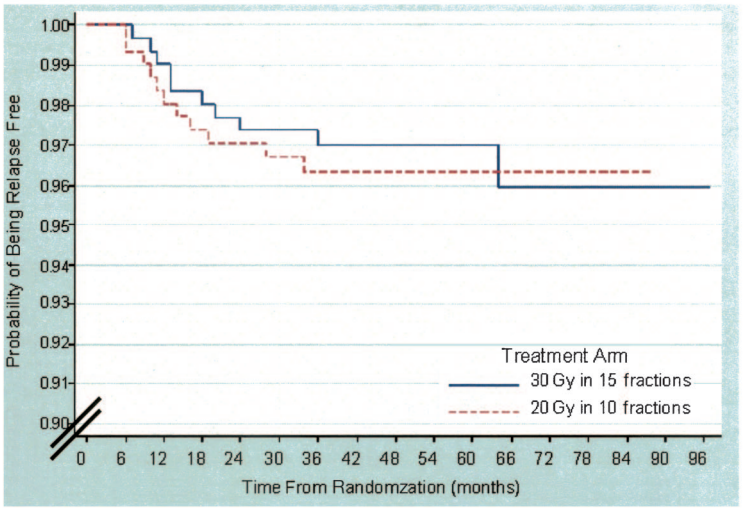

Number of patients at risk:

Treatment Arm	Time From Randomization (months)								
	0	12	24	36	48	60	72	84	96
30 Gy in 15 fractions	313	302	290	281	266	207	71	21	2
20 Gy in 10 fractions	312	298	287	275	257	193	71	13	-

Fig 3. Relapse-free rates by allocated treatment.

serum marker (HCG, 48 U/L) only in one patient, abdominal nodes only in one patient, and mediastinum only in three patients. An additional three patients experienced relapse in multiple sites (abdomen and lung, bone and pleura, and mediastinum and neck, respectively). Again, the majority were treated with bleomycin, etoposide, and cisplatin, or etoposide and cisplatin, and two patients received radiotherapy to the involved site. One patient died as a result of recurrent seminoma but the remaining patients who experienced disease relapse all remain alive and disease free. An additional three (relapse free) patients have died from unrelated causes, two as a result of cardiovascular disease and one in a car accident.

The intent-to-treat HR for relapse is 1.11 (90% CI, 0.54 to 2.28; log-rank $P = .81$) and the per-protocol analysis results were almost identical (HR, 1.10; $P = .83$). Relapse-free rates at 2 years are 97.7% (95% CI, 95.2% to 98.9%) and 97.0% (95% CI, 94.4% to 98.4%) in the 30- and 20-Gy groups respectively. The corresponding 5-year rates are 97.0% (95% CI, 94.3% to 98.3%) and 96.4% (95% CI, 93.5% to 98.0%) respectively. The observed difference in relapse-free rate (30 − 20 Gy) at 2 years is 0.7%, with the lower 90% confidence limit 2.9% by both methods. Thus, the estimated difference in relapse rates is less than 1%, and at the 5% level (one sided) we can exclude an increase in 2-year relapse rates associated with the lower radiotherapy dose of 3% or more.

Six new non–germ cell primary cancer diagnoses have been confirmed, all in patients treated with 30 Gy: two skin cancers of the scalp (one malignant melanoma, one basal cell carcinoma), two prostate cancers, one bladder cancer, and one low-grade non-Hodgkin's lymphoma. Nine new germ cell primaries have been reported, with three among patients allocated to receive 30 Gy (all seminoma) and six in patients allocated to receive 20 Gy (three seminoma, three nonseminoma).

Addition of Early Data From TE19/30982

After the closure of TE18, 469 additional patients allocated radiotherapy in trial TE19/30982 were randomly assigned with respect to radiotherapy dose (20 *v* 30 Gy). Median follow-up is shorter at 2.5 years, but to date 15 relapses have been reported among patients allocated 30 Gy compared with only four relapses in those patients allocated 20 Gy. Combining these data with those from TE18 gives a total of 1,094 patients, 550 allocated to receive 30 Gy and 544 allocated to receive 20 Gy. The updated HR is 0.62 (90% CI, 0.36 to 1.07) and the 2-year relapse-free rates are 96.8% (95% CI, 94.8% to 98.0%) and 97.5% (95.8% to 98.6%), respectively. The observed difference in relapse-free rates at 2 years (30 − 20 Gy) is therefore 1.3% in favor of 20 Gy, and at the 5% significance level (one sided), we can exclude an increase in relapse rates associated with the lower radiotherapy dose of 0.5% or more.

DISCUSSION

Postoperative radiotherapy has been the main adjuvant therapy for seminoma testis for more than 50 years.[15]

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During that time, better equipment has been developed and techniques have become more refined. Similarly, improved diagnostic imaging (especially computed tomography and magnetic resonance imaging scanning) has led to a more accurate definition of clinical stage.[16] Seminoma is regarded as one of the most radiosensitive tumors, and radiation doses required to eradicate small metastatic deposits are low in comparison to those required for other solid tumors. Cure rates are high—of the order of 98%. However, the therapy still carries a degree of morbidity and, surprisingly, the extent of this and its impact on the patient and his daily life has been poorly documented in the medical literature.

This large randomized study simply set out to compare the results of a standard dose of 30 Gy in 15 fractions of radiotherapy with the lower dose of 20 Gy in 10 fractions, and to study the morbidity of the therapies and their impact on quality of life. The treatment arms were evenly matched by patient characteristics and treatment compliance was excellent.

Our trial demonstrates that 20 Gy in 10 daily fractions during 2 weeks is highly effective adjuvant treatment for stage I testicular seminoma. In comparison with 30 Gy given in 15 daily fractions of 2 Gy, acute morbidity is reduced. Treatment-related lethargy and inability to carry out normal work is significantly reduced in the short term. With median follow-up of more than 5 years, data from TE18 alone allows an absolute increase in relapse rates of more than 3% to be excluded reliably, and cancer-specific survival exceeds 99%. Furthermore, early data from randomly assigned patients with respect to radiotherapy dose within the subsequent TE19 trial add additional confidence in these conclusions, enabling absolute differences of more than 1% to be excluded reliably.

There is published evidence of an increased risk of new, treatment-induced, primary non–germ cell cancers in testicular cancer patients treated with radiotherapy.[7,17-19] In addition, a recent report from M.D. Anderson Cancer Center[20] (Houston, TX) concluded that survivors of testicular seminoma, treated with surgery and radiotherapy only, had a significant excess risk of death from cardiac disease as well as from second cancers. It must be acknowledged that these reports include patients treated in an era of less sophisticated radiotherapy equipment and techniques, and that radiation-induced cancers may take 20 to 30 years to manifest themselves. Collectively, they suggest at least a three-fold relative increase in risk of gastric cancers in patients undergoing radiotherapy compared with those on surveillance.

Participants in the TE18 trial will be observed over a long period to document the incidence of new primaries, to determine whether there is an excess over the rate expected, and to see if there is a difference in new primary non–germ cell tumor rates by treatment arm. With a median follow-up of 5 years, all six new non–germ cell primary cancers have occurred in patients allocated to receive 30 Gy. Although it is too soon to draw conclusions about dose-response in this study, there is evidence of such an effect in other sites; for example, breast cancer incidence after radiotherapy for Hodgkin's lymphoma.[21]

New germ cell primaries are more likely to be related to the causative factors of the first tumor than the therapy, and generally occur earlier than treatment-induced malignancies; up to 5% of patients with unilateral testis cancer develop bilateral tumors, with a median time between diagnoses of 5 years.[22] The incidence noted to date within this study is therefore in the range expected in this patient group.

The absolute risk of additional primary malignancies is low. However, at least 80% of patients treated adjuvantly receive unnecessary treatment. This encourages the study of treatment schedules, which minimize radiotherapy dose without compromising efficacy, and of alternative approaches, including surveillance and adjuvant chemotherapy. All of these approaches aim to reduce the sequelae of treatment for these patients, the great majority of whom will have a normal life span.

Identifying the 20% to 25% of patients destined to experience relapse after orchidectomy alone is not currently possible, although the recent publication[23] of combined data on postorchidectomy surveillance for stage I seminoma has identified possible risk factors. However, even the high-risk group has a 5-year relapse-free rate of approximately 70%, and focusing adjuvant treatment only on these patients, with surveillance for the rest, would prevent only a third of all relapses. Surveillance is not a straightforward management option, and requires radiologic surveillance to be intensive and prolonged if relapse is to be diagnosed at an early stage. Radiotherapy (or chemotherapy, if shown to be effective) is therefore likely to remain the treatment of choice in countries and health care systems where such follow-up schedules are difficult to apply. The MRC/EORTC TE19/30892 trial, in which nearly 1,500 stage I seminoma patients have been randomly assigned between postoperative radiotherapy (20 to 30 Gy) or a single dose of carboplatin (area under the time-concentration curve of 7), will demonstrate whether this simple chemotherapy can provide a satisfactory alternative to irradiation. Preliminary results of this trial[24] indicate that this may indeed be so; with a median follow-up time of 3 years, absolute increases in the 2-year relapse rate of more than 3% among patients allocated carboplatin could be excluded reliably and early data on second germ cell cancers strongly favors the carboplatin-treated group.

In conclusion, this study has shown that, compared with 30 Gy given in 15 fractions during 3 weeks, 20 Gy given in 10 fractions during 2 weeks produces excellent results, with less inconvenience to the patient in terms of the numbers of hospital visits and severity of adverse effects, allowing a speedier resumption of normal living. There is also a minor financial advantage to the health care provider. Longer term follow-up may indicate whether early suggestions of a dose-response relationship with respect to new primary cancers, seen also in Hodgkin's lymphoma, are confirmed.

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Appendix

The following investigators participated in this trial: The chief investigator was Dr W.G. Jones, Leeds; the EORTC principal investigator was Dr Wijnmaalen, Rotterdam. The trial was coordinated by the MRC Clinical Trials Unit: senior statistician, Sally Stenning; statistician, Sarah Kirk; trial managers, Rupert Jakes, Eric Lallemand, Sharon Naylor, Neil Kelk, and Robert Owens.

The following centers and clinicians entered patients onto the trial (number of patients appears in parentheses): Aberdeen Royal Infirmary, Bissett D (4 patients); Academic Hospital, Nijmegen, NL, Bekker J (6 patients), Pop L (5 patients); Academisch Ziekenhuis, Leiden, NL, Keizer HJ (1 patient); Academisch Ziekenhuis VUB, Brussels, BE, Keuppens F (1 patient); Addenbrooke's Hospital, Cambridge, Williams MV (4 patients); Beatson Oncology Centre, Glasgow, Dodds D (4 patients), Harnett A (1 patient), Junor E (3 patients); Belvoir Park Hospital, Belfast, Clarke J (1 patient), Moore K (4 patients); Box Hill Hospital, Australia, McKendrick J (3 patients); Bristol Oncology Centre, Falk S (1 patients), Graham J (24 patients); Bristol Royal Infirmary, Newman H (4 patients). Circolo Hospital, Italy, Bono A (4 patients); Clatterbridge Hospital, Liverpool, Errington R (3 patients), Littler J (6 patients), Maguire J (1 patient), Slater A (2 patients), Smith D (1 patient), Syndikus I (7 patients); Cookridge Hospital, Leeds, Bottomley D (1 patient), Close H (1 patient), Jones W (39 patients); Dr Bernard Verbeeten Institute, Tilberg, NL, de Winter (1 patient), Poortmans PH (2 patients); Dunedin Hospital, New Zealand, North J (3 patients); Hospitale B.Ramazzini, Italy, Brausi M (8 patients); Ipswich Hospital, LeVay J (2 patients); Leicester Royal Infirmary, Madden F (16 patients); Middlesex Hospital, Duchesne G (11 patients), Harland S (2 patients), Payne H (1 patient); Mount Vernon Hospital, Hoskin P (7 patients), Makepeace A (1 patients), Rustin G (14 patients); Newcastle General, Branson A (1 patient), Podd T (1 patient), Ritchie D (1 patient), Roberts JT (42 patients); Norfolk and Norwich, Baillie-Johnson H (1 patient); North Middlesex, Karp S (1 patient); Northampton General, Houghton A (10 patients), Levy D (1 patient); Norwegian Radium Hospital, Oslo, Norway, Aass N (12 patients), Fossa S (69 patients). Nottingham City Hospital, Sokal M (33 patients); Queen Elizabeth Hospital, Birmingham, Coulter C (1 patient), Cullen M (4 patients), James ND (3 patients), Peake D (3 patients); Raigmore Hospital, Inverness, Whillis D (6 patients); Royal Berkshire, Barrett J (2 patients); Royal Devon & Exeter, Hong A (5 patients), Nethersell AEW (1 patient); Royal Marsden Hospital, Dearnaley D (11 patients), Horwich A (28 patients); Royal Shrewsbury, Agrawal R (7 patients); Royal South Hants, Mead G (58 patients); Royal Sussex County, Hodson N (5 patients); Royal United Hospital, Gilby E (1 patient); Singleton Hospital, Swansea, Askill C (8 patients); South Cleveland, Rathmell A (5 patients); Southend General, Robinson A (7 patients); St Mary's Hospital, Portsmouth, Mead G (1 patient); Sussex Oncology Centre, Newman G; (1 patient) The Churchill Hospital, Oxford, Alcock C (2 patients), Cole D (5 patients), Rowell N (2 patients), Sugden E (1 patient); University Hospital Antwerp, Belgium, Hoekx L (2 patients); Velindre Hospital, Cardiff, Mason M (21 patients); Western General Hospital, Edinburgh, Howard G (24 patients); Western Infirmary, Glasgow, Canney P (2 patients), Harnett A (1 patient), Russell J (5 patients), Yosef H (2 patients). Weston Park Hospital, Sheffield, Champion A (24 patients), Coleman R (5 patients), Robinson M (1 patient).

The independent Data Monitoring Committee comprised: Judith Bliss (Institute of Cancer Research, Chair), Graham Read (Royal Preston Hospital) and Hans-Joachim Schmoll (Universität Halle-Wittenberg).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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