Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial

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Summary

Background The standard treatment for spinal cord compression caused by metastatic cancer is corticosteroids and radiotherapy. The role of surgery has not been established. We assessed the efficacy of direct decompressive surgery.

Methods In this randomised, multi-institutional, non-blinded trial, we randomly assigned patients with spinal cord compression caused by metastatic cancer to either surgery followed by radiotherapy (n=50) or radiotherapy alone (n=51). Radiotherapy for both treatment groups was given in ten 3 Gy fractions. The primary endpoint was the ability to walk. Secondary endpoints were urinary continence, muscle strength and functional status, the need for corticosteroids and opioid analgesics, and survival time. All analyses were by intention to treat.

Findings After an interim analysis the study was stopped because the criterion of a predetermined early stopping rule was met. Thus, 123 patients were assessed for eligibility before the study closed and 101 were randomised. Significantly more patients in the surgery group (42/50, 84%) than in the radiotherapy group (29/51, 57%) were able to walk after treatment (odds ratio 6·2 [95% CI 2·0–19·8] p=0·001). Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days *vs* 13 days, p=0·003). 32 patients entered the study unable to walk; significantly more patients in the surgery group regained the ability to walk than patients in the radiation group (10/16 [62%] *vs* 3/16 [19%], p=0·01). The need for corticosteroids and opioid analgesics was significantly reduced in the surgical group.

Interpretation Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.

Introduction

Metastatic epidural spinal cord compression (MESCC) is a debilitating and common complication of cancer, occurring in 5–14% of cancer patients. More than 20 000 new cases are reported every year in the USA.[1,2] Acute onset of MESCC needs immediate treatment.[3,4] Standard treatment for MESCC consists of corticosteroids and radiotherapy,[3,4] with which only about 50% of patients are able to walk and few non-ambulatory patients ever walk again.[1–9] The role of surgery in the management of MESCC has not been established. Before radiation became available, surgery (in the form of simple laminectomy) was the only treatment. With the introduction of radiotherapy, results with laminectomy plus radiation did not seem to differ from results with radiation alone. Surgical treatment was largely abandoned when several retrospective studies[5–10] and a small randomised trial[11] did not show any benefit for laminectomy alone or in combination with radiotherapy. However, laminectomy might not be the best operation for MESCC. Most spinal metastases causing MESCC are located in the vertebral body, anterior to the spinal cord.[1,2] Laminectomy involves the removal of posterior elements of the spinal column and does not remove tumour, and thus often does not result in immediate decompression. Furthermore, the procedure can cause destabilisation of the spine because often only the

posterior elements are intact and removal of these elements causes instability.

In the 1980s, another type of surgical procedure was developed for the treatment of MESCC. The tumour was removed and immediate circumferential decompression was achieved, usually through an anterior approach. When needed, reconstruction of the spine intraoperatively was possible to provide immediate stabilisation. Several uncontrolled surgical series[12–16] and a meta-analysis[17] reported that direct decompressive surgery, with or without postoperative radiotherapy, was superior to radiation alone. However, these non-randomised studies were subject to patient selection bias, heterogeneous tumour types, unclear inclusion criteria, and imprecise endpoints. Consequently, these studies have not established direct decompressive surgery as an effective treatment. To determine the value of surgery in the management of MESCC, we undertook a randomised trial comparing the efficacy of direct decompressive surgery plus postoperative radiotherapy with that of radiotherapy alone.

Methods

Patients

Patients at least 18 years old with a tissue-proven diagnosis of cancer (not of CNS or spinal column origin) and MRI evidence of MESCC were eligible for the study.

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MESCC was defined radiographically as a true displacement of the spinal cord (by an epidural mass) from its normal position in the spinal canal. Patients also had to have at least one neurological sign or symptom (including pain) and not have been totally paraplegic for longer than 48 h before study entry. The MESCC had to be restricted to a single area, which could include several contiguous spinal or vertebral segments. Patients with a mass that compressed only the cauda equina or spinal roots were excluded. Those with multiple discrete compressive lesions were also excluded (unless they had one area of compression and multiple non-compressive lesions). Patients with certain radiosensitive tumours (lymphomas, leukaemia, multiple myeloma, and germ-cell tumours) were excluded, as were patients with pre-existing or concomitant neurological problems not related directly to their MESCC (eg, brain metastases). Additionally, patients with previous MESCC and those who had received spinal radiation such that they were unable to receive the study dose were excluded. Patients also had to have a general medical status good enough to be acceptable surgical candidates and an expected survival of at least 3 months.

The study was approved by the institutional review boards of the University of Kentucky and other participating institutions, and written informed consent was obtained from all patients before study entry.

Procedures
The study was a randomised, multi-institutional, non-blinded trial with two treatment groups. Before randomisation, all patients had imaging of the entire spinal cord. The imaging technique consisted of MRI with whole spine sagittal T1 and T2 imaging and axial T1 imaging. Additional MRI techniques were used as clinically appropriate. There was a central review of all MRI scans for confirmation of MESCC.

When diagnosed, all patients were given 100 mg dexamethasone immediately, then 24 mg every 6 h until the start of radiotherapy or surgery. Corticosteroids were then reduced and continued until completion of radiotherapy. Patients with severe diabetes or other relative contraindications to high-dose corticosteroids were treated with reduced doses when appropriate.

Before randomisation, patients were stratified according to treating institution, tumour type, ambulatory status, and relative stability of the spine. Spinal stability was ascertained according to Cybulski's guidelines.[18] Patients with pathological spine fractures or evidence of bone in the spinal canal were also judged to have spinal instability. Randomisation within strata by permutated blocks was done separately at each institution with a computerised technique, which ensured immediate randomisation at study entry. The study was undertaken by the Bluegrass Neuro-Oncology Consortium with seven participating institutions (University of Kentucky [n=70 patients], MD Anderson [n=14], Brown University [n=12], University of Alabama-Birmingham [n=2], University of Michigan [n=1], University of Pittsburgh [n=1], University of South Florida [n=1]).

For patients randomised to the radiation group, radiotherapy was started within 24 h after randomisation. The total dose was 30 Gy given in ten fractions ($3 \cdot 0$ Gy$\times$10 fractions). Treatments were delivered to a port that encompassed one vertebral body above and below the visible lesion. There was a central review of radiotherapy treatment plans to monitor protocol compliance. Patients allocated to surgery were operated on within 24 h after randomisation. The protocol did not specify operative techniques or fixation devices. However, the aim of surgery was to provide immediate direct circumferential decompression of the spinal cord. The operation was tailored for each patient depending on the level of the spine involved and the patient's circumstances. In general, for anteriorly-located tumours the approach in the cervical spine was anterior, and in the thoracic and lumbar spine, depending on the tumour location, the approach was through a transversectomy or anterior approach. For laterally-located tumours, a lateral approach was used, and for posteriorly-located tumours, a laminectomy was done and any other posterior elements involved were removed. Stabilisation of tumours in all locations was performed if spinal instability was present; cement (methyl methacrylate), metallic rods, bone grafting, or other fixation devices were used. Within 1 month of treatment Phillip Tibbs reviewed operative reports and William Regine reviewed plans for post-surgery radiotherapy to monitor protocol compliance. Patients were given radiotherapy, as in the radiation group, within 14 days after surgery. Steroids were given on the same schedule for both groups.

Patients had neurological assessments before treatment, weekly during radiotherapy, and within 1 day after completion of treatment. Patients then had regular study follow-up assessments every 4 weeks until the end of the trial or death. Patients were also reassessed at any time they had symptoms suggestive of neurological progression.

The primary endpoint of the study was the ability to walk after treatment. A patient was deemed ambulatory if he or she could take at least two steps with each foot unassisted (4 steps total), even if a cane or walker was needed. We assessed ambulatory status in two ways, and both methods were prespecified. The combined ambulatory rate was the percentage of patients who maintained or regained the ability to walk immediately after completion of radiotherapy and quantified the initial success rate of treatment. Ambulatory time after treatment was a measure of long-term success. Secondary endpoints were urinary continence, changes in Frankel functional scale scores[19] and American Spinal Injury Association (ASIA) motor scores,[20] and use of

corticosteroids and opioid analgesics. Corticosteroid use was assessed by calculating and comparing mean daily dexamethasone equivalent doses. Pain relief was assessed by calculating and comparing mean daily morphine equivalent doses. Survival time after treatment was also recorded. All time dependent endpoints were measured from the day of randomisation until death or last follow up.

Statistical analysis

Results from previous uncontrolled studies have suggested that the expected combined post-treatment ambulatory rate in patients treated with radiation alone is about 45%,[1–9] and uncontrolled surgical series, in which direct decompressive surgery was used, reported post-treatment ambulatory rates of about 75%.[12–16] These studies suggest that the advantage from surgery is an additional 30% increase in the post-treatment ambulatory rate compared with radiation alone. To determine sample size for this study, we used a more conservative expected difference in post-ambulatory rate between study groups of 20%. With this assumption and with 100 patients in each treatment group, the chance of achieving overall statistically significant results at the $p<0.05$ level, using a two-sided test, was 82%.[21] The study design also included provision for an interim analysis to be done at the halfway point (after 100 patients were entered into the trial) according to the O'Brien-Fleming rule.[22]

An intention-to-treat analysis was used throughout. Multivariate analyses were based on a Cox regression model.[23] The covariates used were treatment group, age, sex, primary tumour type, spinal level involved, predominant position of metastasis in vertebra, stability of spine, Frankel and ASIA scores at study entry, length of time motor symptoms associated with cord compression were present before treatment, and length of time between diagnosis of the primary tumour and development of cord compression. All these analyses were prespecified.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We compared combined ambulatory rates after treatment between the two groups using a Cochran-Mantel-Haenszel statistic based on ambulatory status. This comparison yielded a p value of 0·001, which fell below the predetermined significance level for early termination of the trial according to the O'Brien Fleming rule ($p<0.0054$). Because of proven superiority of surgical treatment, the data safety and monitoring committee deemed the trial should be stopped early.
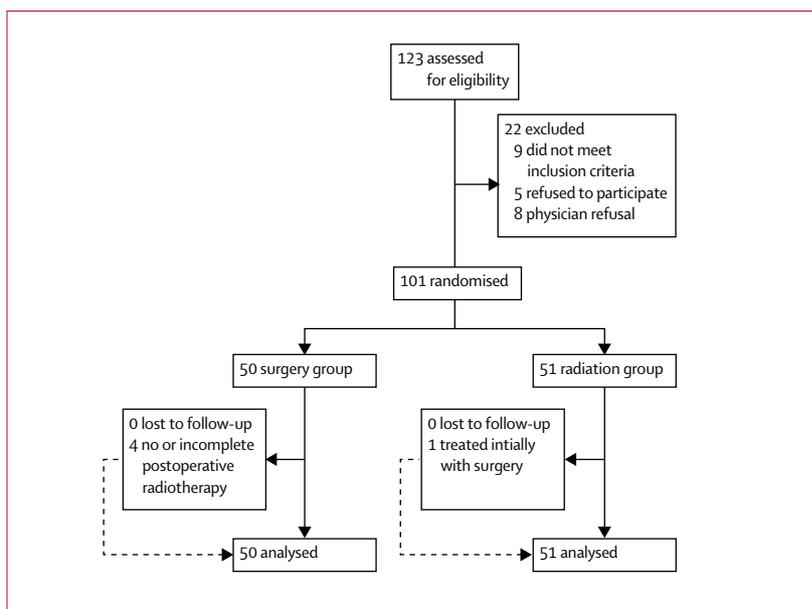

Figure 1: Trial profile

Between Sept 1, 1992, and Dec 31, 2002, 123 patients were assessed for eligibility and, of these, 101 were entered into the trial before it closed (figure 1). Protocol violations occurred with five patients. In the surgery group, three patients did not receive postoperative

	Radiation group (n=51)	Surgery group (n=50)
Men/women	37/14	33/17
Median age, years	60	60
Primary tumours		
Lung	13	13
Breast	6	7
Prostate	10	9
Other genitourinary	6	5
Gastrointestinal	4	2
Melanoma	3	3
Head and neck	2	1
Unknown	3	5
Other	4	5
Walking at entry	35	34
Continent at entry	32	30
Median Frankel score at entry	D	D
Median ASIA score at entry	90	89
Spinal level of compression		
Cervical	5	8
T1-T6	18	20
T7-T12	28	22
Position of spinal tumour		
Anterior	33	28
Lateral	11	9
Posterior	7	13
Unstable spine	18	20
Median time between diagnosis of primary tumour and development of MESCC	7 months	3 months
Median time between development of motor symptoms and treatment of MESCC	12 days	10 days

D=ambulatory but with neurological symptoms.

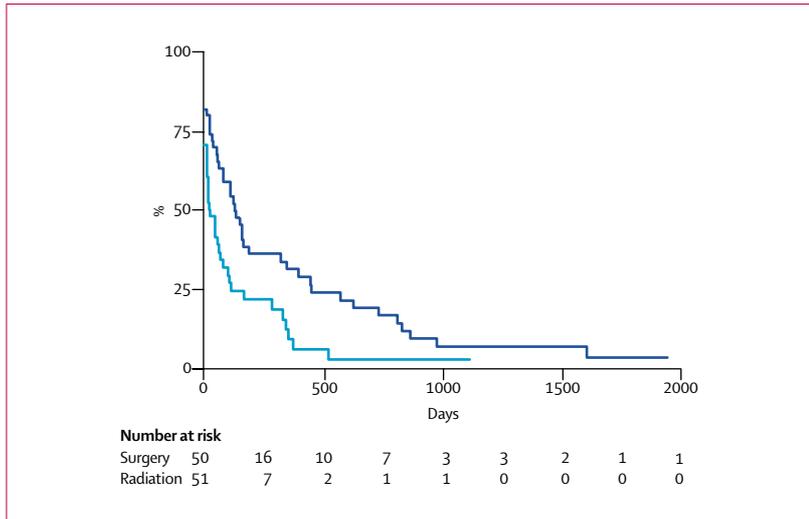**Table 1: Baseline characteristics of study patients**

Figure 2: Kaplan–Meier estimates of length of time all study patients remained ambulatory after treatment
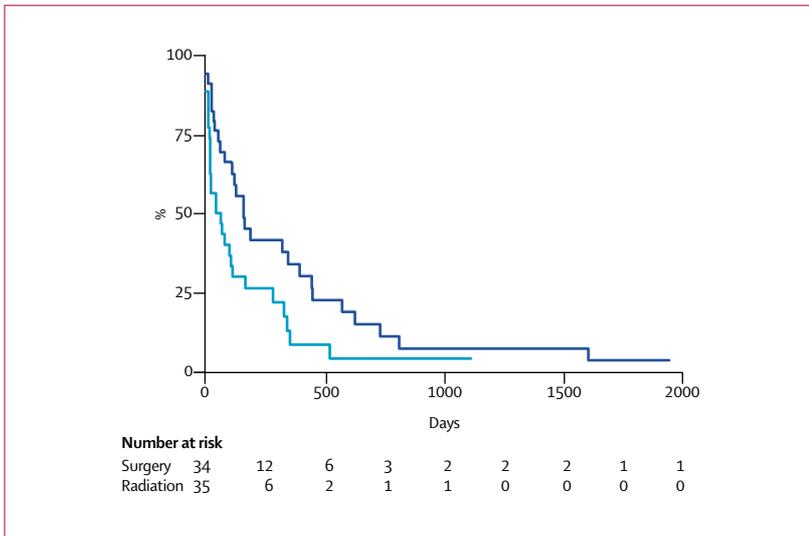

Figure 3: Kaplan–Meier estimates of length of time patients who were ambulatory at study entry remained ambulatory after treatment

radiotherapy and a fourth patient stopped radiotherapy before receiving the complete course. In the radiation group, one patient was treated with surgery as well as postoperative radiotherapy. Table 1 shows baseline characteristics of patients entered in the study. Overall median follow-up times were 102 days (IQR 0–1940) in the surgery group and 93 days (0–1117 days) in the radiation group (p=0·10).

The combined post-treatment ambulatory rate in the surgery group was 84% (42/50) and 57% (29/51) in the radiation group. Ambulatory rates were compared between the two groups using a Cochran-Mantel-Haenszel statistic after stratifying by pretreatment ambulatory status. This analysis yielded a p value of 0·001 with an odds ratio of 6·2 (95% CI 2·0–19·8). Patients in the surgery group retained the ability to walk for significantly longer than did those in the radiation group (median 122 days *vs* 13 days, p=0·003; figure 2). Multivariate analysis showed surgery (p=0·0017) and pretreatment Frankel score (p=0·0008) to be associated with longer ambulatory time.

In the subgroup of patients who could walk at study entry, 94% (32/34) in the surgery group continued to walk after treatment compared with 74% (26/35) in the radiation group (p=0·024). Patients in the surgical group were able to walk for a median of 153 days compared with 54 days in the radiation group (odds ratio 1·82 [95% CI 1·08–3·12] p=0·024; figure 3). Multivariate analysis showed surgery (p=0·0048), Frankel score (p=0·016), and breast primary tumour (p=0·029) to be associated with longer ambulatory times.

32 patients (16 in each group) entered the study unable to walk; of these, ten patients (62%) in the surgery group regained the ability to walk compared with three patients (19%) in the radiation group (p=0·012). Additionally, non-ambulatory patients treated with surgery walked for a median of 59 days compared with a median of 0 days for patients in the radiation group (p=0·04).

Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA

	Radiation group (n=51) median	Surgery group (n=50) median	Relative risk*	95% CI*	P*	Significant predictors**
Maintenance of continence	17 days	156 days	0·47	0·25–0·87	0·016	Surgery RR=0·51 (0·29–0·90)
						Baseline Frankel Score RR=0·56 (0·3–0·73)
Maintenance of ASIA score	72 days	566 days	0·28	0·13–0·61	0·001	Surgery RR=0·30 (0·14–0·62)
						Stable Spine RR=0·43 (0·22–0·83)
						Cervical Spinal Level RR=0·49 (0·26–0·90)
						Baseline Frankel Score RR=0·65 (0·46–0·91)
Maintenance of Frankel score	72 days	566 days	0·24	0·11–0·54	0·0006	Surgery RR=0·26 (0·12–0·54)
						Stable Spine RR=0·39 (0·20–0·75)
						Cervical Spinal Level RR=0·53 (0·74–0·98)
						Baseline Frankel Score RR=0·62 (0·44–0·88)
Survival time	100 days	126 days	0·60	0·38–0·96	0·033	Surgery RR=0·60 (0·40–0·92)
						Breast Primary Tumour RR=0·29 (0·13–0·62)
						Lower Thoracic Spinal Level RR=0·65 (0·43–0·99)

*Based on a Cox model with all covariates included. **Based on a Cox model with only significant predictors included (stepwise selection).

Table 2: Secondary endpoints

scores), functional ability (Frankel scores), and increased survival time (table 2). The surgical group also had a substantial reduction in use of corticosteroids and opioid analgesics. In the surgery group, the median mean daily dexamethasone equivalent dose was 1·6 mg (IQR 0·1–44·0) compared with 4·2 mg (0·0–50·0) in the radiation group (p=0·0093). In the surgery group, the median mean daily morphine equivalent dose was 0·4 mg (0·0–60·0) compared with 4·8 mg (0·0–200·0) in the radiation group (p=0·002).

The 30-day mortality rates were 6% in the surgery group and 14% in the radiation group (p=0·32). 30-day morbidity rates were calculated by deterioration in ASIA and Frankel scores. At 30 days, surgery group patients maintained or improved their pretreatment ASIA muscle strength scores at a significantly (p=0·0064) higher rate than did patients in the radiation group (86% vs 60%). Also, at day 30 after treatment, the percentage of patients with Frankel scores at or above study entry level was significantly (p=0·0008) higher in the surgery group than in the radiation group (91% vs 61%). Surgery did not result in prolonged hospitalisation; the median hospital stay was 10 days in both the surgery group (IQR 2–51 days) and the radiation group (0–41 days; p=0·86). Extended hospital stays (greater than 20 days) occurred in seven patients in the surgery group and 11 in the radiation group.

Ten patients in the radiation group (20%) had a substantial decline in motor strength during radiotherapy and crossed over to receive surgery. The primary tumour histologies of these crossover patients were: lung (four), gastrointestinal (two), prostate (one), other genitourinary (two), sarcoma (one). At the time of surgery, none of these patients could walk. Three (30%) regained the ability to walk. Of the crossover patients, four (40%) had surgical complications consisting of three wound infections and one failure of fixation that needed additional surgery.

Discussion

This prospective randomised trial shows that patients with MESCC treated with direct decompressive surgery plus postoperative radiotherapy retain the ability to walk for longer and regain the ability more often than do patients treated with radiotherapy alone. Surgery allows most patients to remain ambulatory for the remainder of their lives, whereas patients treated with radiation alone spend a substantial proportion of their remaining time paraplegic. Surgical treatment also results in increased survival time. The better survival time in the surgical group was probably because a greater proportion of patients in this group were ambulatory and remained so for longer than those in the radiation group. Therefore, patients in the surgery group were less susceptible to infections, blood clots, and other problems that result in the death of paraplegic patients. Surgical treatment also reduces the need for corticosteroids and opioid pain relief.

The cause of damage to the spinal cord from compression is complex and multifactorial, although two mechanisms predominate.[1,2] Direct compression results in oedema, venous congestion, and demyelination. If the compression is of short duration, the effects are reversible; remyelination and recovery of function is possible. However, with prolonged compression, secondary vascular injury occurs with infarction of the spinal cord. After this type of injury, no meaningful recovery is possible. Surgical decompression is immediate, whereas radiotherapy takes several days to have an effect. Surgery was probably able to provide relief from compression before irreversible vascular injury occurred in a substantial number of patients in our study. Thus a higher percentage of patients were able to recover function in this treatment group, which explains the number of patients who regained the ability to walk after treatment and the initial success of the treatment. The fact that surgery preserved the ability to walk much longer than did radiation is because of the ability of surgery to remove tumour. In patients treated with radiation alone, tumour was left behind and regrowth with secondary compression was more likely.

With any surgical procedure, operative mortality and morbidity have to be weighed against any possible benefit from surgery. Surprisingly, surgery did not result in an increase in length of hospital stay. 30-day mortality rates did not differ significantly between the two groups, and 30-day morbidity was substantially worse in the radiation group. Therefore, there was no excess mortality or morbidity due to surgery.

A possible limitation of the study was patient selection bias. Any study that has exclusion criteria selects a subset of the total number of patients with a disease for study. Our study was designed to reflect the way patients with MESCC were being treated routinely in community and academic medical centres. The patient population studied consisted of those patients for whom surgery would be regarded as a realistic treatment option. Patients with very radiosensitive tumours, multiple areas of spinal cord compression, or total paraplegia for longer than 48 h were excluded. Therefore, the results of this trial cannot be used to justify surgery in all patients with MESCC and apply only to patients comparable to those included in our study. Even in this group of patients, reasonable clinical judgment should be used in the selection of patients for surgery.

Our trial shows that surgery is an effective treatment for MESCC, but should surgery be the initial treatment for all patients similar to those in the study who have operable lesions? An argument could be made that ambulatory patients should be treated with radiation first, and surgery reserved for those patients who progress. This approach would reduce the number of surgeries done and might be as effective. However, the results of our trial do not lend support to the use of

radiation alone as first-line treatment. In the subgroup of patients who were ambulatory at the start of therapy, initial treatment with surgery was significantly better at preserving the ability to walk. Further evidence comes from the radiation patients who crossed over to surgery. These patients were treated initially with radiation and then operated on when they failed radiation and lost the ability to walk. In these patients, only 30% regained the ability to walk. This result compares unfavourably with the 62% post-treatment ambulatory rate of the patients who were originally not able to walk and received surgery as their first treatment. Clearly, first-line treatment with surgery was superior. For these reasons, the best treatment for spinal cord compression caused by metastatic cancer is surgery as initial treatment followed by radiotherapy.

Contributors
R A Patchell had the idea for the study and designed and wrote the protocol in collaboration with colleagues from various disciplines (P A Tibbs and B Young for neurosurgery, W F Regine and M Mohiuddin for radiation oncology, and R J Kryscio for statistics). R Payne and S Saris were principal investigators at their institutions and made substantial contributions of patients to the study.

Conflict of interest statement
We declare that we have no conflict of interest.

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